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Process Research on the Asymmetric Hydrogenation of a Benzophenone for Developing the Manufacturing Process of the Squalene Synthase Inhibitor TAK-475

Mitsutaka Goto,*,† Takahiro Konishi, Shinji Kawaguchi, Masatoshi Yamada, Toshiaki Nagata, and Mitsuhisa Yamano

†Chemical Technology Department, Takeda Pharmaceutical Co. Ltd., 4720, Takeda, Mitsui, Hikari, Yamaguchi 743-8502, Japan

Chemical Development Laboratories, CMC center, Takeda Pharmaceutical Co. Ltd., 2-17-85, Juso-Honmachi, Yodogawa-ku, Osaka 532-8686, Japan

Supporting Information

ABSTRACT: A practical synthetic method for the synthesis of the chiral benzhydrol **8**, which is the key intermediate of the squalene synthase inhibitor TAK-475 (**1**), has been developed. The method, via asymmetric hydrogenation of the benzophenone **7**, employed Noyori's ruthenium precatalyst of the type [$RuCl_2$(diphosphine)(diamine)]. We focused on tuning of the chiral diphosphine, and have discovered a novel ligand, DADMP-BINAP (**18c**), for the catalyst that has allowed reduction of the operating pressure in the asymmetric hydrogenation. The precatalyst containing **18c** performed effectively at low hydrogen pressure (<1 MPa) with sufficient enantioselectivity, and the result enabled us to successfully obtain enantiomerically pure **8** on a multikilogram scale.

INTRODUCTION

TAK-475 (**1**)[1] is a potent squalene synthase inhibitor and was expected to be a good candidate to lower plasma cholesterol.[2] In cholesterol biosyntheses, the inhibition of squalene synthase is a unique target to control cholesterol without inhibiting the biosynthesis of biologically important isoprenoids. Therefore, it was supposed that squalene synthase inhibitors might be free from side effects and effective in the treatment of hyperlipemia.[3]

TAK-475 (**1**) has a 4,1-benzoxazepine core structure (Scheme 1), which has been constructed by intramolecular Michael addition followed by condensation of the *N*-alkylated benzhydrol derivative **9** with a fumaric acid derivative.[2,4] In this reaction, the thermodynamically stable 3,5-*trans*-isomer **10** was obtained diastereoselectively by the screening of appropriate reaction conditions. Therefore, the development of an efficient synthesis of the enantiopure benzhydrol **8** was a significant challenge in order to achieve the asymmetric synthesis of **1**. The optical resolution of the acetylated ***rac*-8** with esterase was conducted at early stage development.[5] However, a catalytic enantioselective method was needed for more efficient synthesis of **8** on a large scale.

Catalytic enantioselective syntheses of substituted benzhydrols like **8** involve either reduction of prochiral benzophenones or addition of air-sensitive phenyl nucleophiles to benzaldehyde derivatives.[6] Although the reduction methodologies are often practical, they require discrimination between the two phenyl moieties in order to achieve high enantioselectivity and have only been reported for an extremely limited substrate range via enantioselective borohydride and borane reduction,[7] β-hydride transfer,[8] enantioselective hydrosilylation,[9] enantioselective hydrogen transfer,[10] asymmetric hydrogenation,[11] and bioreduction.[12]

For asymmetric synthesis of the benzhydrol **8**, an attempt at enantioselective borohydride reduction of prochiral benzophenone **7**, using $LiBH_4$ in the presence of a chiral bimetallic Lewis acid, was conducted, but only moderate enantioselectivity was obtained.[7e] An alternative enantio selective reduction of **7** via β-hydride transfer with (−)-DIP-Chloride achieved high enantioselectivity.[13] The enantioselective hydrogenation of substituted benzophenones using [$RuCl_2${(*S*)-xylbinap}{(*S*)-daipen}] (**12b**)[14] as a Ru precatalyst has generally given excellent results in terms of catalyst efficiency (Scheme 2).[11d] Moreover, this technology has been applied to the synthesis of **8** using [$RuCl_2${(*S*)-xylbinap}{(*S*,*S*)-dpen}] (**13b**)[14] for large-scale preparation and has achieved high enantioselectivity (80−90% ee) and high catalyst efficiency (S/C = 1700).[15]

However, further improvement was needed for large-scale production, especially with regards to the use of high pressure. The fine-tuning approach for Ru precatalyst, [$RuCl_2${(*S*)-xylbinap}{(*S*,*S*)-dpen}] (**13b**) was conducted for optimizing the diphosphine moiety, while the diamine moiety was strictly optimized to DPEN. For the chiral diphosphine, while there are numerous ligands, a few ligands (e.g., BINAP,[16] MeOBIPHEP[17]) are known for general use. Thus, we conducted modification of BINAP analogues to develop a fine-tuned Ru precatalyst (**13**), which performed well under low hydrogen pressure for asymmetric hydrogenation of **7**, retaining enantioselectivity

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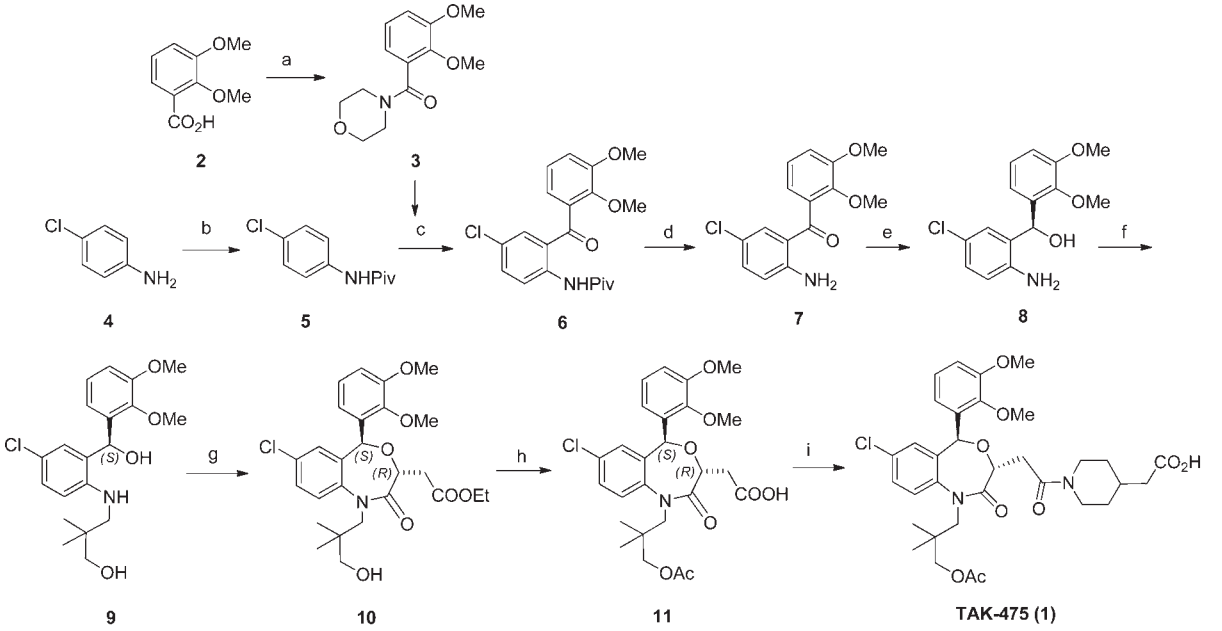
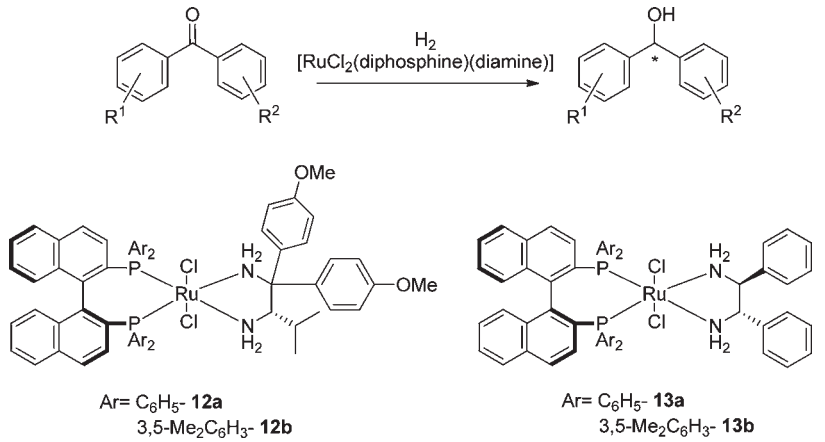
Scheme 1. Synthetic route of TAK-475 (1)



Reagents and conditions: (a) i) $SOCl_2$, DMF, ii) morphorine, toluene; (b) Piv-Cl, $NaHCO_3$, AcOEt; (c) i) ^nBuLi, THF, ii) **3**; (d) KOH, MeOH; (e) asymmetric reduction; (f) i) 3-hydroxy-2,2-dimethylpropanal, HCl, THF, ii) $NaBH_4$, DMAc; (g) i) (*E*)-ethyl 4-chloro-4-oxobut-2-enoate, 1 mol/L NaOH, AcOEt; ii) DBU, EtOH; (h) i) NaOH, CH_3CN, ii) AcCl, pyridine, iii) H_2O; (i) i) Piv-Cl, Et_3N, CH_3CN, ii) 2-(piperidin-4-yl)acetic acid.

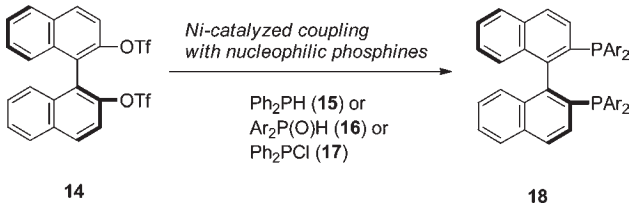
Scheme 2. Asymmetric hydrogenation of prochiral benzophenone derivatives



Ar= C_6H_5- **12a**
3,5-$Me_2C_6H_3$- **12b**

Ar= C_6H_5- **13a**
3,5-$Me_2C_6H_3$- **13b**

Scheme 3. Precedent for synthesis of BINAP and BINAP analogues



Ni-catalyzed coupling with nucleophilic phosphines

Ph_2PH (**15**) or
$Ar_2P(O)H$ (**16**) or
Ph_2PCl (**17**)

14 **18**

and catalyst efficiency. In this paper, we report a novel fine-tuned Ru precatalyst that contains a novel BINAP analogue, and a large-scale asymmetric hydrogenation for synthesis of the chiral key intermediate (**8**) of TAK-475 (**1**).

RESULTS AND DISCUSSION

Preparation of BINAP Analogues for Phosphine Ligand Tuning. After the first synthesis of BINAP was achieved in 1980 by Noyori,[18] several methods for the preparation of BINAP have been developed,[11a] which are nickel-catalyzed phosphine insertion with diphenylphosphine (**15**) or diarylphosphine oxides (**16**). Similarly, the Monsanto method,[19] which is characterized by a nickel-catalyzed coupling reaction of diphenylchlorophosphine (**17**) in the presence of zinc, has been implemented for large-scale production (Scheme 3). On the basis of these methods, a large number of BINAP analogues have been synthesized in a bid to increase catalyst activity.[20] The successful improvement was achieved by modification of the aryl groups on phosphorus.

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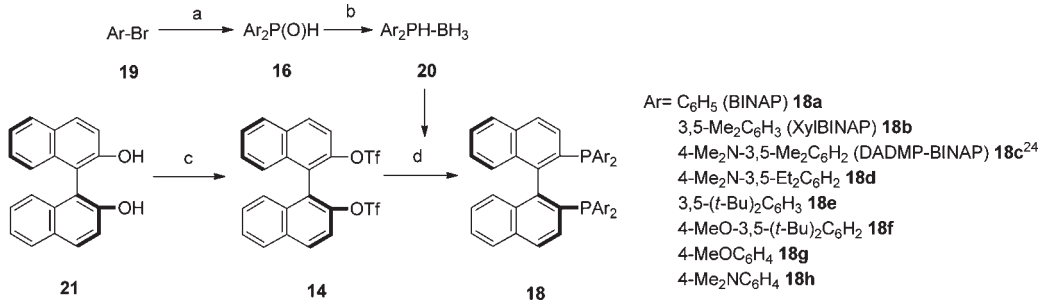
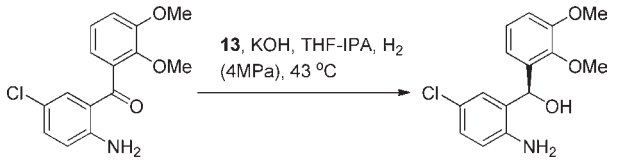
Scheme 4. Our method for synthesis of BINAP analogues 18



Reagents and conditions: (a) i) Mg, THF, ii) $(EtO)_2P(O)H$, (b) $CeCl_3$, $LiAlH_4$, $NaBH_4$, THF or BH_3-THF, Toluene, (c) Tf_2O, Pyridine, CH_3CN, (d) **20**, $NiCl_2$(dppe), DABCO, DMF

Table 1. Screening of BINAP analogues[a]



entry	13[b] L: 18[c]	% conv.	% ee (*S*)
1	**18a**	100	59
2	**18b**	100	94
3	**18c**	100	95
4	**18d**	>99	90
5	**18e**	6	6 (*R*)
6	**18f**	7	36
7	**18g**	56	35
8	**18h**	17	15

[a] Reactions were carried out at 4 MPa of H_2 for 24 h at 43 °C using 3 mmol of the substrate **7** with Ru complex[25] and (*S*,*S*)-DPEN in 2-propanol/THF. Substrate/Ru/(*S*,*S*)-DPEN/KOH = 1000:1:10:20. [b] **13** was prepared *in situ* by charging (*S*,*S*)-DPEN with the Ru complex[25] containing the corresponding BINAP analogue (**18**). [c] **18a**−**18h** was prepared with our method for synthesis of BINAP analogues, which is shown in scheme 4.

We developed an alternative method for the preparation of BINAP analogues in our previous studies (Scheme 4).[20c,21] The advantage of our method is that phosphine−borane complexes are used as a phosphine source and these are easier to handle because of their greater stability towards oxygen and moisture, compared to other phosphine sources such as diphenylphosphine and diphenylchlorophosphine. A large number of phosphine−borane complexes (**20**) were directly synthesized from the corresponding phosphine oxides (**16**) using a simple reaction involving treatment with lithium aluminum hydride and sodium borohydride activated by cerium chloride,[22] or a reduction in borane−tetrahydrofuran solution (Scheme 4).[23] More than 30 BINAP analogues, including novel compounds, were prepared using the corresponding phosphine−borane complexes, and some of them were synthesized on multihundred gram scale.

Screening of BINAP Analogues for Fine-Tuning of the Ru Precatalyst 13. Optimization of the Ru precatalyst **13** for asymmetric hydrogenation of the benzophenone **7** has been studied, utilizing the available BINAP ligand diversity. The screening of BINAP analogues was conducted for the asymmetric hydrogenation of **7** using *in situ* prepared **13**, by charging (*S*,*S*)-DPEN with the Ru complex[25] containing the corresponding BINAP analogues (**18**). On the first screening, the lower alkyl group substituents (such as methyl and ethyl groups) at the 3,5-positions of the aryl moieties of the BINAPs (**18b**−**d**) were found to markedly increase the enantioselectivity (Table 1, entries 2−4). Among the BINAPs, **18b** and **18c**[24] led to the highest enantioselectivity, affording 94−95% ee (entries 2, 3). This "3,5-dialkyl *meta*-effect" has been described in several reports,[26] and it was supposed to arise from steric and electronic effects on the phosphorus atom. Hence, when the *meta* substituents were bulkier (such as *tert*-butyl group; **18e** and **18f**), both the enantioselectivity

Table 2. Asymmetric hydrogenation of 7 under mild conditions; influence of hydrogen pressure[a]

entry	13[b] L: 18	H_2 [MPa]	time [h]	% conv.	%ee(*S*)
1	**18b**	4	65	>99	94
2	**18b**	1	65	>99	90
3	**18c**	4	48	>99	95
4	**18c**	1	50	>99	96

[a] Reactions were carried out at 43 °C using 10 mmol of the substrate **7** with Ru complex[25] and (*S*,*S*)-DPEN in 2-propanol/THF. Substrate/Ru/(*S*,*S*)-DPEN/KOH = 1000:1:10:20. [b] **13** was prepared *in situ* by charging (*S*,*S*)-DPEN with the Ru complex[25] containing the corresponding BINAP analogue (**18**).

Table 3. Asymmetric hydrogenation of 7 using 13c under low hydrogen pressure; influence of reaction temperature[a]

entry	temp. [°C]	time [h]	% conv.	% ee (*S*)	TOF[b] [h^{-1}]
1[c]	23	60	85	96	29.0
2	30	50	>99	95	55.4
3	40	45	>99	93	81.7
4	60	24	>99	81	191.3

[a] Reactions were carried out at 1 MPa of H_2 using 10 mmol of the substrate **7** with **13c** in 2-propanol/THF. Substrate/Ru/KOH = 1000:1:20. [b] Turnover frequency, which is defined as moles of the product per mole of the catalyst per hour. [c] Entry 1 using Ru complex[25] and (*S*,*S*)-DPEN instead of **13c**.

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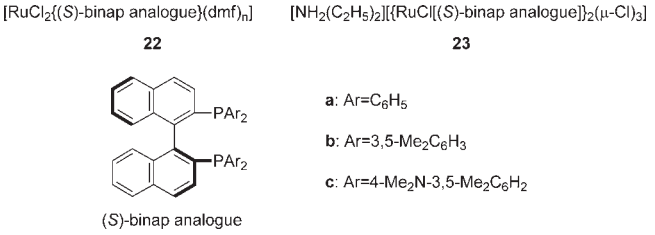


Figure 1. Ru complexes for precursor of **13**.

Table 4. Asymmetric hydrogenation of 7; comparison of Ru complexes[a]

entry	Ru complexes	time [h]	% conv.	% ee (*S*)	TOF[b] [h^{-1}]
1[c]	**13c**	39	>99	95	55.4
2	**22c**	40	86	86	34.6
3	**23c**	60	>99	96	41.3

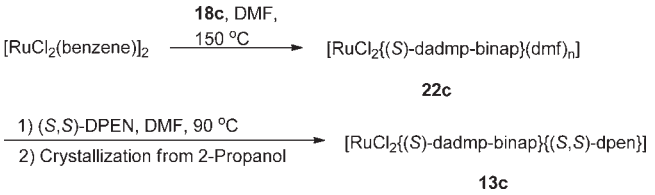
[a] Reactions were carried out at 1 MPa of H_2 at 30 °C using 10 mmol of the substrate **7** with Ru complex and (*S*,*S*)-DPEN in 2-propanol/THF. Substrate/Ru/(*S*,*S*)-DPEN/KOH = 1000:1:10:20. [b] Turnover frequency, which is defined as moles of the product per mole of the catalyst per hour. [c] (*S*,*S*)-DPEN was not added.

Table 5. Asymmetric hydrogenation of 7 using 13c; influence on the residual amount of 22c[a]

entry	**22c**/ **13c**[b]	% conv.	% ee (*S*)	TOF[c] [h^{-1}]
1	<0.01	>99	95	55.4
2	0.05	>99	94	–
3	0.11	>99	89	37.2

[a] Reactions were carried out at 1 MPa of H_2 at 30 °C using 10 mmol of the substrate **7** with **13c** in 2-propanol/THF. Substrate/Ru/KOH = 1000:1:20−30. [b] The ratio was calculated from the integral area of ^{31}P NMR. [c] turn over frequency, which is defined as moles of the product per mole of the catalyst per hour.

Scheme 5. Preparation of highly pure 13c



and the conversion rate of this reaction decreased remarkably (entries 5, 6).

In the next step, we compared **18b** and **18c** under the mild conditions that had given the best results on the first screening. Interestingly, hydrogen pressure affected the enantioselectivity in this reaction (Table 2). When the hydrogen pressure was decreased to 1 MPa, **18c** gave a slightly increased ee value, up to 96% ee, whereas **18b** gave a lower ee at this condition. Moreover, the reaction rate when using **18c** was shown to be three times higher than that for **18b**. Therefore, it is suggested that increasing the electron density on the phosphorus, which will occur when using aryl substituents with 4-dimethylamino groups, has a desirable effect on the asymmetric hydrogenation of **7**.[27]

Table 6. Optimization of other conditions for scale-up[a]

entry	amount of water[b] [% v/v]	S/C	time [h]	% conv.	% ee (*S*)	TOF[c] [h^{-1}]
1	–	1000	45	99.9	93	81.7
2	0.35%	1000	45	99.8	91	84.8
3	0.70%	1000	45	99.6	91	64.0
4	–	2000	65	99.9	90	68.5
5	–	3000	96	99.3	90	73.5

[a] Reactions were carried out at 1 MPa of H_2 at 40 °C using 10 mmol of the substrate **7** with **13c** in 2-propanol/THF. Ru/KOH = 1:20−30. [b] To entries 2 and 3 were added 0.35% and 0.70% of water, respectively. [c] Turnover frequency, which is defined as moles of the product per mole of the catalyst per hour.

Furthermore, we evaluated the influence of reaction temperature for Ru precatalyst **13c** containing **18c**, and found that it also strongly influenced the enantioselectivity (Table 3). There was a clear tendency for increased enantioselectivity of **8** under milder conditions, similar to that seen for reduced hydrogen pressure. However, the reaction rate decreased at lower temperature. Thus, the optimum reaction temperature was 30−40 °C, which gave a balance of both selectivity and productivity. In the case of reacting at higher temperatures, such as 60 °C, the enantioselectivity sharply decreased to 81% ee.

Examination of Ru Precatalyst Preparation. To the best of our knowledge, Noyori's ruthenium precatalyst of the type [$RuCl_2$(diphosphine)(diamine)] is generally synthesized via the Ru complexes, [$RuC1_2$(diphosphine)$(dmf)_n$], [$NH_2(C_2H_5)_2$]-[{RuCl(diphosphine)}$_2(\mu$-Cl)$_3$], or [RuC1(diphosphine)(η^6-arene)]Cl by treatment with a chiral diamine (Figure 1).[28] Some of the Ru precatalysts containing BINAP analogues have been obtained as isolated compounds, while many of them have been prepared *in situ*.[29] In the case of the *in situ* preparation of Ru precatalyst (**13**), however, the reaction rate is remarkably decreased compared to that obtained with the isolated ones.[28,30] Regarding the asymmetric hydrogenation of **7**, we also confirmed that the isolated **13c** gave the fastest reaction among these Ru complexes (Table 4). Therefore, we decided to use the isolated **13c** as the Ru precatalyst.

The synthesis of **13c** was conveniently accomplished by the reaction of **22c** with (*S*,*S*)-DPEN. This reaction was incomplete in 2-propanol at 25 °C, and 10−15% of **22c** remained (observed by ^{31}P NMR). This incomplete formation of **13c** has been recognized as a major problem, as even a slight contamination of **13c** by **22c** causes a decrease in the enantioselectivity. (Table 4, entry 2) To further study the effect of contamination of **13c** by **22c**, we confirmed that the presence of **22c** adversely affected the enantioselectivity by spike testing the asymmetric hydrogenation with **22c** (Table 5).

In a bid to complete the conversion to **13c**, we found that it was important to select the appropriate reaction conditions of temperature and solvent (Scheme 5), and the reaction went to completion in DMF at 90 °C. After crystallization from 2-propanol, pure **13c** was obtained in 79% yield.

On the other hand, the precursor **23** was generally synthesized by treatment of [$RuCl_2$(cod)]$_n$ with the diphosphine ligand in the presence of triethylamine.[31] However, the synthesis of [NH_2-$(C_2H_5)_2$][{RuCl[(*S*)-dadmp-binap]}$_2(\mu$-Cl)$_3$] (**23c**) gave only low yield by the general method.

Development of Robust Conditions for Scale-Up. It was found that the asymmetric hydrogenation of **7** could be performed

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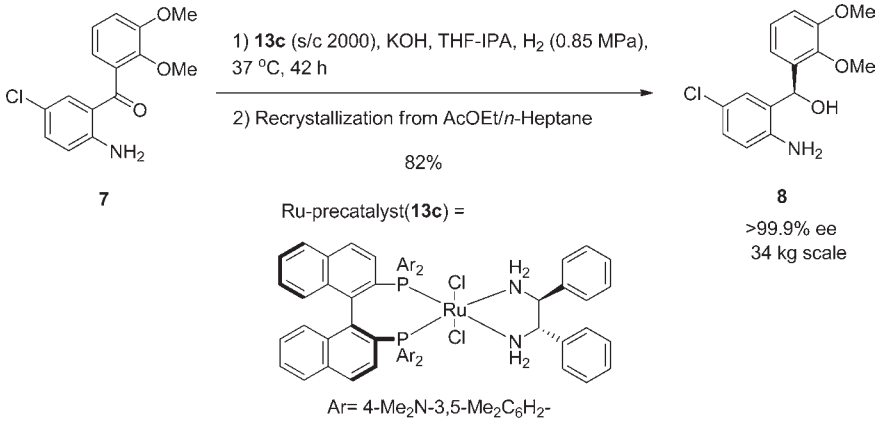
Scheme 6. Scale-up synthesis of 8



at high concentration by the addition of THF to the 2-propanol solvent, to improve the solubility of **7**. Next, we investigated the effect of water on the reaction, and it was found that it slowed the reaction significantly. This tendency was revealed by the fact that the turnover frequency (TOF) dropped to 64 h^{-1} with a slight presence (0.70%) of water. Thus, the concentration of water in the reaction system must be controlled to less than 0.35% to achieve sufficient reaction rate in scale-up operations (Table 6, entries 2, 3). Therefore, we decided to use dehydrated solvents and careful protocols as to degas and purge on large-scale operations in order to prevent an invasion of water.

During our studies for optimization, the reaction could be conducted easily on a preparative scale with a substrate to catalyst (S/C) mole ratio of 1000. We challenged the reduction of catalyst loading, and robust and reproducible conversion could be achieved at a lower loading level up to S/C 3000 (entries 4, 5). However, when the catalyst loading was lower, the reaction rate was slowed significantly, and TOF dropped to 69−74 h^{-1}. Consequently, we decided to implement scale-up operations at S/C 2000.

Subsequently, for the purpose of confirming the robustness and reproducibility on the optimum conditions, we could carry out scale-up reaction in a pilot plant. Under these optimum conditions, we successfully manufactured **8** on a large scale using a catalyst loading of S/C 2000 and a hydrogen pressure of 0.85 MPa (Scheme 6) without any incidents. The reaction gave full-conversion in 94% ee.[32] After recrystallization from ethylacetate/*n*-heptane, the perfectly enantiopure **8** (>99.9% ee) was obtained in 82% yield.

CONCLUSION

In conclusion, a highly enantioselective synthesis of the chiral benzhydrol **8**, which is the key intermediate of TAK-475 (**1**), was established via asymmetric hydrogenation developed using the fine-tuned Noyori's ruthenium precatalyst (**13c**), which consisted of a BINAP analogue **18c** as the novel diphosphine ligand. Using the precatalyst, asymmetric hydrogenation of the prochiral benzophenone (**7**) proceeded with high enantioselectivity under low hydrogen pressure (<1 MPa). Pure **13c** was isolated by crystallization for large-scale production to achieve sufficient reaction rate and enantioselectivity in the asymmetric hydrogenation. Finally, the large-scale synthesis of **8** was implemented, and we obtained 34 kg of **8** in high yield and excellent enantioselectivity, using the optimized conditions.

EXPERIMENTAL SECTION

^{1}H NMR spectra were recorded on a Bruker DPX-300 (300 MHz) spectrometer or Bruker AVANCE III (500 MHz) spectrometer with chemical shifts given in ppm (with tetramethylsilane as an internal standard). ^{13}C NMR spectra were recorded on a Bruker DPX-300 (75 MHz) spectrometer or Bruker AVANCE III (126 MHz) spectrometer with chemical shifts given in ppm (with tetramethylsilane and $CDCl_3$ as an internal standard). ^{31}P NMR spectra were recorded on a Bruker DPX-300 (121 MHz) spectrometer or Bruker AVANCE III (202 MHz) spectrometer with chemical shifts given in ppm (with 85% H_3PO_4 as an external standard). Infrared absorption spectra were recorded on a Shimadzu IRPrestige-21. Elemental analyses were carried out by Takeda Analytical Laboratories, Ltd. and are within ±0.4% of the theoretical values. Inductively coupled plasma (ICP) analysis performed on a Hitachi P-4010 ICP instrument gave the contents of ruthenium. HPLC was performed using an Inertsil ODS-3 (150 mm × 4.6 mm I.D.). Conditions were as follows: mobile phase, 30% 0.05 M KH_2PO_4 and 70% acetonitrile; flow rate, 1.0 mL/min; detection, UV 254 nm; temperature, 25 °C. Typical relative retention times for **8** and **7** were 0.63 and 1.00, respectively. Chiral HPLC was performed using a Chiralcel OJ-RH (150 mm × 4.6 mm I.D.). Conditions were as follows: mobile phase, 60% 0.05 M KH_2PO_4 and 40% acetonitrile; flow rate, 1.0 mL/min; detection, UV 254 nm; temperature, 25 °C. Typical relative retention times for (***S***)-**8** and (***R***)-**8** were 1.00 and 1.20, respectively. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad.

Preparation of (*S*)-2,2′-Bis[bis(4-dimethylamino-3,5-dimethylphenyl)phosphino]-1,1′-binaphthyl (18c). To a stirred mixture of magnesium (2.43 g, 0.10 mol) in THF (15 mL) was added a solution of 4-dimethylamino-3,5-dimethylbromobenzene (**19c**) (31.25 g, 0.136 mol) in THF (50 mL). After being stirred for 1 h at 40 °C, to the reaction mixture was added a solution of diethyl phosphite (4.69 g, 0.034 mol) in THF (15 mL) at 25 °C. The reaction mixture was stirred for 1.5 h at 25 °C and then quenched with water (60 mL) at 5−10 °C. After extraction with toluene (100 mL), the organic extracts were washed with water (30 mL). Subsequently, the solvent was removed under reduced pressure. After purification by flash chromatography on silica gel (*n*-hexane/ethyl acetate, 6:4), the corresponding phosphine oxide (**16c**) (4.64 g, 40% yield) was isolated as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.29 (12H, s), 2.82 (12H, s), 7.31 (4H, d, J_{PH} = 13.8 Hz), 7.89 (1H, d, J_{PH} = 474.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.3 (d, J_{CP} = 4.4 Hz), 42.3, 126.8 (d, J_{CP} = 103.4 Hz), 131.1 (d,

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J_{CP} = 11.9 Hz), 137.2 (d, J_{CP} = 13.7 Hz), 153.8. ^{31}P NMR (121 MHz, $CDCl_3$, 85% H_3PO_4): δ 22.51(dm, J_{PH} = 474.2 Hz).

To a solution of **16c** (4.64 g, 0.014 mol) in toluene (30 mL) was added borane−tetrahydrofuran solution (71 mL, 0.076 mol) upon slow addition for 2 h. After addition of borane−tetrahydrofuran solution, the reaction mixture was quenched with silica gel (8.7 g), and stirred at room temperature for 1.5 h. The silica gel was filtered off, and then the filtrate was concentrated under reduced pressure. After purification by flash chromatography on silica gel (toluene) and crystallization from *n*-hexane, the corresponding phosphine−borane complex (**20c**) (3.00 g, 65% yield) was isolated as a white crystalline powder. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.30−1.75 (3H, brdd, J = ca. 95.5 Hz, 81.9 Hz), 2.28 (12H, s), 2.81 (12H, s), 6.11 (1H, dq, J_{PH} = 376.9 Hz, J_{BH} = 6.8 Hz), 7.26 (4H, d, J_{PH} = 11.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.7, 42.7, 121.8 (d, J_{CP} = 58.9 Hz), 133.7 (d, J_{CP} = 9.8 Hz), 137.8 (d, J_{CP} = 11.2 Hz), 153.5. ^{31}P NMR(121 MHz, $CDCl_3$, 85% H_3PO_4): δ −0.66 (dm, J_{PH} = 376.9 Hz).

(*S*)-2,2′-Di(trifluoromethylsulfonyl)-1,1′-binaphthyl (**14**) (1.76 g, 3.21 mmol) and **20c** (2.52 g, 7.38 mmol) in DMF (25 mL) was treated at 105 °C with [1,2-bis(diphenylphosphino)ethane]dichloro nickel (0.17 g, 0.321 mmol) and 1,4-diazabicyclo[2.2.2]octane (2.13 g, 19.26 mmol). The reaction mixture was stirred for 96 h and then concentrated under reduced pressure. The resulting residue was washed with methanol to give **18c** (1.86 g) in 64% yield as a white crystalline powder: mp 265 °C. $[\alpha]_D$ = −76.5° (25 °C, c = 1.00, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ1.97 (12H, s), 2.00 (12H, s), 2.66 (24H, s), 6.58 (4H, d, J = 8.0 Hz), 6.67 (2H, d, J = 8.5 Hz), 6.77−6.81 (6H, m), 7.21−7.25 (2H, m), 7.48−7.50 (2H, m), 7.72 (2H, d, J = 8.5 Hz), 7.77 (2H, d, J = 8.5 Hz). ^{13}C NMR (126 MHz, $CDCl_3$): δ 18.0, 18.1, 41.4, 41.5, 124.0, 124.9, 126.4, 126.7, 126.8, 129.6, 131.7−131.8 (m), 132.1, 132.3−132.7 (4C, m), 133.9−134.2 (2C, m), 134.6 (d, J = 23.9 Hz), 134.8−135.0 (2C, m), 136.2−136.3 (m), 143.6 (d, J = 20.1 Hz), 143.7 (d, J = 21.4 Hz), 148.0, 148.9. ^{31}P NMR (202 MHz, $CDCl_3$, 85% H_3PO_4): δ −15.7 (s). IR (ATR, cm^{-1}): 2779, 1443, 1414, 1333, 1209, 1099, 1059, 1049, 1024, 953, 860, 812, 742, 692. Anal. Calcd for $C_{60}H_{68}N_4P_2$ 0.5 CH_3OH: C, 78.71; H, 7.64; N, 6.07; P, 6.71. Found: C, 78.67; H, 7.40; N, 6.12; P, 6.75.

[(*S*)-2,2′-Bis[bis(4-dimethylamino-3,5-dimethylphenyl) phosphino]-1,1′-binaphthyl][(1*S*,2*S*)-1,2-diphenylethylenediamine]ruthenium(II); [$RuCl_2${(*S*)-dadmp-binap}{(*S*,*S*)-dpen}] (13c). In a 20-mL Schlenk flask, a mixture of $[RuCl_2(C_6H_6)]_2$ (132 mg, 0.264 mmol) and **18c** (484 mg, 0.533 mmol) was degassed. Subsequently, anhydrous DMF (4.8 mL) was added via a cannula under argon atmosphere. Then, the resulting mixture was stirred at 150 °C for 3 h. (*S*,*S*)-DPEN (121 mg, 0.570 mmol) was prepared in a 10-mL Schlenk flask and dissolved by anhydrous DMF (2.0 mL). This solution was added to the 20-mL Schlenk flask via a cannula. After being stirred for 1 h at 90 °C, the solvent was removed under reduced pressure. The resulting residue was dried under reduced pressure at 50 °C to give crude **13c** (753 mg) as a yellow powder. The crude **13c** was suspended with anhydrous 2-propanol (3.0 mL) and stirred for 3 h at 80 °C, for 1 h at room temperature, and for 3 h at 10 °C under argon atmosphere. The resulting precipitate was filtered off under argon atmosphere to give **13c** (535 mg) in 79% yield as yellow powder. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.68 (12H, s), 2.13 (12H, s), 2.38 (12H, s), 2.45 (12H, s), 2.77 (2H, brt, J = 9.3 Hz, NH), 2.99 (2H, brd, J = 8.7 Hz, NH), 4.06−4.09 (2H, m), 5.98 (2H, d, J = 8.6 Hz), 6.54−6.58 (2H, m), 6.69−6.71 (4H, m), 6.91−6.98 (6H, m), 6.99−7.03 (2H, m), 7.13−7.22 (4H, brm), 7.49−7.51 (4H, brm), 7.56 (2H, d, J = 7.9 Hz), 7.75 (2H, d, J = 8.6 Hz), 8.34−8.37 (2H, m). ^{13}C NMR (126 MHz, $CDCl_3$): δ 17.8, 18.5, 41.1, 41.5, 61.8, 122.2, 124.5, 124.6, 125.4, 125.65, 125.71, 125.5−126.0 (m), 126.3, 126.4, 127.3, 129.3−129.9 (m), 131.7, 132.6−132.7 (m), 133.0 (brm), 133.0−133.5 (m), 133.8−133.9 (m), 134.5−134.7 (m), 136.0, 137.2 (d, J = 6.1 Hz), 137.3 (d, J = 6.1 Hz), 139.7, 148.1, 149.0. ^{31}P NMR(202 MHz, $CDCl_3$, 85% H_3PO_4): δ 42.9 (s). MS m/z 1290 (M^+). Anal. Calcd for $C_{74}H_{84}N_6Cl_2P_2Ru$: C, 68.82; H, 6.56; N, 6.51; Cl, 5.49. Found: C, 68.42; H, 6.75 ;N, 6.44; Cl, 5.36.

Scale-Up Synthesis of (*S*)-(2-Amino-5-chlorophenyl)(2,3-dimethoxyphenyl)methanol (8). In a 500-L autoclave, **7** (41.1 kg, 140.9 mol) and potassium hydroxide (118.7 g, 2.1 mol) were placed and degassed by seven cycles of vacuum filling with argon. Subsequently, anhydrous THF (72 L) and anhydrous 2-propanol (72 L) were added to a 500-L autoclave via cannula. The precatalyst **13c** (91.1 g, 0.0705 mol) was transferred by Schlenk techniques as a suspension in anhydrous THF (500 mL) and anhydrous 2-propanol (500 mL) into a 500-L autoclave. The autoclave was then purged with hydrogen (0.1 MPa, 10 times), and then pressurized with hydrogen to 0.84−0.86 MPa, and stirring for 42.5 h at 37−43 °C. After cooling to 25 °C, the autoclave was carefully vented and completely replaced by argon. To the reaction mixture was added activated carbon (481 g), and the slurry was stirred for 3 h at 25 °C. After further addition of Celite (70 g), the suspension was filtered and rinsed with THF (15 L). The filtrate was removed under reduced pressure. The resulting residue was dissolved in 2-propanol (75 L) at 75 °C. Subsequently, to the mixture was added water (41 L) over 45 °C, and stirred 1 h at 25 °C, and 3 h below 10 °C. The precipitate was separated by centrifugation and rinsed with 2-propanol (31 L). The collected compound was dried under reduced pressure at 60 °C to give crude **8** (38.0 kg, 96.1% ee). The crude **8** was dissolved in ethyl acetate (103 L) at 70 °C. To the solution was added *n*-heptane (72 L) over a 30-min period, and then the solution was cooled to 25 °C. The mixture was stirred for 15 h at ambient temperature and cooled to 0−10 °C for 3 h. The precipitate was collected by filtration and dried under reduced pressure at 60 °C to give **8** (34.0 kg, 82.2% yield, >99.9% ee). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.30 (1H, m), 3.80 (3H, s), 3.86 (3H, s), 4.17 (2H, s), 6.00 (1H, d, J = 4.9 Hz), 6.54 (1H, d, J = 8.4 Hz), 6.88 (2H, d, J = 8.0 Hz), 6.99−7.08 (3H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.8, 61.0, 69.2, 112.3, 117.5, 119.7, 122.8, 124.6, 127.3, 128.2, 129.0, 134.8, 143.4, 146.3, 152.5. IR (KBr), cm^{-1}: 3418, 1585, 1039, 789. Anal. Calcd for $C_{15}H_{16}NO_3Cl$: C, 61.33; H, 5.49; N, 4.77; Cl, 12.07. Found: C, 61.32; H, 5.40; N, 4.67; Cl, 12.13. Residual amount of ruthenium: 0.15 ppm.

■ ASSOCIATED CONTENT

Supporting Information. NMR spectra of **8**, **13c**, **18c**, **18d**, **18f**, and **18h** and crystallographic information files for **13c**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Telephone: +81-6-6300-6433. Fax: +81-6-6300-6251. E-mail: Goto_Mitsutaka@takeda.co.jp.

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(13) Unpublished results. The chiral benzhydrol (**7**) was obtained by the following procedure, [(i) LDA/THF, −55 °C; (ii) (−)-DIP-Chloride, −55 °C to rt, 21 h; (iii) 3 N NaOH, H_2O_2, 85% yield, 96% ee]. (−)-DIP-Chloride is a trademark of Sigma-Aldrich Corporation.

(14) Abbreviations: (*S*)-XylBINAP (**18b**) = (*S*)-2,2′-bis[bis(3,5-dimethylphenyl)phosphino]-1,1′-binaphthhyl. (*S*)-DAIPEN = (2*S*)-1,1-bis(4-methoxyphenyl)-3-methyl-1,2-butanediamine. (*S*,*S*)-DPEN = (1*S*,2*S*)-1,2-diphenylethylenediamine.

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(24) Abbreviation: (*S*)-DADMP-BINAP (**18c**) = (*S*)-2,2′-bis[bis-(4-dimethylamino-3,5-dimethylphenyl)phosphino]-1,1′-binaphthyl.

(25) Ru complex containing $[NH_2(C_2H_5)_2][\{RuCl(diphosphine)\}_2(\mu\text{-}Cl)_3]$ was prepared by treatment of $[RuCl_2(cod)]_n$ with the diphosphine (L) in the presence of triethylamine under toluene reflux. After removing the solvent, the concentrated residue was used for reaction without further purification.

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(32) There was slight unevenness of the ee ratio of **8** for different lots of **13c**. We supposed that there could be another potential impurity affecting **13c**, e.g. dimethylamine that is generated by thermal decomposition of DMF.