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An Enantioselective Hydrogenation of an Alkenoic Acid as a Key Step in the Synthesis of AZD2716

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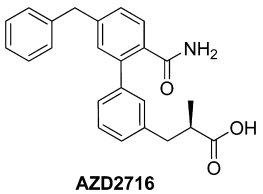
Supporting Information

ABSTRACT: A classical resolution of a racemic carboxylic acid through salt formation and an asymmetric hydrogenation of an α,β-unsaturated carboxylic acid were investigated in parallel to prepare an enantiomerically pure alkanoic acid used as a key intermediate in the synthesis of an antiplaque candidate drug. After an extensive screening of rhodium- and ruthenium-based catalysts, we developed a rhodium-catalyzed hydrogenation that gave the alkanoic acid with 90% ee, and after a subsequent crystallization with (*R*)-1-phenylethanamine, the ee was enriched to 97%. The chiral acid was then used in sequential Negishi and Suzuki couplings followed by basic hydrolysis of a nitrile to an amide to give the active pharmaceutical ingredient in 22% overall yield.

INTRODUCTION

In one of our drug development programs, we planned to run a full toxicological study on **AZD2716**, a candidate drug for the treatment of coronary artery disease (Figure 1).[1] Several hundred grams of the compound was needed for this purpose.



AZD2716

Figure 1. Structure of **AZD2716**.

The first-generation synthesis of **AZD2716** commenced with an alkylation of diethyl methylpropanedioate with 1-bromo-3-(bromomethyl)benzene followed by saponification and decarboxylation of the intermediate **1** to give the racemic carboxylic acid (±)-**2** (Scheme 1). Compound (±)-**2** was next transformed to the corresponding pinacolborate[2] (±)-**3**, which then was ready for a Suzuki coupling[3] with chloride **4** to give compound (±)-**5**. Compound **4** was obtained from commercially available 4-bromo-2-chlorobenzonitrile via a Negishi coupling.[4] The synthesis was finalized with a hydrolysis of nitrile (±)-**5** using NaOH followed by separation of the enantiomers using chiral HPLC to give **AZD2716**.

Given limited time for further optimization of the first-generation route, in the scale-up we decided to keep the major part of the first-generation synthesis, but a few issues had to be addressed. We realized that separation of the racemic mixture of the active pharmaceutical ingredient (API) as the last step, which resulted in more than 50% loss of material, was not suitable for further scale-up. Thus, we decided to direct our efforts toward the development of an asymmetric synthesis of this chiral α-methyl carboxylic acid moiety. This could in theory be achieved through asymmetric alkylation, asymmetric hydrogenation of an alkenoic acid, and resolution of a racemic α-methyl alkanoic acid building block. Furthermore, we wanted to avoid the use of chromatography and instead identify crystalline intermediates that could be purified through crystallization. Alternatively, noncrystalline intermediates could be used as such and/or telescoped. We believed that the rest of the first-generation synthesis could be used as such in the scale-up with only minor modifications such as in the workup.

RESULTS AND DISCUSSION

In order to obtain the enantiomerically pure carboxylic acid (*R*)-**2**, two different approaches were investigated in parallel: resolution of racemic acid (±)-**2** through salt formation with chiral amines and asymmetric hydrogenation of alkenoic acid **8** (Scheme 2). On a large scale, the racemic carboxylic acid (±)-**2** was prepared using the procedure from the first-generation synthesis with small modifications (Scheme 2). The alkenoic acid required for the asymmetric hydrogenation was prepared via a Baylis−Hillman reaction[5] between 3-bromobenzaldehyde and methyl acrylate to give **7** followed by reduction[6] to give **8**.

For the resolution of carboxylic acid (±)-**2**, a selection of chiral amines were screened (Table 1). From this screen we found (*R*)-1-phenylethylamine to be the best choice for resolution of the racemate (±)-**2**. Thus, starting from 1.6 kg of the racemate (±)-**2** and using EtOAc as the solvent, we obtained the salt with 64% ee, which is a slightly better result than that obtained in the primary small screen (Table 1, entry 7). We found it necessary to perform two recrystallizations of this salt from a mixture of EtOH and EtOAc to obtain an acceptable ee (>95% ee). After acidification using HCl and extractions, (*R*)-**2** was isolated in 27% overall yield with 97% ee.

As mentioned above, in parallel with the work on the resolution of acid (±)-**2** we searched for a more efficient method for long-term supply of the enantiomerically pure acid

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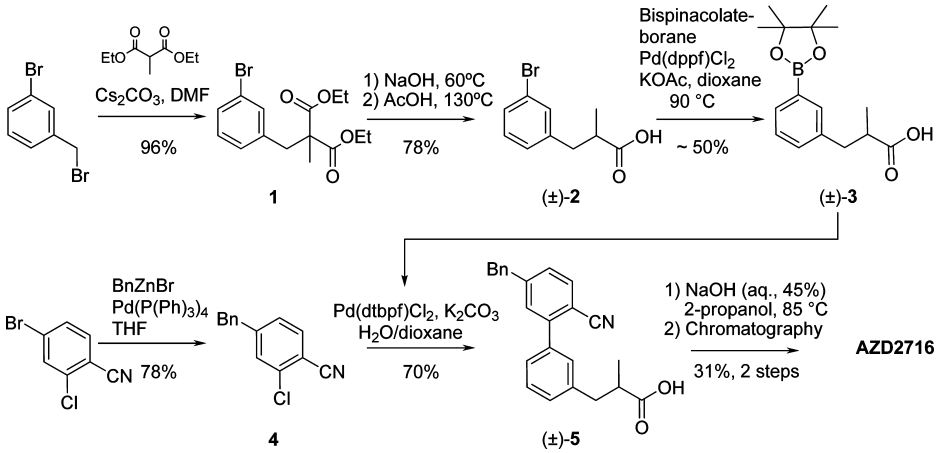
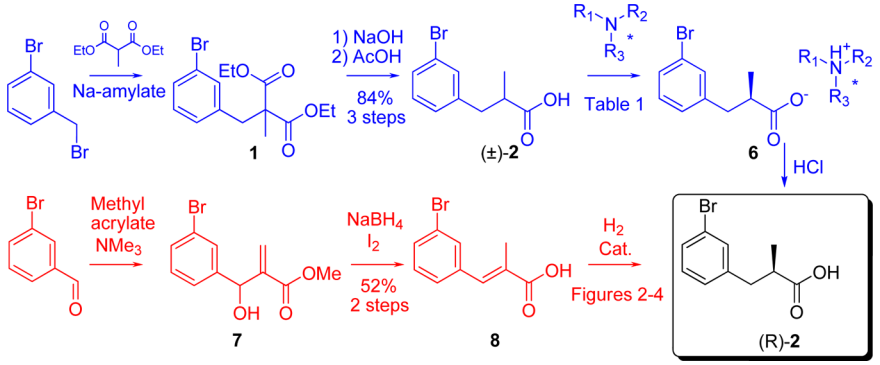
Scheme 1. First-Generation Synthesis of AZD2716



Scheme 2. Two Different Approaches for the Synthesis of Carboxylic Acid (*R*)-2



(*R*)-**2**. Asymmetric hydrogenation of alkenoic acids is a powerful methodology for the preparation of enantiomerically pure carboxylic acids.[7] The substrate scope is broad, and a wide variety of carboxylic acids with different substitution patterns have been prepared on a multikilogram scale by asymmetric hydrogenation using both ruthenium- and rhodium-based catalysts.[8] As a part of our efforts to develop a more sustainable approach for the synthesis of enantiomerically pure carboxylic acid (*R*)-**2**, our plan was to identify an efficient catalyst for the asymmetric hydrogenation of α,β-unsaturated acid **8** (Scheme 2). A literature survey showed that α-methylcinnamates are difficult substrates in asymmetric hydrogenations and constitute an exception to the otherwise broad substrate scope. In fact, only a few examples were found that gave useful enantioselectivities for a range of different α-methylcinnamates.[9] Those reports used chiral ligands that had to be synthesized through a multistep sequence, and at the time when this work was conducted, those ligands were not commercially available. For this reason and to avoid the dependence on patented protocols to obtain catalysts, we wanted to identify a commercially available catalyst that also could give a satisfactory enantioselectivity (>95% ee). A broad screen of both Ru- and Rh-based catalysts in combination with a wide range of different ligands representing all of the important ligand families was set up (Figures 2–4).[10] The hydrogenation screen of **8** was performed on a Chemspeed high-throughput experimentation robot with a high-pressure parallel autoclave.[11]

As illustrated in Figures 2 and 4, both the conversion and enantioselectivity varied considerably among the catalysts. However, the Rh catalysts showed overall higher reactivity and enantioselectivity, and the majority of the Rh catalysts gave complete conversion to product, in contrast to the Ru catalysts. Consistently good performance was observed for almost the entire series of Walphos ligands (W001–W022) with enantioselectivities in the range of 80–85% ee. Also, some of the Mandyphos ligands (M001–M012) showed good selectivity. The overall best hit was for the Josiphos ligand J505-1, which afforded the product with 94% ee. Interestingly, out of the 11 Josiphos ligands that were included in the screen (J001–J505), only the J-505 ligand gave >30% ee.

On the basis of these results, the Rh–J505 catalyst was selected for further optimization, and the influence of various solvents and additives on the performance at gradually decreasing catalyst loadings was investigated. The effect of solvents, including methanol, isopropanol, *n*-butanol, and tetrahydrofuran (THF) was investigated, as was the effect of additives such as triethylamine, *tert*-butylamine, and trifluoroacetic acid (TFA).[12] It was found that methanol was the best solvent for the reaction with regard to both enantioselectivity and catalyst activity. At catalyst loadings below 1 mol %, addition of TFA had a clear positive effect on the catalyst activity, and at a loading of 0.5 mol % the reaction stopped at <30% conversion in absence of added TFA but went to full conversion when 1 mol % TFA was added. A further decrease in the catalyst loading to 0.2 mol % or less led to incomplete conversion even in the presence of added TFA (Figure 5).

Furthermore, upon scaling up to 70 g and using the Rh–J505 catalyst, we found that a slightly lower enantioselectivity was obtained (90% ee) and a higher catalyst loading (1 mol %) was required to reach full conversion. However, with the efforts

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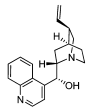
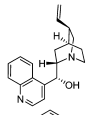
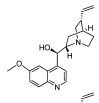
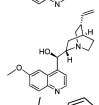
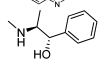
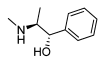
Table 1. Salt Screen for the Resolution of (±)-2

Entry	Amine[a]	Solvent	Yield (%)	Ee (2)[b]
1		EtOAc/heptane	53%	0%
2		MIBK/heptane	55%	0%
3		EtOAc	57%	24%
4		EtOH	29%	56%
5		EtOAc	0%	-
6		EtOH	0%	-
7		EtOAc	40%	34%
8		EtOH	40%	74%
9		EtOAc/heptane	15%	20%
10		MIBK/heptane	5%	20%
11		EtOAc	0%	-
12		EtOH	0%	-

[a]A 70 mol % loading of the resolving amine was used. [b]Determined using chiral HPLC of the free acid.

already invested in trying to identify a chiral amine for the resolution of racemic acid (±)-**2**, we knew that the ee could be enhanced through salt formation with (*R*)-1-phenylethanamine. Thus, after the hydrogenation was complete, this amine was added to the crude mixture, which resulted in precipitation. After filtration of the salt obtained, followed by acidification and extraction, carboxylic acid (*R*)-**2** was isolated in 75% isolated yield with 98% ee (Scheme 3).

In order to obtain **AZD2716**, sequential Negishi and Suzuki couplings followed by hydrolysis of the nitrile were required (Scheme 3). The Negishi coupling[13] of commercially available 4-bromo-2-chlorobenzonitrile and benzylzinc bromide was found to furnish the homocoupled dimer 3,3′-dichlorobiphenyl-4,4′-dicarbonitrile (20% w/w) as a major byproduct along with the desired product **4**. We tried to suppress this side reaction through variation of the temperature, the loadings of the catalyst and BnZnBr, and the rate of addition of the latter. However, no significant positive effect could be observed. Instead, we searched for conditions to remove this byproduct from the crude mixture through crystallizations, but because of the highly crystalline properties of this dimer, that search was not successful. Although we aimed for a chromatography-free process, we decided to purify the mixture through preparative HPLC followed by one crystallization from MeOH/water, which gave 321 g (>99% by HPLC) of the desired compound **4**. In the subsequent steps to the API, we could not identify a suitable intermediate for crystallization. Instead, we developed a three-step sequence to **AZD2716** in which none of the intermediates were isolated or purified other than by extractions. The sequence included the formation of the boronate ester (*R*)-**3** from (*R*)-**2** followed by a telescoping sequence in which a Suzuki coupling[3] with **4** resulted in compound (*R*)-**5**. After extractions of the crude mixture of (*R*)-**5**, this was concentrated and then directly hydrolyzed to furnish, after crystallization from EtOAc, the desired API **AZD2716** in 57% isolated yield over three steps with >98% ee.[14]

CONCLUSION

In comparison with the first-generation synthesis of **AZD2716** in 8% overall yield, we developed an enantioselective large-scale route with an overall yield of 22%. The main improvement was the replacement of a late-stage enantiomeric separation of a racemic mixture with an enantioselective hydrogenation of an

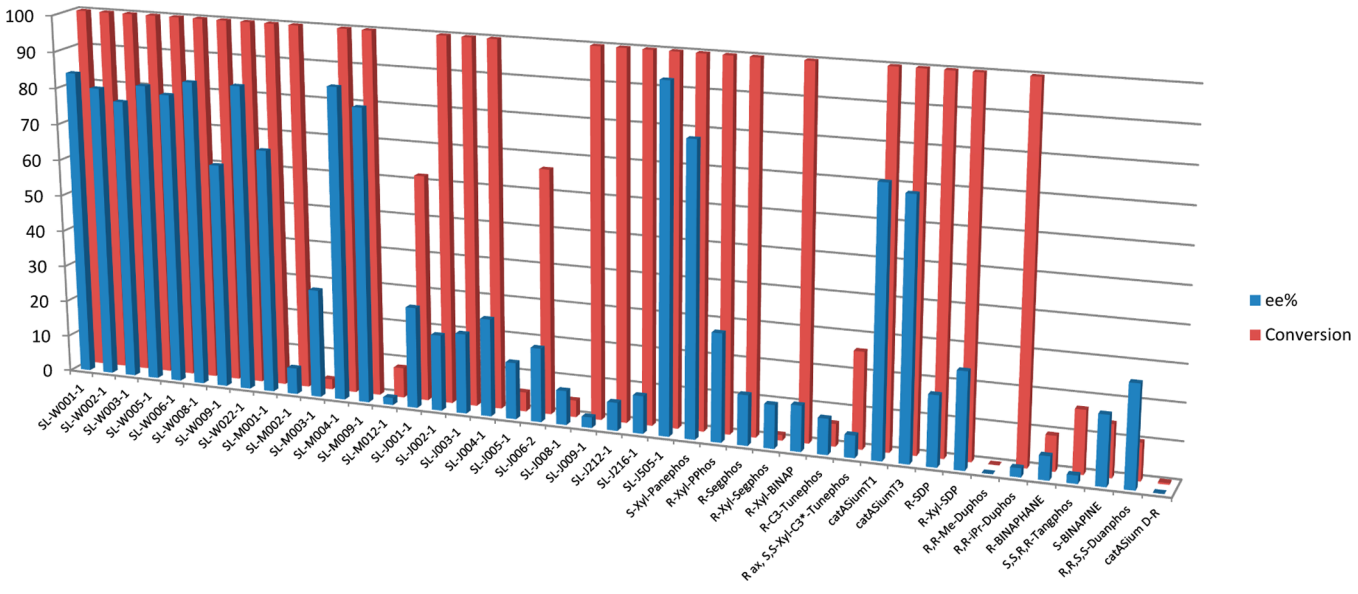


Figure 2. Results from the hydrogenation screen of **8** using various rhodium catalysts.

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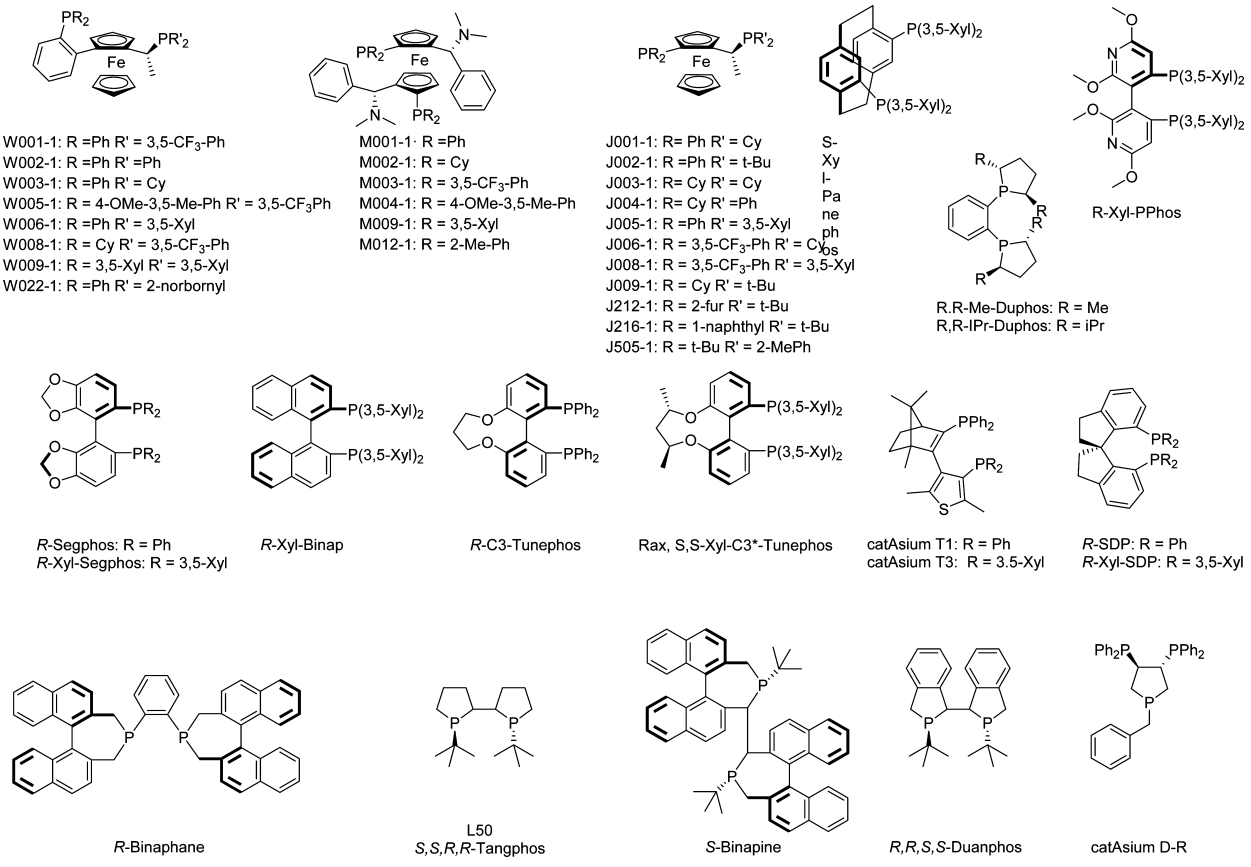

Figure 3. Ligands screened for the asymmetric hydrogenation.

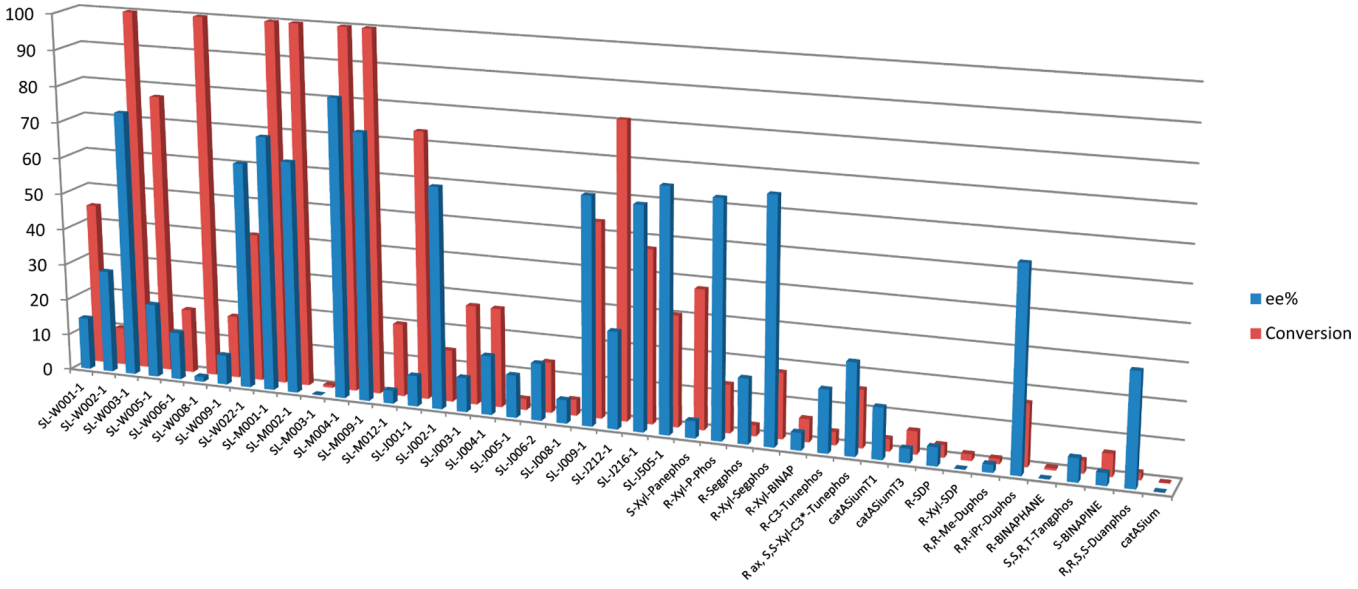

Figure 4. Results from the hydrogenation screen of **8** using various ruthenium catalysts.

early-stage alkenoic acid **8**. Using the Josiphos ligand (*R*)-1-[(*S*)-2-(di-*tert*-butylphosphino)ferrocen-1-yl]ethylbis(2-methylphenyl)phosphine in combination with rhodium as the catalyst in the hydrogenation, we obtained (*R*)-**2** with 90% ee. Salt formation with (*R*)-1-phenylethylamine followed by crystallization improved the enantioselectivity to 97% ee. Another key step in the synthesis was a sequential Negishi/Suzuki coupling. By using crude intermediates directly in the next steps without purifications, we avoided chromatography in all but one step. A final crystallization of the API gave 347 g of **AZD2716** with >99% purity and >98% ee.

EXPERIMENTAL SECTION

Materials and Instrumentation. All materials were purchased from commercial suppliers and used as such without further purification. All reactions were performed under an atmosphere of nitrogen. Large-scale reactions were performed

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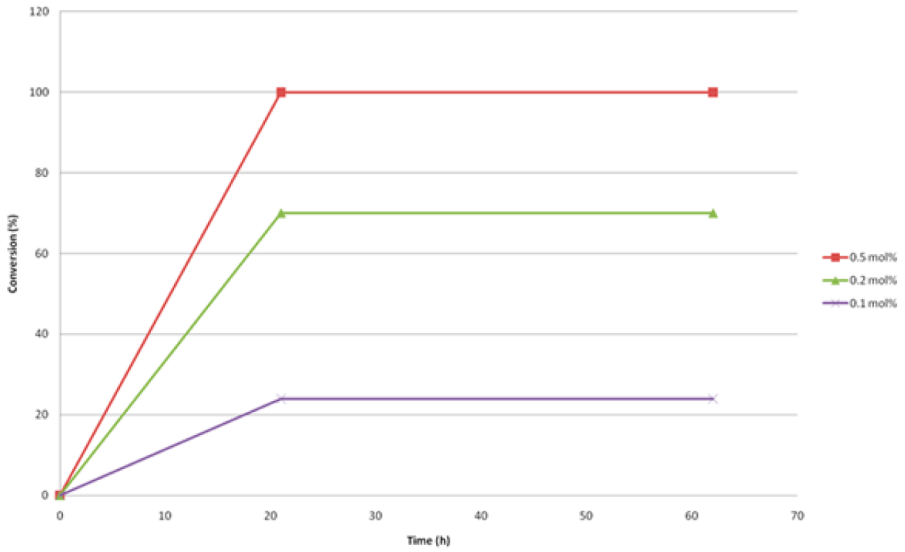
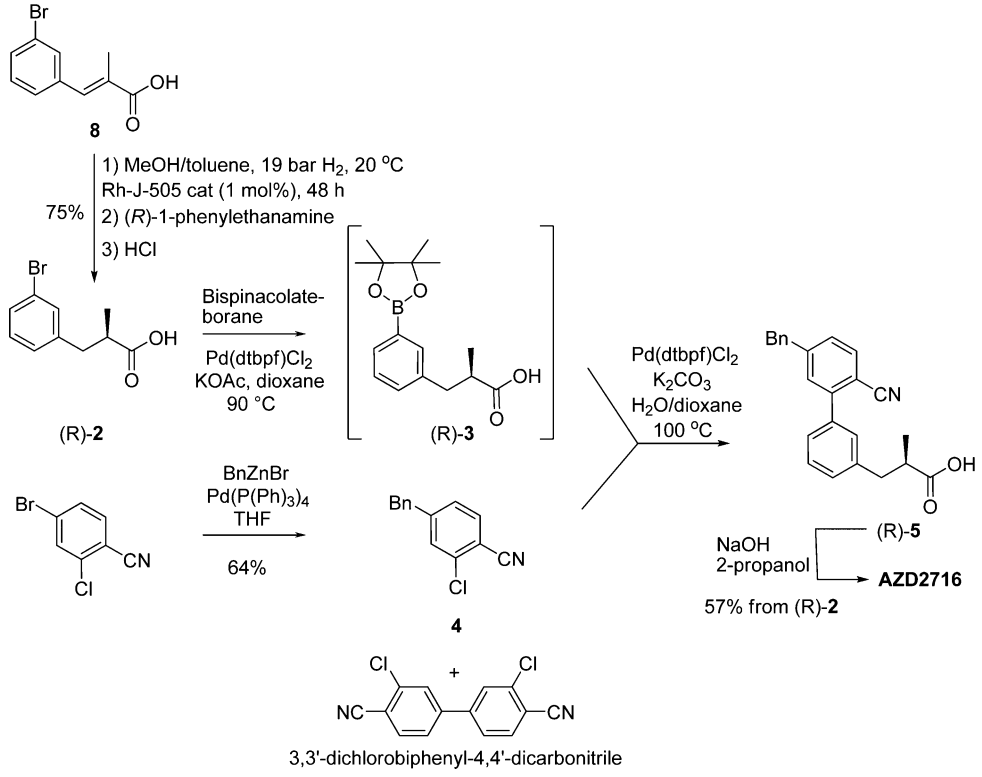


Figure 5. Conversion of **8** as a function of the loading of the Rh–J505 catalyst.

Scheme 3. Second-Generation Synthesis of AZD2716



using glass reactors equipped with an overhead stirrer. IPCs were recorded either by HPLC or ^{1}H NMR analysis of the crude reaction mixtures. Assays were determined by ^{1}H NMR integration using benzyl benzoate as an internal standard. The enantiomeric purity of (*R*)-**2** was determined using HPLC [*t*-Bu-CQN column (4.6 mm × 250 mm) with CH_3CN/2-propanol/AcOH 90/10/0.3 as the eluent]. The enantiomeric purity of **AZD2716** was determined using HPLC [Chiralcel OJ column (4.6 mm × 250 mm) with heptane/EtOH/formic acid 10/90/0.1 as the eluent]. High-resolution mass spectrometry was performed on a QTOF 6530 instrument (Agilent) with a mass precision of ±5 ppm. NMR measurements were performed using a Bruker Avance III spectrometer. LC/MS analyses were recorded on a Waters ZMD, LC column x Terra MS C_8 (Waters) with detection using an HP 1100 MS-detector diode array.

Catalyst Screening. Catalyst screening was performed on a Chemspeed high-throughput experimentation robot equipped with a high-pressure parallel autoclave. To each of the wells in a 96-well microtiter plate was added 50 μL of methanol followed by 50 μL of either a 0.00700 M MeOH solution of $Rh(COD)_2BF_4$ or a 0.00700 M MeOH solution of $Ru(COD)(TFA)_2$. Finally, 50 μL aliquots of 0.0077 M solutions of the ligands in toluene were added to the wells to give a total of 43 different Rh catalysts and 43 different Ru catalysts. The mixtures were agitated at 40 °C for 2 h, after which 200 μL of a

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0.28 M solution of **8** in MeOH was added to each well and the reaction plate was inserted into the autoclave. The autoclave was pressurized to 15 bar H_2 and agitated for 16 h. The reaction mixtures were diluted with isopropanol and then analyzed by chiral HPLC for determination of the conversion and enantiomeric excess.

3-(3-Bromophenyl)-2-methylpropanoic Acid [(±)-2]. A 25 L reactor was charged with diethyl 2-methylmalonate (1.8 kg, 10.4 mol) and ethanol (99.5%, 12 L). The mantle temperature was set at 0 °C. When the reaction temperature had reached 8 °C, sodium 2-methylbutan-2-olate (1.2 kg, 10.4 mol) was added portionwise over 20 min. The reaction temperature reached 22 °C during this addition. The mantle temperature was then set at 20 °C. To the homogeneous solution was then added within 10 min a suspension of 1-bromo-3-(bromomethyl)benzene (2.0 kg, 8.0 mol) in ethanol (99.5%, 2 L). This addition raised the reaction temperature to 39 °C, and a white suspension was obtained. The mantle temperature was set at 60 °C. When the reaction temperature reached 57 °C, a 25% aqueous solution of sodium hydroxide (4.5 kg, 28.2 mol) was added, and the white suspension was allowed to stir for 30 min. EtOH (∼5 L) was then allowed to distill off (400 mbar/60 °C). With the mantle temperature set at 20 °C, methyl *tert*-butyl ether (MTBE) (7.5 L) and water (5 L) were added. The layers were separated, and water (5 L) and MTBE (2.5 L) were added to the organic layer. The pooled aqueous layer was washed with MTBE (5 L + 2.5 L). The mantle temperature was set at 0 °C, and to the aqueous layer was added MTBE (2.5 L) followed by the addition of 12 M HCl(aq) (3.5 L) within 10 min until a pH of ∼1 was obtained. The reaction temperature increased to 39 °C during this addition. The organic layer (6 L) was concentrated to give the intermediate diacid as a pale-yellow solid. This was charged into a 25 L reactor, and acetic acid (3.2 L) was added. The yellow suspension was then heated at reflux for 17 h, during which gas evolution was observed. The mantle temperature was set at 20 °C, and water (4 L) and MTBE (4 L) were added. The organic layer was washed with water (3 × 1 L) and then concentrated. Residual acetic acid and propionic acid were azeotropically removed using toluene (3 × 500 mL). This furnished the title acid (±)-**2** (1.64 kg, 6.75 mol, 84%) as a viscous oil which was used as such in the next step (resolution). Analytical data were in accordance with those given for (*R*)-**2** in the literature.[9c]

(2*R*)-3-(3-Bromophenyl)-2-methylpropanoic Acid (*R*)-1-Phenylethylammonium Salt (6). A 25 L reactor was charged with the crude racemic 3-(3-bromophenyl)-2-methylpropanoic acid [(±)-**2**] from the previous step (1.5 kg, 6.3 mol) followed by the addition of ethyl acetate (15 L). The mixture was heated to 60 °C. (*R*)-1-Phenylethanamine (0.5 kg, 4.1 mol) was added, and a rapid precipitation occurred. The mixture was heated to reflux, which furnished a homogeneous solution. The mantle temperature was then allowed to reach 20 °C over 120 min. Seeding crystals were added when the reaction temperature had reached 65 °C, which initiated a slow crystallization. After 1 h at 20 °C, the thick suspension was filtered, and the white salt collected was washed with EtOAc (3 × 1 L). Chiral HPLC analysis of the salt showed an enantiomeric excess of 64% for the acid. This salt was recrystallized from hot ethyl acetate (7 L) and 99.5% EtOH (3 L) using a temperature ramp from 80 to 20 °C over 10 h, a constant temperature of 20 °C for 3 h, and then filtration and washing with EtOAc (3 × 800 mL). This gave the acid with an enantiomeric excess of 92%. A second recrystallization was performed from hot EtOH/EtOAc (3 L/5 L) using a temperature ramp from 80 to 20 °C over 120 min followed by filtration of the salt and washing with EtOAc (3 × 500 mL). After drying under reduced pressure, the title salt **6** was obtained as a white solid (0.61 kg, 1.7 mol, 27%) with 97% ee (free acid) as determined by chiral HPLC analysis. ^{1}H NMR (400 MHz, CD_3OD): δ 1.08 (d, J = 6.6 Hz, 3H), 1.59 (d, J = 6.8 Hz, 3H), 2.49−2.58 (m, 2H), 2.92−3.00 (m, 1H), 4.38 (q, J = 6.8 Hz, 1H), 7.12−7.46 (m, 9H).

(2*R*)-3-(3-Bromophenyl)-2-methylpropanoic Acid [(*R*)-2] via the Resolved Salt 6. (2*R*)-3-(3-Bromophenyl)-2-methylpropanoic acid (*R*)-1-phenylethylammonium salt (**6**) (0.61 kg, 1.67 mol) was partitioned between MTBE (1 L) and 4 M HCl (0.5 L). The aqueous layer was extracted with MTBE (0.4 L), and the pooled organic layer was then washed with water (100 mL) followed by concentration. Residual water was azeotropically removed using MTBE (2 × 200 mL). This gave the title compound (*R*)-**2** as a colorless oil (407 g, 1.67 mol, 100%) with 97% ee and assay 100% (w/w). Analytical data were in accordance with those in the literature.[9c]

Methyl 2-((3-Bromophenyl)(hydroxy)methyl)acrylate (7). With the mantle temperature set at 25 °C, the reactor was charged with 3-bromobenzaldehyde (100 g, 0.54 mol) and methyl acrylate (140 g, 1.63 mol) followed by the addition of methanol (0.5 L). A solution of trimethylamine (25% in H_2O, 128 g, 0.54 mol) was added, and the mixture was allowed to stir at 25 °C for 5 days, after which almost full conversion had been obtained (checked by LC/MS). Most of the MeOH was removed under reduced pressure. MTBE (0.5 L) was added, and the pH was then adjusted to ∼3 using HCl solution. The layers were separated, and the organic layer was washed with water (0.2 L) and then concentrated under reduced pressure. Water was azeotropically removed with toluene (2 × 0.4 L) until the water content was <0.15% (w/w) as determined by Karl Fischer titration. The title compound **7** was obtained as a clear oil (144 g) and was used as such directly in the next step. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.74 (s, 3H), 5.52 (s, 1H), 5.84 (s, 1H), 6.36 (s, 1H), 7.18−7.24 (m, 1H), 7.30−7.32 (m, 1H), 7.40−7.43 (m, 1H), 7.53−7.55 (m, 1H).

(*E*)-3-(3-Bromophenyl)-2-methylacrylic Acid (8). To the crude methyl 2-((3-bromophenyl)(hydroxy)methyl)acrylate (**7**) from the previous step (144 g) were added THF (1 L) and I_2 (304 g, 1.2 mol). The resulting brown solution was cooled to 0 °C. $NaBH_4$ (40 g, 1.06 mol) was added in small portions over 1 h to maintain the reaction temperature below 20 °C. **Caution: exothermic reaction!** The mantle temperature was then set at 20 °C, and the white suspension was allowed to stir for 17 h. MeOH (180 mL) was slowly added over 1.5 h. The mixture was then concentrated. MeOH (360 mL) was added, and the mantle temperature was set at 0 °C. To the clear solution was added a 50% aqueous solution of sodium hydroxide (143 mL, 2.7 mol). When all had been added, the mixture was allowed to reach a temperature of 25 °C and was stirred for 1 h. The mixture was then concentrated to almost dryness. Toluene (500 mL) and water (500 mL) were added. The aqueous layer was acidified to pH 2 using 37% aqueous HCl (162 mL, 1.97 mol), and toluene (1 L) was added. The organic layer was concentrated, followed by the addition of ethanol (500 mL) and water (450 mL). The mantle temperature was set at 20 °C. Crystallization initiated, and more ethanol (450 mL) was added. The suspension was stirred at 20 °C for 16 h. The solids were filtered off and dried to afford the title compound **8** as a white solid (67.6 g, 0.28 mol,

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52% over two steps). Analytical data were in accordance with those in the literature.[9c]

Synthesis of 6 via Asymmetric Hydrogenation of 8. Under an atmosphere of nitrogen, to a solution of bis(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate (1.16 g, 2.9 mmol) in methanol (350 mL) was added a solution of (*R*)-1-[(*S*)-2-(di-*tert*-butylphosphino)ferrocen-1-yl]ethylbis(2-methylphenyl)phosphine (1.78 g, 3.2 mmol) in toluene (350 mL). To the resulting active catalyst mixture was added a solution of (*E*)-3-(3-bromophenyl)-2-methylacrylic acid (**8**) (71.1 g, 295 mmol) in methanol (700 mL). The dark-red mixture was hydrogenated under hydrogen (19 bar) for 48 h, after which full conversion had been obtained as determined by LC/MS with 90% ee as determined by chiral HPLC analysis of the crude mixture. The mixture was concentrated, and to the residual brown oil were added ethyl acetate (700 mL) and (*R*)-1-phenylethanamine (9.4 g, 78 mmol), after which crystallization initiated. The mantle temperature was set at 80 °C and more (*R*)-1-phenylethanamine (26 g, 217 mmol) was added. Ethanol (99.5%, 350 mL) was added at a process temperature of 72 °C, which resulted in a homogeneous solution. The mixture was then allowed to reach 20 °C over a period of 2 h. The suspension was filtered, and the salt collected was washed with EtOAc (2 × 200 mL). After drying under reduced pressure, the title salt **6** was obtained as a white solid (80.7 g, 220 mmol, 75%) with 97% ee (free acid) as determined by chiral HPLC analysis. The analytical data agreed with those given above for **6**.

4-Benzyl-2-chlorobenzonitrile (4). The reactor was charged with $Pd(Ph_3P)_4$ (38 g, 0.032 mol) and 4-bromo-2-chlorobenzonitrile (0.48 kg, 2.2 mol) followed by the addition of THF (1.2 L). At 20 °C, a solution of benzylzinc(II) bromide (0.5 M in THF, 4.8 L, 2.4 mol) was added within 15 min. A slightly exothermic reaction initated, and the reaction temperature was kept below 57 °C by adjusting the mantle temperature in the interval of 35 to 45 °C. After 2 h of stirring, full conversion of the starting material had been obtained, and the mixture was cooled to 15 °C. A 0.4 M aqueous solution of hydrochloric acid (1.5 L) was added, followed by the addition of brine (1.5 L). The organic layer was washed with brine (3 × 1.5 L), followed by concentration of the mixture. EtOAc (2 L) was added in order to precipitate the byproduct 3,3′-dichlorobiphenyl-4,4′-dicarbonitrile. The suspension was stirred over the weekend and then filtered. The filtrate was concentrated to give a crude impure mixture (>700 g) of **4**. This was further purified by chromatography (column kromasil-SIL, 250 mm × 100 mm) using 20−100% EtOAc in heptane as the eluent. Fractions were pooled and concentrated. To the residue was added methanol (3.5 L) followed by heating to 40 °C. The homogeneous solution was allowed to reach 20 °C, after which a suspension had been formed. Water (0.9 L) was added. The mixture was cooled at 0 °C for 2 h and filtered, and the solid was washed with a 50% aqueous solution of methanol (0.5 L). After drying under reduced pressure at 40 °C, the title compound **4** was obtained as a white solid (321 g, 1.4 mol, 64%) wth 99.4% purity as determined by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.02 (s, 2H), 7.15−7.37 (m, 7H), 7.58 (d, J = 7.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 41.6, 110.8, 116.0, 126.8, 127.7, 128.8, 128.9, 130.2, 133.8, 136.6, 138.5, 148.5.

(*R*)-2-Methyl-3-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoic Acid [(*R*)-3]. Under an atmosphere of nitrogen, a 10 L reactor was charged with potassium acetate (494 g, 5.04 mol), diboron pinacol ester (543 g, 2.14 mol), (*R*)-3-(3-bromophenyl)-2-methylpropanoic acid [(*R*)-**2**] (400 g, 1.64 mol), and 1,4-dioxane (4 L). To the white suspension was then added 1,1′-bis(di-*tert*-butylphosphino)-ferrocene palladium dichloride (10.5 g, 0.016 mol). The suspension immediately turned brown/orange. The mantle temperature was set at 70 °C, and stirring was performed for 17 h. LC/MS analysis of the crude mixture showed full conversion of the starting material. The mantle temperature was set at 20 °C, and the mixture of (*R*)-**3** (477 g) was then used as such in the next step. MS: m/z 289 $[M - H]^+$.

(*R*)-3-(5′-Benzyl-2′-cyanobiphenyl-3-yl)-2-methylpropanoic Acid [(*R*)-5]. To the crude mixture of (*R*)-2-methyl-3-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-propanoic acid [(*R*)-**3**] (477 g) in dioxane (4 L) was added a degassed solution of potassium carbonate (682 g, 4.93 mol) in water (680 mL) followed by the addition of a degassed suspension of 4-benzyl-2-chlorobenzonitrile (**4**) (376 g, 1.64 mol) in 1,4-dioxane (700 mL) and 1,1′-bis(di-*tert*-butylphosphino)ferrocene palladium dichloride (10.8 g, 0.016 mol). The reaction mixture was degassed and then heated to 90 °C for 48 h, after which approximately 50% conversion had been obtained. More 1,1′-bis(di-*tert*-butylphosphino)ferrocene palladium dichloride [10.8 g, 0.016 mol + 2 × (7 g, 0.0109 mol)] had to be added sequentially over the next 48 h to reach almost full conversion of the starting material. The reaction mixture was concentrated. With the mantle temperature set at 20 °C, toluene (5 L) was added, and to the resulting dark-brown solution was added a 3.8 M aqueous solution of HCl (3 L, 11.4 mol) over 10 min followed by the addition of water (1 L). The organic layer was washed with 4 L of 15% NaCl solution. The mantle temperature was then set at 10 °C, and the mixture was stirred for an additional 17 h. Undissolved precipitates were removed through filtration (25 μm filter), and water (2 L) was added to the filtrate. The organic layer was then concentrated to give the crude title compound (*R*)-**5** (584 g), which was directly used as such in the next step. MS: m/z 354 $[M - H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 (d, J = 6.8 Hz, 3H), 2.74−2.91 (m, 2H), 3.20 (dd, J = 6.0, 13.2 Hz, 1H), 4.11 (s, 2H), 7.22−7.45 (m, 11H), 7.70 (d, J = 8.0 Hz, 1H).

(2*R*)-3-(5′-Benzyl-2′-carbamoylbiphenyl-3-yl)-2-methylpropanoic Acid (AZD2716). To the crude (*R*)-3-(5′-benzyl-2′-cyanobiphenyl-3-yl)-2-methylpropanoic acid [(*R*)-**5**] from the previous step (584 g) was added 2-propanol (7.5 L) followed by 50% aqueous NaOH (657 g, 8.2 mol). The mantle temperature was set at 80 °C, and the mixture was stirred for 14 h, after which full conversion of the nitrile had been obtained. The mixture was concentrated to almost dryness (7.5 L was distilled off). To the residue were added water (6 L) and toluene (6 L). The organic layer was extracted with water (1 L). To the pooled aqueous layer was added 37% aqueous HCl (805 g, 8.17 mol) until a pH of 2.6 was obtained. Toluene (5 L) was added. The layers were separated, and the organic one was stirred at 20 °C for 1 h, after which crystallization initiated. The solid was filtered off through a sintered glass funnel (P3), washed with toluene (1 L), and then suspended in ethyl acetate (9.5 L). The mixture was heated to reflux, which resulted in a clear solution that was filtered through a sintered glass filter (P3). EtOAc (4 L) was distilled off under atmospheric pressure, after which crystallization initiated. The mixture was allowed to reach 20 °C over 120 min and was then stirred for an additional 16 h. The suspension was filtered, and the solid collected was dried under reduced pressure at 20 °C for 20 h to give 347 g

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(0.93 mol, 57% over three steps) of the title compound **AZD2716** with >98% ee (chiral HPLC), assay 100% (w/w), and 99.6% purity (HPLC). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.04 (d, J = 6.6 Hz, 3H), 2.55−2.68 (m, 2H), 2.95 (dd, J = 6.1, 12.8 Hz, 1H), 4.00 (s, 2H), 7.13−7.37 (m, 13H), 7.49−7.54 (m, 1H), 12.2 (s, br, 1H). ^{13}C NMR (151 MHz, DMSO): δ 16.7, 39.1, 40.7, 41.0, 126.3, 126.4, 127.3, 127.8, 128.0, 128.2, 128.7, 128.9, 129.2, 130.3, 135.3, 139.2, 139.5, 140.5, 141.2, 142.7, 171.3, 177.1. HRMS (ESI): $[M + H]^+$ m/z calcd for $C_{24}H_{24}NO_3$ 374.1751, found 374.1748.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.5b00382.

^{1}H NMR, ^{13}C NMR, HRMS, and HPLC analyses and extended screen of solvents and additives in the hydrogenation of **8** (PDF)

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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(11) The detailed experimental setup is described in the Experimental Section

(12) Details are given in the Supporting Information

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(14) CCDC 1437667 contains the supplementary crystallographic data for **AZD2716**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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