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Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 17 (2006) 184–190

Approach to the stereoselective synthesis of melatonin receptor agonist Ramelteon via asymmetric hydrogenation

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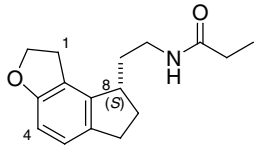
Received 30 August 2005; revised 2 November 2005; accepted 4 November 2005

Abstract—Asymmetric synthesis of a novel non-benzodiazepine hypnotic drug Ramelteon (TAK-375) was accomplished via asymmetric hydrogenation. Development of the substrate design revealed that a novel class of substrate, allylic acylamine **4a**, was hydrogenated with a Ru-BINAP catalyst in 95% ee and 98% yield. The effectiveness and robustness of the reaction were demonstrated on a 700-g scale.

1. Introduction

The chemical synthesis of enantiomerically pure compounds is crucial in the development of new drugs. The pertinent question in this context is not only how to prepare them in a pure state, but also how to prepare them economically. In addition, safety and environmental issues as well as the availability of the starting materials and key intermediates are important factors that determine the reaction feasibility. When a new chemical entity is selected as a drug candidate, the preliminary exploration of a wide range of possible reactions is inevitable in the early stages. Ramelteon (TAK-375) [(*S*)-*N*-[2-(1,6,7,8-tetrahydro-2*H*-indeno[5,4-*b*]furan-8-yl)ethyl]-propionamide] is a novel, selective melatonin MT_1/MT_2 receptor agonist and is expected to be useful in the treatment of circadian rhythm sleep disorders (Scheme 1). It constitutes a new class of prescription drugs that do not cause adverse effects typically associated with the use of benzodiazepine, such as learning and memory impairment and drug dependence.[1] Recently, the US Food and Drug Administration (FDA) approved a new drug application (NDA) for Ramelteon (ROZEREM™) for the treatment of insomnia characterized by difficulty with sleep onset. It is also the first and only prescription sleep medication that is not designated as a controlled substance by the US Drug Enforcement Administration (DEA).



Ramelteon

Scheme 1.

Ramelteon has a simple but unique chemical structure, comprising of a three-fused-ring system with an asymmetric center at the benzylic position. In order to obtain enantiomerically pure Ramelteon, we investigated various synthetic approaches based on asymmetric hydrogenation,[2] enzymatic resolution,[3] diastereomer salt resolution, and simulated moving bed (SMB) resolution.[4] With the objective of obtaining a practical synthesis, we focused our efforts on asymmetric hydrogenation using readily available and versatile Ru-BINAP catalysts.[5] We presumed that excellent yield, enantioselectivity, and productivity could be achieved by the appropriate design of substrates rather than the screening of catalysts. Herein, we report our synthetic approaches to Ramelteon based on chelation-controlled asymmetric hydrogenation using Ru-BINAP catalysts.

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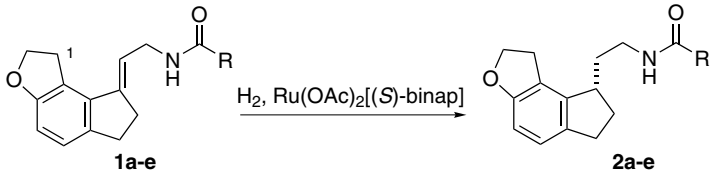
doi:10.1016/j.tetasy.2005.11.005



Scheme 2.

2. Results and discussion

2.1. Hydrogenation of allylic acylamines 1a–e

Prioritizing synthetic effectiveness, we selected tricyclic *exo* allylic acylamines **1a**–**e**,[6] which were the most direct precursors for Ramelteon, as shown in Scheme 2 and Table 1. Substrates with various acyl groups (RCO), including the propionyl group, which is the substituent on Ramelteon, were examined. However, none of them yielded satisfactory enantioselectivities and conversions. Enantioselective hydrogenation with Ru-BINAP catalysts is generally considered to proceed via metal complexes in which an unsaturated bond and an electron-donating heteroatom are simultaneously coordinated to the Ru atom.[2] According to the proposed reaction mechanism, the poor enantioselectivities in the reactions with **1a**–**e** might suggest that the steric hindrance of the C1 methylene moiety in **1a**–**e** inhibited the desired chelation. In addition, the faint effect of the R groups on the reactivities and enantioselectivities indicates that any R group located outside the metal chelation could not contribute to improving the outcome of the reaction.

Table 1. Asymmetric hydrogenation of allylic acylamines **1a**–**e**[a]

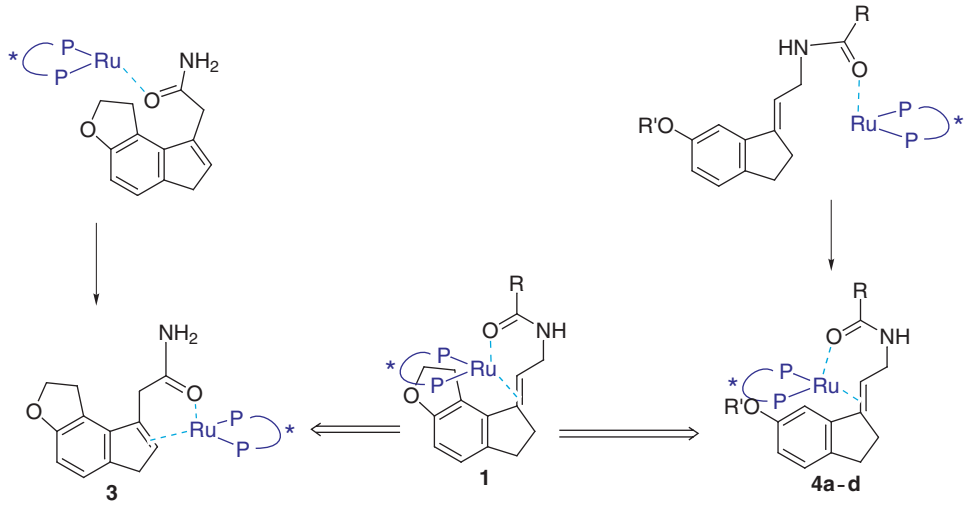
R	ee[b] (%)	Yield[b] (%)
Et (**1a**)	42	37
H (**1b**)	12	18
n-Pr (**1c**)	32	35
n-Bu (**1d**)	18	23
OBz (**1e**)[c]	Racemic	29

[a] The reaction was conducted with 10 mol % $Ru(OAc)_2$(binap) at 50 °C for 6 h under H_2 (10 MPa).
[b] Determined by HPLC analysis with chiral stationary phases.
[c] $[Et_2NH_2]^+[Ru_2Cl_5(binap)_2]^-$ was utilized.

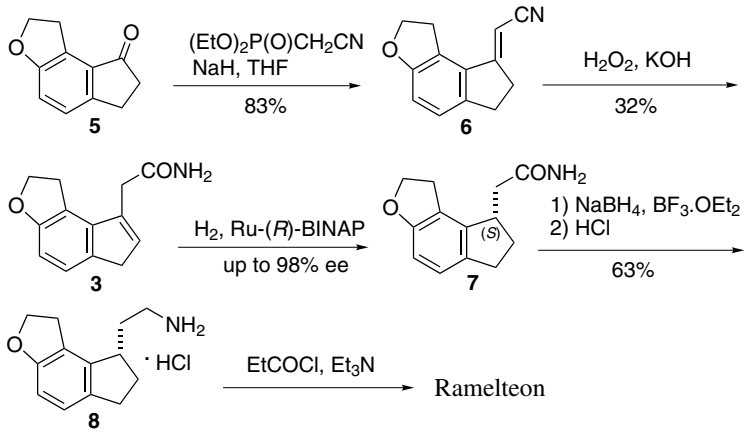
The objective of our substrate design was to realize effective chelation for hydrogenation, as outlined in Scheme 3. When the carbonyl group in **1** coordinated to Ru in the usual manner, chelation was presumed to be realized at the congested side according to the trajectory of coordination. Therefore, we presumed that relocation of the double bond and the carbonyl group, as depicted in amide **3** would result in a change in the coordination, thereby favoring the less hindered side. On the other hand, the bicyclic substrates **4a**–**d** that lack the undesirable C1 methylene moiety were expected to chelate in a less congested fashion.

2.2. Hydrogenation of carboxamide 3

The synthesis of carboxamide **3** was carried out as shown in Scheme 4. 1,2,6,7-Tetrahydro-8*H*-indeno[5,4-*b*]-furan-8-one **5**[1] was converted to nitrile **6** by Horner–Emmons condensation. The treatment of nitrile **6** with alkaline hydrogen peroxide yielded *endo*-amide **3** via hydration and isomerization. The *endo* geometry was established by a NOESY experiment by ^1H NMR. The results of the asymmetric hydrogenation of carboxamide **3** using (*R*)-BINAP catalysts are summarized in Table 2. The binuclear complex $[Et_2NH_2]^+$-$[Ru_2Cl_5(binap)_2]^-$,[7] which is a highly effective catalyst for the asymmetric hydrogenation of ketones such as



Scheme 3.



Scheme 4.

Table 2. Asymmetric hydrogenation of carboxamide **3**[a]

Ru-BINAP	H_2 (MPa)	Temp (°C)	ee[b] (%)	Yield[b] (%)
$[Et_2NH_2]^+[Ru_2Cl_5(binap)_2]^-$	10	50	98	20
$[Et_2NH_2]^+[Ru_2Cl_5(binap)_2]^-$	10	70	97	21
$Ru(OAc)_2[(R)\text{-binap}]$	10	50	92	92
$Ru(OAc)_2[(R)\text{-binap}]$	5	50	96	86

[a] The reaction was conducted with 5 mol % Ru for 6 h.
[b] Determined by HPLC analysis with a chiral stationary phase.

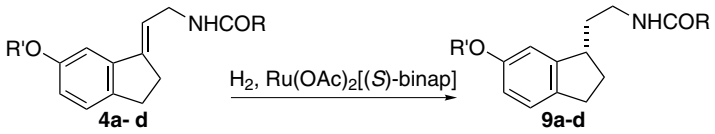
3-oxobutanoate, gave excellent ees but poor yields. Conversely, satisfactory ees and yields were obtained when the mononuclear complex $Ru(OAc)_2[(R)$-binap] was utilized. The effects of pressure and temperature were insignificant. It is noteworthy that (*R*)-BINAP generated the desired enantiomer with *S*-configuration. The opposite stereochemistry obtained in the hydrogenation of **1a–e** and in the hydrogenation of **3** is most likely due to a difference in the coordination mode of the chiral catalyst, as depicted in Scheme 3.[8] Hence, the six-membered chelate complex **3**, in which the Ru(II) atom interacts with carbonyl oxygen, and an olefinic double bond would be formed on the right side of the existing olefinic double bond. The reduction of carboxamide **7** followed by acylation in a conventional manner yielded Ramelteon. However, carboxamide **3** appeared to be inadequate for large-scale application because of its insufficient solubility.

2.3. Hydrogenation of allylic acylamines 4

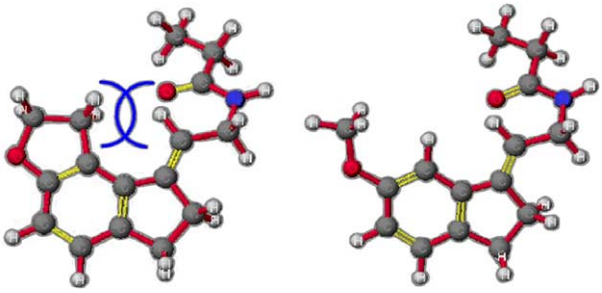
The bicyclic *exo* allylic acylamines **4a–d**[1,9] were subjected to asymmetric hydrogenation (Scheme 5).

The reaction proceeded successfully with 10 mol % of the catalyst precursor at 50–70 °C under an initial H_2 pressure of 9–10 MPa with an excellent enantioselectivity of 95%. The alkoxy groups (OR′), which were located outside the chelation, had little effect on the enantioselectivities. However, the amide alkyl groups (R) had a substantial effect on both the enantioselectivity and reactivity. The replacement of the methyl group with the electron-withdrawing trifluoromethyl group (**9c** vs **9d**) resulted in a drastic deterioration in ee and yield. This finding clearly indicates that the chelation of Ru onto the carbonyl group is crucial for the reaction (Table 3). Allylic acylamines **4a–d** required (*S*)-BINAP in order to obtain the desired stereochemistry in accordance with acylamine **1**. This observation also reinforces the feasibility of the working hypothesis depicted in Scheme 3. The steric hindrance of a rather remote moiety in **1**—C1 methylene—exerts a decisive influence on the chelation, as shown in Scheme 6. It is clear that a consideration of the entire structure of the compounds is essential for designing an effective asymmetric hydrogenation process.

The sense of chirality can be rationalized by the two presumed transition structures schematically illustrated in Scheme 7. The protruding *quasi*-equatorial phenyl rings (colored light blue) are believed to play a crucial role in stereoselection with BINAP.[2,10] The reaction presum-



Scheme 5.

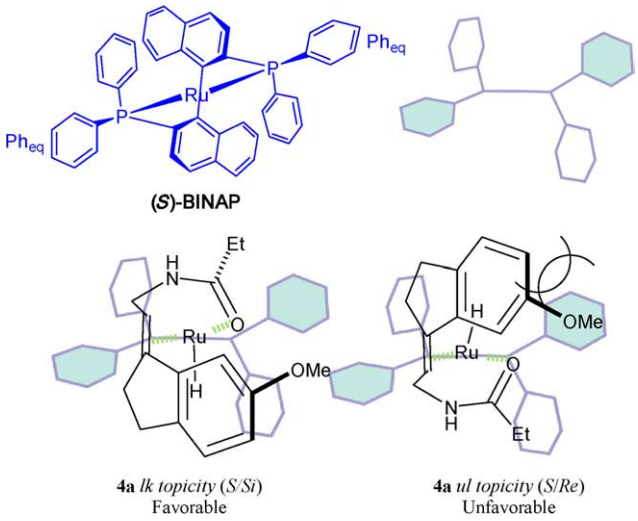


Scheme 6.

Table 3. Asymmetric hydrogenation of allylic acylamines **4a–d**[a]

R	R′	Product	ee[b] (%)	Yield[b] (%)
Et	Me	**9a**	95	98
Et	Et	**9b**	95	88
Me	Me	**9c**	81	82
CF_3	Me	**9d**	22	16

[a] The reaction was conducted with 10 mol % $Ru(OAc)_2$(binap) at 50 °C for 6 h under H_2 (9–10 MPa).
[b] Determined by HPLC analysis with chiral stationary phases.



Scheme 7.

ably proceeds via the transition structure having *lk* topicity avoiding steric repulsion between the quasi-equatorial phenyl groups of (*S*)-BINAP and indane moiety, as can be seen in Scheme 7, irrespective of the amide carbonyl oxygen coordination mode.

The effectiveness and robustness of the reaction were undiminished on a preparative scale. In a 20-L autoclave, 700 g of allylic acylamine **4a** was smoothly hydrogenated with an ee of 93% and a chemical yield of 99%. From a practical viewpoint, it is noteworthy that a reduction in loading of the catalyst was achieved by employing a higher reaction temperature; this resulted in an increase in the reaction rate while maintaining the selectivity. To the best of our knowledge, this is the first example of the asymmetric hydrogenation of allylic acylamines. The conversion of the hydrogenated product **9a** to Ramelteon was carried out without racemization.[1]

3. Conclusions

Among the three types of substrates, **1a–e**, **3**, and **4a–d** designed for the practical synthesis of Ramelteon, carboxamide **3** and allylic acylamines **4a** and **b** were found to exhibit superior performances. Additionally, an acylamine in the allylic position proved to play a role as a directive functional group for asymmetric hydrogenation with the Ru-BINAP catalyst. In conclusion, the development of highly effective chiral ligands along with the sophisticated design of substrates has fulfilled the goal of excellent yields and ees by asymmetric hydrogenation. This is encouraging for the development of more efficient processes.

4. Experimental

4.1. General

Melting points were determined using a Yanako micro melting point apparatus and are uncorrected. Infrared spectra were obtained using PARAGON 1000—a Perkin–Elmer FT-IR spectrometer. ^{1}H NMR spectra were recorded on JEOL JMTC0400/5 (400 MHz), JEOL JNM-A500 (500 MHz), or Bruker DMX-600 (600 MHz) with tetramethylsilane as an internal reference. MS were recorded using Hitachi M-2000. $Ru(OAc)_2$[(*S*)-binap] and $[Et_2NH_2]^+[Ru_2Cl_5(binap)_2]^-$ were prepared according to the methods described in the literature.[11] All manipulations involving air- and moisture-sensitive organometallic compounds were carried out by using the standard Schlenk technique under purified argon by passing them through a column of activated copper at 80 °C. Chiral stationary phase columns—CHIRALPAK AS and CHIRALCEL OB-H—were obtained from Daicel Chemical Industries, Ltd. The chiral stationary phase column Ceramospher Chiral RU-1 was obtained from Shiseido Co., Ltd.

4.2. Materials

Methanol and ethanol were distilled under argon after being dried over magnesium alkoxides.

4.3. Asymmetric hydrogenation of *N*-[2-(1,6,7,8-tetrahydro-2*H*-indeno[5,4-*b*]furan-8-ylidene)ethyl]propionamide 1a

A solution of *N*-[2-(1,6,7,8-tetrahydro-2*H*-indeno[5,4-*b*]-furan-8-ylidene)ethyl]propionamide **1a** (257 mg, 1 mmol) and $Ru(OAc)_2$[(*S*)-binap] (86 mg, 0.1 mmol) in methanol (70 mL) was degassed by three freeze–thaw cycles and then charged into a stainless-steel autoclave. Hydrogen was introduced (10 MPa), and the mixture stirred at 50 °C. After 6 h, the ee (42%) and chemical yield

(37%) were determined by HPLC analysis (Ceramospher Chiral RU-1, eluted with methanol, 0.5 mL/min).

4.4. 2-(1,2,6,7-Tetrahydro-8*H*-indeno[5,4-*b*]furan-8-ylidene)acetonitrile 6

Sodium hydride (65% dispersion in mineral oil, 17.7 g) was added to a solution of diethyl cyanomethylphosphonate (84.5 g, 0.477 mol) in tetrahydrofuran (600 mL) at room temperature. The mixture was stirred at room temperature for 30 min and this added dropwise to a solution of 1,2,6,7-tetrahydro-8*H*-indeno[5,4-*b*]furan-8-one **5** (69.3 g, 0.398 mol) in tetrahydrofuran (1300 mL). After being stirred at room temperature for 2 h, ice water (500 mL) was added and the mixture was concentrated to dryness under reduced pressure. The residue was dissolved in ethyl acetate (2000 mL), and the solution was washed twice with water (1000 mL) and once with brine in succession and then dried over magnesium sulfate. The filtrate was treated with activated charcoal (14 g) and the resulting solution concentrated under reduced pressure to yield crystals, which were washed with diisopropyl ether (1000 mL) to afford 2-(1,2,6,7-tetrahydro-8*H*-indeno[5,4-*b*]furan-8-ylidene)acetonitrile **6** (49.6 g, 63%). Diisopropyl ether washings were concentrated to yield crystals, which were washed again with diisopropyl ether to afford the second crop (15.8 g, 20%). mp: 146–151 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.05–3.12 (4H, m), 3.30 (2H, t, J = 8.8 Hz), 4.66 (2H, t, J = 8.8 Hz), 5.45 (1H, s), 6.85 (1H, t, J = 8.0 Hz), 7.10 (1H, t, J = 8.0 Hz). IR (KBr): ν_{max} cm^{-1} 2207, 1602.

4.5. 2-(1,6-Dihydro-2*H*-indeno[5,4-*b*]furan-8-yl)acetamide 3

A 30% hydrogen peroxide solution (10 mL) was added dropwise to a solution of 2-(1,2,6,7-tetrahydro-8*H*-indeno[5,4-*b*]furan-8-ylidene)acetonitrile **6** (1.14 g, 5.93 mmol) and potassium hydroxide (5.0 g) in DMSO (25 mL) and water (30 mL); the mixture was then stirred at room temperature for 3 h. The reaction mixture was extracted with ethyl acetate, and the extract dried over sodium sulfate. Concentration under reduced pressure afforded solids, which were recrystallized from ethyl acetate to yield 2-(1,6-dihydro-2*H*-indeno[5,4-*b*]furan-8-yl)acetamide **3** (0.395 g, 32%). mp: 204 °C (ethyl acetate). ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.39 (2H, s), 3.40 (2H, t, J = 8.6 Hz), 3.58 (2H, s), 4.60 (2H, t, J = 8.6 Hz), 5.37 (1H, br s), 5.67 (1H, br s), 6.51 (1H, s), 6.70 (1H, d, J = 7.9 Hz), 7.20 (1H, d, J = 7.9 Hz). NOESY cross-peaks were observed between H-1 to H-2, H-2 to H-7′, H-7′ to H-6′, and H-6′ to H-5′. IR (KBr): ν_{max} cm^{-1} 3400, 3200, 1650. MS (SIMS): m/z 215 (MH$^+$).

4.6. Asymmetric hydrogenation of 2-(1,6-dihydro-2*H*-indeno[5,4-*b*]furan-8-yl)acetamide 3

A solution of 2-(1,6-dihydro-2*H*-indeno[5,4-*b*]furan-8-yl)acetamide **3** (214 mg, 0.994 mmol) and Ru(OAc)$_2$-[(*R*)-binap] (42 mg, 0.0499 mmol) in EtOH (70 mL) was degassed by three freeze–thaw cycles and then charged into a stainless-steel autoclave. Hydrogen was introduced (10 MPa), and the mixture stirred at 50 °C. After 6 h, the ee (92%) and chemical yield (92%) were determined by HPLC analysis (Ceramospher Chiral RU-1, eluted with methanol, 0.7 mL/min). The reaction mixture was concentrated under reduced pressure to yield solids (216 mg). A part of the resulting solids (136 mg) was subjected to preparative thin-layer chromatography to afford (*S*)-2-(1,6,7,8-tetrahydro-2*H*-indeno[5,4-*b*]furan-8-yl)acetamide **7** (106 mg). mp: 218 °C (ethyl acetate). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.72–1.78 (1H, m), 2.03–2.17 (2H, m), 2.44–2.50 (1H, m), 2.67 (1H, m), 2.77–2.83 (1H, m), 3.06–3.10 (1H, m), 3.14–3.22 (1H, m), 3.42–3.44 (1H, m), 4.43–4.51 (2H, m), 6.52 (1H, d, J = 7.8 Hz), 6.81 (1H, s), 6.90 (1H, d, J = 7.8 Hz), 7.33 (1H, s). IR (KBr): ν_{max} cm^{-1} 3400, 3200, 2950, 1665.

4.7. (*S*)-2-(1,6,7,8-Tetrahydro-2*H*-indeno[5,4-*b*]furan-8-yl)ethylamine hydrochloride 8

Boron trifluoride diethyl etherate (3.47 mL, 27.6 mmol) was dissolved in dry tetrahydrofuran (25 mL) and stirred at −10 °C. Sodium borohydride (1.04 g, 27.6 mmol) was added portionwise to this solution, and the mixture stirred at room temperature for 1 h. After cooling to 0 °C, (*S*)-2-(1,6,7,8-tetrahydro-2*H*-indeno[5,4-*b*]-furan-8-yl)acetamide **7** (1.0 g, 4.6 mmol) was added and stirred at room temperature for 24 h. The mixture was concentrated under reduced pressure to yield solids, which were dissolved in ethyl acetate and treated with 1 M hydrochloric acid (25 mL). The mixture was concentrated to dryness, and the resulting residue was washed with diisopropyl ether to afford (*S*)-2-(1,6,7,8-tetrahydro-2*H*-indeno[5,4-*b*]furan-8-yl)ethylamine hydrochloride **8** (0.70 g, 63% yield). mp: 270 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.60–1.75 (2H, m), 2.08–2.23 (2H, m), 2.65–2.84 (4H, m), 3.10–3.21 (2H, m), 4.42–4.57 (2H, m), 6.55 (1H, d, J = 8.0 Hz), 6.91 (1H, d, J = 8.0 Hz), 8.09 (2H, br s). IR (KBr): ν_{max} cm^{-1} 2920, 2000. The absolute stereochemistry of **8** was established by X-ray crystallographic analysis of its salt with L-malic acid. Crystallographic data for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 286073. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0)123 336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.8. Asymmetric hydrogenation of *N*-[2-(6-methoxy-2,3-dihydro-1*H*-inden-1-ylidene)ethyl]propionamide 4a

N-[(2*E*)-2-(6-Methoxy-2,3-dihydro-1*H*-inden-1-ylidene)-ethyl]propionamide **4a** (700 g, 2.85 mol), Ru(OAc)$_2$[(*S*)-binap] (24 g, 28.7 mmol), and methanol (15 L) were charged into a stainless-steel autoclave. The mixture was bubbled with nitrogen. Hydrogen was introduced (9 MPa), and the mixture stirred at 70 °C. After 1 h,

the ee (93%) and chemical yield (99%) were determined by HPLC analysis (CHIRALPAK AS, eluted with *n*-hexane/2-propanol/trifluoroacetic acid = 9:1:0.01, 1.0 mL/min). In the same manner, 300 g of *N*-[(2*E*)-2-(6-methoxy-2,3-dihydro-1*H*-inden-1-ylidene)ethyl]propionamide **4a** was treated to obtain 95% ee and 98% chemical yield. The combined reaction mixture was concentrated under reduced pressure to yield a residue, which was subjected to silica-gel column chromatography (*n*-hexane/ethyl acetate = 4:1) followed by recrystallization from *n*-hexane and ethyl acetate (4:1) to afford (*S*)-*N*-[2-(6-methoxy-2,3-dihydro-1*H*-inden-1-yl)ethyl]propionamide **9a** (801 g, 79%, 99% ee). mp: 76–77 °C (*n*-hexane/ethyl acetate). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.15 (3H, t, $J = 8$ Hz), 1.57–1.78 (2H, m), 2.02–2.09 (1H, m), 2.19 (2H, q, $J = 8$ Hz), 2.29–2.36 (1H, m), 2.74–2.89 (2H, m), 3.08–3.14 (1H, m), 3.37–3.41 (2H, m), 3.34 (3H, s), 5.53 (1H, br s), 6.71 (1H, dd, $J = 2$ and 8 Hz), 6.75 (1H, d, $J = 2$ Hz), 7.10 (1H, d, $J = 8$ Hz). $[\alpha]_D^{25} = -4.4$ (*c* 1, $CHCl_3$). IR(KBr): ν_{max} cm^{-1} 3317, 2940, 1633, 1550. Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.59; H, 8.50; N, 5.84. The absolute configuration of **9a** was deduced from X-ray crystallographic analysis of the *p*-bromobenzoate derivative, as described in the previous literature.[1]

4.9. Asymmetric hydrogenation of *N*-[(2*E*)-2-(6-ethoxy-2,3-dihydro-1*H*-inden-1-ylidene)ethyl]propionamide 4b

A solution of *N*-[(2*E*)-2-(6-ethoxy-2,3-dihydro-1*H*-inden-1-ylidene)ethyl]propionamide **4b** (240 mg, 0.93 mmol) and Ru(OAc)$_2$[(*S*)-binap] (78 mg, 0.093 mmol) in methanol (70 mL) was degassed by three freeze–thaw cycles and then charged into a stainless-steel autoclave. Hydrogen was introduced (10 MPa), and the mixture was stirred at 50 °C. After 6 h, the ee (95%) and chemical yield (88%) were determined by HPLC analysis (CHIRALPAK AS, eluted with *n*-hexane/2-propanol = 9:1, 1.0 mL/min).

4.10. Asymmetric hydrogenation of *N*-[(2*E*)-2-(6-methoxy-2,3-dihydro-1*H*-inden-1-ylidene)ethyl]acetamide 4c (synthesis of an intermediate for the distomer)

A solution of *N*-[(2*E*)-2-(6-methoxy-2,3-dihydro-1*H*-inden-1-ylidene)ethyl]acetamide **4c** (119 mg, 0.5 mmol) and Ru(OAc)$_2$[(*R*)-binap] (40 mg, 0.050 mmol) in methanol (70 mL) was degassed by three freeze–thaw cycles and then charged into a stainless-steel autoclave. Hydrogen was introduced (10 MPa), and the mixture stirred at 50 °C. After 6 h, the ee (81%) and chemical yield (82%) were determined by HPLC analysis (CHIRALPAK AS, eluted with *n*-hexane/2-propanol = 9:1, 1.0 mL/min).

4.11. Asymmetric hydrogenation of 2,2,2-trifluoro-*N*-[(2*E*)-2-(6-methoxy-2,3-dihydro-1*H*-inden-1-ylidene)ethyl]acetamide 4d

A solution of 2,2,2-trifluoro-*N*-[(2*E*)-2-(6-methoxy-2,3-dihydro-1*H*-inden-1-ylidene)ethyl]acetamide **4d** (159 mg, 0.56 mmol) and Ru(OAc)$_2$[(*R*)-binap] (40 mg, 0.048 mmol) in methanol (70 mL) was degassed by three freeze–thaw cycles and then charged into a stainless-steel autoclave. Hydrogen was introduced (10 MPa), and the mixture was stirred at room temperature. After 6 h, the ee (22%) and chemical yield (16%) were determined by HPLC analysis (CHIRALCEL OB-H, eluted with *n*-hexane/2-propanol = 4:1, 0.7 mL/min).

Acknowledgements

We are indebted to Dr. Shohei Hashiguchi for constructive discussions. We also thank Mr. Akira Fujishima and Ms. Keiko Higashikawa for their help in the determination of the single-crystal X-ray structure.

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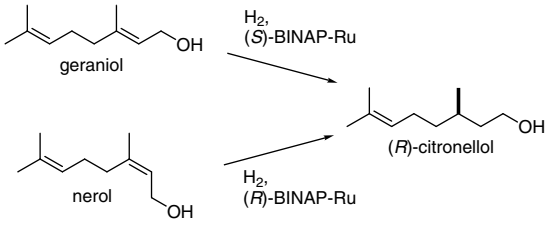
chirality, and configuration of the products is distinct, as shown below.



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