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Large-Scale Candoxatril Asymmetric Hydrogenation

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Abstract:

Ruthenium-catalyzed asymmetric hydrogenation was used to prepare tons of a key chiral succinate intermediate for clinical trials quantities of candoxatril. MeOBiphep was used as the ligand, and the catalyst was generated in situ from RuCOD-Bismethylallyl. THF was the best cosolvent for the reaction leading to a selective hydrogenation and a process which was readily amenable on large scale.

Introduction

Candoxatril is a cardiovascular drug (ANF potentiator) developed by Pfizer in the mid 1990s.[1] PPG-SIPSY was involved in the production of the quantities (2 metric tons) needed for phase III clinical trials. The candoxatril process involved a ruthenium-catalyzed asymmetric hydrogenation. Thanks to a continuous collaboration with Professor Genêt's laboratory, PPG-SIPSY had acquired the know-how to perform asymmetric hydrogenation on large scale.[2] MeO-Biphep[3] was used as the chiral ligand.

Extensive scientific background on ruthenium-catalyzed asymmetric hydrogenation is accessible in Professor Noyori's group,[4] Professor Genêt's group and Roche's catalysis group.

Overall Process

The chiral acid **4** is a key intermediate in the preparation of candoxatril and is obtained after a four-step synthesis[5] (Scheme 1). A modified Baylis−Hillman reaction afforded 2-substituted acrylate **1** starting from *tert*-butyl acrylate. The crude acrylate **1** was directly used in the next addition−elimination reaction which led to pure *trans*-vinyl sulfone **2** being isolated as an oil with a 65% yield over the two steps. Michael addition of di-lithiated cyclopentanecarboxylic acid to the vinyl sulfone was achieved after transmetalation with zinc chloride. The enolate intermediate rapidly collapsed to lead to the lithium salt of the corresponding olefin acid. Acidification followed by caustic treatment led to the sodium salt of the olefin acid **3** isolated as crystals. The first version of the process allowed us to run the three steps in 32% overall yield.

The fourth step consisted of an asymmetric hydrogenation which was followed by a recrystallization of the cyclohexylamine salt to improve the purity. The original Pfizer process using Binap as ligand and methanol as solvent produced the cyclohexyamine salt **4** in 35% yield and 99% enantiomeric excess after recrystallization.

Clearly, this process had to be improved so that it could be used to produce at least 2 metric tons for the phase III quantities. We were involved at this stage and decided to investigate separately the asymmetric hydrogenation and then the three early steps.

Our Work on Enantioselective Hydrogenation

A series of ligands had been previously tested by Pfizer, and the results have been published[6] after large quantities were produced. Despite a tendency to lead to the isomerisation by-product **5**, Binap was selected because it gave a very good enantiomeric excess when compared with other readily available ligands. To produce 2 metric tons rapidly, we needed to improve the process so that the required capacity and time to deliver would be acceptable. Access to a reasonably priced ligand which would be readily available on large scale (up to 10 kg) was a key issue. Patents were also a concern, and we needed to have the right to use the ligand and the catalyst in-house. As Sipsy was already involved in asymmetric technologies, we had a supply and licence agreement in place to use Roche's MeOBiphep ligand. Thus, our work was focused on using MeOBiphep and investigating the hydrogenation conditions to reduce formation of the cis enol ether **5**.

Catalyst and Pressure

Because Binap and MeOBiphep have somewhat similar atropisomeric structures, we expected similar behavior in the hydrogenation of intermediate **3**. Having the ligand in hand, we were looking for an appropriate way of using it. Thanks to our collaboration with Genêt, we were able to implement the in situ ruthenium catalytic hydrogenation[2] and compare the performance of the different catalysts relative to both the enantiomeric excess, and also to the level of the isomerisation by-product **5** (Table 1).

Under the above reaction conditions, all ruthenium catalysts showed similar behavior except for the reaction kinetics. The best catalysis was achieved with ruthenium diacetylacetonate and dibromide (in situ method) since this provided a good compromise between reaction rate and

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Scheme 1. **Candoxatril process**

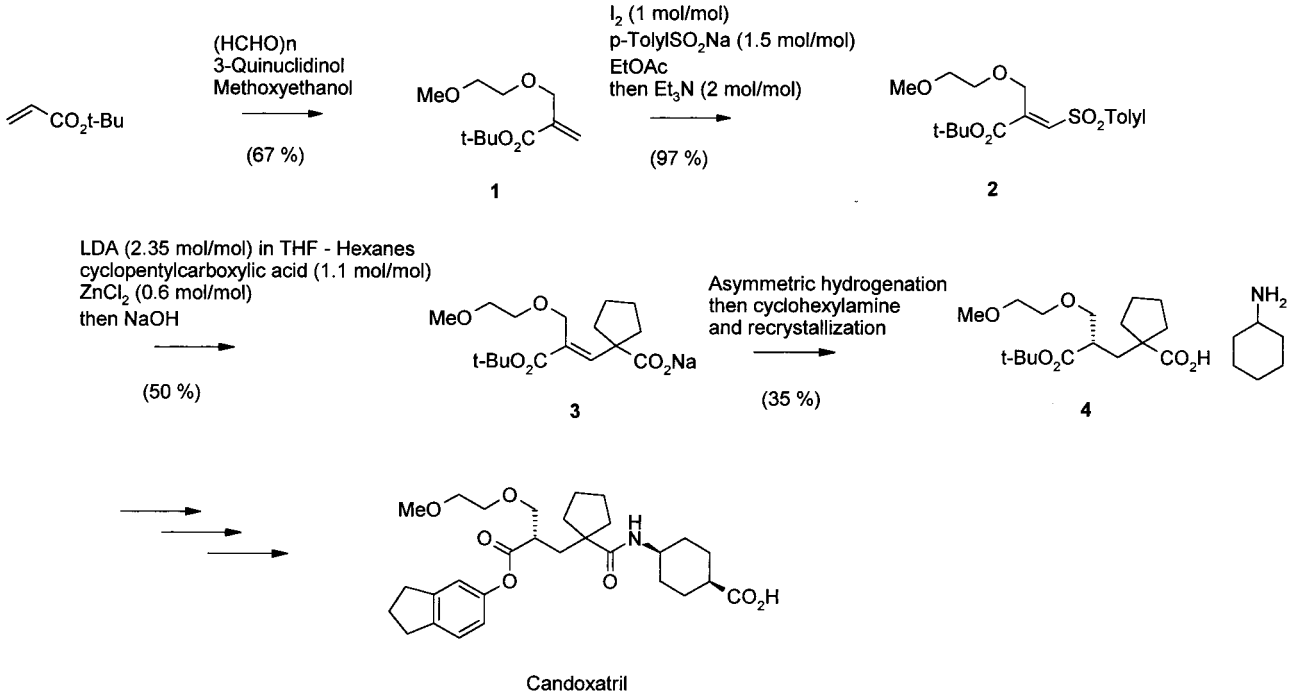


Table 1. **Catalyst screening**[a]

entry	catalyst	reaction time (h)	**4:5**[b]	yield (%)[c]	ee (%)[d]
1	((*R*)-BinapRuClp-Cymene)Cl	3	78:22	57	97
2	(*R*)-MeOBiphepRuCl$_2$−Et$_3$N	3	78:22	44	95
3	(*R*)-MeOBiphepRuAcac$_2$	2	77:23	59	94
4	(*R*)-MeOBiphepRuBismethallyl	7	79:21	49	91
5	(*R*)-MeOBiphepRuBr$_2$	2	78:22	53	97

[a] Conditions: 15 g scale, 0.1% mol of catalyst, 4 atm H_2 in methanol:water, 50 °C, 1−7 h. [b] Determined by HPLC on the crude mixture. [c] As cyclohexylammonium salt. [d] Enantiomeric excess measured by chiral HPLC.

enantiomeric excess. This result demonstrated the catalyst precursor's ability to generate the active species under mild conditions (50 °C, slightly acidic) and therefore to the concentration of active catalytic species in the reaction mixture. However, a very disappointing **4:5** ratio was obtained whatever catalyst was used.

Formation of **5** occurs during the hydrogenation reaction and is due to a competitive isomerisation (Scheme 2). Asymmetric hydrogenation of **5** is possible but requires higher pressures and leads to the opposite enantiomer so that lower enantiomeric excesses are obtained at higher pressure with ruthenium Binap catalysts in the same reaction conditions. When formed, by-product **5** had to be removed by recrystallization to ensure that intermediate **4** was obtained within specifications (less that 0.5% remaining **5**). Starting from a 25% level of **5** in the reaction mixture, one or two recrystallizations were necessary to meet the specifications. Considerable loss of yield resulted and from a 56% yield after the first crystallization, only 35% yield was finally obtained after purification. Reduction of the amount of **5** in the hydrogenation mixture was necessary to achieve an economic process on large scale (Table 2).

Solvent Choice

Ruthenium-catalyzed hydrogenations are generally run in alcoholic solvents and preferably methanol (protonation of the insertion intermediate appears to be the rate-determining step in many cases). In our case, the starting material solubility forced us to use water as cosolvent. We took into account that water is an acceptable source of protons for the catalytic cycle and that ruthenium intermediate **6** may require more coordination to prevent β-elimination. We were looking for a solvent with better coordinating properties than methanol. Ethers, ketones, and amides were selected as possible alternatives. A rapid solvent screen was executed (Table 3).

DMF was rejected because of the formation of numerous impurities and work-up difficulties. THF/water was selected as the best solvent system for this reaction, and **4** was obtained in 68% yield on small scale. It was also found that only one recrystallization was necessary to reach the specification level of less than 0.5% of by-product **5** in intermediate **4**.

Scale-Up and Manufacturing Issues

Having solved the catalyst and ligand access problem and improved the hydrogenation process, we faced several scale-up and manufacturing issues.

Production of 2 metric tons necessitated the preparation of 3.0 kg of CODRuBismethylallyl. No large-scale preparation had been reported, and the laboratory suppliers (Acros and Heraeus) were not able to supply quantities larger than a few tens of grams. Quality of CODRuBismethylallyl from lab suppliers was also questionable since use-tests of the different samples led to variable results. We realized that Professor Genêt's group had the best know-how to effectively prepare CODRuBismethylallyl. Synthesis of CODRuBismethylallyl consists of transforming ruthenium trichloride

Scheme 2. **Competitive formation of 4 and 5**

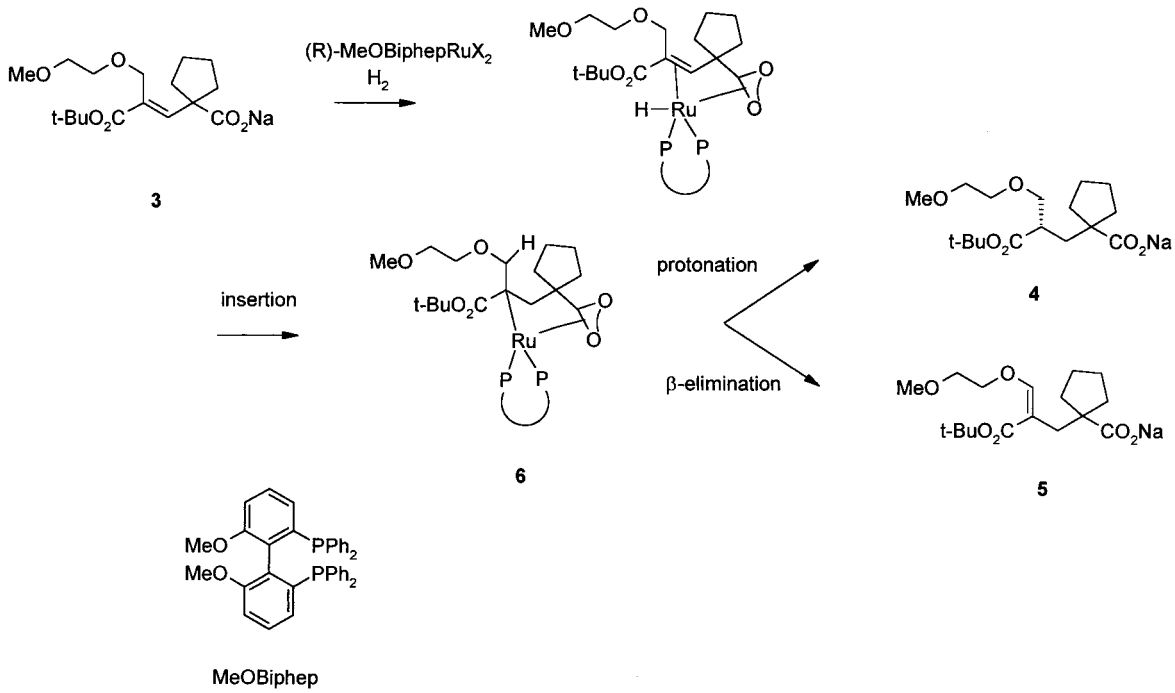


Table 2. **Pressure effect**[a]

entry	pressure (atm)	temperature (°C)	reaction time (h)	**4:5**[b]	yield (%)[c]	ee (%)[d]
1	4	50	3	78:22	57	99.4
2	10	50	1	85:15	59	91.7
3	10	20	10	92:8	66	85.3

[a] Conditions: 15 g scale, 0.1% mol ((*R*)-BinapRuClp-Cymene)Cl, methanol: water. [b] Determined by HPLC on the crude mixture. [c] As cyclohexylammonium salt. [d] Enantiomeric excess measured by chiral HPLC on the crude reaction mixture.

Table 3. **Solvent selection**[a]

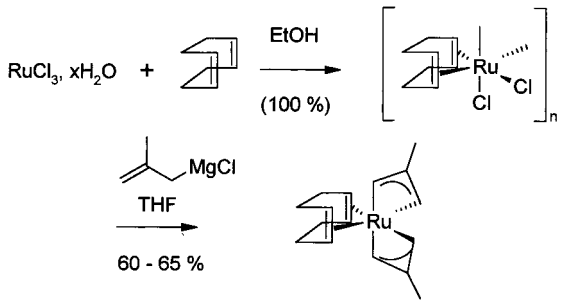
entry	solvent	solvent:water	**4:5**[b]	ee (%)[c]
1	methanol	6:2	78:22	97.4
2	acetone	6:2	87:13	97.6
3	acetone	5:5	62:38	98.4
4	dioxane	6:2	88:12	99.4
5	THF	6:2	92:8	98.1
6	DMF[d]	6:2	96:4	99.1
7	*N*-methypyrrolidone	6:2	No reaction	ND

[a] Conditions: 0.1% mol (*R*)-MeOBiphepRuBismethylallyl and (*R*)-MeOBiphep in acetone then HBr−MeOH, and then 15 g **3** in the solvent mixture as above specified, 4 atm H_2, 50 °C, 1−6 h. [b] Determined by HPLC on the crude mixture. [c] Enantiomeric excess measured by chiral HPLC on the crude reaction mixture. [d] Decarboxylation impurity and many other side-products present in the crude.

into ruthenium cyclooctadiene dichloride polymer and then preparing and adding methylallyl magnesium chloride[7] (Scheme 3).

Because Professor Genêt's laboratory was not equipped to process 3.0 kg of CODRuBismethylallyl, we choose to contract out this preparation at Arran Chemical Company (Ireland) where the process was scaled up. Batches up to 500 g were produced in 20 L reactors. Batches of CO-DRuBismethylallyl were of consistent quality and were checked by NMR and use-test before large-scale hydrogenation.

Scheme 3. **Preparation of bis-(2-methylallyl)cycloocta-1,5-diene ruthenium(II)**



The scale-up of the hydrogenation reaction was simpler than expected. As we wanted to secure the supply of at least 2 metric tons of **4**, we did not try to increase the S/C ratio yet, and we kept it to a conservative 1000 although very short reaction times (1 h to 1 h 40 min) were recorded during the 14-batch campaign. This indicated that less catalyst could be used, and a supportive experiment with S/C = 2000 was tested successfully at laboratory scale. Batch size was 231 kg, and the stainless steel hydrogenator had a capacity of 4000 L.

An initial crystallization yielded crude **4**, but a second recrystallization was necessary to meet the specifications (less than 0.5% of **5** in **4**). Enantiomeric excess was never an issue, and values systematically greater than 99% were obtained on crude **4** (Table 4).

Conclusions

Asymmetric hydrogenation using the in situ Genêt's method was successfully scaled up. Basic solvents tend to reduce the isomerisation by-product. We took advantage of

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Table 4. **Impurity profile on a large-scale hydrogenation**[a]

	4 (%)[b]	*cis*-**5** (%)[b]	*trans*-**5** (%)[b]	yield (%)[c]	ee (%)[d]
crude **4**	96.5	3.54	nd	83.8	99.4
purified **4**	99.6	0.4	nd	69.5	99.7

[a] Conditions: 231 kg scale, see Experimental Section. [b] w/w assay determined by HPLC (nd = not detectable). [c] Combined yield. [d] Enantiomeric excess measured by chiral HPLC.

the availability of MeOBiphep and the relatively low cost of ruthenium metal to design rapidly a cost-efficient process which allowed us to manufacture more than two metric tons of Candoxatril intermediate for phase III clinical trials.

Experimental Section

General Procedure. All solvents and chemicals were technical grades available on PPG-SIPSY's site. In our hands, no oxygen sensitivity was recorded on large scale. CODRuBismethylallyl must be stored at less than 0 °C under nitrogen as it decomposes with oxygen. HPLC impurity profile and weight by weight assay was performed using a Hypercarb column (100 × 4.6 mm) with 5 μm particle size. Conditions employed were as follows: mobile phase, 50% water + 0.5 mL/L H_3PO_4 and 50% acetonitrile; flow rate, 1.0 mL/min; detection, UV 210 nm, temperature, 20 °C. Typical relative retention times for **3**, *cis*-**5**, *trans*-**5**, and **4** respectively 0.59, 0.83, 0.92, and 1. Chiral HPLC was performed using a Chiralpack AD (250 × 4.6 mm). Conditions were as follows: mobile phase, 5% hexane and 95% 2-propanol and 0.1% TFA; flow rate, 1.0 mL/min; detection, UV220 nm; temperature: 20 °C. Typical relative retention times for **(S)-4** and **(R)-4** were 1 and 1.19, respectively.

Hydrogenation of Sodium Salt 3. A solution of sodium salt **3** (231 kg, 660 mol) in purified water (500 L) and THF (600 L) was prepared in a stainless steel tank, degassed, and kept under nitrogen. The tank was connected to the hydrogenator.

(a) Catalyst Preparation. In a 4000 L stainless steel hydrogenator was charged acetone (580 L), and the reactor was degassed with nitrogen. CODRuBismethylallyl (0.217 kg, 0.680 mol) and (*R*)-(6,6′-dimethoxybiphenyl-2,2-diyl)-bis(diphenylphosphine) ((*R*)-MeOBiphep) (0.397 kg, 0.681 mol) were introduced in the reactor which was degassed again with nitrogen. Hydrobromic acid (3 L, 120 mL of 62% aqueous solution HBr in 3 L of methanol) was then added, and the mixture was stirred for 30 min at 20 °C.

(b) Hydrogenation. The previously prepared solution of sodium salt **3** in THF/water was introduced to the hydrogenator, and then nitrogen was replaced by hydrogen (4 atm pressure), and the reaction mixture was heated to 53 °C. The reaction was monitored by hydrogen consumption and by HPLC. The reaction was complete after 1 h 40.

(c) Workup and Purification. The reaction mixture was cooled to 27 °C, and hydrogen was replaced by nitrogen. The solution was transferred to a glass-lined reactor and combined with three identical hydrogenation batches and concentrated in vacuo. Isopropyl acetate (^{i}PrOAc) (3150 L) was added and then hydrochloric acid (175 kg, 36% aqueous solution) until the pH reached 2.9. The solution was washed with brine (180 kg of sodium chloride in 1200 L water) to neutrality. The solution was dried by distillation of ^{i}PrOAc which was replaced with fresh and dry ^{i}PrOAc. Cyclohexylamine (187 kg, 1885 mol) was then added at 30 °C. The crystals were filtered, rinsed with ^{i}PrOAc (2520 L), and then dried in vacuo. Crude **4** was obtained: 712 kg (83.8%), identical to a reference sample (HLPC assay see Table 4). Crude **4** was recrystallized from ^{i}PrOAc (1390 L). Pure **4** is obtained: 591 kg (69.5% combined yield) (HPLC see Table 4).

Acknowledgment

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