Organic Process Research & Development

Communication

pubs.acs.org/OPRD

Asymmetric Hydrogenation of 3,5-Bistrifluoromethyl Acetophenone in Pilot Scale with Industrially Viable Ru/Diphosphine–Benzimidazole Complexes

Liang Xu,[†,‡] Zhi-Hong Huang,[‡] Christian A. Sandoval,[‡] Lian-Quan Gu,[†] and Zhi-Shu Huang*[,†]

[†]School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou 510006, People's Republic of China

[‡]Enantiotech Corp., Ltd., Zhongshan Torch Hi-Tech, Industrial Development Zone, Zhongshan 528437, Guangdong Province, People's Republic of China

Supporting Information

ABSTRACT: A novel efficient asymmetric hydrogenation (AH) process was developed for the preparation of (*R*)-1-(3,5-bis(trifluoromethyl)phenyl)ethanol (**3**), using a catalyst Ru/(4*R*,5*R*)-(+)-4,5-bis(diphenylphosphinomethyl)-2,2-dimethyl-1,3-dioxoane-(*R*,*R*-Diop)-2*R*-(α-methylmethanamine)-4,7-dimethyl-1*H*-benzo[*d*]imidazole (*R*-D-Me-BIMAH) in toluene in the presence of potassium *t*-butoxide. Various hydrogenation parameters, such as ligand, solvent, and substrate-to-catalyst (S/C) ratio, were investigated. The hydrogenation was carried out for four times on a 5 kg scale at 30 atm and 25 °C with S/C of 20 000 with an enantiomeric excess of >89%.

INTRODUCTION

Optically active secondary alcohols are useful building blocks for many biologically active compounds in the pharmaceutical industry.[1] Asymmetric hydrogenation (AH) of prochiral ketones is a practical and simple method to obtain enantiomerically pure secondary alcohols.[2−4] (*R*)-1-(3,5-Bistrifluoromethyl)phenyl)ethanol (**3**) (Figure 1) is a key intermediate in the synthesis of human neurokinin-1 (NK-1) receptor blockers,[5−7] such as Aprepitant[6,7] (Figure 1, **1**) and Fosaprepitant[8] (Figure 1, **2**). Market demand of **3** might be increased greatly after expiration of the drug patents. Although the methods for preparation of optically pure **3** through AH have aroused wide interest in both academic and industrial research,[9−13] most studies remained in a small scale or difficult to operate in large-scale production because of the complicated catalyst or the harsh conditions. Noteworthily, a scaled-up AH process has been reported by Naud and co-workers.[14] Since many AH processes for the preparation of **3** have been protected by patents, a novel technically feasible AH process need to be developed for company to be able to compete in this market.

Previously, we have developed a novel and efficient ruthenium-(4*S*,5*S*)-(+)-4,5-bis(diphenylphosphinomethyl)-2,2-dimethyl-1,3-dioxoane)-1*H*-benzimidazole-2-methanamine ($RuCl_2$[(*S*)-Diop][(*S*)-BIMAH]) catalyst for aryl ketones reduction in the presence of potassium *t*-butoxide, and good conversion and enantioselectivity have been obtained on meta substituted acetophenone with either electron-withdrawing or electron-donating[15] substituent. The BIMAH ligands and $RuCl_2$[Diop][BIMAH] catalysts (Supporting Information, Figure S2) have been sold to Strem Chemical Inc. Inspired by this previous result, we further developed a novel process for the preparation of **3** by using $RuCl_2$[(*R*)-Diop][(*R*)-BIMAH] as a catalyst in the present study.

RESULTS AND DISCUSSION

Our previous research of the $RuCl_2$[(*S*)-Diop][(*S*)-BIMAH] complex catalyst has shown that the steric bulk of R^1 (Figure 2) has a slight influence on conversion and enantioselectivity in the AH process.[15,16] Besides, the previous study has shown that both electron-withdrawing and electron-donating substituents on the C6 can decrease the enantioselectivity or conversion.[15] However, the influence of substituents on the C4 and C7 of the benzene ring has not been studied so far.

Hereby, (*R*)-**6a**, and (*R*)-**6b** (Figure 2) were synthesized to further evaluate the influence of the steric bulk of R^1 (Figure 2). (*R*)-**6d** (Figure 2) was selected due to its excellent performance in our previous study for further investigation on the influence of R^3. To prepare (*R*)-**6a**, (*R*)-**6b**, and (*R*)-**6d**, the corresponding ligands (*R*)-**5a**, (*R*)-**5b**, and (*R*)-**5d** (Figure 2) were synthesized respectively according to the previously reported protocol using the corresponding *R*-isomer amino acids as starting materials.[15,16] To further investigate the influence of the substituents on the other position of the benzene ring, the same substituents of C4 and C7 were introduced first. The subsequent study for influence of substituents on the C4 and C7 of the benzene ring of $RuCl_2$[(*S*)-Diop][(*S*)-BIMAH] showed that the methyl group was preferred as summarized in our another unpublished manuscript. As shown in Scheme 1, the method for synthesizing 1,4-dimethyl-2,3-dinitrobenzene (**8**) was adopted from a previous report.[17] Reduction of **8** was carried out using 10% Pd/C as catalyst under H_2 at 1 bar for 24 h to give 3,6-dimethylbenzene-1,2-diamine (**9**), and the reduction product was used directly to synthesize (*R*)-**5c** according to the established methods for (*R*)-**5a**, (*R*)-**5b**, and (*R*)-**5d**.[18] The catalysts (*R*)-**6a**, (*R*)-**6b**, (*R*)-**6c**, and (*R*)-**6d** (Figure 2) were synthesized according to the established method for $RuCl_2$[(*S*)-Diop][(*S*)-BIMAH] catalysts with modification of the benzimidazole and phosphorus ligands.[15]

Received: May 10, 2014

   dx.doi.org/10.1021/op500148k | *Org. Process Res. Dev.* XXXX, XXX, XXX−XXX

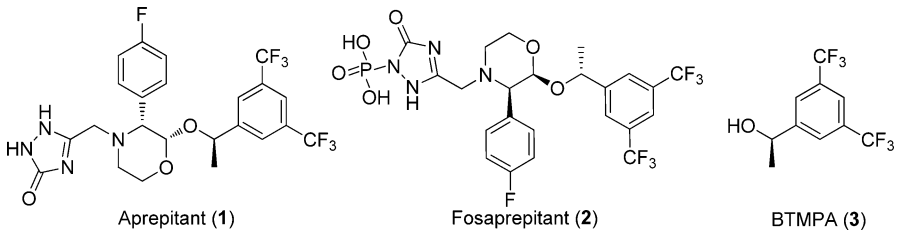
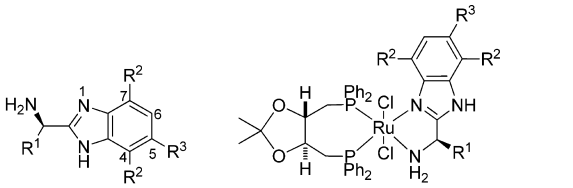


Figure 1. Chemical structure of Aprepitant, Fosaprepitant, and **3**.

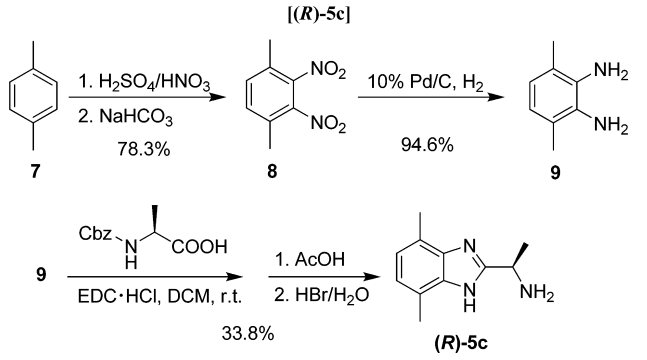


(R)-**5a**: R^1= CH_3, R^2 = H, R^3= H
(*R*)-**5b**: R^1= $CH(CH_3)_2$, R^2 = H, R^3= H
(*R*)-**5c**: R^1= CH_3, R^2 = CH_3, R^3= H
(*R*)-**5d**: R^1= CH_3, R^2 = H, R^3= OMe

(R)-**6a**: R^1= CH_3, R^2 = H, R^3= H
(*R*)-**6b**: R^1= $CH(CH_3)_2$, R^2 = H, R^3= H
(R)-**6c**: R^1= CH_3, R^2 = CH_3, R^3= H
(R)-**6d**: R^1= CH_3, R^2 = H, R^3= OMe

Figure 2. Structure of the BIMAH ligands and catalysts.

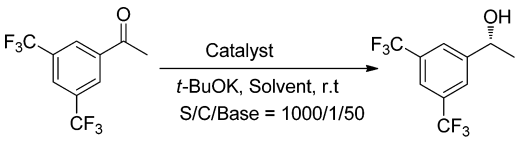
Scheme 1. Synthesis of (*R*)-1-(4,7-dimethyl-1*H*-benzo[*d*]imidazol-2-yl)ethanamine [(*R*)-5c]



1. Catalyst Screening and Optimization of the Hydrogenation Conditions. The screening hydrogenations were carried out in 100 mL glass autoclaves under various conditions being established during the research of $RuCl_2$[(*S*)-Diop][(*S*)-BIMAH] complex using anhydrous 1-(3,5-bis-(trifluoromethyl)phenyl)ethanone (**4**) in the presence of potassium *t*-butoxide with or without an equivalent (relative to catalyst) of PPh_3 as an additive.[16]

Table 1 details the AH of **4** using similar in situ generated catalyst [S/C/Base = 1000:1:50, $P(H_2)$ = 8 atm, t = 4 h, T = 25 °C] in classical solvent systems. For most combinations, **3** was quantitatively obtained through AH of **4**. The catalyst activity and enantioselectivity were not influenced by the steric bulk of R^1 (entry 2, entry 5). The ee of **3** was nearly unaffected by adding PPh_3 in mixed solvent of toluene/*t*-BuOH (entries 1−5). Notably, the ee value of **3** was slightly decreased by adding PPh_3 (entries 6−13), which was different from our previous study that the ee value was increased by adding PPh_3 as additive during the asymmetric hydrogenation,[16] while (*R*)-**6c** showed better result in toluene than (*R*)-**6a**, (*R*)-**6b**, and (*R*)-**6d** (entries 6−13). Importantly, hydrogenation catalyzed by (*R*)-**6c** was considerably more selective in toluene without PPh_3 (entry 10 and 11); meanwhile, the methyl groups on the C4 and C7 were favorable to the AH in toluene. Protic solvents always possess high water content, which are not favorable to AH, while purified alcohols lead to high cost. Here, in order to further develop a novel AH process for **3** and minimize the cost of the process, (*R*)-**6c** was selected[19] for further study since the relatively high ee of **3** could be obtained in toluene with low solvent cost.

Table 1. Effect of catalyst structure (see Figure 2), solvent, and additive on ee screening[a]



entry	catalyst	solvent (v/v)[b]	additive	conv. %[c]	ee %[c]
1	(*R*)-**6a**	toluene/*t*-BuOH	PPh_3	99.9	92.0
2	(*R*)-**6a**	toluene/*t*-BuOH		99.8	90.2
3	(*R*)-**6c**	toluene/*t*-BuOH		97.7	90.0
4	(*R*)-**6b**	toluene/*t*-BuOH	PPh_3	94.6	90.5
5	(*R*)-**6b**	toluene/*t*-BuOH		99.8	90.3
6	(*R*)-**6a**	toluene	PPh_3	99.7	85.8
7	(*R*)-**6a**	toluene		99.9	84.0
8	(*R*)-**6b**	toluene	PPh_3	99.2	85.1
9	(*R*)-**6b**	toluene		99.9	86.5
10	(*R*)-**6c**	toluene		99.6	91.3
11	(*R*)-**6c**	toluene	PPh_3	99.7	85.9
12	(*R*)-**6d**	toluene		99.1	88.7
13	(*R*)-**6d**	toluene	PPh_3	100	87.8

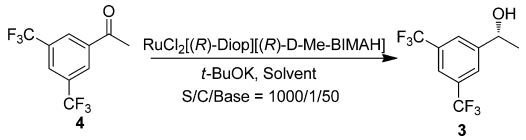
[a]Reaction conditions: S/C/Base = 1000:1:50, base = *t*-BuOK, V_T = 3 mL, $P(H_2)$ = 8 atm, T = 25 °C, t = 4 h; the substrate **4** was freshly distilled over CaH_2 prior to use. [b]Toluene/*t*-BuOH: 9:1 (v/v) ratio used; the toluene and *t*-BuOH were freshly distilled over CaH_2 prior to use. [c]Determined by GC analysis.

2. Screening the Solvents of Hydrogenation. It has been known that the solvents often affect the catalyst activity and the enantioselectivity during asymmetric hydrogenation. To figure out the solvent influence on catalytic efficiency, AH profiles were obtained in different solvent systems. Hydrogenations were carried out in toluene, *t*-BuOH, methyl *tert*-butyl ether, and toluene/alcohol (9:1 or 19:1, v/v) mixtures using (*R*)-**6c** as catalyst in the presence of potassium *t*-butoxide.

The subsequent evaluation of (*R*)-**6c** using in situ generated catalyst in different solvent systems is shown in Table 2 and Figure S4.[20] It was found that the amount of water could significantly affect the proceeding of the reaction. The hydrogenation proceeded smoothly in the commercially available toluene with a moisture content of 0.03% (entry 1), which indicated that commercial toluene could be used directly without further drying. To investigate the influence of the water, the experiment was also carried out at the moisture of

dx.doi.org/10.1021/op500148k | Org. Process Res. Dev. XXXX, XXX, XXX−XXX

Table 2. Screening the solvents of hydrogenation[a]



entry	solvent[b]	moisture (%)[c]	time (h)	conv. %[d]	ee %[d]
1	toluene	[e]	3	100	91.3
2	toluene	0.4	16	NR	NR
3	toluene/*t*-BuOH	0.13	16	99.7	91.0
4	toluene/*n*-BuOH	0.13	2	99.9	84.0
5	toluene/*i*-PrOH	0.07	16	67.5	86.8
6	toluene/EtOH	0.12	16	47.9	70.9
7	toluene/MeOH	0.03	16	48.5	58.6
8	methyl *tert*-butyl ether	[f]	3	99.7	85.4
9	*t*-BuOH	0.03	3	99.7	89.5

[a]Reaction conditions: S/C/Base = 1000:1:50, base = *t*-BuOK, V_T = 3 mL, $P(H_2)$ = 8 atm, T = 25 °C; the substrate **4** was freshly distilled over CaH_2 prior to use. [b]Entry 3: toluene/*t*-BuOH(9:1, v/v), entries 4−7: toluene/alcohol (19:1, v/v). [c]The moisture contents of different alcohols were determined by a Karl Fischer moisture meter. [d]Determined by GC analysis. [e]The moisture content of commercial toluene was 0.03%. [f]Methyl *tert*-butyl ether was freshly distilled over CaH_2 prior to use.

Table 3. Pilot scale and optimization of hydrogenation process[a]

entry	solvent (V/V)	S/C[b]	conv. %[c]	ee %[c]
1[d]	toluene	1840	99.8	89.9
2[d]	toluene	5520	99.9	90.0
3[d]	toluene	10 900	99.9	90.3
4[d]	toluene	20 700	99.7	89.5
5[e]	toluene	20 700	99.9	89.4
6[f]	toluene	20 700	99.2	88.7
7[d]	toluene	40 138	99.9	83.0
8[d]	toluene/*t*-BuOH (9:1)	20 700	99.7	85.3
9[d]	*t*-BuOH	20 700	99.8	85.6
10[d]	toluene	20 700	99.9	88.8

[a]Reaction conditions: C/Base = 1:50, $V_{Solvent}$ = 1 L, $P(H_2)$ = 30 atm, T = 25 °C; t = overnight; entries 1−9: substrate = 170 g; entry 10: substrate = 540 g. [b]S/C = substrate-to-catalyst molar ratio. [c]Determined by GC analysis. [d]**4** from Supplier 1, as supplied, the water content was not more than 0.05% determined by Karl Fischer moisture meter, and the purity was not less than 99.0% determined by using GC. [e]**4** from Supplier 2, as supplied, the water content was not more than 0.05% determined by Karl Fischer moisture meter, and the purity was not less than 99.0% determined by using GC. [f]**4** from Supplier 3, as supplied, the water content was not more than 0.05% determined by Karl Fischer moisture meter, and the purity was not less than 99.0% determined by using GC.

0.4% by means of additional water to toluene. The result showed that the hydrogenation could not happen (entry 2). More importantly, when using mixed solvent of toluene/*t*-butanol, the ee value of **3** was not improved or even slightly decreased (from 91.3% to 91%) under the moisture content of 0.13% (entry 3). Also, noticeable decrease in conversion and ee was observed in entries 4−7 with the decrease of bulk and the number of carbons of alcohol added in toluene (1:19, v/v), which was similar result as previous reported.[15] Noteworthy, **3** was smoothly obtained in 85.4% and 89.5% ee in freshly distilled methyl *tert*-butyl ether and *t*-BuOH, respectively (entry 8 and 9). The solvent screening results showed that commercial toluene could be used directly, which was very beneficial for amplification on the industrial production.

3. Pilot Scale and Optimization of Hydrogenation Process. From an industrial point of view, a good process should be stable, scalable, ecological, and cost efficient. Hereby, pilot processes of **4** catalyzed by (*R*)-**6c** at different S/C were conducted and the conversions and enantioselectivities were investigated. Table 3 displays the outcome for AH of **4** in 170 g scale catalyzed by (*R*)-**6c** under various reaction conditions. In terms of enantioselectivity, the outcome of the reaction was only slightly affected by the catalyst loading (entries 1−4) until the S/C was up to 40 000 (entry 7). To investigate the influence of **4** from different suppliers, three suppliers were tested (entries 4−6), and all of the AH proceeded smoothly without significant change in conversion or enantioselectivity. As a control, AH of **4** in *t*-BuOH and mixed solvent of toluene/*t*-BuOH (9/1, v/v) catalyzed by (*R*)-**6c** were carried out (entry 8 and 9), and both of the results showed lower ee (entry 8:85.3%, entry 9:85.6%) than that in toluene (entry 4, 89.5%) at the same S/C ratio of 20 700. This outcome was consistent with exploratory experiments. To further verify the stability of the process, we scaled the process up to 540 g with a S/C ratio of 20 700 (entry 10). The AH proceeded smoothly without significant change in ee of **3**. Meanwhile, the process was repeatable even at 540 g scale using (*R*)-**6c** as a catalyst in toluene in the presence of potassium *t*-butoxide with S/C of 20 000 under 30 atm of H_2.

4. Scale-up of the Hydrogenation. To produce the required amount of **3** for further preparation of the subsequent intermediate of Aprepitant and further verify the process, the optimized process was run four times on 5 kg scale in a 100 L hydrogenation autoclave with a S/C ratio of 20 000 under 30 atm H_2 at 25 °C (Supporting Information, Table 1). All four batches proceeded smoothly in 99.9% conversion after 16 h periods and afforded crude **3** with 89.3−89.4% ee. The combined batches of crude product were recrystallized from heptane with 1,4-diazabicyclo[2.2.2]octane (DABCO) to afford pure **3** (yield 60−65%, ee 98−98.75%) according to the reported Hansen protocol.[21] Heavy metal detection (by microcolorimetry) result of the subsequent intermediate synthesized from **3** was lower than 20 ppm (Figure S3) and met the customer requirement. Typically, catalyst removal is an issue that always achieved by absorption, crystallization, distillation, or extraction, which lead to a loss of product.

CONCLUSION

In summary, we have described an efficient and practical pilot process for the synthesis of (*R*)-1-(3,5-bis(trifluoromethyl)-phenyl)ethanol, a key intermediate for the synthesis of Aprepitant and Fosaprepitant. Started from the commercially available inexpensive materials, three catalysts were prepared. Critical parameters of the asymmetric hydrogenation such as catalyst selection, additive effect, solvent influence, S/C ratio, and pilot scale were investigated, and the process was demonstrated to be a robust catalytic process for the preparation of (*R*)-1-(3,5-bis(trifluoromethyl)phenyl)ethanol in the presence of potassium *t*-butoxide in toluene. Scale-up to 5 kg scale was experimentally performed for four times, and a total amount of 14.2 kg of optically pure (*R*)-1-(3,5-bis(trifluoromethyl)phenyl)ethanol was obtained (yield 65−70%, ee 98−98.75%) in a reasonably acceptable cost.

dx.doi.org/10.1021/op500148k | Org. Process Res. Dev. XXXX, XXX, XXX−XXX

EXPERIMENTAL SECTION

General Methods. All of the experiments sensitive to moisture and air were conducted using standard Schlenk techniques under an argon atmosphere. Toluene (Industrial grade, purity ≥99.5%, water content ≤0.05%, Shanghai Demand Chemical Co., Ltd.) was used as purchased or distilled over CaH_2 prior to use. MeOH (GR grade, Aladdin Reagent Co.), EtOH (GR grade, Aladdin Reagent Co.), *i*-PrOH (GR grade, Aladdin Reagent Co.), *t*-BuOH (GR grade, Aladdin Reagent Co.), hexane (HPLC grade, Aladdin Reagent Co.), and CH_2Cl_2 (HPLC grade, Aladdin Reagent Co.) were used as purchased. Methyl *tert*-butyl ether (GR grade, Aladdin Reagent Co.) and DMF (AR grade, Aladdin Reagent Co.) were distilled over CaH_2 prior to use. 1-(3,5-Bis(trifluoromethyl)phenyl)-ethanone (Industrial grade) was used as purchased from supplier 1 (Beijing Pure Chem. Co., Ltd.), supplier 2 (Fuxin Jintelai Fluoring Chemical Co., Ltd.), and supplier 3 (Beijing Golden Olive Co., Ltd.).

All reactions were monitored by gas chromatography (GC), and the conversions and ee values were determined by using GC. GC analysis was conducted on Agilent 7890A with Supelco BETA-DEXP^{TMP} 225 column (30 m × 250 μm, 0.25 μm).

^{1}H NMR, ^{13}C NMR, and ^{31}P NMR spectra were recorded on a Bruker BioSpin GmbH spectrometer at 400 and 100 MHz using TMS as the internal standard, respectively. Mass spectra (MS) was recorded on a Shimadzu LCMS-2010A instrument with an ESI or ACPI mass selective detector. Melting points (m.p.) were determined using an SRS-OptiMelt automated melting point instrument without correction. Flash column chromatography was performed with silica gel (200−300 mesh) purchased from Qingdao Haiyang Chemical Co., Ltd. The chiral purity of synthesized ligand was confirmed to be higher than 99.5% by using analytical HPLC with a dual pump Shimadzu LC-20AB system equipped with an OD-H column (DAIEL OD-H column, 4.6 cm × 250 mm, λ = 254 nm, v = 1.0 mL/min, hexane/i-PrOH = 90:10). All exploratory experiments were carried out following the previously established method.[15]

Preparation of (*R*)-5. Ligands (*R*)-**5a**, (*R*)-**5b**, and (*R*)-**5d** were prepared according to the established method for (*S*)-BIMAH[16] with modification of the starting material of *R*-isomer amino acids. (*R*)-**5c** was synthesized by the (*R*)-**5a** method using 3,6-dimethylbenzene-1,2-diamine (**9**) instead of *o*-diaminobenzene (Scheme 1).

*(R)-**5a***. Off-white powder. Yield 37%. M.p.: 188−190 °C; chiral purity: 99.67%; MS (ESI): m/z = 161 $[M + H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.56−7.53 (m, 2H), 7.23−7.19 (m, 2H), 4.46−4.41 (m, 1H), 1.58 (d, J = 6.8, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.27, 138.39, 122.33, 114.94, 46.30, 23.80.

*(R)-**5b***. Off-white powder. Yield 35%. M.p.: 193−195 °C; chiral purity: 99.54%; MS (ESI): m/z = 190 $[M + H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.50−7.48 (m, 2H), 7.16−7.14 (m, 2H), 4.04 (d, J = 4.8, 1H), 2.26−2.21 (m, 1H), 0.92−0.85 (dd, J_1 = 6.8, J_2 = 24, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 1557.77, 138.21, 122.20, 114.96, 56.50. 33.98, 19.36, 17.58.

*(R)-**5c***. Off-white powder. Yield 25%. M.p.: 184−185.5 °C; chiral purity: 99.75%; MS (ESI): m/z = 190 $[M + H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.93 (s, 2H), 4.55−4.50 (m, 1H), 2.54 (s, 6H),1.57 (d, J = 6.4, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.07, 122.71, 46.43, 24.09, 16.86.

*(R)-**5d***. Light yellow powder (hygroscopic). Yield 27%. chiral purity: 99.81%; ^{1}H NMR (400 MHz, DMSO) δ = 7.34 (d, J = 11.2, 1H), 6.98 (s, 1H), 6.72−6.750 (m, 1H), 4.08−4.13 (m, 1H), 3.75 (s, 1H),1.39 (d, J = 8.8, 1H); ^{13}C NMR (100 MHz, DMSO) δ = 167.73, 159.68, 157.40, 155.55, 115.97, 110.72, 97.79, 55.74, 46.22, 23.43.

Preparation of Catalysts. The catalysts were synthesized according to the established method for $RuCl_2$[(*S*)-Diop][(*S*)-BIMAH] by modifying the benzimidazole and phosphorus ligands.[15]

*(R)-**6c***. Yellow powder. Yield 75%. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 11.60 (br, 1H), 7.98−6.50 (m, 22H), 5.40−4.68 (m, 2H), 3.69−3.47 (m, 1H), 2.94−2.12 (m, 13H), 1.35−0.76 (m, 13H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 161.87, 139.19−125.10 (m, aromatic carbons), 122.52, 122.28, 117.61, 106.77, 94.27, 87.76, 87.52, 79.78, 71.59, 35.48, 30.86, 30.50 (J = 20.1), 26.03 (J = 7.4), 25.77, 25.64, 25.39, 22.53, 21.62, 21.27, 15.96, 13.09; ^{31}P NMR (161 MHz, $CDCl_3$), major isomer: δ = 46.93 (d, ^2J(P,P) = 36.5), 34.74 (d, ^2J(P,P) = 36.5).

Typical Pilot Hydrogenation Procedure. 1-(3,5-Bis-(trifluoromethyl)phenyl)ethanone (170 g) was dissolved in a solvent (1 L) in a 5 L autoclave (BÜCHI), and the solution was degassed by running argon through the solution (1 h). Stoichiometric amounts of solid catalyst and potassium *t*-butoxide were added to the autoclave under argon atmosphere. The charged autoclave was purged three times with 5 atm of hydrogen and then pressurized to 30 atm of hydrogen. The resulting mixture was stirred at room temperature. After the reaction completed, the hydrogen was released, and the conversion and ee were determined by using GC. GC (Supelco BETA-DEXP^{TMP} 225 column (30 m × 250 μm, 0.25 μm)); P = 118.6 kPa; T = 105 °C; t_R of (*R*)-isomer, 22.9 min (major); t_R of (*S*)-isomer, 19.9 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.85 (s, 2H), 7.80 (s, 1H), 5.06−5.02 (m, 1H), 1.57 (d, J = 5.2, 3H).

Scale-up Hydrogenation Representative Procedure. 1-(3,5-Bis(trifluoromethyl)phenyl)ethanone (5.1 kg) was introduced to the 100 L autoclave under argon atmosphere, followed with 30 L of toluene. A bubbler was connected to the autoclave, and the resulting mixture was charged with argon and bubbled with argon for 2 h to degas the oxygen of the mixture. After degassing completed, a suspension of the catalyst (1.0 g) and potassium *t*-butoxide (5.6 g) in toluene (0.5 L) was transferred by means of standard Schlenk technique. The charging port was shut up quickly, and the valve of the argon pipeline was closed up. After washing the hydrogen pipeline with hydrogen for 3 times, the charged autoclave was purged three times with 10 atm of hydrogen and then pressurized to 30 atm of hydrogen. The resulting mixture was stirred at 25 °C at an agitation speed of 800 rpm. After completion of the reaction, the hydrogen was released, and the mixture was filtered, and the filtrate was evaporated to give crude product. The crude product was recrystallized from hexane/isopropanol according to a protocol reported by Hansen et al.[16] to afford pure **3** (yield 65−70%, ee 98−98.75%).

ASSOCIATED CONTENT

Supporting Information

Table S1: Scale-up batches of crude 3, mass, ^{1}H NMR, ^{13}C NMR spectrum of **5a**, mass, ^{1}H NMR, ^{13}C NMR spectrum of **5b**, mass, ^{1}H NMR, ^{13}C NMR spectrum of **5c**, ^{1}H NMR, ^{13}C NMR spectrum of **5d**, ^{1}H NMR spectrum of **3**, ^{1}H NMR, ^{31}P NMR, ^{13}C NMR spectrum of **6c**, spectrum of chiral purity of **5a**, **5b**, **5c**, and **5d**, representative GC spectrum of Table 1 and

dx.doi.org/10.1021/op500148k | Org. Process Res. Dev. XXXX, XXX, XXX−XXX

S1, Figure S1: 5 L autoclave, Figure S2: stream catalog of Enantiotech ligands and catalysts, Figure S3: COA of Aprepitant N-1 intermediate in house, method of testing heavy metals, Figure S4: AH data of different solvents. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-mail: ceshzs@mail.sysu.edu.cn.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We are thankful for the contributions of Shiliang Huang, Shenrong Liao (Sun-Yat Sen University) and experimental work of Qinghong Lin, Yuyun Zeng, and Yanxiong Li (Enantiotech Corp., Ltd.).

ABBREVIATIONS

R,*R*-Diop: 2*R*,3*R*-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane; CAS No. 32305-98-9; *R*-D-Me-BIMAH: 2*R*-(α-methyl methanamine)-4,7-dimethyl-1*H*-benzo[*d*]imidazole; S/C: substrate-to-catalyst; AH: asymmetric hydrogenation

REFERENCES

(1) Ohkuma, T. Asymmetric hydrogenation of ketones: Tactics to achieve high reactivity, enantioselectivity, and wide scope. *P. Jpn. Acad. B-Phys.* **2010**, *86*, 202−219.

(2) Yang, X. H.; Xie, J. H.; Liu, W. P.; Zhou, Q. L. Catalytic asymmetric hydrogenation of delta-ketoesters: highly efficient approach to chiral 1,5-diols. *Angew. Chem.* **2013**, *52*, 7833−7836.

(3) Abdur-Rashid, K.; Faatz, M.; Lough, A. J.; Morris, R. H. Catalytic cycle for the asymmetric hydrogenation of prochiral ketones to chiral alcohols: direct hydride and proton transfer from chiral catalysts trans-Ru(H)(2)(diphosphine)(diamine) to ketones and direct addition of dihydrogen to the resulting hydridoamido complexes. *J. Am. Chem. Soc.* **2001**, *123*, 7473−7474.

(4) Püntener, K.; Scalone, M. *Asymmetric Catalysis on Industrial Scale; Challenges, Approaches and Solutions*, 2nd ed.; Blaser, H.-U., Federsel, H.-J., Eds.; Wiley-VCH: Weinheim, 2010.

(5) Reichard, G. A.; Stengone, C.; Paliwal, S.; Mergelsberg, I.; Majmundar, S.; Wang, C.; Tiberi, R.; McPhail, A. T.; Piwinski, J. J.; Shih, N. Y. Asymmetric synthesis of 4,4-disubstituted-2-imidazolidinones: potent NK_1 antagonists. *Org. Lett.* **2003**, *5*, 4249−4251.

(6) Brands, K. M. J.; Payack, J. F.; Rosen, J. D.; Nelson, T. D.; Candelario, A.; Huffman, M. A.; Zhao, M. M.; Li, J.; Craig, B.; Song, Z. G. J.; Tschaen, D. M.; Hansen, K.; Devine, P. N.; Pye, P. J.; Rossen, K.; Dormer, P. G.; Reamer, R. A.; Welch, C. J.; Mathre, D. J.; Tsou, N. N.; McNamara, J. M.; Reider, P. J. Efficient synthesis of NK_1 receptor antagonist aprepitant using a crystallization-induced diastereoselective transformation. *J. Am. Chem. Soc.* **2003**, *125*, 2129−2135.

(7) Zhao, M. M.; McNamara, J. M.; Ho, G. J.; Emerson, K. M.; Song, Z. J.; Tschaen, D. M.; Brands, K. M.; Dolling, U. H.; Grabowski, E. J.; Reider, P. J.; Cottrell, I. F.; Ashwood, M. S.; Bishop, B. C. Practical asymmetric synthesis of aprepitant, a potent human NK-1 receptor antagonist, via a stereoselective Lewis acid-catalyzed trans acetalization reaction. *J. Org. Chem.* **2002**, *67*, 6743−6347.

(8) Dorn, C. P.; Hale, J. J.; MacCoss, M.; Mills, S. G. Preparation of morpholine tachykinin receptor antagonist prodrugs. WO9523798A1, 1995.

(9) Zuo, W.; Lough, A. J.; Li, Y. F.; Morris, R. H. Amine(imine)-diphosphine iron catalysts for asymmetric transfer hydrogenation of ketones and imines. *Science* **2013**, *342*, 1080−1083.

(10) Li, W.; Sun, X.; Zhou, L.; Hou, G.; Yu, S.; Zhang, X. Highly efficient and highly enantioselective asymmetric hydrogenation of ketones with TunesPhos/1,2-diamine-ruthenium(II) complexes. *J. Org. Chem.* **2009**, *74*, 1397−1399.

(11) Genov, D. G.; Ager, D. J. Asymmetric hydrogenation of ketones catalyzed by RuII-bicp complexes. *Angew. Chem.* **2004**, *43*, 2816−2819.

(12) Naud, F.; Malan, C.; Spindler, F.; Ruggeberg, C.; Schmidt, A. T.; Blaser, H. U. Ru-(phosphine-oxazoline) complexes as effective, industrially viable catalysts for the enantioselective hydrogenation of aryl ketones. *Adv. Synth. Catal.* **2006**, *348*, 47−50.

(13) Soni, R.; Jolley, K. E.; Clarkson, G. J.; Wills, M. Direct formation of tethered Ru(II) catalysts using arene exchange. *Org. Lett.* **2013**, *15*, 5110−5113.

(14) Naud, F.; Spindler, F.; Rueggeberg, C. J.; Schmidt, A. T.; Blaser, H. U. Enantioselective ketone hydrogenation: From R&D to pilot scale with industrially viable Ru/phosphine-oxazoline complexes. *Org. Process Res. Dev.* **2007**, *11*, 519−523.

(15) Li, Y. H.; Zhou, Y. G.; Shi, Q. X.; Ding, K. L.; Noyori, R.; Sandoval, C. A. An efficient diphosphine/hybrid-amine combination for Ruthenium(II)-catalyzed asymmetric hydrogenation of aryl ketones. *Adv. Synth. Catal.* **2011**, *353*, 495−500.

(16) Li, Y.; Ding, K.; Sandoval, C. A. Hybrid NH_2-benzimidazole ligands for efficient Ru-catalyzed asymmetric hydrogenation of aryl ketones. *Org. Lett.* **2009**, *11*, 907−910.

(17) Yan-Hong, L.; Tong-Lai, Z.; Jian-Guo, Z.; Jin-Yu, G.; Kai-Bei, Y. Synthesis and characterization of nitro-*p*-xylenes. *Molecules* **2005**, *10*, 978−989.

(18) Dinitration of *p*-xylene was prepared according to previously reported method,[16,17] and the crude product could be used directly to synthesize **5c** without purification. The conc. H_2SO_4 used was less than 500 mL in each batch, and it was easy to control safety. The synthesis of the **5c** was prepared according to established methods. **5c** was purified by using column chromatography. It was convenient and safe to obtain the **5c**.

(19) According to our experimental results, if **6a** was adopted for the processing study, the AH product was required to do recrystallization at least twice to reach the required chiral purity (98%), because it is ee value was only 84%. Generally, the ee value of product should be decreased when the process was scaled up and it would lead to lower yield. After all things considered, **6c** would be preferred to minimize the cost.

(20) According to Figure 1 of *Adv. Synth. Catal.* **2011**, *353*, 495−500, there is not a platform period suggesting there is not an induction period and product inhibition in the solvent with base. The catalyst degradation behavior should have happened since the catalyst required activation by base, and the catalyst was pre-catalyst; nevertheless, such behavior could not be detected by current methods.

(21) Hansen, K. B.; Chilenski, J. R.; Desmond, R.; Devine, P. N.; Grabowski, E. J. J.; Heid, R.; Kubryk, M.; Mathre, D. J.; Varsolona, R. Scalable, efficient process for the synthesis of (*R*)-3,5-bistrifluoromethylphenyl ethanol via catalytic asymmetric transfer hydrogenation and isolation as a DABCO inclusion complex. *Tetrahedron: Asymmetry* **2003**, *14*, 3581−3587.