General Asymmetric Synthesis of Isoquinoline Alkaloids. Enantioselective Hydrogenation of Enamides Catalyzed by BINAP-Ruthenium(II) Complexes

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In the presence of a small amount of RuX_2[(*R*)- or (*S*)-BINAP] (X = anionic ligand) a wide range of (*Z*)-2-acyl-1-benzylidene-1,2,3,4-tetrahydroisoquinolines are hydrogenated to give the saturated products in nearly quantitative yields and in high (up to 100%) optical yields. The enamide substrates are selectively prepared by N-acylation of the corresponding 1-benzylated 3,4-dihydroisoquinolines under suitable acylation conditions; some crystalline materials having low solubility are obtained by a second-order *Z*/*E* stereomutation technique utilizing the double-bond photolability and lattice energy effects. This asymmetric hydrogenation sets the key stereogenic center in a predictable manner, either *R* or *S* flexibly, at the C(1) position of the benzylated tetrahydroisoquinolines. The chiral products are converted by standard functional group modification to tetrahydropapaverine, laudanosine, tretoquinol, norreticuline, etc. Hydrogenation of the simple 1-methylene substrate is used for synthesis of salsolidine. This enantioselective hydrogenation is applied to the synthesis of morphine and its artificial analogues such as morphinans and benzomorphans of either chirality. A mnemonic device is presented for predicting the reactivity and enantiofacial selection of the BINAP-Ru catalyzed hydrogenation. Reaction with BINAP-Rh catalyst proceeds with a lower enantioselectivity and an opposite sense of asymmetric induction.

Introduction

Isoquinolines are found abundantly in the plant kingdom, comprising the largest family of alkaloids.[1] In particular, 1-benzyl-1,2,3,4-tetrahydroisoquinolines, or often simply called benzylisoquinolines, occupy a central place from which a multitude of structural groups are derived, typified by protoberberines, aporphines, bis(benzylisoquinolines), phthalide isoquinolines, morphine, etc., as illustrated in Figure 1. Some natural alkaloids possess the 1*S* absolute configuration, while the others possess the 1*R* geometry. Since many of these alkaloids exhibit important physiological activities, the naturally occurring products provide a basis for the development of useful therapeutic medicines possessing antihypertensive, hemostatic, smooth or skeletal muscle relaxant, antispasmodic, antitussive, antimalarial, narcotic, analgesic, or antipyretic activities.[2] Such a situation has attracted the attention of synthetic organic chemists for over a century, and consequently, many efficient synthetic procedures have been explored. Unfortunately, although many benzylisoquinolines show totally different biological or physiological functions between the 1*R* and 1*S* enantiomers, most existing methods are suitable only for the synthesis of the racemic compounds requiring resolution of the products by chiral acids[3] or via derivatization with amino

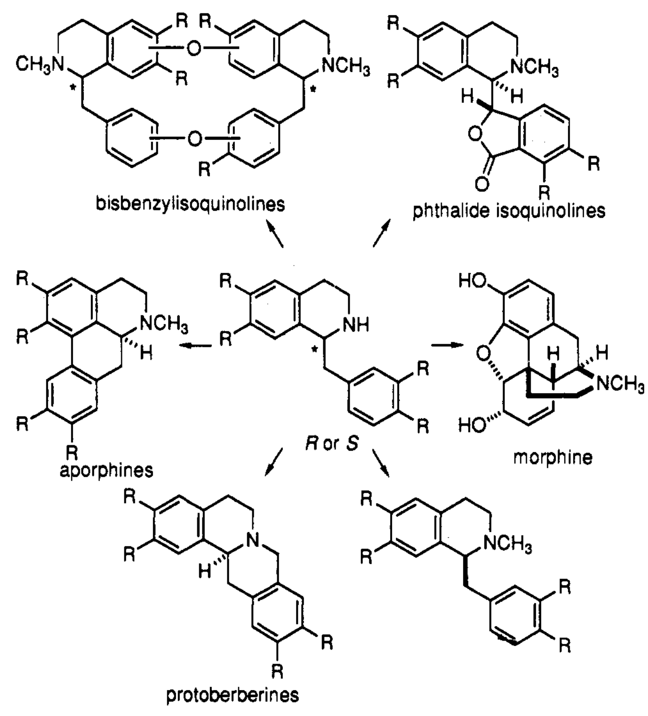

Figure 1. Benzylisoquinoline alkaloids.

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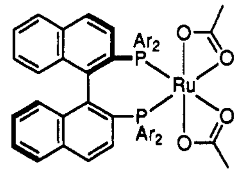
acids or carbohydrates.[4] For supplying the optically active alkaloids, development of an enantioselective synthesis is highly desirable. An elegant solution along this line was provided by Meyers and his collaborators who found diastereoselective alkylation of 1-lithiated tetrahydroisoquinolines containing an amino acid-derived *N*-imino function which leads to the 1*S* enantiomers.[5] Some other examples based on stoichiometric chirality transfer include asymmetric syntheses using as the key step sodium borohydride reduction of optically active α-alkylbenzylamine derivatives,[6] diastereoselective hydrogenation of chiral enamides,[7] addition of organometallic reagents to chiral iminium compounds,[8] intramolecular addition of amines to chiral vinyl sulfoxides,[9] addition of chiral sulfoxide anions to imines or nitrones,[10] asymmetric Pictet–Spengler reaction,[11] and reduction of 1-alkyl-3,4-dihydroisoquinolines by chiral sodium (triacyloxy)borohydrides.[12] Although these asymmetric syntheses are sometimes attained in high chemical and optical yields, an obviously ideal way is asymmetric catalysis by which a large quantity of the chiral compound can be produced using a small amount of a chiral catalyst. Catalytic enantioselective synthesis of 1-benzylated tetrahydroisoqinolines, if feasible, realizes a general synthesis of the large family of isoquinoline alkaloids. Kagan provided the first example toward this end by finding an enantioselective hydrosilylation of a 1-alkyl-3,4-dihydroisoquinoline catalyzed by a DIOP–Rh(I) complex, though the highest optical yield remained 39%.[13] A recently found high-pressure hydrogenation (140 atm) of the 1-methyl derivative using a chiral titanocene catalyst gives salsolidine in up to 98% ee.[14] Hyrogenation of 2-acetyl-1-methylene-1,2,3,4-tetrahydroisoquinoline catalyzed by a chiral phosphine–Rh complex afforded, after deacetylation, salsolidine with 45% ee.[15] Thus, in view of the general significance of chiral isoquinoline alkaloids, development of a truly efficient stereoselective synthesis is imperative.

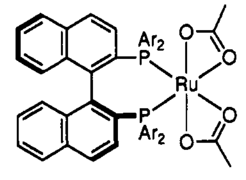
Some years ago we preliminarily reported the highly enantioselective synthesis bsed on BINAP–Ru(II)[16]-catalyzed hyrogenation of 2-acyl-1-alkylidene-1,2,3,4-tetrahydroisoquinolines.[17] The new method is general, chirally flexible, and very practical. In response to numerous inquiries which we have received since then, this paper describes the details of the asymmetric hydrogenation including the selective preparation of the enamide substrates, reaction conditions, and scope and limitations. The origin of the high degree of enantioselection is also discussed.

Results and Discussion

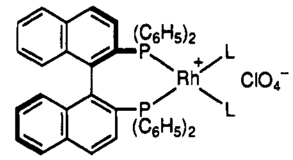
Planning. The efficiency of the enantioselective synthesis of amino acids with the aid of BINAP–transition metal complexes such as 1 and 2 prompted this study.[18]



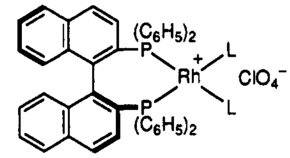
(R)-**1a**, Ar = C_6H_5
(R)-**1b**, Ar = p-$CH_3C_6H_4$



(S)-**1a**, Ar = C_6H_5
(S)-**1b**, Ar = p-$CH_3C_6H_4$



(R)-**2a**, L–L = 1,5-cyclooctadiene
(R)-**2b**, L = CH_3OH
(R)-**2c**, L–L = (R)-BINAP



(S)-**2a**, L–L = 1,5-cyclooctadiene
(S)-**2b**, L = CH_3OH
(S)-**2c**, L–L = (S)-BINAP

We selected (Z)-2-acyl-1-benzylidene-1,2,3,4-tetrahydroisoquinolines **3** as precursors of the desired products **4** because hydrogenation of the structurally related olefins **5** catalyzed by a BINAP–Rh(I)[19] or –Ru(II) complex[20] gives the protected phenylalanines **6** in high ee. The extensive study of the Rh catalyzed reaction[21] revealed that (1) the presence of the *N*-acyl function in **5** is crucial for the reaction because it acts as a binding tether to the catalytic

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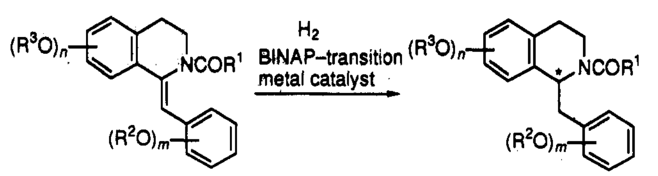

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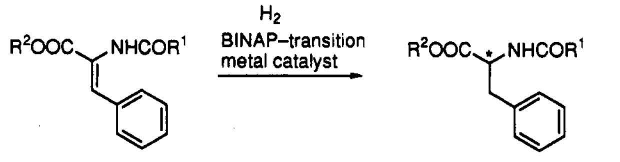

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Figure 2. Enantioselective hydrogenation of enamides.

metal center, (2) the Z olefin geometry is important for high reactivity and high enantioselection, and (3) the carboxyl or ester group may be replaced by other electronegative groups. Later, certain β-alkoxycarbonylated enamides were also found to be good substrates giving optically active β-amino acids.[22] Thus, the enamides of type **3** seemed to satisfy the requirements of good substrates.

Catalysts. In most hydrogenation experiments, we used $Ru(CH_3COO)_2$[(R)- or (S)-BINAP] or analogues of type **1** as catalysts. The pure Ru(II) diacetate complex **1a** was prepared by treating $[RuCl_2(cod)]_n$ first with (R)- or (S)-BINAP and triethylamine in toluene at 110 °C and then with sodium acetate in *tert*-butyl alcohol at 80 °C.[23] It is now most conveniently prepared by a one-pot, two-stage reaction of $[RuCl_2(benzene)]_2$ and BINAP in DMF at 100 °C and then sodium acetate.[24] The intermediary crude $RuCl_2(BINAP)(dmf)_n$ complex as well as isolated $[RuCl_2(BINAP)]_2N(C_2H_5)_3$[20a] was also used. Cationic BINAP–Rh(I) complexes **2** were synthesized by the standard method.[19b,25]

Substrates. The enamide substrates were generally prepared in 50–80% overall yield by acylation of the dihydroisoquinolines **7** which are readily accessible by the Bischler–Napieralski reaction. Since purification procedures of **7** often drastically reduce the yield owing to the formation of the enamine isomers and/or disproportionation to the tetrahydro and aromatic compounds, crude **7** obtained by the ring closure was immediately subjected to acylation using acyl chlorides or acid anhydrides and triethylamine or pyridine as promoters. The asymmetric hydrogenation required stereoselective preparation of Z-configurated 1-benzylidene substrates **3** (Figure 2) because the 1E stereoisomers are inactive to the hydrogenation conditions (vide infra). The Z/E stereoselectivity in the enamide formation was highly dependent on the acylation conditions as well as the substrate structures, ranging from 100:0 to 14:86. For example, formylation of the imine **7** ($R^1 = R^3 = R^4 = CH_3O$; $R^2 = H$) with formic–pivalic mixed anhydride and pyridine led to a 92:8 mixture of the stereoisomeric N-formylenamide **8a** in favor of the desired Z isomer, whereas use of formic–acetic mixed anhydride afforded a 69:31 mixture of (Z)- and (E)-**8a**. The Z enamides were usually much less soluble in ethanol than the E isomers, and hence, the requisite Z substrates could easily be purified by recrystallization.

Thus, high Z selectivity is accomplishable by selection of the appropriate acylating agents. But this was not always feasible. Fortunately, the geometrical isomers are interconvertible by irradiation with a tungsten lamp. Therefore the second-order stereomutation technique[26] utilizing the photolability and lattice-energy effects provided a more convenient method for selective preparation of the Z enamides. A typical example is seen in the preparation of (Z)-**8b**: When **7** ($R^1 = R^3 = R^4 = CH_3O$; $R^2 = H$) was treated with acetyl chloride and triethylamine in dichloromethane, stereoisomeric **8b** was produced in 95% yield with the undesired E isomer predominating, Z:E = 18:82. However, exposure of a 0.05 M solution of this mixture in ethanol or methanol at 25 °C for 2 h to a 500-W tungsten lamp resulted in precipitation of the less soluble (Z)-**8b**. The mother liquor contained a photostationary 3:4 mixture of the Z and E isomers. Repetitions of this procedure four times gave (Z)-**8b** in 75% total yield.

Although photoisomerization of (E)-**8a** occurred in acetone, ethyl acetate, acetonitrile, benzene, or chloroform, the preparative efficiency was low because of the high solubility of the enamide in these solvents. Attempted thermal equilibration failed to obtain a high Z:E ratio. Thus, heating of a 2:98 mixture of (Z)- and (E)-**8a** in methanol-d_4 at 80 °C for 2 h resulted in a 23:77 mixture. With **8b**, a Z:E ratio of only 3:97 was obtained.

The Z and E isomers, (Z)- and (E)-**8**, have very different spectroscopic properties, for which the following general trends have been found:[27] (1) The Z isomer having a *trans*-stilbene chromophore absorbs UV light at a longer wavelength and with a higher intensity than the E isomer, as seen with unsubstituted stilbene isomers. (2) In ^{1}H NMR spectra, the benzylidene aromatic ring strongly affects the chemical shift of the neighboring protons. All the Z stereoisomers have a sickle conformation with respect to the enamide conjugation system. Consequently, the signals of N-formyl, -acetyl, and -pivaloyl protons of the Z isomers occur at a higher field, owing to aromatic shielding, than those of the E isomers. The configurational assignment was confirmed by single-crystal X-ray analyses of the N-pivaloyl and -(p-bromobenzoyl) derivatives [(Z)-**8d** and (Z)-**8f**, respectively].[28] When only one stereoisomer could be isolated, the geometry was assigned by comparison of the spectral data with those of the stereo-defined analogues.

Product Analysis. The structures of the hydrogenation products of type **9** were confirmed by routine spectroscopic methods or by comparison with authentic samples. The amide products exist as a mixture of two rotamers as revealed by ^{1}H- and ^{13}C-NMR spectra.[29] The

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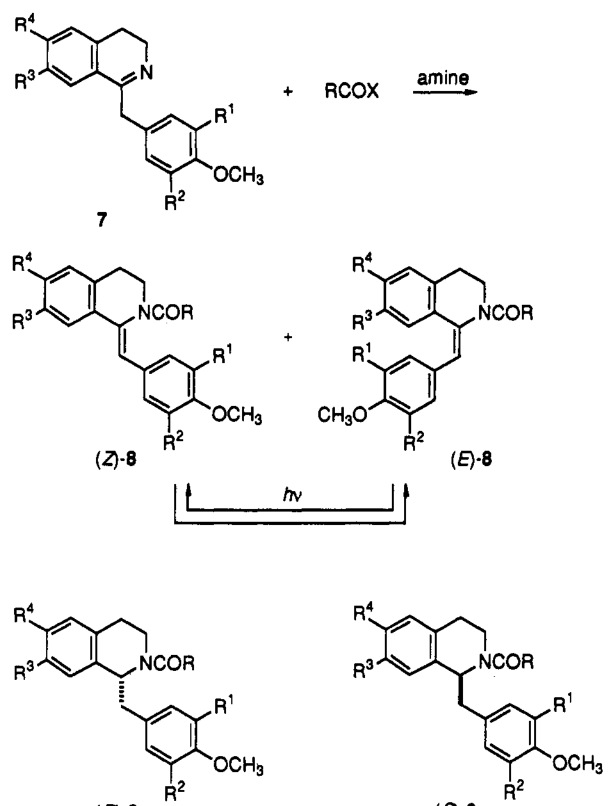
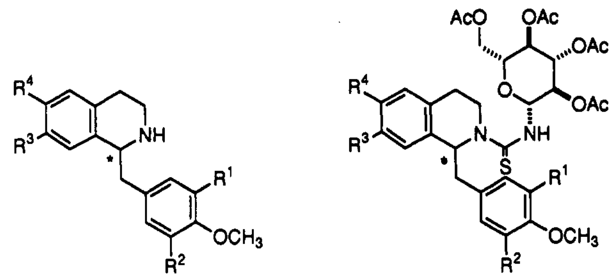


7, (Z)-8, (E)-8, (R)-9, (S)-9

	R	R^1	R^2	R^3	R^4
a	H	CH_3O	H	CH_3O	CH_3O
b	CH_3	CH_3O	H	CH_3O	CH_3O
c	CF_3	CH_3O	H	CH_3O	CH_3O
d	t-C_4H_9	CH_3O	H	CH_3O	CH_3O
e	C_6H_5	CH_3O	H	CH_3O	CH_3O
f	p-BrC_6H_4	CH_3O	H	CH_3O	CH_3O
g	CH_3	CH_3O	CH_3O	$C_6H_5CH_2O$	$C_6H_5CH_2O$
h	H	HO	H	HO	CH_3O
i	CH_3	CH_3COO	H	CH_3COO	CH_3O
j	H	$C_6H_5CH_2O$	$C_6H_5CH_2O$	H	CH_3O
k	H	HO	H	H	CH_3O

ee values were normally determined after conversion to the thioureas 11 by deacylation followed by condensation of 10 with 2,3,4,6-tetra-O-acetyl-D-glucopyranosyl isothiocyanate (GITC).[30] Reversed-phase HPLC analysis of the GITC adducts is highly reliable. The diastereomeric thiourea mixture derived from a sample in 99.5% ee, prepared by mixing a 611 mM solution of (*R*)-**9a** and a 5.91 mM solution of *S* enantiomer, indeed showed two peaks in a 99.75 ± 0.06:0.25 ± 0.06 ratio on an average of 10 measurements.

Hydrogenation Conditions. The efficiency of the catalyst and reaction conditions was examined by hydrogenation of (*Z*)-**8a** or (*Z*)-**8b** as substrate giving the protected tetrahydropapaverines **9a** or **9b**. We first used the BINAP–Rh complexes of type **2** as catalysts which exhibit excellent chiral efficiency in asymmetric hydrogenation of (*Z*)-α-(acylamino)cinnamates **5**.[19] Unfortunately, however, as shown in Table 1 the asymmetric reaction did not work well. Thus, the reaction of (*Z*)-**8b** in benzene containing (*R*)-**2a** at 30 °C under initial hydrogen pressure of 4 atm gave (*S*)-**9b** in 100% yield but in only 68% ee. Variation of the catalyst as well as reaction conditions failed to improve the result. Use of [Rh((*S*)-TolBINAP)(cod)]ClO_4[31] as catalyst, for example, gave (*R*)-**9b** in 95% yield and in 75% ee. [Rh((*R*)-BINAP)$_2$]ClO_4[25] afforded (*S*)-**9b** in 45% yield and in merely 2% ee. Structural modification of the substrate did not help either. Hydrogenation of a simpler substrate **12b** in the presence of (*R*)-**2b** afforded (*S*)-**13b** in 82% chemical yield and 60% ee. The *N*-formyl substrates (*Z*)-**8a** and **12a** were not hydrogenated under similar conditions.



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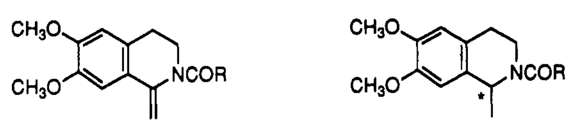


12a, R = H
12b, R = CH_3

13a, R = H
13b, R = CH_3

The chiral efficiency displayed by the BINAP–Ru(II) complexes,[23,24] however, was remarkable. Table 2 lists the results of the screening experiments. When the reaction was conducted with a 5:1 methanol- or ethanol–dichloromethane solution containing 15 mM of the substrate (*Z*)-**8a** and 0.075 mM of (*R*)-**1a** [substrate/catalyst (S/C) mole ratio = 200] under 1–4 atm of hydrogen at 30 °C, the saturated product, (*R*)-**9a**, was obtained in nearly quantitative yield and with >99.5% ee. The GITC method showed only a single peak, and the minor enantiomer could not be detected. It should be noted that the direction of asymmetric induction is opposite that observed with the Rh catalyst having the same BINAP chirality.

The Ru-catalyzed reaction of **8a** at 100 °C gave **9a** in 95% ee quantitatively. In this particular reaction, increase in hydrogen pressure tends to decrease the enantioselectivity to some extent. The reaction under atmospheric pressure of hydrogen gave (*R*)-**9a** in >99.5% ee, but under 100 atm the ee was lowered to 96% ee. In reducing the hydrogen pressure from 4 atm to 1 atm, the reaction rate was approximately halved. Use of aprotic solvents such as THF, benzene, acetonitrile, or dichloromethane drastically retarded the reaction at 30 °C. Hydrogenation of (*Z*)-**8a** in dichloromethane containing (*R*)-**1a** proceeded at 100 °C and at 100 atm to give (*S*)-**9a** in 38% yield and in 10% ee. Thus, the best media appeared to be a mixture of methanol or ethanol and dichloromethane (>1:1). Alcohols are essential to effect the hydrogenation smoothly, though they are poor solvents for the substrate; dichlo-

(30) (a) Nimura, N.; Ogura, H.; Kinoshita, T. *J. Chromatogr.* **1980**, *202*, 375. (b) Gal, J. *J. Chromatogr.* **1984**, *307*, 220. (c) Nishi, H.; Fujimura, N.; Yamaguchi, H.; Fukuyama, T. *J. Chromatogr.* **1991**, *539*, 71.

(31) TolBINAP = 2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl. Takaya, H.; Mashima, K.; Koyano, K.; Yagi, M.; Kumobayashi, H.; Taketomi, T.; Akutagawa, S.; Noyori, R. *J. Org. Chem.* **1986**, *51*, 629.

(32) Stenlake, J. B.; Williams, W. D.; Dhar, N. C.; Marshall, I. G. *Eur. J. Med. Chem.* **1974**, *9*, 233.

(33) CyBINAP = 2,2′-bis(dicyclohexylphosphino)-1,1′-binaphthyl. Inoue, S.-I.; Osada, M.; Koyano, K.; Takaya, H.; Noyori, R. *Chem. Lett.* **1985**, 1007.

Table 1. BINAP–Rh(I)-Catalyzed Asymmetric Hydrogenation of 2-Acyl-1-alkylidene-1,2,3,4-tetrahydroisoquinolines[a]

				product		
substrate	catalyst	solvent	time, h	% yield	% ee[b]	confign
(*Z*)-**8b**	[Rh((*R*)-BINAP)(cod)]ClO_4[(*R*)-**2a**]	C_6H_6	34	100	68[c]	*S*
(*Z*)-**8b**	[Rh((*S*)-CyBINAP)(cod)]ClO_4[d]	C_6H_6	18	100	35[e]	*R*
(*Z*)-**8b**	[Rh((*R*)-BINAP)$(CH_3OH)_2$]ClO_4[(*R*)-**2b**]	C_6H_6	42	80	76[f]	*S*
(*Z*)-**8b**	[Rh((*R*)-BINAP$)_2$]ClO_4[(*R*)-**2c**]	C_6H_6	192	45	2[g]	*S*
(*Z*)-**8b**	[Rh((*S*)-TolBINAP)(cod)]ClO_4[h]	C_6H_6	64	95	75[i]	*R*
(*Z*)-**8b**	(*R*)-**2a**	C_2H_5OH–CH_2Cl_2 (5:1)	24	100	29[j]	*S*
(*Z*)-**8b**	(*R*)-**2a**	CH_2Cl_2	16	100	10[k]	*R*
(*Z*)-**8b**	(*R*)-**2a**	THF	16	100	36[l]	*S*
12b	(*R*)-**2b**	C_6H_6	40	82	60[m,n]	*S*

[a] Reaction was carried out at 30 °C under 4 atm of initial hydrogen pressure using a 0.15 mM solution of the catalyst and a 15 mM solution of the substrate in the stated solvent (5–9 mL). [b] Based on the optical rotation ($[\alpha]^{20}_D$ +89.8° (*c* 1.045, $CHCl_3$) for (*S*)-**9b**).[32] [c] $[\alpha]^{24}_D$ +61.5° (*c* 1.15, $CHCl_3$). [d] See ref 33. [e] $[\alpha]^{24}_D$ −31.0° (*c* 0.83, $CHCl_3$). [f] $[\alpha]^{24}_D$ +68.0° (*c* 1.10, $CHCl_3$). [g] $[\alpha]^{24}_D$ +1.8° (*c* 1.15, $CHCl_3$). [h] See ref 31. [i] $[\alpha]^{24}_D$ +67.6° (*c* 1.08, $CHCl_3$). [j] $[\alpha]^{24}_D$ +26.2° (*c* 1.02, $CHCl_3$). [k] $[\alpha]^{24}_D$ −8.6° (*c* 0.95, $CHCl_3$). [l] $[\alpha]^{24}_D$ +32.3° (*c* 1.32, $CHCl_3$). [m] $[\alpha]^{24}_D$ +113.5° (*c* 1.21, $CHCl_3$). [n] HPLC analysis of the diastereomeric GITC derivatives of **19**.

Table 2. BINAP–Ru(II)-Catalyzed Asymmetric Hydrogenation of 2-Acyl-1-benzylidene-1,2,3,4-tetrahydroisoquinolines [(*Z*)-8]

		concn, mM			condns			product		
substrate	catalyst	catalyst	substrate	solvent	H_2, atm	temp, °C	time, h	% yield	% ee	confign
(*Z*)-**8a**	$Ru(CH_3COO)_2$[(*R*)-BINAP] [(*R*)-**1a**]	0.075	15	CH_3OH–CH_2Cl_2 (5:1)	1	30	140	100	>99.5	*R*
(*Z*)-**8a**	(*R*)-**1a**	0.075	15	CH_3OH–CH_2Cl_2 (5:1)	4	30	48	100	>99.5	*R*
(*Z*)-**8a**	(*R*)-**1a**	0.075	15	C_2H_5OH–CH_2Cl_2 (5:1)	4	30	48	100	>99.5	*R*
(*Z*)-**8a**	(*R*)-**1a**	0.075	15	CH_3OH–CH_2Cl_2 (5:1)	50	30	24	94	97	*R*
(*Z*)-**8a**	(*R*)-**1a**	0.075	15	CH_3OH–CH_2Cl_2 (5:1)	100	30	24	100	96	*R*
(*Z*)-**8a**	(*R*)-**1a**	0.075	15	CH_3OH–CH_2Cl_2 (5:1)	4	0	24	0		
(*Z*)-**8a**	(*R*)-**1a**	0.075	15	CH_3OH–CH_2Cl_2 (5:1)	4	50	24	100	97	*R*
(*Z*)-**8a**	(*R*)-**1a**	0.075	15	CH_3OH–CH_2Cl_2 (5:1)	4	100	24	100	95	*R*
(*Z*)-**8a**	(*R*)-**1a**	0.03	15	CH_3OH–CH_2Cl_2 (5:1)	100	60	72	98	91	*R*
(*Z*)-**8a**	(*R*)-**1a**	0.75	150	CH_3OH–CH_2Cl_2 (1:1)	4	30	24	70	99	*R*
(*Z*)-**8a**	(*R*)-**1a**	0.075	15	CH_2Cl_2	4	30	48	0		
(*Z*)-**8a**	(*R*)-**1a**	0.075	15	CH_2Cl_2	100	100	48	38	10	*S*
(*Z*)-**8a**	(*R*)-**1a**	0.075	15	THF	4	30	24	0		
(*Z*)-**8a**	(*R*)-**1a**	0.075	15	C_6H_6	4	30	24	0		
(*Z*)-**8a**	(*R*)-**1a**	0.075	15	CH_3CN	4	30	24	0		
(*Z*)-**8a**	$RuCl_2$[(*R*)-BINAP](dmf)$_n$	0.075	15	CH_3OH–CH_2Cl_2 (5:1)	4	30	48	97	99	*R*
(*Z*)-**8a**	[$RuCl_2$((*R*)-BINAP)$]_2N(C_2H_5)_3$	0.075	15	CH_3OH–CH_2Cl_2 (5:1)	4	30	48	98	99	*R*
(*E*)-**8a**	(*S*)-**1a**	0.075	15	CH_3OH–CH_2Cl_2 (5:1)	4	30	48	<3		
(*Z*)-**8b**	(*R*)-**1a**	0.41	31	C_2H_5OH–CH_2Cl_2 (5:1)	4	24	48	100	>99.5	*R*
(*E*)-**8b**	(*S*)-**1a**	0.39	30	C_2H_5OH–CH_2Cl_2 (5:1)	4	24	48	0		
(*Z*)-**8c**	(*S*)-**1a**	0.34	25	C_2H_5OH–CH_2Cl_2 (5:1)	4	24	167	10		
(*Z*)-**8d**	(*S*)-**1a**	0.37	25	C_2H_5OH–CH_2Cl_2 (5:1)	4	24	47	100	50	*S*

romethane assists in making a homogeneous phase. In addition to the Ru(II) diacetate complex **1a**,[23,24b] preformed and in situ prepared dichloro Ru(II) complexes[24] also gave satisfactory results as hydrogenation catalysts.

N-Acetyl substrate (*Z*)-**8b** can equally be used, but the strongly electron-withdrawing trifluoroacetyl group decreases the reactivity to a great extent. With the introduction of a sterically demanding pivaloyl group at nitrogen, the optical yield decreased to 50%. The 1*E* substrates, (*E*)-**8a** and (*E*)-**8b**, were almost inert (<3% yield) under the standard conditions (4 atm, 30 °C, 48 h, 5:1 methanol–dichloromethane as solvent).

Generality. The wide generality of the asymmetric hydrogenation is illustrated in Table 3. This method using purely artificial ligand BINAP is chirally flexible; the (*R*)-BINAP–Ru-catalyzed reaction of the benzylidene substrates (*Z*)-**8** consistently yields predominantly the 1*R* benzylated products, whereas 1*S*-dominant products are obtained by the reaction with (*S*)-BINAP-based catalysts.

The *N*-formyl substrate (*Z*)-**8a** can be hydrogenated smoothly with the Ru diacetate **1a** with S/C ratios ranging from 100 to 500 at room temperature to 100 °C and at hydrogen pressure of 1–100 atm. *N*-Acetyl and -benzoyl derivatives such as (*Z*)-**8b**, (*Z*)-**8e**, and (*Z*)-**8f** can also be utilized. Use of an *N*-formyl group among various protective groups has an eminent synthetic advantage because of the versatility of its conversion into other functional groups.[34] Particularly, reduction of the *N*-formyl group easily affords naturally ubiquitous *N*-methylated tetrahydroisoquinolines. In addition, removal of the formyl group from the hydrogenation products is accomplished without loss of optical activity under mild conditions with a 2 M ethanolic solution of NaOH at 80 °C. In constrast, the *N*-acetyl and -benzoyl derivatives are extremely resistant toward both acidic and basic deblocking conditions, and the chiral products sometimes racemize during hydrolysis.[4a,35]

Hydrogenation of (*Z*)-**8a** catalyzed by (*R*)-**1a** and subsequent deformylation gave (*R*)-tetrahydropapaverine [(*R*)-**14**] of nearly 100% enantiomeric purity. Lithium aluminum hydride reduction of the hydrogenation product afforded laudanosine (**15**). The (*R*)-BINAP–Ru-catalyzed reaction of (*Z*)-**8g** followed by deacetylation produced (*R*)-**16** in 97% ee. Hydrogenolysis of the two benzyl groups on Pd/C in ethanol gave, after recrystallization, enantiomerically pure (*R*)-tretoquinol [(*R*)-**17**], which acts as an inhibitor of platelet aggregation. The enantiomer, (*S*)-**17**, obtained by using (*S*)-**1a** as a hydrogenation catalyst

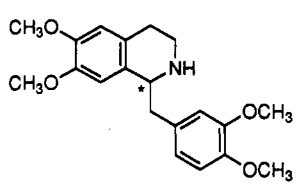
(34) (a) Rice, K. C., Ripka, W. C.; Reden, J.; Brossi, A. *J. Org. Chem.* **1980**, *45*, 601. (b) Beyerman, H. C.; Van Bommel, L.; Maat, L.; Olieman, C. *Recl. Trav. Chim. Pays-Bas* **1976**, *95*, 312.
(35) Kametani, T.; Ihara, M.; Shima, K. *J. Chem. Soc. C* **1968**, 1619.

Table 3. BINAP–Ru(II)-Catalyzed Asymmetric Hydrogenation of Enamides[a]

substrate	catalyst	product % yield	product % ee	product config
(*Z*)-8a	$Ru(CH_3COO)_2$[(*R*)-BINAP][(*R*)-1a]	100	>99.5	*R*
(*Z*)-8a	$Ru(CH_3COO)_2$[(*S*)-BINAP][(*S*)-1a]	100	>99.5	*S*
(*Z*)-8b	(*R*)-1a	100	>99.5	*R*
(*Z*)-8b	(*S*)-1a	100	>99.5	*S*
(*Z*)-8e	(*S*)-1a	100	96	*S*
(*Z*)-8f	(*S*)-1a	100	98	*S*
(*Z*)-8g	(*R*)-1a	93	97	*R*
(*Z*)-8g	(*S*)-1a	100	96	*S*
(*Z*)-8h	(*R*)-1a[b]	98	99	*R*
(*Z*)-8i	(*R*)-1a	92	95	*R*
(*Z*)-8i	(*S*)-1a	97	96	*S*
(*Z*)-8j	(*R*)-1a	86	97	*R*
(*Z*)-8k	(*R*)-1a	98	99	*R*
12a	(*S*)-1a	100	97	*S*
12b	(*S*)-1a	100	96	*S*
(*Z*)-26	(*S*)-1b[b]	38	95	*S*
(*Z*)-26	$Ru(CF_3COO)_2$[(*R*)-TolBINAP][c,d]	99	96	*R*
(*Z*)-26	$Ru(CF_3COO)_2$[(*S*)-TolBINAP][c,d]	98	97	*S*
(*Z*)-29	$Ru(CF_3COO)_2$[(*R*)-TolBINAP][c,d]	98	98	*R*
(*Z*)-29	$Ru(CF_3COO)_2$[(*S*)-TolBINAP][c,d]	98	97	*S*

[a] Reaction at 4 atm of H_2 with S/C = 50–200. For detailed reaction conditions, see Experimental Section. [b] Reaction at 50 atm of hydrogen. [c] Reaction at 100 atm of hydrogen. [d] See ref 31.

is a commercial bronchodilating agent.[36] Enamides (*Z*)-8h and (*Z*)-8i were converted in two steps to (*R*)-norreticuline [(*R*)-18] in 99 and 95% ee, respectively, acting as the central intermediate in isoquinoline biosynthesis.[1]



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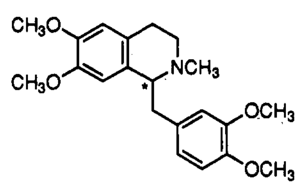

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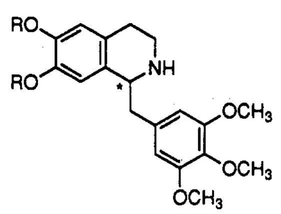
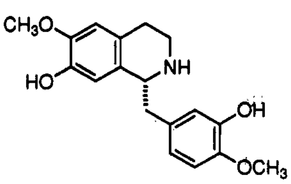
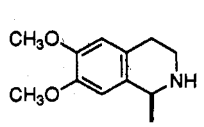


16, R = $C_6H_5CH_2$
17, R = H



(*R*)-18



(*S*)-19

In a like manner, the simple 1-methylene substrate 12 is hydrogenated in the presence of (*S*)-1a to give the (*S*)-1-methylated compound, whose deacylation produced (*S*)-salsolidine [(*S*)-19] in 97% ee.

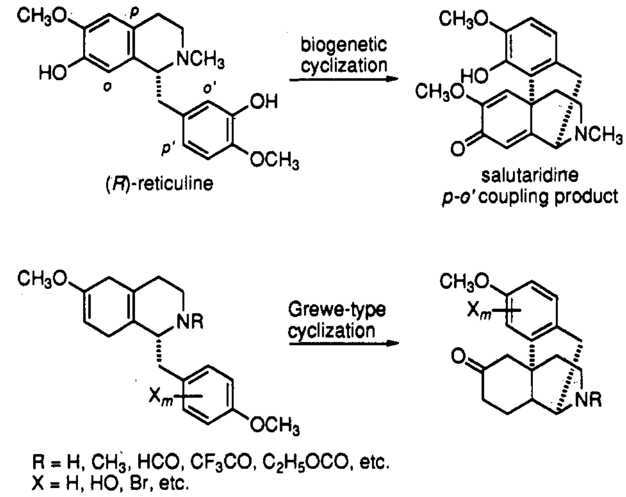
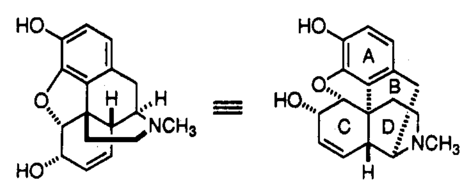


Figure 3. Biogenetic vs Grewe-type cyclization.

Synthesis of Morphine, Morphinans, and Benzomorphans. Morphine (20) is biosynthesized in nature from (*R*)-18 via (*R*)-reticuline through intramolecular oxidative coupling of the electron-rich aromatic rings at the *p* and *o*′ positions (Figure 3).[37] Such position-selective transformation among four possibilities, however, is difficult by conventional chemical or electrochemical oxidation.[38] The most convenient synthesis of 20 perhaps



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consists of partial saturation of the appropriately substituted isoquinoline benzene ring by the Birch reduction followed by an acid-catalyzed Grewe-type cyclization leading to the required tetracyclic carbon skeleton (Figure 3).[39] The Beyerman intermediate (*R*)-21possessing a symmetrically substituted benzyl substituent at the C(1) position[40] was obtained with 97% ee on the basis of (*R*)-BINAP–Ru-catalyzed hydrogenation of (*Z*)-8j. The asymmetric hydrogenation of (*Z*)-8k provides a straightforward way to the Rice intermediate (*R*)-22 of high enantiomeric purity which can be converted to the 6′-bromo derivative

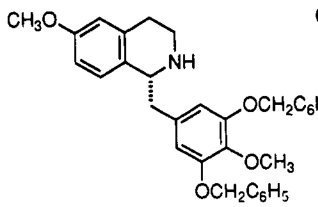
(36) (a) Iwasawa, Y.; Kiyomoto, A. *Jpn. J. Pharmacol.* **1967**, *17*, 143. (b) Dalton, C.; Crowley, H. J.; Czyzewski, L. B. *Biochem. Pharmacol.* **1976**, *25*, 2209. (c) Shin, Y.; Romstedt, K. J.; Doyle, K.; Harrold, M. W.; Gerhardt, M. A.; Miller, D. D.; Patil, P.; Feller, D. R. *Chirality* **1991**, *3*, 112.

(37) (a) Gulland, J. M.; Robinson, R. *Mem. Proc. Manchester Lit. Philos. Soc.* **1925**, *69*, 79. (b) Barton, D. H. R.; Cohen, T. *Festschrift Prof. Dr. Arthur Stoll zum Siebzigsten Geburtstag*; Birkhäuser Verlag: Basel, Switzerland, 1957; p 117.

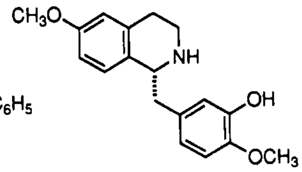
(38) (a) Barton, D. H. R.; Kirby, G. W.; Steglich, W.; Thomas, G. M.; Battersby, A. R.; Dobson, T. A.; Ramuz, H. *J. Chem. Soc.* **1965**, 2423. (b) Battersby, A. R. In *Oxidative Coupling of Phenols*; Battersby, A. R., Taylor, W. I., Eds.; Marcel Dekker: New York, 1967. (c) Stuart, K. L. *Chem. Rev.* **1971**, *71*, 47. (d) Kametani, T.; Kozuka, A.; Fukumoto, K. *J. Chem. Soc. C* **1971**, 1021. (e) Szántay, C.; Bárczai-Beke, M.; Péchy, P.; Blaskó, G.; Dörnyei, G. *J. Org. Chem.* **1982**, *47*, 594. (f) White, J. D.; Caravatti, G.; Kline, T. B.; Edstrom, E.; Rice, K. C.; Brossi, A. *Tetrahedron* **1983**, *39*, 2393. (g) Schwartz, M.; Mami, I. S. *J. Am. Chem. Soc.* **1975**, *97*, 1239. (h) Bobbitt, J. M.; Noguchi, I.; Ware, R. S.; Chiong, K. N.; Huang, S. J. *J. Org. Chem.* **1975**, *40*, 2924. (i) Schäfer, H. J. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 911. (j) Kerr, J. B.; Jempty, T. C.; Miller, L. *J. Am. Chem. Soc.* **1979**, *101*, 7338.

(39) Grewe, R.; Friedrichsen, W. *Chem. Ber.* **1967**, *100*, 1550.

(40) (a) Lie, T. S.; Maat, L.; Beyerman, H. C. *Recl. Trav. Chim. Pays-Bas* **1979**, *98*, 419. (b) DeGraw, J. I.; Christensen, J. C.; Brown, V. H.; Cory, M. J. *J. Heterocycl. Chem.* **1974**, *11*, 363.



(*R*)-**21**

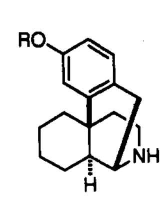


(*R*)-**22**

suitable for the selective Grewe cyclization.[41] The compounds (*R*)-**21** and (*R*)-**22** are readily converted to morphine and other natural opiates.[41b]

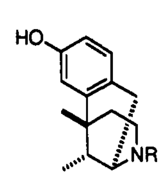
Naturally occurring morphine (**20**) is extremely important as an analgesic but exhibits serious addictive side effects.[42] Potent but nonaddicting analgesics might result from modifing the basic structure by partial ring removal from the original full pentacyclic system.[43] Among the most successful artificial morphine analogues are tetracyclic morphinans **23**, which have lost the furan ring from **20**, as well as tricyclic benzomorphans **24** lacking the C and furan rings.[44] The present stereoselective methodology provides a powerful tool for preparation of such clinically effective artificial analgesics of either chirality. Since the existing commercial production of **23** and **24** usually involves optical resolution of an amine intermediate, this asymmetric hydrogenation would enhance greatly the overall synthetic efficiency.

The hydrogenation substrates, **26** and **29**, were prepared via **25** and **28**, respectively, by combination of the standard Bischler–Napieralski reaction and N-formylation. These substrates resist hydrogenation under the standard low-pressure conditions using the diacetate catalyst **1b**. Fortunately, however, hydrogenation was effectively accomplished by use of $Ru(CF_3COO)_2$[(*S*)-TolBINAP], generated by the reaction of **1b** and 2 equiv of trifluoroacetic acid and by applying high hydrogen pressure. Thus, when the reaction of **26** was performed in methanol containing 0.5 mol % of the bistrifluoroacetate complex at 25 °C under initial hydrogen pressure of 100 atm, (*S*)-**27a** was obtained with 97% ee and in 98% yield. Notably, hydrogenation of the diene substrate occurred regioselectively at the enamide part leaving the simple tetrasubstituted olefinic linkage intact. The formyl base, (*S*)-**27a**, directly undergoes the acid-catalyzed Grewe cyclization giving a morphinan structure which is convertible to dextromethorphan (**23a**), an important commercial antitussive agent.[45] In addition **27b** acts as an intermediate leading to dextrophan (**23b**), an anticough drug.[46] The levorotatory isomer, (*R*)-**27a**, can be transformed to levallorphan and oxilorphan, narcotic antagonists, as well



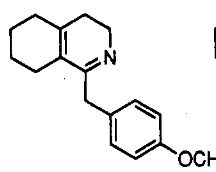
morphinan

23a, R = CH_3
23b, R = H



benzomorphan

24a, R = CH_3
24b, R = $(CH_3)_2C{=}CHCH_2$
24c, R = cyclopropylmethyl
24d, R = $C_6H_5CH_2CH_2$



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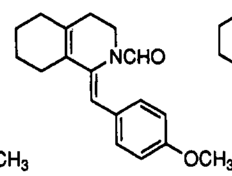

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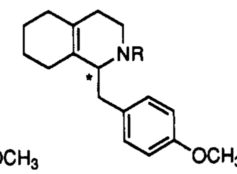
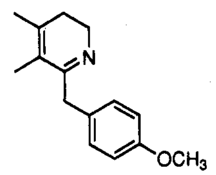


27a, R = CHO
27b, R = H



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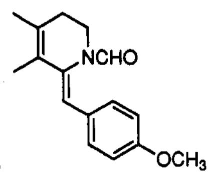

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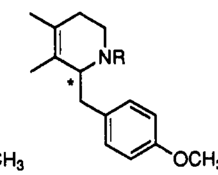

30a, R = CHO
30b, R = H

as the analgesic butorphanol.[45,47] Later Ru complexes which were prepared from $Ru_2(CF_3COO)_4(cod)_2$, $Ru(CH_3COO)_2(cod)$, or $Ru_2Cl_4(CH_3CN)(cod)_2$ and BIPHEMP ligand, a relative of BINAP, were also found to be good asymmetric catalysts for hydrogenation of **26**.[48]

In a similar manner, **29** was hydrogenated with the aid of the (*R*)-TolBINAP–Ru catalyst to form desired (*R*)-**30a** in 98% ee. This chiral tetrahydropyridine derivative is a useful intermediate for the synthesis of (−)-metazocin (**24a**), (−)-pentazocine (**24b**), (−)-cyclazocine (**24c**), (−)-phenazocine (**24d**), etc.[44b,49,50] Thus, this method allows for the flexible synthesis of various morphine-based analgesics, either natural or artificial and dextorotatory or levorotatory.

Sense of Asymmetric Induction. Hydrogenation of (1*Z*)-benzylidene substrates (*Z*)-**8** catalyzed by an (*S*)-BINAP–Ru complex leads predominantly to the 1*S*-benzylated products, while the (*R*)-BINAP–Ru catalyst forms the 1*R*-enriched products. The enantioface selection is almost perfect. Although the mechanism of the Ru-catalyzed hydrogenation of enamides has not yet been

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(42) (a) Johnson, M. R.; Michne, G. M. In *Medicinal Chemistry*, 4th ed.; Wolff, M. E., Ed.; Wiley Interscience: New York, 1981; Part III, p 699. (b) Ehrhardt, G.; Ruschig, H. *Arneimittel*; Verlag Chemie: Weinheim, 1968; Vol. 1, p 316. (c) Palmer, D. C.; Strauss, M. J. *Int. Eng. Chem. Prod. Res. Dev.* **1980**, *19*, 172.

(43) Braenden, O. J.; Eddy, N. B.; Halbach, H. *Bull. Wld. Hlth. Org.* **1955**, *13*, 937.

(44) Review: (a) Casy, A. F.; Parfitt, R. T. *The Opioid Analgesics*, Plenum Press: New York, 1986. (b) Palmer, D. C.; Strauss, M. J. *Chem. Rev.* **1977**, *77*, 1. (c) Eddy, N. B.; May, E. L. *Synthetic Analgesics*; Pergamon Press: London, 1966; Part 2.

(45) Schnider, O.; Grüssner, A. *Helv. Chim. Acta* **1951**, *34*, 2211.

(46) Schnider, O.; Grüssner, A. *Helv. Chim. Acta* **1949**, *32*, 821.

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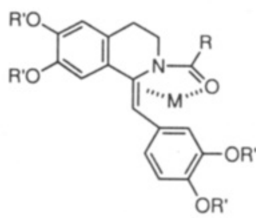
(48) Heiser, B.; Broger, E. A.; Crameri, Y. *Tetrahedron: Asymmetry* **1991**, *2*, 51. BIPHEMP = (6,6′-dimethylbiphenyl-2,2′-diyl)bis(diphenylphosphine). See also: Miyashita, A.; Karino, H.; Shimamura, J.-I.; Chiba, T.; Nagano, K.; Nohira, H.; Takaya, H. *Chem. Lett.* **1989**, 1849.

(49) (a) May, E. L.; Eddy, N. B. *J. Org. Chem.* **1959**, *24*, 1435. (b) Murphy, J. G.; Ager, J. H.; May, E. L. *J. Org. Chem.* **1960**, *25*, 1386. (c) May, E. L.; Kugita, H. *J. Org. Chem.* **1961**, *26*, 188. (d) May, E. L.; Kugita, H.; Ager, J. H. *J. Org. Chem.* **1961**, *26*, 1621. (e) Saito, S.; May, E. L. *J. Org. Chem.* **1961**, *26*, 4536. (d) May, E. L.; Eddy, N. B. *J. Org. Chem.* **1959**, *24*, 294.

(50) (a) Archer, S.; Albertson, N. F.; Harris, L. S.; Pierson, A. K.; Bird, J. G. *J. Med. Chem.* **1964**, *7*, 123. (b) Albertson, N. F.; Wetterau, W. F. *J. Med. Chem.* **1970**, *13*, 302. (c) Kametani, T.; Kigasawa, K.; Hiiragi, M.; Wagatsuma, N. *Heterocycles* **1974**, *2*, 79. (d) Kametani, T.; Huang, S.-P.; Ihara, M.; Fukumoto, K. *Chem. Pharm. Bull.* **1975**, *23*, 2010. (e) Kametani, T.; Honda, T.; Huang, S.-P.; Fukumoto, K. *Can. J. Chem.* **1975**, *53*, 3820.

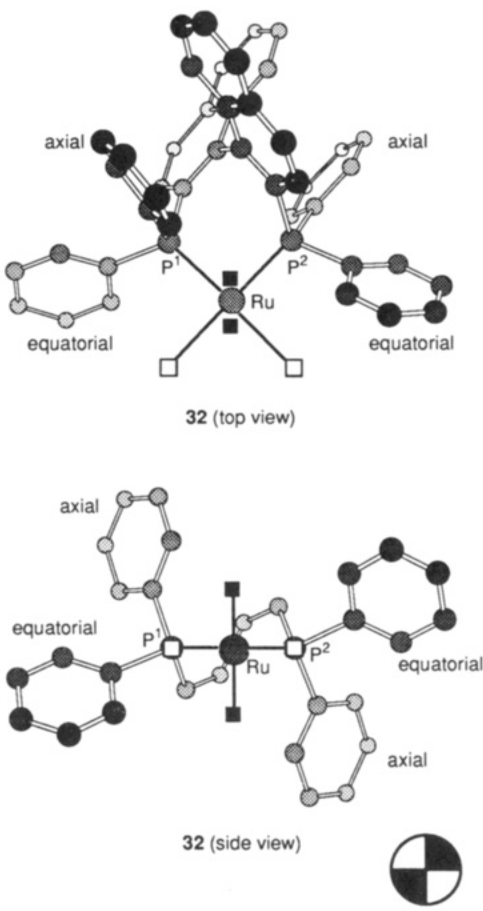
elucidated,[51] this general sense of asymmetric induction can be understood in terms of chelate model **31** [M = Ru(BINAP)X_2]. The standard enamide substrate (*Z*)-**8**



31

is rather unambiguous structurally. The reacting C=C linkage is directly connected with an aryl group and a constrained 6/6 bicyclic system, while the *N*-acyl directing group is conformationally flexible. In hydrogenation, the BINAP–Ru template[23] efficiently recognizes a chirality of the enamide in the enantio-determining step by forming a stereo-complementary complex **31** or a transition state which approximates it.

The chiral environment created by an (*S*)-BINAP–Ru element approximates C_2 symmetry and is schematically illustrated in Figure 4.[18c,e] The chirality originally issued from the binaphthyl skeleton is transmitted to the coordination sites, shown by □ and ■, through the *P*-phenyl rings. The sites in the P^1–Ru–P^2 plane, □, are significantly affected by the "equatorial" phenyl substituents, while the out-of-plane sites, ■, are influenced by the "axial" phenyls. Thus, the two sets of quadrants of **32** (first and third vs second and fourth) are clearly differentiated spatially. Since d^6 Ru(II) complexes normally have an octahedral geometry and the central metal can accommodate up to six ligands, a variety of diastereomers are conceivable for the enamide chelate complex. Actually, however, simple model inspection suggests that the structure $\mathbf{33}_S$ in Figure 5 is highly favored for the simultaneous complexation of the congested (*S*)-BINAP and enamide ligands to the Ru(II) center. The enamide occupies the in-plane sites, □, of **32**, where the $C(1)_{re}$=C_{si}HAr face and C=O oxygen have interaction with Ru; the out-of-plane coordination sites, ■, are used for accommodation of the dihydrogen molecule, hydride, and other anions or solvent molecules. Delivery of hydrogen atoms from the Ru center to the coordinated olefin face leads to the 1*S* product. The diastereomeric complex $\mathbf{33}_R$ using the enantiomeric $C(1)_{si}$=C_{re}HAr face and C=O is highly unlikely because, in the first quadrant, the tetrahydroisoquinoline aromatic ring suffers serious nonbonded interaction with the equatorial phenyl substituent in (*S*)-BINAP. In a like manner, steric constraints caused by the *P*-phenyl groups do not allow the substrate accommodation in the out-of-plane sites, ■. Thus, hydrogenation of the enamide occurring in such a coordination sphere consistently explains the general sense of asymmetric induction, *S* to *S* or *R* to *R*.



□ = coordination site in the P^1–Ru–P^2 plane
■ = coordination site out of the P^1–Ru–P^2 plane

Figure 4. Chiral environment of an (*S*)-BINAP–Ru(II) complex. All atoms are shaded by depth. In the side view, the binaphthyl skeleton is omitted.

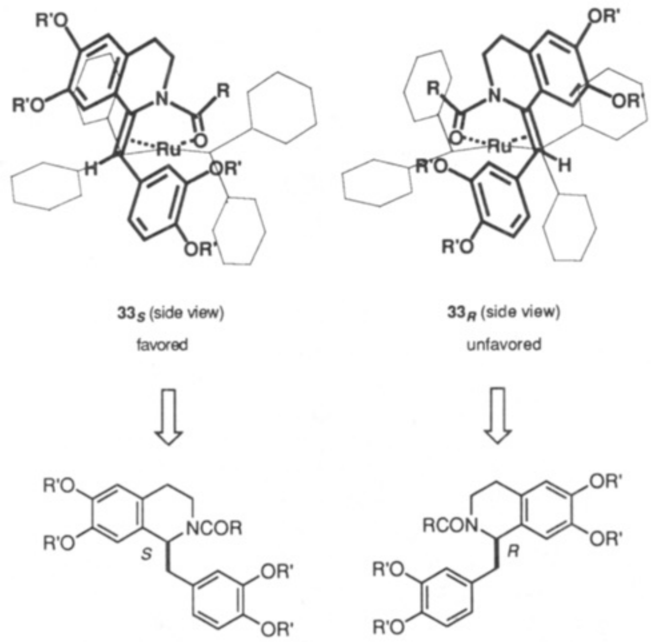


Figure 5. Enantioface discrimination of (*Z*)-2-acyl-1-benzylidene-1,2,3,4-tetrahydroisoquinolines by the (*S*)-BINAP–Ru element.

Mnemonic device A in Figure 6 is convenient for the prediction of enantioface selection.[52] Model B is its extension for explaining the general behavior of related

(51) For the mechanism of the hydrogenation of α,β-unsaturated carboxylic acids, see: Ohta, T.; Takaya, H.; Noyori, R. *Tetrahedron Lett.* **1990**, *31*, 7189. Ashby, M. T.; Halpern, J. *J. Am. Chem. Soc.* **1991**, *113*, 589.

(52) A related model was given for the Sharpless asymmetric dihydroxylation: Sharpless, K. B.; Amberg, W.; Beller, M.; Chen, H.; Hartung, J.; Kawanami, Y.; Lübben, D.; Manoury, E.; Ogino, Y.; Shibata, T.; Ukita, T. *J. Org. Chem.* **1991**, *56*, 4585.

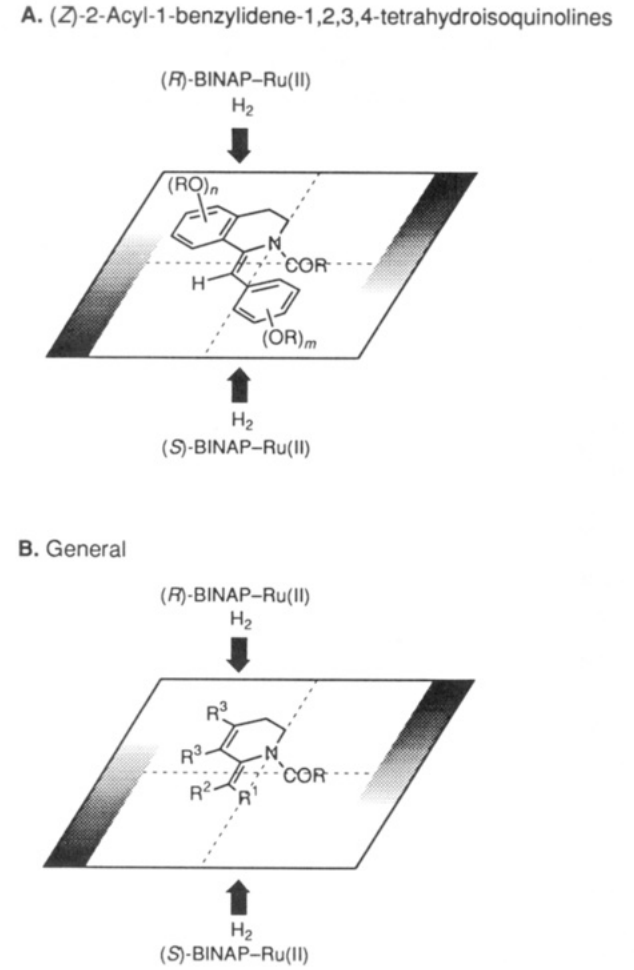


Figure 6. Mnemonics for prediction of the sense of enantioselective hydrogenation. The density code refers to the extent of steric influence of the equatorial *P*-phenyl rings.

substrates. The tetrahydroisoquinoline ring in A may be replaced by dialkylated or ring-fused 3,4-dehydropiperidine rings: Using model B, where $R^3 = CH_3$ or $R^3–R^3 = (CH_2)_4$, the stereochemical outcome of the synthesis of the benzomorphan or morphinan intermediates can be explained. Replacement of the benzylidene moiety by a methylene group, B where $R^1 = R^2 = H$, does not affect the argument, consistent with the stereochemistry of the hydrogenation of **12**. We noted that, while the (1*Z*)-benzylidene substrates **8a** react smoothly, the 1*E* isomers are inert to hydrogenation. This difference is also understandable with model B, $R^1 = H$ and R^2 = aryl. The BINAP–Ru template **32** (or its antipodal structure) is unable to accommodate such substrates owing to the steric repulsion between the bulky aryl substituent and the equatorial *P*-phenyl in the crowded third quadrant.

This *S*-to-*S* or *R*-to-*R* catalyst/product chirality correlation is made empirically on the basis of experimental observations. Obviously homogeneous hydrogenation of olefins proceeds in a stepwise fashion via various intermediates such as olefin π complexes, metal hydrides, and metal alkyls, and both stability and reactivity of these short-lived, diastereomeric complexes affect strongly the overall sense and degree of the enantioselection. The above purely stereochemical argument should be limited to the Ru(II)-catalyzed reaction. Notably, with a given BINAP chirality, Ru(II) and Rh(I) catalyst deliver opposite chirality to the C(1) position through hydrogenation. The stereoselection of the Ru-promoted reaction is simply deduced from the relative stabilities of diastereomeric **31** [M = Ru(BINAP)X_2], where the nature of X is yet to be elucidated. On the other hand, in the Rh-catalyzed reaction, as elegantly demonstrated by Halpern[53] and Brown,[54] the less stable, minor diastereomeric complex **31** [M = Rh^+(BINAP)] with a square planar structure may be more reactive to hydrogen, leading to the antipodal dihydro compound. This reversal of asymmetric orientation between Ru and Rh is also seen in hydrogenation of dehydro amino acids.[18a,19,22]

Conclusion

The BINAP–Ru(II) complexes catalyze hydrogenation of a wide array of 2-acylated 1-alkylidene-1,2,3,4-tetrahydroisoquinolines proceeding in nearly quantitative yield and with a very high optical yield. Figure 6 presents a mnemonic device for the prediction of the reactivity and the sense of enantioface selection. The chiral products thus obtained can be converted to most naturally occurring and also artificial isoquinolines by standard synthetic procedures. Since most of the tetrahydroisoquinoline products are crystalline, the enantiomerically pure materials are readily accessible by single recrystallization. Thus, the present discovery has realized a general, highly practical asymmetric synthesis of isoquinoline alkaloids.

Experimental Section

IR ($CHCl_3$ solution) and UV (C_2H_5OH solution) spectra are expressed by wavenumber (cm^{-1}) and by wavelength (nm). Optical rotations were measured on a digital polarimeter in $CHCl_3$ solution in a 1-dm cell. Chemical shifts of ^{1}H- and ^{13}C-NMR spectra taken in $CDCl_3$ are reported in ppm downfield from TMS, and proton signal patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. HRMS and MS were performed at an ionizing voltage of 70 eV. Elemental analyses were carried out at the Faculty of Agriculture, Nagoya University. Melting points are uncorrected. Chromatographic purification was done with 240–400-mesh silica gel.

Preparation of the 2-Acyl-1-alkylidene-1,2,3,4-tetrahydroisoquinoline 8. The imines **7** were prepared by the known procedure and immediately used.

To a solution of 1-[(3,4-dimethoxyphenyl)methyl]-6,7-dimethoxy-3,4-dihydroisoquinoline [**7** ($R^1 = R^3 = R^4 = CH_3O$; R^2 = H)][55] (8.00 g, 23.4 mmol) in CH_2Cl_2 (50 mL) cooled at 0 °C was added pyridine (7.43 mL, 91.9 mmol) and formic pivalic anhydride[56] (5.98 g, 46.0 mmol). The reaction mixture was allowed to stir at rt for 3 h. After the mixture was partitioned between H_2O (100 mL) and CH_2Cl_2 (100 mL), the aqueous layer was extracted with CH_2Cl_2 (25 mL × 2), and the combined organic extracts were washed with 1 N HCl solution (50 mL × 2), 2 N NaOH solution (50 mL), and brine (50 mL). Drying and concentration afforded a crude 92:8 mixture of (*Z*)- and (*E*)-1-[(3,4-dimethoxyphenyl)methylene]-2-formyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**8a**). Recrystallization from C_2H_5OH (50 mL) gave pure (*Z*)-**8a** (7.80 g, 90% yield) as colorless needles: mp 167–168 °C. Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.18; H, 6.16, N 3.69. The IR, UV, and ^{1}H NMR spectra were consistent with reported values.[27a]

Pure (*E*)-**8a** (1.50 g) was obtained as slightly yellowish crystals by recrystallization of a crude 69:31 mixture of (*Z*)- and (*E*)-**8a** (9.20 g) from C_2H_5OH (50 mL) in the dark: mp 106–109 °C; IR 1660; UV 293 (ϵ 14 670), 222 (39 040); ^{1}H NMR (270 MHz) δ 2.89

(53) Halpern, J. Asymmetric Catalytic Hydrogenation: Mechanism and Origin of Enantioselection. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, Chapter 2.

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(55) Buck, J. S.; Haworth, R. D.; Perkin, W. H. *J. Chem. Soc.* **1924**, *125*, 2176.

(56) Vlietstra, E. J.; Zwikker, J. W.; Nolte, R. J. M.; Drenth, W. *Recl. Trav. Chim. Pays-Bas* **1982**, *101*, 460.

(t, 2, J = 6.3 Hz), 3.39, 3.78, and 3.88 (three s, 12), 3.83 (t, 2, J = 6.3 Hz), 6.37 (s, 1), 6.64 (s, 1), 6.8–6.9 (m, 4), 8.71 (s, 1); ^{13}C NMR (67.8 MHz) δ 28.48, 39.89, 55.31, 55.78, 55.82, 55.91, 110.57, 110.77, 111.18, 112.03, 116.20, 121.82, 123.11, 128.75, 129.27, 133.97, 146.60, 148.24, 148.83, 149.17, 160.86. Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.24; H, 6.17; N, 3.73.

An 18:82 mixture of (*Z*)- and (*E*)-2-acetyl-1-[(3,4-dimethoxyphenyl)methylene]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**8b**) (5.8 g) was obtained under the following conditions: 7 ($R^1 = R^3 = R^4 = CH_3O$; R^2 = H) (5.00 g, 14.6 mmol), triethylamine (8.00 mL, 57.4 mmol), acetyl chloride (4.00 mL, 56.3 mmol), CH_2Cl_2 (100 mL), 23 °C, 2 h. A solution of the crude *Z*/*E* mixture in C_2H_5OH (300 mL) was placed in a round-bottomed Pyrex flask in a water bath and irradiated externally by a 500-W tungsten lamp for 2 h, resulting in a 3:4 *Z*/*E* photostationary ratio. Evaporation of about 200 mL of the solvent and collection of the precipitated crystals afforded (*Z*)-**8b** (2.3 g). Four repetitions of this procedure gave (*Z*)-**8b** (4.5 g). Recrystallization (C_2H_5OH (30 mL)) gave pure (*Z*)-**8b** (4.20 g, 75% yield): mp 196.5–198 °C; IR 1635; UV 332 (ε 31 220), 223 (30 610); ^{1}H NMR (270 MHz) δ 1.81 (s, 3), 2.6–2.8 (m, 1), 3.1–3.3 (m, 2), 3.89 (s, 9), 3.98 (s, 3), 5.0–5.1 (m, 1), 6.62 (s, 1), 6.72 (s, 1), 6.86 (d, 1, J = 8.9 Hz), 7.06 (s, 1), 7.07 (br d, 1), 7.14 (s, 1); ^{13}C NMR (67.8 MHz) δ 21.62, 28.13, 41.58, 55.78, 55.89, 56.14, 106.03, 110.77, 111.32, 111.74, 118.79, 121.42, 125.69, 127.86, 128.21, 135.08, 147.66, 148.63, 148.96, 149.46, 169.95; MS m/z 383 (M^+). Anal. Calcd for $C_{22}H_{25}NO_5$: C, 68.91; H, 6.57; N, 3.65. Found: C, 68.91; H, 6.66; N 3.63.

The stereoisomer (*E*)-**8b** (150 mg) contaminated with 2% of the *Z* isomer was isolated as a slightly yellowish foam by chromatography (20:1–10:1 ether–acetone) of a crude 1:4 *Z*/*E* mixture (900 mg) in the dark: IR 1620; UV 286 (ε 9440), 208 (41 610); ^{1}H NMR (270 MHz) δ 2.30 (s, 3), 2.92 (t, 2, J = 6.3 Hz), 3.47, 3.76, 3.87, and 3.88 (four s, 12), 3.99 (t, 2, J = 6.3 Hz), 6.46 (br s, 1), 6.65 (s, 1), 6.8–6.9 (m, 4); ^{13}C NMR (67.8 MHz) δ 22.25, 27.76, 42.50, 55.38, 55.69, 55.73, 55.78, 110.08, 110.80, 110.96, 111.58, 121.66, 124.25, 124.75, 127.95, 129.36, 135.93, 146.19, 148.42, 148.65, 149.08, 169.19. Anal. Calcd for $C_{22}H_{25}NO_5$: C, 68.91; H, 6.57; N, 3.65. Found: C, 68.83; H, 6.46; N, 3.54.

A crude 25:75 *Z*/*E* mixture of 1-[(3,4-dimethoxyphenyl)methylene]-2-(trifluoroacetyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**8c**) (4.1 g) was obtained under the following conditions: 7 ($R^1 = R^3 = R^4 = CH_3O$; R^2 = H) (3.00 g, 8.79 mmol), triethylamine (4.50 mL, 32.3 mmol), trifluoroacetic anhydride (3.43 mL, 24.3 mmol), CH_2Cl_2 (60 mL), rt, 10 min. Recrystallization (CH_3OH (15 mL)) gave pure (*Z*)-**8c** (0.450 g, 1.03 mmol): mp 196.5–198 °C; IR 1695; UV 331 (ε 28 520), 221 (28 190); ^{1}H NMR (400 MHz) δ 2.8–2.9 (m, 1), 3.2–3.3 (m, 1), 3.4–3.5 (m, 1), 3.85 and 3.96 (two s, 6), 3.88 (s, 6), 5.0–5.1 (m, 1), 6.6–7.2 (m, 6). Anal. Calcd for $C_{22}H_{22}F_3NO_5$, C 60.41, H 5.07, N 3.20; Found C 60.41, H 5.01, N 3.33.

A 2:98 *Z*/*E* mixture of 1-[(3,4-dimethoxyphenyl)methylene]-6,7-dimethoxy-2-pivaloyl-1,2,3,4-tetrahydroisoquinoline (**8d**) (5.0 g) was obtained under the following conditions: 7 ($R^1 = R^3 = R^4 = CH_3O$; R^2 = H) (4.00 g, 11.7 mmol), triethylamine (7.00 mL, 50.2 mmol), pivaloyl chloride (3.50 mL, 28.4 mmol), CH_2Cl_2 (40 mL), rt, 1 h. Three cycles of the irradiation–concentration–separation procedure (500-W tungsten lamp; CH_3OH (300 mL); 2 h) afforded the crude (*Z*)-**8d**. Recrystallization (CH_3OH–CH_2Cl_2) gave pure (*Z*)-**8d** (3.80 g, 76% yield): mp 203.5–205.5 °C; IR 1620; UV 329 (ε 48 080), 220 (44 420); ^{1}H NMR (270 MHz) δ 0.99 (br s, 9), 2.69 (br s, 1), 3.19 (br s, 2), 3.89 and 3.97 (two s, 6), 3.90 (s, 6), 5.11 (br s, 1), 6.54 (s, 1), 6.61 (s, 1), 6.85 (d, 1, J = 8.3 Hz), 7.02 (s, 1), 7.07 (dd, 1, J = 1.8 Hz and 8.3 Hz), 7.13 (s, 1); ^{13}C NMR (67.8 MHz) δ 28.01, 28.51, 41.04, 45.92, 55.69, 55.73, 55.76, 56.07, 106.25, 110.89, 111.29, 111.54, 121.85, 122.05, 127.29, 128.28, 128.66, 136.90, 147.56, 148.58, 148.63, 148.96, 178.08; HRMS m/z (M^+) calcd 425.2202, obsd 425.2205. Anal. Calcd for $C_{25}H_{31}NO_5$: C, 70.55; H, 7.35; N, 3.29. Found: C, 70.65; H, 7.21; N 3.25.

The stereoisomer (*E*)-**8d** (168 mg) containing 2% of the *Z* isomer was isolated as a colorless foam by chromatography (2:1 ether–hexane) of a crude 2:98 *Z*/*E* mixture (750 mg) in the dark: IR 1610; UV 296 (ε 14 420); ^{1}H NMR (270 MHz) δ 1.33 (s, 9), 2.92 (t, 2, J = 6.3 Hz), 3.46, 3.74, 3.86 and 3.87 (four s, 12), 4.07 (br t, 2, J = 6.0 Hz), 6.55 (s, 1), 6.61 (s, 1), 6.70 (s, 1), 6.7–6.9 (m, 3); ^{13}C NMR (67.8 MHz) δ 28.08, 29.45, 40.91, 46.17, 55.56, 55.71, 55.85, 55.89, 110.57, 111.07, 111.72, 121.76, 125.04, 125.54, 128.12, 129.18, 137.46, 146.04, 148.55, 148.73, 149.03, 177.27. Anal. Calcd for $C_{25}H_{31}NO_5$: C, 70.57; H, 7.34; N, 3.29. Found: C, 70.59; H, 7.23; N, 3.24.

A 98:2 *Z*/*E* mixture of 2-benzoyl-1-[(3,4-dimethoxyphenyl)methylene]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**8e**) (6.3 g) was obtained under the following conditions: 7 ($R^1 = R^3 = R^4 = CH_3O$; R^2 = H) (5.00 g, 14.6 mmol), triethylamine (8.00 mL, 57.4 mmol), benzoyl chloride (3.50 mL, 30.2 mmol), CH_2Cl_2 (100 mL), rt, 0.5 h. Recrystallization (C_2H_5OH–CH_2Cl_2) yielded pure (*Z*)-**8e** (4.69 g, 72% yield) as slightly yellowish crystals: mp 217–219.5 °C. Anal. Calcd for $C_{27}H_{27}NO_5$: C, 72.79; H, 6.11; N, 3.14. Found: C, 72.78; H, 6.11; N, 3.14. The IR, UV, and ^{1}H NMR spectra were consistent with reported values.[57]

An 88:12 *Z*/*E* mixture of 2-(*p*-bromobenzoyl)-1-[(3,4-dimethoxyphenyl)methylene]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**8f**) (23 g) was obtained under the following conditions: 7 ($R^1 = R^3 = R^4 = CH_3O$; R^2 = H) (14.0 g, 41.0 mmol), triethylamine (16.6 g, 164 mmol), *p*-bromobenzoyl chloride (18.0 g, 82.0 mmol), CH_2Cl_2 (130 mL), 23 °C, 0.5 h. Recrystallization (50:1 C_2H_5OH–CH_2Cl_2) gave pure (*Z*)-**8f** (16.0 g, 74% yield) as slightly yellowish crystals: mp 205–206 °C; IR 1630; UV 324 (ε 19 700), 205 (35 560); ^{1}H NMR (270 MHz) δ 2.87 (br d, 1, J = 14.5 Hz), 3.1–3.4 (m, 2), 3.78, 3.88, 3.93, and 3.96 (four s, 12), 5.0–5.2 (m, 1), 6.31 (s, 1), 6.35 (s, 1), 6.59 (d, 1, J = 8.3 Hz), 6.70 (s, 1), 6.73 (d, 2, J = 8.3 Hz), 6.76 (d, 1, J = 8.3 Hz), 7.05 (s, 1), 7.16 (d, 2, J = 8.3 Hz); ^{13}C NMR (67.8 MHz) δ 28.85, 41.94, 55.53, 55.71, 55.77, 56.02, 105.59, 110.76, 110.94, 111.60, 118.00, 120.73, 123.59, 124.73, 127.31, 127.79, 128.73, 129.81, 134.43, 134.81, 147.89, 148.69, 149.48, 168.15. Anal. Calcd for $C_{27}H_{26}BrNO_5$: C, 61.84; H, 5.00; N, 2.67. Found: C, 61.70; H, 5.00; N, 2.61.

A 23:77 *Z*/*E* mixture of 2-acetyl-6,7-bis(benzyloxy)-1-[(3,4,5-trimethoxyphenyl)methylene]-1,2,3,4-tetrahydroisoquinoline (**8g**) (3.2 g) was obtained under the following conditions: 7 ($R^1 = R^2 = CH_3O$; $R^3 = R^4 = C_6H_5CH_2O$)[58] (2.80 g, 5.35 mmol), triethylamine (3.50 mL, 25.1 mmol), acetyl chloride (3.00 mL, 42.2 mmol), CH_2Cl_2 (50 mL), 23 °C, 1 h. Three cycles of the irradiation–concentration–separation procedure (500-W tungsten lamp; C_2H_5OH (300 mL); 4 h) afforded crude (*Z*)-**8g**. Recrystallization (C_2H_5OH) gave pure (*Z*)-**8g** (1.93 g, 64% yield) as colorless crystals: mp 205–206.5 °C; IR 1630; UV 332 (ε 27 410), 210 (37 040); ^{1}H NMR (500 MHz) δ 1.80 (s, 3), 2.6–2.7 (m, 1), 3.0–3.2 (m, 2), 3.86 (s, 6), 3.87 (s, 3), 4.9–5.1 (m, 1), 5.16 (s, 2), 5.19 (d, 1, J = 11.6 Hz), 5.23 (d, 1, J = 11.9 Hz), 6.58 (s, 1), 6.71 (s, 3), 7.25 (s, 1), 7.3–7.6 (m, 10); ^{13}C NMR (67.8 MHz) δ 21.65, 28.03, 41.35, 55.94, 60.84, 70.88, 72.12, 105.19, 110.80, 114.73, 118.97, 126.05, 127.13, 127.45, 127.85, 128.40, 128.44, 128.96, 130.76, 135.87, 136.68, 137.08, 137.62, 147.34, 149.79, 153.22, 169.82. Anal. Calcd for $C_{35}H_{35}NO_6$: C, 74.32; H, 6.24; N, 2.48. Found: C, 74.26; H, 6.31; N, 2.49.

Crude (*Z*)-2-formyl-7-hydroxy-1-[(3-hydroxy-4-methoxyphenyl)methylene]-6-methoxy-1,2,3,4-tetrahydroisoquinoline (**8h**) (2.7 g) was obtained under the following conditions: 7 ($R^1 = R^3$ = HO; R^2 = H; $R^4 = CH_3O$)[59] (2.60 g, 8.30 mmol), pyridine (5.5 mL, 68.0 mmol), formic pivalic anhydride (4.30 g, 33.0 mmol), THF (50 mL), rt, 12 h. The intermediary 2,7,3′-triformyl compound was hydrolyzed at the workup stage by 28% NH_4OH solution. Recrystallization (C_2H_5OH) yielded pure (*Z*)-**8h** (1.50 g, 53% yield) as slightly yellowish crystals: mp 190–191 °C; IR (KBr) 3280, 1650; UV 336 (ε 22 790), 223 (33 360); ^{1}H NMR (270 MHz, CD_3OD) δ 2.89 (t, 2, J = 6.0 Hz), 3.87 (s, 3), 3.89 (s, 3), 3.96 (t, 2, J = 6.0 Hz), 6.73 (s, 1), 6.82 (s, 1), 6.8–7.0 (m, 3), 7.26 (s, 1), 8.05 (s, 1); ^{13}C NMR (67.8 MHz, DMSO-d_6) δ 28.14, 38.10, 55.56, 109.59, 112.12, 112.27, 112.93, 115.51, 120.42, 123.50, 125.59, 128.25, 132.01, 145.24, 146.43, 146.68, 148.27, 161.87. Anal. Calcd for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.77; H, 5.60; N, 4.07.

Crude (*Z*)-7-acetoxy-1-[(3-acetoxy-4-methoxyphenyl)methylene]-2-acetyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline (**8i**) (4.4 g) was obtained under the following conditions: 7 ($R^1 = R^3$ =

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HO; R^2 = H; R^4 = CH_3O)[59] (2.88 g, 9.19 mmol), pyridine (30 mL), acetic anhydride (15 mL), 140 °C, 4 h. Recrystallization (C_2H_5OH–CH_2Cl_2) afforded (*Z*)-**8i** (2.50 g, 62% yield): mp 203–205 °C; IR 1630; UV 324 (ϵ 29 640), 213 (27 710); ^{1}H NMR (400 MHz) δ 1.81 (s, 3), 2.32 and 2.34 (two s, 6), 2.7–2.8 (m, 1), 3.1–3.2 (m, 2), 3.84 and 3.84 (two s, 6), 4.9–5.0 (m, 1), 6.66 (s, 1), 6.71 (s, 1), 6.94 (d, 1, *J* = 8.5 Hz), 7.18 (d, 1, *J* = 2.1 Hz), 7.31 (dd, 1, *J* = 8.5 Hz and 2.1 Hz), 7.35 (s, 1); ^{13}C NMR (100 MHz) δ 20.98, 21.05, 21.88, 28.74, 41.76, 56.07, 56.16, 112.48, 112.74, 117.58, 118.56, 122.41, 125.89, 127.05, 127.97, 133.75, 134.63, 138.16, 139.71, 150.48, 150.78, 168.48, 168.78, 169.70. Anal. Calcd for $C_{24}H_{25}NO_7$: C, 65.59; H, 5.73; N, 3.19. Found: C, 65.60; H, 5.85; N, 3.18.

A 1:2 *Z*/*E* mixture of 1-{[3,5-bis(benzyloxy)-4-methoxyphenyl]-methylene}-2-formyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline (**8j**) (4.4 g) was obtained under the following conditions: **7** (R^1 = R^2 = $C_6H_5CH_2O$: R^3 = H; R^4 = CH_3O)[40b] (4.00 g, 8.10 mmol), pyridine (4.08 mL, 50.4 mmol), formic pivalic anhydride (3.30 g, 25.4 mmol), CH_2Cl_2 (30 mL), rt, 12 h. Three cycles of this irradiation–concentration–separation procedure (500-W tungsten lamp; C_2H_5OH (200 mL); 3 h) afforded the crude (*Z*)-**8j**. Recrystallization (C_2H_5OH) gave pure (*Z*)-**8j** (3.42 g, 81% yield): mp 166.5–168 °C; IR (KBr) 1665; UV 327 (ϵ 20 200), 215 (39 470); ^{1}H NMR (270 MHz) δ 2.90 (t, 2, *J* = 6.0 Hz), 3.82 (s, 3), 3.85 (t, 2, *J* = 6.2 Hz), 3.91 (s, 3), 5.12 (s, 4), 6.6–6.7 (m, 3), 6.80 (dd, 1, *J* = 3.0 Hz and 8.9 Hz), 7.2–7.5 (m, 10), 7.64 (d, 1, *J* = 8.9 Hz), 8.14 (s, 1); ^{13}C NMR (67.8 MHz) δ 29.34, 38.07, 55.24, 60.69, 71.22, 108.64, 112.93, 113.47, 123.74, 124.41, 127.04, 127.74, 128.48, 130.55, 133.34, 135.91, 137.15, 138.50, 152.72, 159.58, 162.76. Anal. Calcd for $C_{33}H_{31}NO_5$: C, 75.99; H, 5.99; N, 2.69. Found: C, 76.08; H, 6.02; N, 2.66.

A 5:1 *Z*/*E* mixture of 2-formyl-1-[(3-hydroxy-4-methoxyphenyl)methylene]-6-methoxy-1,2,3,4-tetrahydroisoquinoline (**8k**) (2.1 g) was obtained under the following conditions: **7** (R^1 = HO; R^2 = R^3 = H; R^4 = CH_3O)[60] (2.00 g, 6.73 mmol), pyridine (3.30 mL, 40.8 mmol), formic pivalic anhydride (2.60 g, 20.0 mmol), CH_2Cl_2 (30 mL), rt, 12 h. The intermediary 2,3′-diformyl compound was hydrolyzed at the workup stage by using 28% NH_4OH solution. The crude product was treated with activated charcoal in ethyl acetate (40 mL) and then recrystallized from the filtrate to give (*Z*)-**8k** (1.12 g, 51% yield) as slightly yellowish crystals: mp 148.5–149.5 °C; IR (KBr) 3300, 1660; UV 330 (ϵ 18 530), 210 (28 360); ^{1}H NMR (270 MHz) δ 2.93 (t, 2, *J* = 6.1 Hz), 3.83 and 3.89 (two s, 6), 3.98 (t, 2, *J* = 6.1 Hz), 5.60 (s, 1), 6.66 (d, 1, *J* = 2.6 Hz), 6.77 (s, 1), 6.81 (d, 1, *J* = 8.3 Hz), 6.83 (dd, 1, *J* = 2.6 Hz and 8.9 Hz), 6.89 (dd, 1, *J* = 2.0 Hz and 8.3 Hz), 6.95 (d, 1, *J* = 2.0 Hz), 7.70 (d, 1, *J* = 8.9 Hz), 8.15 (s, 1); ^{13}C NMR (67.8 MHz) δ 29.34, 38.18, 55.20, 55.78, 110.98, 113.14, 113.41, 114.87, 120.68, 124.03, 124.32, 128.40, 132.53, 135.71, 145.70, 145.76, 159.36, 162.84. Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.30. Found: C, 69.92; H, 5.85; N, 4.31.

Crude 2-formyl-6,7-dimethoxy-1-methylene-1,2,3,4-tetrahydroisoquinoline (**12a**) (11 g) was obtained under the following conditions: 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline[61] (10.0 g, 48.7 mmol), triethylamine (40.7 mL, 292 mmol), formic pivalic anhydride (13.0 g, 100 mmol), CH_2Cl_2 (60 mL), rt, 4 h. Recrystallization (1:2 ethyl acetate–hexane) gave pure **12a** (10.6 g, 93% yield) as colorless crystals: mp 136.5–138 °C; IR (KBr) 1665; UV 307 (ϵ 7570), 268 (11 150); ^{1}H NMR (270 MHz) δ 2.84 (t, 2, *J* = 6.1 Hz), 3.89 (t, 2, *J* = 6.1 Hz), 3.89 and 3.91 (two s, 6), 4.83 (d, 1, *J* = 2.0 Hz), 5.20 (d, 1, *J* = 2.0 Hz), 6.60 and 7.11 (two s, 2), 8.64 (s, 1); ^{13}C NMR (67.8 MHz) δ 28.58, 38.46, 55.68, 55.82, 94.47, 106.50, 110.89, 121.78, 127.19, 140.59, 147.81, 149.83, 160.26. Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.85; H, 6.49; N, 6.01.

2-Acetyl-6,7-dimethoxy-1-methylene-1,2,3,4-tetrahydroisoquinoline (**12b**) was prepared according to the known procedure:[61] mp 102–103 °C. Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.97; H, 6.91; N, 5.65.

Crude 2-formyl-1-[(4-methoxyphenyl)methylene]-1,2,3,4,5,6,7,8-octahydroisoquinoline (**26**) was obtained under the following conditions: 1-[(4-methoxyphenyl)methylene]-3,4,5,6,7,8-hexahydroisoquinoline[62] (8.50 g, 33.3 mmol), pyridine (17.0 mL, 210 mmol), formic pivalic anhydride (13.0 g, 100 mmol), THF (100 mL), 0 °C, 8 h. This was chromatographed on a silica gel column (1:6 ethyl acetate–hexane) to give a 6:1 mixture of (*Z*)- and (*E*)-**26** (7.36 g, 78% yield). Recrystallization (CH_3OH (20 mL)) gave pure (*Z*)-**26** (4.85 g, 51% yield) as colorless crystals: mp 88.5–90 °C; IR 1660; UV 297 (ϵ 22 350); ^{1}H NMR (270 MHz) δ 1.6–1.8 (m, 4), 2.07, 2.20, and 2.28 (three m, 6), 3.78 (s, 3), 3.86 (t, 2, *J* = 5.9 Hz), 6.16 (s, 1), 6.83 (dt, 2, *J* = 2.5 Hz and 8.9 Hz), 7.23 (dt, 2, *J* = 2.5 Hz and 8.9 Hz), 8.01 (s, 1); ^{13}C NMR (22.4 MHz) δ 22.11, 22.71, 24.26, 30.49, 31.09, 37.61, 55.03, 113.21, 114.17, 125.42, 127.88, 129.85, 134.35, 158.16, 162.60. Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.30; H, 7.47; N, 4.94. Found: C, 76.37; H, 7.47; N, 4.98.

A 90:<1:4.5:4.5 mixture of (*Z*)-1-formyl-2-[(4-methoxyphenyl)-methylene]-3,4-dimethyl-1,2,5,6-tetrahydropyridine [(*Z*)-**29**], (*E*)-**29**, 2-[(4-methoxyphenyl)methyl]-3,4-dimethylpyridine, and **30b** was obtained under the following conditions: crude HCl salt of 2-[(4-methoxyphenyl)methyl]-3,4-dimethyl-5,6-dihydropyridine (**28**)[63] (5.37 g, 20.2 mmol), pyridine (200 mL), formic pivalic anhydride (25.0 g, 192 mmol), benzene (400 mL), 0 °C, 8 h. Chromatographic purification (1:9 acetone–hexane) and recrystallization (acetone–hexane) yielded pure (*Z*)-**29** (2.60 g, 50% yield) as colorless crystals: mp 96–98 °C; IR (KBr) 1675; UV 298 (ϵ 22 850); ^{1}H NMR (270 MHz) δ 1.84 and 1.93 (two s, 6), 2.28 (br t, 2, *J* = 6 Hz), 3.78 (s, 3), 3.84 (t, 2, *J* = 6.1 Hz), 6.24 (s, 1), 6.83 (d, 2, *J* = 8.9 Hz), 7.23 (d, 2, *J* = 8.6 Hz), 7.99 (s, 1); ^{13}C NMR (22.5 MHz) δ 13.60, 20.53, 31.86, 37.82, 55.26, 114.43, 114.76, 124.40, 127.27, 128.24, 130.09, 132.04, 135.18, 137.51, 158.53, 162.65. Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.62; H, 7.42; N, 5.39.

General Procedure of Asymmetric Hydrogenation. Hydrogenation solvents were distilled from magnesium methoxide (CH_3OH), magnesium ethoxide (C_2H_5OH), sodium benzophenone ketyl (C_6H_6 and THF), or CaH_2 (CH_2Cl_2 and CH_3CN) and degassed. BINAP–Ru[23,24] and –Rh[19b,25] complexes **1** and **2** were prepared according to the reported method. $Ru(CF_3COO)_2$-(TolBINAP) was prepared by mixing $Ru(CH_3COO)_2$(TolBINAP) with 2 equiv of trifluoroacetic acid in CH_2Cl_2 and evaporation of the solvent in vacuo. The entire apparatus was oven-dried at 120 °C overnight before use. The 4-atm hydrogenation was performed in a glass autoclave, and the high-pressure reaction (≥50 atm) was carried out in a glass vessel placed in a stainless steel autoclave. Hydrogenation was done with H_2 gas of a 99.99999% purity under anaerobic conditions using the standard Schlenk technique. The ee's of the hydrogenation products were determined after conversion to the diastereomeric thioureas **11** by HPLC analysis. The details are given in the synthesis of tetrahydropapaverine (**14**). The absolute configuration was determined by comparison of the rotation value or the HPLC retention time of authentic samples.

The procedure is exemplified by reaction using (*Z*)-**8a** as substrate and $Ru(CH_3COO)_2$[(*R*)-BINAP] [(*R*)-**1a**] as catalyst. A dry Schlenk tube was charged with (*Z*)-**8a** (1.00 g, 2.71 mmol), CH_3OH (150 mL), and CH_2Cl_2 (30 mL). The whole mixture was degassed by three freeze–thaw cycles. To this (*R*)-**1a** (11.4 mg, 13.5 μmol) was added under an Ar stream. The resulting yellowish solution was further degassed by two freeze–thaw cycles and then transferred into a dry Ar-filled glass autoclave. Ar gas in the whole system was replaced three times by H_2, and the reaction vessel was pressurized to 4 atm. The yellowish solution was vigorously stirred at 30 °C for 48 h. Transfer of the slightly brownish contents into a round-bottomed flask and evaporation of the solvent gave crude (*R*)-1-[(3,4-dimethoxyphenyl)methyl]-2-formyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline [(*R*)-**9a**]; ^{1}H NMR analysis, with mesitylene as an internal standard, showed 100% yield. Chromatographic purification (ethyl acetate) gave (*R*)-**9a** (1.01 g) in >99.5% ee as a colorless solid. Solution-phase properties were determined after an equilibrium between two amide rotamers had been reached (1 h):[29] $[\alpha]^{24}_D$ −86.4° (*c* 1.02); IR 1660; ^{1}H NMR (270 MHz) δ 2.5–3.4 (m, 5), 3.5–3.6 (m, 0.5), 3.69, 3.76, 3.84, 3.84, 3.85, 3.86, and 3.87 (seven s, 12), 4.4–4.7 (m,

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1), 5.52 (t, 0.5, J = 6.3 Hz), 6.33 (s, 0.5), 6.5–6.9 (m, 4.5), 7.70 (s, 0.5), 8.14 (s, 0.5); ^{13}C NMR (67.8 MHz) δ 27.54, 28.93, 34.02, 40.75, 41.38, 42.95, 51.91, 55.65, 55.73, 55.78, 55.87, 55.96, 58.84, 109.76, 110.24, 110.80, 111.13, 111.27, 111.49, 112.33, 112.71, 121.62, 121.85, 125.27, 126.03, 126.93, 127.22, 129.56, 129.86, 147.18, 147.43, 147.66, 147.75, 148.01, 148.15, 148.53, 148.96, 161.18, 161.22; HRMS m/z (M^+) calcd 371.1732, obsd 371.1730. An analytical sample was prepared by recrystallization (1:1 hexane–ethyl acetate): mp 139.5–140.5 °C (lit.[64] mp 136 °C). Anal. Calcd for $C_{21}H_{25}NO_5$: C, 67.91; H, 6.78, N, 3.77. Found: C, 67.90; H, 6.73; N, 3.71. (S)-BINAP–Ru-catalyzed hydrogenation (substrate, (Z)-**8a** (205 mg, 0.555 mmol), catalyst, (S)-**1a** (5.1 mg, 6.1 μmol), solvent, C_2H_5OH (15 mL) and CH_2Cl_2 (3 mL), H_2, 4 atm, temperature, 24 °C time, 48 h, conversion, 100%) afforded (S)-**9a** in >99.5% ee: $[\alpha]^{24}_D$ +86.3° (c 1.02).

The conditions of hydrogenation of (Z)-**8b**, (Z)-**8c**, (Z)-**8d**, (Z)-**8e**, and (Z)-**8f** listed in Table 3 and the product properties are as follows. (Z)-**8b** (214 mg, 0.558 mmol): (R)-**1a** (6.2 mg, 7.4 μmol), C_2H_5OH (15 mL) and CH_2Cl_2 (3 mL), 4 atm, 24 °C, 48 h, 100% conversion. Product, (R)-2-acetyl-1-[(3,4-dimethoxyphenyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline [(R)-**9b**] in >99.5% ee; $[\alpha]^{24}_D$ −91.3° (c 1.19) [lit.[32] $[\alpha]^{20}_D$ +89.8° (c 1.045) for (S)-**9b**]; IR 1620; ^{1}H NMR (270 MHz) δ 1.59 (s, 1.5), 2.15 (s, 1.5), 2.5–3.2 (m, 5), 3.3–3.5 (m, 0.5), 3.63, 3.77, 3.84, 3.85, 3.85, and 3.87 (six s, 12), 4.7–4.9 (m, 1), 5.62 (dd, 0.5, J = 5.2 Hz and 7.8 Hz), 6.21 (s, 0.5), 6.5–6.9 (m, 4.5); ^{13}C NMR (100 MHz) δ 21.52, 22.45, 28.26, 28.84, 35.29, 42.15, 42.85, 54.29, 55.91, 56.00, 56.07, 56.10, 56.22, 56.28, 59.42, 110.07, 110.77, 111.35, 111.53, 112.65, 112.81, 121.59, 121.81, 125.56, 126.63, 127.81, 128.23, 130.10, 130.58, 130.80, 147.07, 147.41, 147.90, 148.36, 148.77, 168.91, 169.20; MS m/z (M^+) 385. Analytical sample obtained by recrystallization (1:1 hexane–ethyl acetate): mp 139.5–140 °C (lit.[32] mp 135 °C). Anal. Calcd for $C_{22}H_{27}NO_5$: C, 68.55; H, 7.06; N, 3.63. Found: C, 68.30; H, 7.04; N, 3.57. (Z)-**8b** (203 mg, 0.529 mmol): (S)-**1a** (3.9 mg, 4.6 μmol), C_2H_5OH (15 mL) and CH_2Cl_2 (3 mL), 4 atm, 24 °C, 48 h, 100% conversion. Product, (S)-**9b** in >99.5% ee: $[\alpha]^{24}_D$ +84.6° (c 1.01).

(Z)-**8c** (196 mg, 0.448 mmol): (S)-**1a** (5.2 mg, 6.2 μmol), C_2H_5OH (15 mL) and CH_2Cl_2 (3 mL), 4 atm, 24 °C, 167 h, 10% conversion.

(Z)-**8d** (195 mg, 0.458 mmol): (S)-**1a** (5.6 mg, 6.7 μmol), C_2H_5OH (15 mL) and CH_2Cl_2 (3 mL), 4 atm, 24 °C, 47 h, 100% conversion. Product, (S)-1-[(3,4-dimethoxyphenyl)methyl]-6,7-dimethoxy-2-pivaloyl-1,2,3,4-tetrahydroisoquinoline [(S)-**9d**] in 50% ee on the basis of the optical rotation of the authentic (S)-**9d** [$[\alpha]^{24}_D$ +105.3° (c 0.96)]: $[\alpha]^{24}_D$ +52.9° (c 0.97); IR 1610; ^{1}H NMR (270 MHz) δ 1.26 (s, 9), 2.62 (br d, 1, J = 15.5 Hz), 2.89 (ddd, 1, J = 5.3 Hz, 11.6 Hz, and 16.8 Hz), 2.99 (dd, 1, J = 8.2 Hz and 13.5 Hz), 3.08 (dd, 1, J = 5.6 Hz and 13 .5 Hz), 3.36 (ddd, 1, J = 4.0 Hz, 11.9 Hz, and 13.5 Hz), 3.61 and 3.80 (two s, 6), 3.84 (s, 6), 4.12 (br s, 1), 5.68 (br s, 1), 6.16 (br s, 1), 6.57 (s, 1), 6.63 (dd, 1, J = 1.7 Hz and 7.9 Hz), 6.69 (br d, 1, J = 2 Hz), 6.74 (d, 1, J = 7.9 Hz); ^{13}C NMR (67.8 MHz) δ 28.28, 28.73, 29.65, 38.84, 41.62, 55.60, 55.80, 55.87, 110.63, 110.84, 110.89, 112.93, 122.07, 125.27, 128.55, 130.82, 146.73, 147.56, 147.59, 148.58, 176.21; HRMS m/z (M^+) calcd 427.2358, obsd 427.2359. Analytical sample obtained by recrystallization (1:3 ethyl acetate–hexane): mp 147.5–148.5 °C. Anal. Calcd for $C_{25}H_{33}NO_5$: C, 70.23; H, 7.78; N, 3.28. Found: C, 70.23; H, 7.70; N, 3.22.

(Z)-**8e** (208 mg, 0.467 mmol): (S)-**1a** (7.9 mg, 9.4 μmol), C_2H_5OH (11.5 mL) and CH_2Cl_2 (6 mL), 4 atm, 24 °C, 158 h, 100% conversion. Product, (S)-2-benzoyl-1-[(3,4-dimethoxyphenyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline [(S)-**9e**] in 96% ee: $[\alpha]^{24}_D$ +79.9° (c 0.99); IR 1620; ^{1}H NMR (270 MHz) δ 2.53 (br d, 0.6, J = 16 Hz), 2.7–2.9, 3.0–3.5, and 3.6–3.7 (three m, 5), 3.67, 3.69, 3.70, 3.81, 3.85, 3.86, and 3.87 (seven s, 12), 4.7–5.0 (m, 0.8), 5.87 (t, 0.6, J = 6.7 Hz), 6.11 (s, 0.4), 6.27 (br s, 0.4), 6.38 (s, 0.6), 6.46 (br d, 0.4, J = 7.9 Hz), 6.57 (s, 0.6), 6.6–6.8, 6.9–7.0, and 7.2–7.5 (three m, 7.6); ^{13}C NMR (67.8 MHz) δ 27.94, 28.89, 35.51, 41.78, 41.90, 42.93, 53.24, 55.73, 55.83, 55.89, 55.98, 59.67, 109.87, 110.46, 110.86, 111.11, 111.18, 111.56, 112.26, 112.82, 121.91, 125.27, 126.15, 126.42, 126.51, 127.74, 128.15, 128.49, 129.05, 129.38, 129.93, 130.47, 136.34, 136.61, 146.98, 147.16, 147.74, 147.95, 148.10, 148.71, 148.92, 170.41, 170.88. Analytical sample obtained by recrystallization (1:3 ethyl acetate–hexane): mp 154–155 °C. Anal. Calcd for $C_{27}H_{29}NO_5$: C, 72.46; H, 6.53; N, 3.13. Found: C, 72.49; H, 6.54; N, 3.08.

(Z)-**8f** (300 mg, 0.572 mmol): (S)-**1a** (5.3 mg, 6.3 μmol) CH_3OH (7.7 mL) and CH_2Cl_2 (7.7 mL), 4 atm, 30 °C, 40 h, 100% conversion. Product, (S)-2-(p-bromobenzoyl)-1-[(3,4-dimethoxyphenyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline [(S)-**9f**] in 98% ee: $[\alpha]^{27}_D$ +78.1° (c 1.41); IR (KBr) 1630; ^{1}H NMR (270 MHz) δ 2.55 (br d, 0.5, J = 16 Hz), 2.7–2.9 (m, 1.5), 2.9–3.5 (m, 2.5), 3.5–3.7 (m, 1), 3.70, 3.73, 3.80, 3.84, 3.85, 3.87, and 3.88 (seven s, 12), 4.7–4.8 (m, 0.5), 4.8–4.9 (m, 0.5), 5.85 (t, 0.5, J = 6.6 Hz), 6.24 (s, 0.5), 6.31 (s, 0.5), 6.38 (s, 0.5), 6.50 (d, 0.5, J = 6.6 Hz), 6.58 (s, 0.5), 6.5–6.8 (m, 3.5), 7.14 (d, 1, J = 8.3 Hz), 7.38 (d, 1, J = 7.9 Hz), 7.52 (d, 1, J = 8.3 Hz); ^{13}C NMR (67.8 MHz) δ 27.68, 28.62, 35.23, 41.56, 41.69, 42.55, 53.13, 55.51, 55.55, 55.65, 55.80, 59.67, 109.54, 110.23, 110.71, 110.96, 111.02, 111.43, 112.03, 112.62, 121.67, 123.08, 123.42, 124.88, 125.85, 127.40, 127.77, 127.99, 128.06, 129.57, 130.13, 131.01, 131.50, 134.81, 135.19, 147.03, 147.61, 147.86, 148.01, 148.51, 148.80, 169.10, 169.59. Analytical sample obtained by recrystallization (1:3 ethyl acetate–hexane): mp 126–128 °C. Anal. Calcd for $C_{27}H_{28}BrNO_5$: C, 61.60; H, 5.36; N, 2.66. Found: C, 61.51; H, 5.33; N, 2.62.

Tetrahydropapaverine (14). The hydrogenation product (R)-**9a** (1.20 g, 3.23 mmol; $[\alpha]^{24}_D$ −86.4° (c 1.02)), obtained by hydrogenation of (Z)-**8a** in the presence of (R)-**1a**, was dissolved in C_2H_5OH (16 mL) containing 2 N NaOH solution (16 mL) in a sealed tube, and the mixture was heated at 80 °C for 10 h. After being cooled to rt and addition of H_2O (60 mL), the mixture was extracted four times with CH_2Cl_2 (40 mL). Drying of the combined organic layers and removal of the solvent afforded (R)-**14** (1.05 g, 3.06 mmol) in 95% yield as foam: $[\alpha]^{28}_D$ +29.2° (c 1.26)[lit.[32] $[\alpha]^{20}_D$ +32.10° (c 1.528) for (R)-**14**]. ^{1}H NMR and IR spectra were consistent with those reported.[65] Deacylation of **9b**, **9e**, and **9f** was performed according to the procedure described in the synthesis of tretoquinol (vide infra). The conditions and the yields were as follows for **9b** (53.2 mg, 0.138 mmol): KOH (360 mg, 6.42 mmol), 80% NH_2NH_2 (0.14 mL, 3.6 mmol), ethylene glycol (14 mL), 170 °C, 20 h, 81% yield. **9e** (117 mg, 0.261 mmol): KOH (840 mg, 15.0 mmol), 80% NH_2NH_2 (0.30 mL, 7.7 mmol), ethylene glycol (30 mL), 170 °C, 17 h, 47% yield. **9f** (100 mg, 0.190 mmol): KOH (609 mg, 10.9 mmol), 80% NH_2NH_2 (0.22 mL, 5.7 mmol), ethylene glycol (20 mL), 170 °C, 15 h, 55% yield. Under these conditions no deacylation occurred with **9d**.

The ee value was determined as follows: An aliquot of the deformylation product (R)-**14** (5.0 mg, 14.6 μmol; $[\alpha]^{28}_D$ +29.2° (c 1.26)) was dissolved in CH_3CN (1.0 mL), and to this was added 2,3,4,6-tetra-O-acetyl-D-glucopyranosyl isothiocyanate (GITC) (11.5 mg, 29.5 μmol). After being stirred at 25 °C for 10 min, the mixture was directly analyzed by HPLC on a reversed-phase C_{18} silica-gel column (column, Nomura Chemical Co. Develosil ODS-5; eluent, 2:3 CH_3CN–H_2O containing ammonium phosphate (1.4 g/L); flow rate, 1.0 mL/min; detection, 254-nm light) to give a single peak, t_R 59.1 min. The GITC derivative of (S)-**14**, which was obtained by using (S)-**1a**, also exhibited a single peak, t_R 53.1 min. HPLC analysis of the GITC derivative of racemic **14** gave two base-line separated peaks, due to the diastereomeric thioureas of (S)-**14** (t_R 53.2 min) and (R)-**14** (t_R 59.7 min), with equal intensities.

Laudanosine (15). To a suspension of $LiAlH_4$ (24.1 mg, 0.635 mmol) in THF (2 mL) was added synthetic (S)-**9a** (53.1 mg, 0.143 mmol) in THF (3 mL) at −78 °C. After the mixture was refluxed for 20 min saturated K_2CO_3 solution (0.1 mL) was added. Separation of the resulting precipitates and evaporation of the solvent gave the crude oil, which was crystallized from CH_2Cl_2–ether to give (S)-laudanosine [(S)-**15**] (40.7 mg, 80 %): $[\alpha]^{28}_D$ +93.6° (c 0.60, C_2H_5OH) [lit.[66] $[\alpha]^{25}_D$ +96.6° (c 0.41, C_2H_5OH) for (S)-**15**]. IR and ^{1}H NMR spectra were consistent with reported values.[65,67]

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Tretoquinol (17). Hydrogenation conditions for (*Z*)-**8g** (201 mg, 0.355 mmol): (*R*)-**1a** (6.5 mg, 7.7 μmol), C_2H_5OH (15 mL) and CH_2Cl_2 (3 mL), 4 atm, 24 °C, 48 h, 100% conversion. Chromatographic purification (3:1 ethyl acetate–hexane) afforded (*R*)-2-acetyl-6,7-bis(benzyloxy)-1-[(3,4,5-trimethoxyphenyl)-methyl]-1,2,3,4-tetrahydroisoquinoline [(*R*)-**9g**] (188 mg) as a colorless foam: $[\alpha]^{24}{}_D$ −66.9° (*c*, 1.10); IR 1590; ^{1}H NMR (400 MHz) δ 1.62 and 2.14 (two s, 3), 2.4–2.6 (m, 0.5), 2.6–2.8 (m, 1), 2.8–3.1 (m, 3), 3.2–3.4 (m, 0.5), 3.5–3.6 (m, 0.5), 3.71, 3.80, and 3.82 (three s, 9), 4.7–4.8 (m, 0.5), 4.8–5.0 (m, 1.5), 5.1–5.2 (m, 3), 5.5–5.6 (m, 0.5), 6.2–6.4 and 6.6–6.8 (m, 4), 7.2–7.5 (m, 10); ^{13}C NMR (67.8 MHz) δ 20.95, 22.00, 27.74, 28.22, 34.69, 41.76, 42.30, 43.07, 53.84, 55.87, 56.09, 58.82, 60.73, 60.84, 70.99, 71.20, 71.85, 106.32, 106.52, 114.22, 114.44, 114.53, 114.80, 126.44, 126.98, 127.05, 127.11, 127.25, 127.67, 127.72, 128.33, 128.48, 128.85, 133.30, 133.70, 136.38, 136.88, 137.06, 146.87, 146.98, 147.41, 148.22, 152.70, 153.17, 169.23, 169.39; HRMS *m/z* (M^+) calcd 567.2620, obsd 567.2618; ee 97% determined after conversion to (*R*)-**16** (vide infra) by the GITC method (3:4 CH_3CN–H_2O containing ammonium phosphate (1.4 g/L), t_R of the thiourea of (*R*)-**16** and (*S*)-**16**, 51.6 min and 43.7 min, respectively). Analytical sample obtained by recrystallization (1:1 ethyl acetate–hexane): mp 64–65 °C. Anal. Calcd for $C_{35}H_{37}NO_6$: C, 74.05; H, 6.57; N, 2.47. Found: C, 73.98; H, 6.67; N, 2.39. (*S*)-BINAP–Ru-catalyzed hydrogenation ((*Z*)-**8g** (200 mg, 0.354 mmol): (*S*)-**1a** (2.7 mg, 3.2 μmol), C_2H_5OH (15 mL) and CH_2Cl_2 (3 mL), 4 atm, 24 °C, 96 h, 100% conversion) afforded (*S*)-**9g** (202 mg) in 96% ee: $[\alpha]^{24}{}_D$ +63.3° (*c* 1.10).

The hydrogenation product (*S*)-**9g** (58.4 mg, 0.103 mmol) dissolved in ethylene glycol (15 mL) containing KOH (360 mg, 6.42 mmol) and 80% aqueous NH_2NH_2 (0.15 mL, 3.9 mmol) was heated at 180 °C for 17 h under an Ar atmosphere. After the reaction mixture was partitioned between ether (10 mL) and 1 N HCl solution (30 mL), the aqueous layer was washed with ether (10 mL × 2) and mixed with 2 N NaOH solution (30 mL). Extraction with CH_2Cl_2 (15 mL × 3), drying, and evaporation of the solvent afforded (*S*)-6,7-bis(benzyloxy)-1-[(3,4,5-trimethoxyphenyl)methyl]-1,2,3,4-tetrahydroisoquinoline [(*S*)-**16**][68] (42.7 mg, 79% yield). To a solution of the HCl salt of (*S*)-**16** (100 mg, 0.178 mmol) in C_2H_5OH (5 mL) was added 10% Pd/C (5.0 mg), and H_2 was pressurized to 4 atm. The mixture was vigorously stirred at 50 °C for 16 h. Removal of the catalyst by filtration and evaporation of the solvent afforded the HCl salt of (*S*)-tretoquinol [(*S*)-**17**] (65.2 mg, 96% yield): $[\alpha]^{30}{}_D$ −27.1° (*c* 1.09, CH_3OH) [lit.[69] $[\alpha]^{22}{}_D$ −32° (*c* 0.23, CH_3OH) for (*S*)-**17**/HCl].

Norreticuline (18). Hydrogenation conditions. (*Z*)-**8h** (150 mg, 0.439 mmol): (*R*)-**1a** (3.0 mg, 3.6 μmol), CH_3OH (40 mL), 50 atm, 25 °C, 120 h, 100% conversion. Chromatographic purification (1:2 ethyl acetate–hexane) afforded (*R*)-**9h** (148 mg) as a colorless solid: $[\alpha]^{27}{}_D$ −68.9° (*c* 1.07, DMF) [lit.[58] $[\alpha]^{23}{}_D$ +68.7° (*c* 0.69, DMF) for (*S*)-**9h**]; IR (KBr) 3460, 1640; ^{1}H NMR (270 MHz) δ 2.5–3.3 (m, 5), 3.4–3.6 (m, 0.4), 3.85, 3.86, 3.87, and 3.88 (four s, 6), 4.4–4.6 (m, 1.2), 5.4–5.7 (m, 2.4), 6.5–6.9 (m, 5), 7.56 (s, 0.6), 8.08 (s, 0.4); ^{13}C NMR (67.8 MHz, DMSO-d_6) δ 27.21, 28.80, 33.31, 40.68, 41.75, 51.10, 55.64, 55.70, 57.50, 111.84, 112.08, 112.28, 113.88, 113.99, 116.81, 116.87, 120.15, 124.02, 124.07, 128.03, 128.66, 130.53, 130.67, 144.85, 144.90, 146.02, 146.24, 146.32, 146.66, 146.77, 160.84, 161.33; ee 99% assayed after conversion of (*R*)-norreticuline [(*R*)-**18**] (2 N NaOH, C_2H_5OH, 80 °C, 15 h) by the GITC method (1:1 CH_3CN–H_2O containing ammonium phosphate (1.4 g/L); t_R of the thiourea of (*R*)-**18** and (*S*)-**18**, 8.20 min and 7.52 min). Analytical sample obtained by recrystallization (methanol): mp 204.5–205 °C. Anal. Calcd for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16; N, 4.08. Found: C, 66.42; H, 5.98; N, 4.00.

Hydrogenation conditions for (*Z*)-**8i** (210 mg, 0.478 mmol): (*R*)-**1a** (11.6 mg, 13.8 μmol), C_2H_5OH (15 mL) and CH_2Cl_2 (3 mL), 4 atm, 24 °C, 48 h, 100% conversion. Chromatographic purification (2:1 ethyl acetate–hexane) afforded (*R*)-**9i** (194 mg) as a colorless foam: $[\alpha]^{24}{}_D$ −73.0° (*c* 1.25); IR 1760, 1620; ^{1}H NMR (270 MHz) δ 1.58 (s, 1.5), 2.12 (s, 1.5), 2.28, 2.29, 2.31, and 2.33 (four s, 6), 2.5–3.2 (m, 4.5), 3.2–3.4 (m, 0.5), 3.5–3.7 (m, 0.5), 3.79, 3.80, and 3.82 (three s, 6), 4.7–4.9 (m, 1), 5.59 (t, 0.5, *J* = 6.1 Hz), 6.5–7.0 (m, 5); ^{13}C NMR (67.8 MHz) δ 20.61, 20.95, 22.09, 28.31, 28.87, 34.60, 41.08, 41.69, 41.96, 53.55, 55.83, 55.89, 58.86, 111.88, 112.04, 112.49, 112.60, 121.13, 121.80, 123.71, 124.16, 127.76, 127.99, 128.22, 128.49, 130.11, 130.24, 132.54, 133.30, 137.94, 139.19, 139.74, 149.62, 149.70, 149.89, 150.16, 168.92, 168.97, 169.15, 169.44, 169.77; ee 95% assayed by the GITC method after conversion to (*R*)-**18** (KOH, 80% NH_2NH_2, ethylene glycol, 180 °C, 14 h). Analytical sample obtained by recrystallization (1:2 ethyl acetate–hexane): mp 134.5–135.5 °C. Anal. Calcd for $C_{24}H_{27}NO_7$: C, 65.29; H, 6.16; N, 3.17. Found: C, 65.19, H, 6.28; N, 3.13.

(*S*)-BINAP–Ru-catalyzed hydrogenation ((*Z*)-**8i** (202 mg, 0.460 mmol): (*S*)-**1a** (4.4 mg, 5.2 μmol), C_2H_5OH (15 mL) and CH_2Cl_2 (3 mL), 4 atm, 24 °C, 49 h, 100% conversion) afforded (*S*)-**9i** (197 mg) in 96% ee: $[\alpha]^{24}{}_D$ +66.7° (*c*, 0.97).

Salsolidine (19). Hydrogenation conditions for **12a** (500 mg, 2.14 mmol): (*S*)-**1a** (18.0 mg, 21.4 μmol), C_2H_5OH (120 mL) and CH_2Cl_2 (24 mL), 1 atm, 30 °C, 7 h, 100% conversion. Chromatographic purification (5:1 ethyl acetate–hexane) afforded (*S*)-**13a** (504 mg) as a yellow oil: $[\alpha]^{27}{}_D$ +183.1° (*c* 1.22); ee 97% evaluated after conversion to (*S*)-**19**[65] (2 N NaOH, C_2H_5OH, 80 °C, 10 h) by the GITC method (3:2 CH_3CN–H_2O containing ammonium phosphate (1.4 g/L); t_R of the thiourea of (*R*)-**19** and (*S*)-**19**, 67.3 min and 70.6 min). IR and ^{1}H NMR spectra were consistent with those described in the literature.[70] Analytical sample obtained by recrystallization (4:1 CH_3OH–ether): mp 81–82 °C. Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.40; H, 7.55; N, 5.94.

Hydrogenation conditions for **12b** (236.5 mg, 0.956 mmol): (*S*)-**1a** (21.8 mg, 25.9 μmol), C_2H_5OH (15 mL) and CH_2Cl_2 (3 mL), 4 atm, 24 °C, 48 h, 100% conversion. Chromatographic purification (3:1 ethyl acetate–hexane) afforded (*S*)-**13b** (239 mg) as a slightly yellow solid: $[\alpha]^{24}{}_D$ +181.9° (*c* 1.11); ee 96% assayed by the GITC method after conversion to (*S*)-**19**[65] (KOH, 80% NH_2NH_2, ethylene glycol, 180 °C, 17 h). The ^{1}H NMR spectrum was consistent with reported values.[7] Recrystallization (1:1 ethyl acetate–hexane) gave the analytical sample: mp 96–98 °C. Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.48; H, 7.64; N, 5.60.

(*R*)-1-{[3,5-bis(benzyloxy)-4-methoxyphenyl]methyl}-2-formyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline [(*R*)-9j]. Hydrogenation conditions for (*Z*)-**8j** (150 mg, 0.288 mmol): (*R*)-**1a** (2.4 mg, 2.9 μmol), CH_3OH (25 mL) and CH_2Cl_2 (5 mL), 50 atm, 25 °C, 98 h, 100% conversion. Chromatographic purification (ether) afforded (*R*)-**9j** (129 mg) as a colorless glassy oil: $[\alpha]^{27}{}_D$ −9.2° (*c*, 1.00); IR 1665; ^{1}H NMR (270 MHz) δ 2.3–2.5 (m, 0.5), 2.5–3.2 (m, 5), 3.77, 3.79, 3.88, and 3.90 (four s, 6), 4.3–4.5 (m, 1), 4.96 (m, 2), 5.10 (m, 2), 5.46 (t, 0.5, *J* = 5 Hz), 6.14 (s, 1), 6.31 (s, 1), 6.55 (d, 0.5, *J* = 2.6 Hz), 6.66 (d, 0.5, *J* = 3.0 Hz), 6.77 (dd, 0.5, *J* = 2.8 Hz and 8.3 Hz), 6.78 (dd, 0.5, *J* = 2.6 Hz and 8.6 Hz), 6.97 (d, 0.5, *J* = 8.6 Hz), 7.01 (d, 0.5, *J* = 8.6 Hz), 7.3–7.5 (m, 10), 7.53 (s, 0.5), 7.83 (s, 0.5); ^{13}C NMR (67.8 MHz) δ 28.23, 29.53, 33.87, 40.92, 41.58, 43.70, 51.86, 55.16, 55.22, 58.50, 60.92, 60.96, 70.60, 71.30, 109.31, 109.42, 112.76, 112.79, 113.16, 113.54, 126.98, 127.06, 127.17, 127.63, 127.68, 127.77, 127.88, 128.41, 128.49, 132.45, 132.58, 135.27, 135.33, 137.12, 137.29, 138.10, 138.70, 151.87, 152.56, 158.19, 158.52, 161.29, 161.53; ee 97% determined after conversion to (*R*)-**21** (2 N NaOH, C_2H_5OH, 80 °C, 15 h; $[\alpha]^{27}{}_D$ +29.2° (*c* 0.64, $CHCl_3/C_2H_5OH$ (9:1)) [lit.[71] $[\alpha]^{25}{}_D$ −33° (*c* 1.8, $CHCl_3/C_2H_5OH$ (9:1)) for (*S*)-**21**]) by the GITC method (3:2 CH_3CN–H_2O containing ammonium phosphate (1.4 g/L); t_R of the thiourea of (*R*)-**21** and (*S*)-**21**, 65.5 min and 54.2 min). Drying over P_4O_{10} (85 °C, 24 h) afforded the analytical sample. Anal. Calcd for $C_{33}H_{33}NO_5$: C, 75.70; H, 6.35; N, 2.67. Found: C, 75.71; H, 6.47; N, 2.67.

(*R*)-2-Formyl-1-[(3-hydroxy-4-methoxyphenyl)methyl]-6-methoxy-1,2,3,4-tetrahydroisoquinoline [(*R*)-9k]. Hydrogenation conditions for (*Z*)-**8k** (150 mg, 0.461 mmol): (*R*)-**1a** (4.0

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mg, 4.8 μmol), CH_3OH (20 mL) and CH_2Cl_2 (8 mL), 50 atm, 25 °C, 98 h, 100% conversion. Chromatographic purification (ethyl acetate) afforded (*R*)-**9k** (148 mg) as a colorless foam: $[\alpha]^{27}_D$ −42.6° (*c* 1.15); IR 3540, 1670; ^{1}H NMR (270 MHz) δ 2.6–3.4 (m, 5), 3.5–3.6 (m, 0.4), 3.78, 3.80, 3.85, and 3.87 (four s, 6), 4.4–4.7 (m, 1.2), 5.54 (t, 0.4, *J* = 6.3 Hz), 5.59 (d, 0.4, *J* = 1.6 Hz), 5.69 (d, 0.6, *J* = 1.7 Hz), 6.5–6.9 (m, 5), 6.96 (d, 0.4, *J* = 8.6 Hz), 7.11 (d, 0.6, *J* = 8.2 Hz), 7.59 (s, 0.6), 8.11 (s, 0.4); ^{13}C NMR (67.8 MHz) δ 28.21, 29.64, 33.71, 40.53, 41.12, 42.71, 51.88, 55.02, 55.09, 55.69, 58.81, 110.48, 110.83, 112.48, 112.70, 113.21, 113.43, 115.27, 115.98, 120.68, 120.91, 127.37, 127.81, 128.34, 130.21, 130.28, 134.48, 135.07, 145.25, 145.41, 145.69, 145.85, 157.99, 158.32, 161.33, 161.36; ee 99% assayed after conversion to (*R*)-**22**[41a] (2 N NaOH, C_2H_5OH, 80 °C, 15 h; $[\alpha]^{27}_D$ +98.7° (*c* 0.15) [lit.[72] dextrorotatory for (*R*)-**22**]) by the GITC method (1:1 CH_3CN–H_2O containing ammonium phosphate (1.4 g/L); t_R of the thiourea of (*R*)-**22** and (*S*)-**22**, 17.6 min and 15.0 min). Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.69; H, 6.47; N, 4.28. Found: C, 69.63; H, 6.32; N, 4.23.

2-Formyl-1-[(4-methoxyphenyl)methyl]-1,2,3,4,5,6,7,8-octahydroisoquinoline (27a). Hydrogenation conditions for (*Z*)-**26** (150 mg, 0.529 mmol): $Ru(CF_3COO)_2$[(*S*)-TolBINAP] (3 mg, 3.0 μmol), CH_3OH (27 mL), 100 atm, 30 °C, 100 h, 100% conversion. Chromatographic purification (1:3 ethyl acetate–hexane) afforded (*S*)-**27a** (148 mg) as a slightly yellow oil: $[\alpha]^{22}_D$ +21.4° (*c* 1.33, CH_3OH) [lit.[73] $[\alpha]^{22}_D$ +22.2° (*c* 1.33, CH_3OH) for (*S*)-**27a**]; IR 1660; ^{1}H NMR (270 MHz) δ 1.4–2.4 (br m, 10), 2.64 (dd, 0.6, *J* = 10 Hz and 14 Hz), 2.7–3.1 (m, 2.4), 3.30 (dd, 0.4, *J* = 7 Hz and 13 Hz), 3.58 (br d, 0.6, *J* = 10 Hz), 3.77 (s, 3), 4.37 (dd, 0.6, *J* = 7 Hz and 13 Hz), 4.68 (br s, 0.4), 6.7–6.9 (m, 2), 6.9–7.1 (m, 2), 7.40 (s, 0.6), 7.93 (s, 0.4); ^{13}C NMR (67.8 MHz) δ 22.55, 22.63, 22.72, 27.52, 29.50, 29.81, 29.97, 30.67, 33.19, 36.11, 37.35, 40.25, 53.08, 55.01, 60.68, 113.41, 113.93, 127.54, 127.59, 127.70, 128.71, 129.65, 129.81, 130.08, 130.26, 158.01, 158.23, 160.68, 160.91; ee 97% assayed after conversion to (*S*)-**27b**[5e] (2 N NaOH, C_2H_5OH, 80 °C, 10 h) by the GITC method (3:2 CH_3CN–H_2O containing ammonium phosphate (1.4 g/L); t_R of the thiourea of (*R*)-**27b** and (*S*)-**27b**, 32.1 min and 25.4 min). Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.74; H, 8.13; N, 4.91. Found: C, 75.41; H, 8.30; N, 4.90. ^{1}H- and ^{13}C-NMR spectra of synthetic (*S*)-**27a** were consistent with those obtained with the authentic sample from Hoffmann-La Roche Co.[48,73] (*R*)-BINAP–Ru-catalyzed hydrogenation ((*Z*)-**26** (150 mg, 0.529 mmol): $Ru(CF_3COO)_2$[(*R*)-TolBINAP] (3 mg, 3 μmol), CH_3OH (27 mL), 100 atm, 30 °C, 164 h; 100% conversion) afforded (*R*)-**27a** in 96% ee: $[\alpha]^{22}_D$ −18.0° (*c* 2.03, CH_3OH).

1-Formyl-2-[(4-methoxyphenyl)methyl]-3,4-dimethyl-1,2,5,6-tetrahydropyridine (30a). Hydrogenation conditions for (*Z*)-**29** (150 mg, 0.583 mmol): $Ru(CF_3COO)_2$[(*S*)-TolBINAP] (3 mg, 3.0 μmol), CH_3OH (27 mL), 100 atm, 30 °C, 120 h, 100% conversion. Chromatographic purification (1:3 ethyl acetate–hexane) afforded (*S*)-**30a** (148 mg) as a slightly yellow oil: $[\alpha]^{23}_D$ +34.4° (*c* 1.54, CH_3OH); IR 1660; ^{1}H NMR (270 MHz) δ 1.65, 1.68, 1.75, and 1.80 (four s, 6), 1.8–2.0 (m, 1), 2.0–2.4 (br m, 1), 2.62 (dd, 0.6, *J* = 14 Hz and 11 Hz), 2.7–3.1 (m, 2.4), 3.31 (dd, 0.4, *J* = 7 Hz and 13 Hz), 3.61 (br d, 0.6, *J* = 10 Hz), 3.77 (s, 3), 4.36 (dd, 0.6, *J* = 7 Hz and 13 Hz), 4.72 (br s, 0.4), 6.7–6.9 (m, 2), 6.9–7.1 (m, 2), 7.39 (s, 0.6), 7.91 (s, 0.4); ^{13}C NMR (67.8 MHz) δ 16.80, 18.95, 19.01, 30.56, 31.73, 33.32, 36.36, 37.35, 40.27, 53.80, 55.11, 55.17, 61.56, 113.57, 114.11, 125.16, 125.34, 125.67, 126.86, 129.79, 129.95, 130.19, 130.35, 158.17, 158.41, 160.77, 160.96; ee 97% determined after conversion to (*S*)-**30b** (2 N NaOH, C_2H_5OH, 80 °C, 10 h; $[\alpha]^{26}_D$ −91.3° (*c* 0.95, ether) [lit.[5d] $[\alpha]^{25}_D$ −88.0° (*c* 1.8, ether) for (*S*)-**30b**]) by the GITC method (1:1 CH_3CN–H_2O containing ammonium phosphate (1.4 g/L); t_R of the thiourea of (*R*)-**30b** and (*S*)-**30b**, 54 min and 44 min). Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.11; H, 8.40; N, 5.44. ^{1}H-NMR spectrum of the deformylation product (*S*)-**30b** was in agreement with the reported value.[5d] (*R*)-BINAP–Ru-catalyzed hydrogenation ((*Z*)-**29** (150 mg, 0.583 mmol): $Ru(CF_3COO)_2$[(*R*)-TolBINAP] (3.0 mg, 3.0 μmol), CH_3OH (27 mL), 100 atm, 25 °C, 120 h, 100% conversion) afforded (*R*)-**30a** in 98% ee: $[\alpha]^{27}_D$ −35.6° (*c* 1.67, CH_3OH).

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