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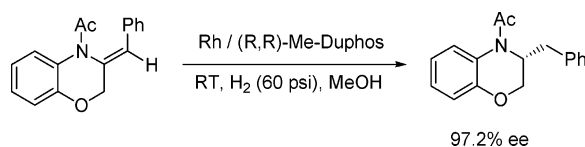# Synthesis and Highly Enantioselective Hydrogenation of Exocyclic Enamides: (Z)-3-Arylidene-4-acetyl-3,4-dihydro-2H-1,4-benzoxazines

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Highly enantioselective hydrogenation of exocyclic enamides, (Z)-3-arylidene-4-acyl-3,4-dihydro-2H-benzoxazines, was achieved in up to 98.6% ee by using Rh/(R,R)-Me-Duphos complex as the catalytic system. The absolute configuration of the product was assigned as R by chemical interrelations.

Optically active 3-substituted-3,4-dihydro-2H-1,4-benzoxazines represent the structure motifs of many naturally occurring substances and chiral drugs. They can also be employed as building blocks in the synthesis of a wide range of biologically active molecules.[1] As shown in Figure 1, levofloxacin, a potent antibacterial agent on the market, possesses the structural unit of 3-substituted-3,4-dihydro-2H-1,4-benzoxazines. It exhibits excellent activities against Gram-positive and -negative bacteria. In addition, some natural aspidosperma-type alkloids also have this structural unit.[1a] The stereoconfiguration at the C-3 position of the 1,4-benzoxazine ring plays an important role for its pharmacological properties.[1e] For example, it is found that levofloxacin is less toxic than its enantiomer.[1e] To get enantiopure compounds, chiral acids[2] and acyl chlorides[3] were employed in the kinetic resolution of racemic products. Furthermore, several stoichiometric and catalytic methods have been developed for the synthesis of this type of building blocks.[4] Elegant examples include Ir/BPPM/BiI$_3$-catalyzed asymmetric hydrogenation of prochiral imine with 90% ee,[4f] and Ru-BINAP-catalyzed asymmetric hydrogenation of acetol as
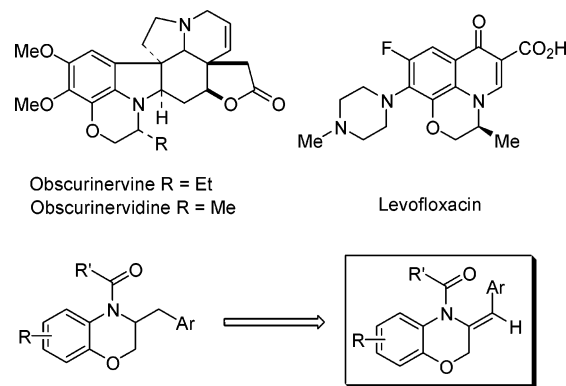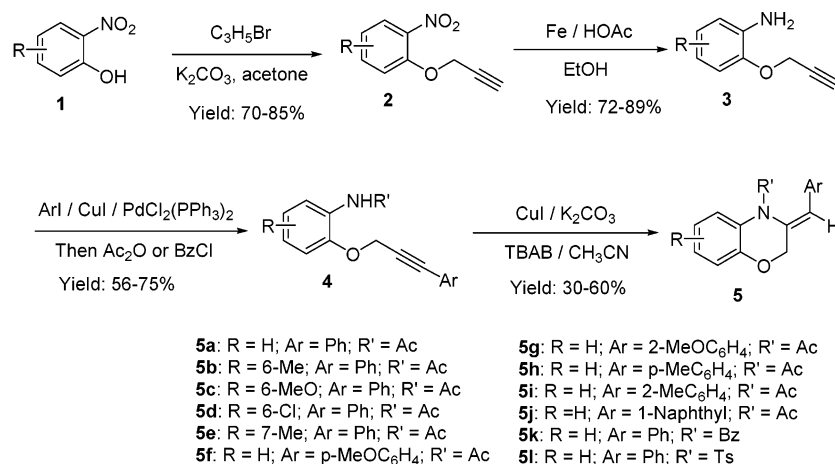

FIGURE 1. Design of cyclic enamides containing 1,4-benzoxazines.

a key intermediate for the synthesis of levofloxacin.[4e] However, the search for an efficient catalytic synthesis of 3-substituted-3,4-dihydro-2H-1,4-benzoxazines is still highly desirable. Recently, catalytic asymmetric hydrogenation of prochiral enamides with Ru- or Rh-complexes

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SCHEME 1. Synthesis of Exocyclic Enamides 5

5a: R = H; Ar = Ph; R' = Ac
5b: R = 6-Me; Ar = Ph; R' = Ac
5c: R = 6-MeO; Ar = Ph; R' = Ac
5d: R = 6-Cl; Ar = Ph; R' = Ac
5e: R = 7-Me; Ar = Ph; R' = Ac
5f: R = H; Ar = p-MeOC$_6$H$_4$; R' = Ac

5g: R = H; Ar = 2-MeOC$_6$H$_4$; R' = Ac
5h: R = H; Ar = p-MeC$_6$H$_4$; R' = Ac
5i: R = H; Ar = 2-MeC$_6$H$_4$; R' = Ac
5j: R = H; Ar = 1-Naphthyl; R' = Ac
5k: R = H; Ar = Ph; R' = Bz
5l: R = H; Ar = Ph; R' = Ts

together with chiral bisphosphine ligands,[5] such as BINAP, BICP, PennPhos, Binapine, DIOP*, *o*-Ph-hexaMeO-BIPHEP, TangPhos, BPE, BisP, BDPMI, BDPAB, or some monodentate phosphorus ligands,[6] has attracted much attention as an efficient method for the synthesis of the corresponding chiral amines. The presence of a secondary donor acyl group in the substrate, which will allow the chelation of the substrate to the central metal, is crucial for the reactivity and enantioselectivity.[7] Ac-

cording to retrosynthetic analysis, we envisioned that direct asymmetric hydrogenation of exocyclic enamides, 3-arylidene-4-acetyl-3,4-dihydro-2*H*-1,4-benzoxazines, should be a convenient and efficient route to the corresponding chiral saturates. Herein, we report the synthesis and highly enantioselective hydrogenation of (*Z*)-3-arylidene-4-acyl-3,4-dihydro-2*H*-benzoxazines.

All enamide substrates in this study were synthesized by a modification of a published procedure.[8] As shown in Scheme 1, the treatment of *o*-nitrophenol derivatives **1** with propargyl bromide in the presence of K$_2$CO$_3$ in acetone afforded **2** in 70–85% yield, and then **2** was reduced with iron powder in acetic acid to give 2-(prop-2′-ynyloxy)aniline derivatives **3**. Compound **3** underwent palladium-catalyzed C-arylation with aryl iodides in the present of Cu(I) and triethylamine to provide the disubstituted alkynes, which were directly converted to the corresponding acetamides with acetic anhydride under base condition in dichloromethane. The acetamides **4** could then be cyclized with CuI in the presence of K$_2$CO$_3$ and tetrabutylammonium bromide in acetonitrile at 80 °C to produce the corresponding hydrogenation substrates **5** with low to moderate yields.[8] Instead of acetic anhydride, benzoyl chloride and tosyl chloride were employed to synthesize compounds **5k** and **5l**, respectively, under the same conditions. It is noted if the aryl group at the carbon–carbon triple bond was replaced with alkyl group, the Cu-catalyzed cyclization (*N*-(2-hept-2-ynyloxyphenyl)acetamide) could not occur under the above reaction conditions. The *Z*-sterochemistry of the exocyclic double bond of the substrate **5a** was assigned according to NOE experiments. When methylenic protons of the heterocyclic ring of compound **5a** were irradiated, a strong enhancement of the vinylic proton signal of the exocyclic double bond was observed.

Since Rh/Me-DuPhos has been successfully applied to asymmetric hydrogenation of acyclic and cyclic enamides,[5e,f] we initially examined the [Rh(COD)$_2$]BF$_4$/(*R,R*)-Me-DuPhos complex for hydrogenation of the enamide substrate **5a**. The reaction was carried out under 60 psi of H$_2$ at room temperature with a ratio of

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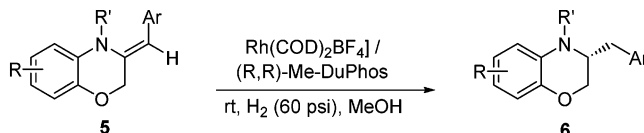
TABLE 1. Rh-Catalyzed Asymmetric Hydrogenation of Exocyclic Enamide 5a[a]
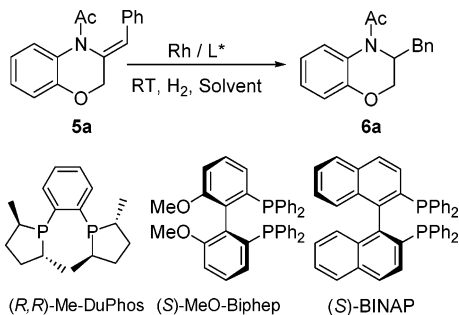
entry	Rh precursor	ligand	solvent	P (psi)	yield[b] (%)	ee[c] (%)
1	Rh(COD)$_2$BF$_4$	(R,R)-Me-DuPhos	CH$_2$Cl$_2$	60	98	39.0
2	Rh(COD)$_2$BF$_4$	(R,R)-Me-DuPhos	toluene	60	45	76.3
3	Rh(COD)$_2$BF$_4$	(R,R)-Me-DuPhos	THF	60	75	96.7
4	Rh(COD)$_2$BF$_4$	(R,R)-Me-DuPhos	MeOH	60	97	97.2
5	Rh(COD)$_2$BF$_4$	(R,R)-Me-DuPhos	i-PrOH	60	96	72.0
6	Rh(COD)$_2$BF$_4$	(R,R)-Me-DuPhos	MeOH	30	97	96.8
7	Rh(COD)$_2$BF$_4$	(R,R)-Me-DuPhos	MeOH	200	97	93.8
8	[Rh(COD)Cl]$_2$	(R,R)-Me-DuPhos	MeOH	60	90	83.2
9	Rh(NBD)$_2$BF$_4$	(R,R)-Me-DuPhos	MeOH	60	96	96.3
10	Rh(COD)$_2$BF$_4$	(S)-MeO-Biphep	MeOH	60	94	80.8
11	Rh(COD)$_2$BF$_4$	(S)-BINAP	MeOH	60	24	66.8

[a] Reactions were carried out at room temperature for 16 h. The catalysts were made in situ by stirring a solution of Rh precursor and bisphosphine ligand in MeOH for 10 min. Substrate/Rh/ligand = 1/0.01/0.011. [b] Isolated yields based on substrate **5a**. [c] Enantiomeric excess was determined by chiral HPLC using a Chiralcel OD-H column.

TABLE 2. Rh/(R,R)-Me-DuPhos-Catalyzed Asymmetric Hydrogenation of 5[a]

entry	R in 5	Ar in 5	R′ in 5	ee[b](%)	config[c]
1	H (**5a**)	Ph	Ac	97.2	R
2	6-Me (**5b**)	Ph	Ac	98.0	(R)
3	6-MeO (**5c**)	Ph	Ac	97.2	(R)
4	6-Cl (**5d**)	Ph	Ac	98.2	(R)
5	7-Me (**5e**)	Ph	Ac	97.2	(R)
6	H (**5f**)	p-MeOC$_6$H$_4$	Ac	98.6	(R)
7	H (**5g**)	2-MeOC$_6$H$_4$	Ac	96.4	(R)
8	H (**5h**)	p-MeC$_6$H$_4$	Ac	98.2	(R)
9	H (**5i**)	2-MeC$_6$H$_4$	Ac	90.6	(R)
10	H (**5j**)	1-naphthyl	Ac	92.2	(R)
11[d]	H (**5k**)	Ph	Bz	90.5	(R)
12[e]	H (**5l**)	Ph	Ts	N/A	N/A

[a] The reaction was run in methanol under hydrogen pressure of 60 psi for 16 h, subtrate/[Rh(COD)$_2$]BF$_4$/(R,R)-Me-DuPhos = 1/0.01/0.011. [b] Enantiomeric excess was determined by HPLC with chiral column. [c] Absolute configurations of these products were assigned by analogy. [d] (S)-MeO-Biphep was used. [e] No reaction.

substrate/Rh/(R,R)-Me-DuPhos of 100:1:1.1. The results are summarized in Table 1. It was observed that the reaction was dependent on solvent. The catalytic hydrogenation goes to completion in dichloromethane, methanol, and 2-propanol under 60 psi of H$_2$ in 16 h (entries 1, 4, and 5), while only 45% yield was achieved in toluene (entry 2). Enantioselectivities dropped to 39% and 72% when dichloromethane and 2-propanol were used as solvents, respectively (entries 1 and 5). Systematic investigation showed that methanol was the best solvent for this transformation. Increasing the pressure of H$_2$ resulted in a slight decrease of enantioselectivity. For example, 93.8% ee was obtained under 200 psi of H$_2$ while 96.8% ee was achieved under 30 psi of H$_2$ (entries 6 and 7). Different catalyst precursors and chiral bisphosphine ligands were also examined for hydrogenation of **5a** under the above optimized conditions, and it was found that a cationic Rh(I) species gave better results than a neutral Rh(I) complex (97.2% ee, entry 4 vs 83.2% ee, entry 8). On the basis of the result shown in entry 4, other chiral bisphosphines were tried for asymmetric hydrogenation of **5a**. It could be concluded that hydrogenation of **5a** with Rh/BINAP (66.8% ee, entry 11) and Rh/MeO-Biphep species (80.8% ee, entry 10) gave lower ee values than the reaction with Rh/(R,R)-Me-Duphos complex (97.2% ee, entry 4) did.

Under the optimal conditions, several (Z)-3-arylidene-4-acyl-3,4-dihydro-2H-1,4-benzoxazines **5a**−**k** were investigated (Table 2). Hydrogenation gives high enantioselectivities (>97% ee) regardless of the substituents on the aromatic ring of 1,4-benzoxazines. In the case of the compounds with an ortho substituent of aryl on exocyclic
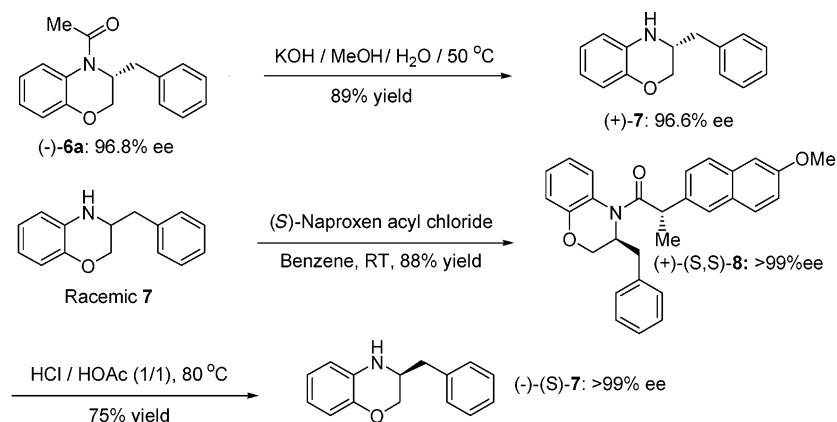
double bond, a slightly low enantioselectivity was obtained (90.6% ee, entry 9 and 92.2% ee, entry 10). Replacement of the N-Ac of (Z)-**5a** with an N-Bz group led to a significant drop in the enantioselectivity (90.5% ee, entry 11 vs 97.2% ee, entry 4). No reduction was observed with (Z)-3-benzylidene-4-tosyl-3,4-dihydro-2H-benzoxazine as the hydrogenation substrate under standard condition, and the reason is not clear.

It was noted that the resolution of ^{1}H and ^{13}C NMR was dependent on the temperature. The ^{1}H and ^{13}C NMR spectra of the hydrogenation products measured at room temperature are broadening (see the Supporting Information), while the spectral lines become narrow with increasing temperature. The best resolution ^{1}H and ^{13}C NMR spectra were obtained in DMSO-d_6 at 100 °C. This phenomenon was also observed in other acyl-protected 2-methyl-1,2,3,4-tetrahydroquinolines, 2-methylindoles, and 3-methyl-3,4-dihydro-2H-1,4-benzoxazines in recent publications.[3]

The absolute configuration of chiral products was figured out by chemical interrelation comparing with the known absolute configuration of (S)-naproxen acyl chloride, and was comfirmed by X-ray crystallographic analysis (Scheme 2). Racemic product **6a** was hydrolyzed with KOH/MeOH to give amine **7**, which then reacted with (S)-naproxen acyl choride[9] to afford the amide **8** with a known absolute configuration in 88% yield, using Chupakhin's condition[3c] (benzene, room temperature). Recrystallization from DCM/hexane gave amide **8** (>99% ee) as a colorless crystal, and its absolute configuration was assigned as (S,S)-(+)-**8** by X-ray diffraction analysis (see the Supporting Information). The (S,S)-amide **8** was hydrolyzed by heating in a mixture of concentrated hydrochloric and acetic acids to afford (S)-(−)-**7** in 88% yield with high enantiomeric purity (>99% ee). The chiral hydrogenation product (−)-**6a** (96.8% ee) was hydrolyzed

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SCHEME 2 The Determination of the Absolute Configuration of 6a

(10) Vogel, A. I. *A Text Book of Practical Organic Chemistry*, 4th ed.; ELBS, Longman Group Limited; London, UK, 1978; p 658.

in a mixture of KOH/MeOH to give (+)-**7** (96.6% ee) without loss of optical purity. By comparison of the sign of optical rotation, it was found that the absolute configuration of the product (+)-**7** was *R*. Thus the absolute configuration of the product (−)-**6a** was unambiguously assigned as the *R* configuration. The configurations of other compounds **6** are deduced based on the signs of the optical rotations because of the structure similarity.

In summary, we have designed and synthesized a new type of cyclic enamide from the cheap starting material *o*-nitrophenol derivatives, which can be hydrogenated with high enantioselectivity by using commercially available Rh/(*R*,*R*)-Me-DuPhos complex as the catalyst. The absolute configuration of the hydrogenation product was also assigned by chemical interrelation. This method provides an efficient access to a variety of optically active 3-substituted-3,4-dihydro-2*H*-1,4-benzoxazines.

Experimental Section

General Procedure for Propargylation of 2-Nitrophenol Derivatives. A mixture of 2-nitrophenol **1a** (6.95 g, 50 mmol) and anhydrous K_2CO_3 (7.05 g, 51 mmol) in dry acetone (50 mL) was stirred for 3 h at room temperature. Propargyl bromide (7.14 g, 60 mmol) in acetone (15 mL) was then added during 1 h. The mixture was then refluxed for 16 h with constant stirring under nitrogen atmosphere, and TLC analysis indicated all the starting materials had been consumed. After removal of acetone under reduced pressure, the reaction mixture was poured into water (50 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic layer was washed successively with hydrochloric acid (3%), water, and brine and dried over anhydrous Na_2SO_4. After removal of solvent, the residue was purified by recrystallization from hexane−dichloromethane to give the desired product **2a** as a light yellow to yellow solid (6.64 g, 75%). **2-(Prop-2′-ynyloxy)-nitrobenzene (2a)**:[8] ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.84 (dd, J_1 = 1.6 Hz, J_2 = 8.0 Hz, 1H), 7.58−7.54 (m, 1H), 7.26(d, J = 8.4 Hz, 1H), 7.11−7.08 (m, 1H), 4.85 (d, J = 2.4 Hz, 2H), 2.60 (t, J = 2.4 Hz, 1H).

General Procedure for Reduction of Nitro Compounds 2 with Fe/Ac$_2$O. 3a−e were prepared by the reduction of **2a−e** with Fe/AcOH following the known procedure.[10] **2-(Prop-2′-ynyloxy)aniline (3a)**:[8] yield 80%; ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.96−6.92 (m, 1H), 6.88−6.81 (m, 1H), 6.74 (t, J = 8.2 Hz, 2H), 4.73 (d, J = 2.3 Hz, 2H), 2.53 (t, J = 2.2 Hz, 1H).

General Procedure for Sonogashira Coupling and Acylation. A mixture of iodobenzene (5.10 g, 25 mmol), (PPh$_3$)$_2$PdCl$_2$ (0.526 g, 0.75 mmol), and CuI (0.238 g, 1.25 mmol) in triethylamine (50 mL) was stirred under nitrogen atmosphere for 40 min, and then aniline derivative **3a** (4.413 g, 30 mmol) in triethylamine (40 mL) was added slowly. The resulting reaction mixture was stirred at room temperature for 16 h under nitrogen atmosphere. After removal of triethylamine under reduced pressure, the reaction mixture was poured into water (150 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic layer was washed successively with water and brine and dried over anhydrous Na$_2$SO$_4$. After removal of solvent, the residue was used in the next step without further purification. The residue was dissolved in dry dichloromethane (50 mL). Then under ice-cold conditions, pyridine (2.43 mL, 30 mmol) and acetic anhydride (2.64 mL, 28 mmol) were added. After being stirred at room temperature for about 2 h under nitrogen atmosphere, the reaction was quenched with brine (50 mL). The separated aqueous layer was then extracted with dichloromethane (3 × 50 mL). The combined organic layer was washed successively with hydrochloric acid (3%), water, and brine and dried over anhydrous Na$_2$SO$_4$. After removal of solvent, the residue was purified by recrystallization from hexane−dichloromethane to give the desired product **4a** (4.438 g, 67%). **N-[2-(3′-Phenyl-prop-2′-ynyloxy)phenyl]acetamide (4a)**: ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.39 (d, J = 7.6 Hz, 1H), 7.82 (s, 1H), 7.43−7.41 (m, 2H), 7.34−7.30 (m, 2H), 7.06−7.00 (m, 3H), 4.97 (s, 2H), 2.19 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 24.9, 57.5, 83.6, 87.8, 112.0, 120.2, 121.9, 122.0, 123.6, 128.4, 128.9, 131.8, 146.0, 168.2; HRMS calcd for C$_{17}$H$_{16}$NO$_2$ (M + 1) 266.1176, found 266.1161.

General Procedure for Cyclization to Benzoxazines. A mixture of the acetamide **4a** (5.30 g, 20 mmol), CuI (761 mg, 4.0 mmol), anhydrous K$_2$CO$_3$ (6.91 g, 50 mmol), and *n*-Bu$_4$-NBr (6.447 g, 20 mmol) in dry acetonitrile (150 mL) was stirred for about 20 min under nitrogen atmosphere, and the resulting mixture was refluxed for 12 h under nitrogen atmosphere. After removal of acetonitrile under reduced pressure, the reaction mixture was poured into water (150 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic layer was washed successively with water, saturated NH$_4$Cl aqueous solution, and brine and dried over anhydrous Na$_2$-SO$_4$. After removal of solvent, the residue was subjected to column chromatography to give the desired product and the recovered material. The product was finally recrystallized from hexane−dichloromethane to give the desired enamide **5a** as a white solid (1.59 g, 30%) and recovered **4a** (3.18 g, 60%). **(Z)-3-Benzylidene-4-acetyl-3,4-dihydro-2*H*-1,4-benzoxazine (5a)**: mp 119−120 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.99 (d, J = 7.9 Hz, 1H), 7.45−7.33 (m, 5H), 7.11−7.09 (m, 1H), 7.03−6.99 (m, 1H), 6.93 (dd, J_1 = 0.8 Hz, J_2 = 8.2 Hz, 1H), 6.63 (s, 1H), 4.81 (s, 2H), 1.94 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ

22.1, 70.9, 116.7, 120.5, 124.4, 126.0, 126.6, 128.5, 128.9, 129.0, 130.5, 133.7, 146.7, 168.2; HRMS calcd for $C_{17}H_{16}NO_2$ (M + 1) 266.1176, found 266.1162.

General Procedure for Asymmetric Hydrogenation of 5. In a glovebox, the Rh-(R,R)-Me-DuPhos complex was made in situ by mixing [Rh(COD)$_2$]BF$_4$ (2.0 mg, 0.005 mmol) and (R,R)-Me-DuPhos (1.7 mg, 0.0055 mmol) in MeOH (2.0 mL). After the mixture was stirred at room temperature for 10 min, substrate **5a** (133 mg, 0.5 mmol) in MeOH (2.0 mL) was added via a syringe. The hydrogenation was performed at room temperature under 60 psi of H$_2$ for 16 h. After the hydrogen was carefully released, the reaction mixture was passed through a short silica gel column to remove the catalyst. Purification was performed by a silica gel column eluted with hexanes/EtOAc to give pure products **6a** (129 mg, 97%). **(R)-3-Benzyl-4-acetyl-3,4-dihydro-2H-1,4-benzoxazine(6a):** 97.2% ee; [α]^{20}$_D$ −90.8 (*c* 0.80, CHCl$_3$); ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ 7.67 (d, *J* = 8.0 Hz, 1H), 7.31−7.21(m, 3H), 7.14−7.07 (m, 3H), 6.95−6.92 (t, *J* = 7.5 Hz, 2H), 4.77 (s, 1H), 4.29 (t, *J* = 5.5 Hz, 1H), 4.15 (dd, J_1 = 2.9 Hz, J_2 = 11.0 Hz, 1H), 2.81 (dd, J_1 = 6.3 Hz, J_2 = 13.8 Hz, 1H), 2.68 (dd, J_1 = 8.9 Hz, J_2 = 13.7 Hz, 1H), 1.99 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, 100 °C) δ 22.3, 35.0, 50.9, 67.7, 116.2, 119.9, 124.1, 124.9, 125.1, 126.2, 128.1, 128.8, 137.6, 145.8, 168.2; HRMS calcd for $C_{17}H_{17}NO_2$ (M + 1) 268.1332, found 268.1325; HPLC, UV 254 nm, Chiralcel OD-H, 1.0 mL/min, 30% 2-propanol/70% hexane, (*R*) t_1 = 5.89 min; (*S*) t_2 = 7.34 min.

The Determination of the Absolute Configuration: (±)-3-Benzyl-3,4-dihydro-2H-1,4-benzoxazine (7). A mixture of (±)-**6a** (905 mg, 3.4 mmol), potassium hydroxide (1.28 g, 22.8 mmol), water (1.2 mL), and methanol (5 mL) was stirred at 50−60 °C under nitrogen atmosphere for 12 h. The mixture was then poured into water and extracted with ether. The combined organic layer was washed successively with water and brine and dried over anhydrous Na$_2$SO$_4$. After removal of solvent, the residue was subjected to column chromatography to give the desired product (±)-**7** (612 mg). Yield 80%: mp 71−72 °C [lit.[11]mp 63 °C (*n*-pentane)]; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.32 (t, *J* = 7.4 Hz, 2H), 7.24 (dd, J_1 = 7.2 Hz, J_2 = 11.2 Hz, 3H), 6.68−6.59 (m, 3H), 6.46 (t, *J* = 7.4 Hz, 1H), 5.76 (s, 1H), 3.97 (d, *J* = 10.4 Hz, 1H), 3.74 (dd, J_1 = 6.6 Hz, J_2 = 10.6 Hz,1H), 3.52 (d, *J* = 6.0 Hz, 1H), 2.81 (dd, J_1 = 6.0 Hz, J_2 = 13.6 Hz, 1H), 2.70 (dd, J_1 = 7.8 Hz, J_2 = 13.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 38.1, 50.1, 67.5, 114.8, 115.8, 116.7, 121.2, 126.3, 128.4, 129.3, 134.2, 137.8, 142.8; HRMS calcd for $C_{15}H_{16}NO$ (M + 1) 226.1226, found 226.1238.

Similar Condition for the Synthesis of (R)-(+)-3-Benzyl-3,4-dihydro-2H-1,4-benzoxazine (7). Yield 89%; 96.6% ee, [α]^{20}$_D$ +46.1 (*c* 0.46, CHCl$_3$), HPLC (Chiralcel OD-H, elute: 5% 2-propanol/95% hexane, flow rate: 1.0 mL/min, detector: UV 254 nm), (*R*) t_1 = 11.67 min; (*S*) t_2 = 12.87 min.

(11) Fusco, R.; Garanti, L.; Zecchi, G. *J. Org. Chem.* **1975**, *40*, 1906.

N-[(2S)-2-(6-Methoxynaphthyl-2)propionyl]-(3S)-2,3-dihydro-3-benzyl-4H-1,4-benzoxazine (8). To a stirred solution of racemate **7** (112 mg, 0.5 mmol) in anhydrous benzene (1.0 mL) was added a solution of (*S*)-naproxen acyl chloride[9] (62 mg, 0.25 mmol) in benzene (2.0 mL) at 5 °C. The mixture was stirred at room temperature for 5 h, then 2 mL of 1 N HCl was added to the reaction mixture at 5 °C followed by extraction with benzene. The combined organic layer was washed successively with water, 5% aqueous NaHCO$_3$ solution, and brine and dried over anhydrous Na$_2$SO$_4$. After removal of solvent, the residue was subjected to column chromatography to give the desired white solid **8** (98 mg, yield based on (*S*)-naproxen acyl chloride: 88%). The product was finally recrystallized from hexane−dichloromethane to give the colorless crystals. Mp 143−144 °C; [α]^{25}$_D$ +36.7 (*c* 1.0, CHCl$_3$); ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ 7.66 (d, *J* = 8.8 Hz, 2H), 7.60 (d, *J* = 8.8 Hz, 1H), 7.39 (s, 1H), 7.23−7.10 (m, 7H), 6.98 (t, *J* = 7.2 Hz, 3H), 6.83 (dd, J_1 = 1.0 Hz, J_2 = 8.2 Hz, 1H), 4.92 (t, *J* = 7.0 Hz, 1H), 4.52 (q, *J* = 6.8 Hz, 1H), 4.11 (d, *J* = 11.2 Hz, 1H), 3.89 (d, *J* = 2.8 Hz, 1H), 3.87 (s, 3H), 2.60 (dd, J_1 = 7.6 Hz, J_2 = 13.6 Hz, 1H), 2.36 (dd, J_1 = 8.0 Hz, J_2 = 13.6 Hz, 1H), 1.47 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, 100 °C) δ 18.6, 34.2, 41.5, 49.9, 45.7, 66.8, 105.9, 115.7, 117.8, 119.4, 123.5, 125.0, 125.4, 125.7, 126.2, 127.5, 128.0, 128.3, 132.7, 135.8, 136.7, 146.1, 156.8, 172.2; HRMS calcd for $C_{29}H_{27}$-NO$_3$ (M + 1) 438.2064, found 438.2045.

(S)-(-)-3-Benzyl-3,4-dihydro-2H-1,4-benzoxazine (7). (*S,S*)-(+)-**8** (24 mg, 0.055 mmol) was refluxed in a mixture of 1 mL of acetic acid and 1.0 mL of hydrochloric acid for 5 h under nitrogen atmosphere. The reaction mixture was evaporated to dryness in vacuo. Water (10 mL) was then added and the resulting mixture was cooled in an ice bath. The precipitate was filtered off and washed with water. The combined filtrates were alkalized by 10 N NaOH up to pH 8−9 under ice-cooling, and extracted with CH$_2$Cl$_2$ (3 × 10 mL). The combined organic layer was washed successively with water and brine and dried over anhydrous Na$_2$SO$_4$. After removal of solvent, the residue was subjected to column chromatography to give the desired white solid (*S*)-(−)-**7** (9 mg, 75%); [α]^{25}$_D$ −39.8 (*c* 0.1, CHCl$_3$); >99.5% ee. The HPLC analysis showed only a single peak, and the minor enantiomer could not be detected. HPLC (Chiralcel OD-H, elute: 5% 2-propanol/95% hexane, flow rate: 1.0 mL/min, detector: UV 254 nm), t_S = 12.63 min.

Supporting Information Available: X-ray crystal structure of **8**, spectroscopic characterization of the unknown compounds, and HPLC data. This material is available free of charge via the Internet at http://pubs.acs.org.

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