Me-DuPHOS-Rh-Catalyzed Asymmetric Synthesis of the Pivotal Glutarate Intermediate for Candoxatril

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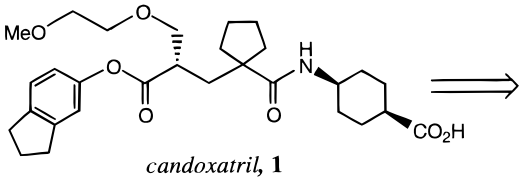
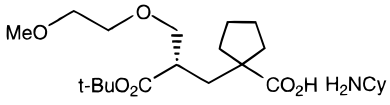
A greatly improved process has been developed for synthesis of the glutarate derivative **2**, a key intermediate required for Pfizer's drug candoxatril. The cationic (*R*,*R*)-Me-DuPHOS-Rh catalyst was found to allow highly efficient and enantioselective hydrogenation of a unique carboxylate substrate (**5**) to afford the desired product in >99% ee and high yield (95%). The robust nature of the process was validated on a 12 kg reaction scale. A novel mechanism for the hydrogenation process is proposed. Through use of a labile η^6-benzene-Rh-Me-DuPHOS complex, the postulated catalytic intermediates have been synthesized by independent means. Detailed spectroscopic analyses of these intermediates corroborate the mechanistic hypotheses. Interconversion of these key catalytic intermediates has been demonstrated.

Introduction

Candoxatril **1** is the orally active prodrug of candoxatrilat, a potent atrial natriuretic factor (ANF) potentiator useful in the treatment of hypertension and congestive heart failure.[1] Candoxatril contains a single stereogenic center, and like many chiral drugs, only one enantiomer of the drug displays the desired activity. The essential intermediate required for the synthesis of candoxatril is (*S*)-cyclopentaneglutarate salt **2**.[2]



candoxatril, **1**



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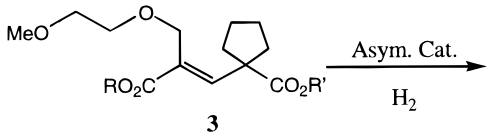
Various syntheses of enantiomerically pure **2** have been identified, including classical resolution of the racemate using (1*S*,2*S*)-(+)-pseudoephedrine.[3] The inherent inefficiency of resolution processes, however, led to a search for alternative methods that would allow practical manufacture of this important building block. Asymmetric catalytic hydrogenation of a suitable prochiral precursor such as **3** was divined as a plausible route to **2** via **4**.[4] Although olefinic substrates typified by **3** were unique, and their utility in asymmetric catalytic hydrogenation reactions was unexplored, the potential advantages of this approach inspired further inquiry. Moreover, it was envisaged that success in this singular case could provide incentive for development of a general method for prepartion of valuable 2-alkylglutarate derivatives.



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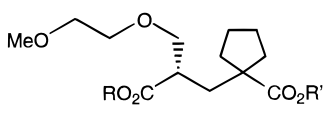

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Herein, we disclose a full account of studies that led to the development of a highly effective catalyst for enantioselective hydrogenation of olefinic precursor **5**. The optimized process utilizes the cationic (*R*,*R*)-Me-DuPHOS-Rh catalyst system,[5] which operates with high catalytic efficiency (S/C = 3500) and directly affords the reduction product **6** with very high enantioselectivity (>99% ee). Importantly and in contrast to other catalyst systems, no isomerization of the starting substrate **5** occurs with the Me-DuPHOS-Rh catalyst, thus allowing the desired intermediate **2** to be isolated in very high yield (>90%). Rhodium complexes containing both substrate (**5**) and product (**6**) have been prepared and spectroscopically characterized. These complexes are postulated to be key intermediates in the catalytic cycle

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(1) James, K.; Alabaster, C. T.; Barclay, P. L.; Barnish, I. T.; Blackburn, K. J.; Brown, D.; Campbell, S. F.; Cussans, N. J.; Danilewicz, J. C.; Palmer, M. J.; Terrett, N. K.; Samuels, G. M. R.; Wythes, M. J. *Perspect. Med. Chem.* **1993**, Chapter 4, pp 45−60.

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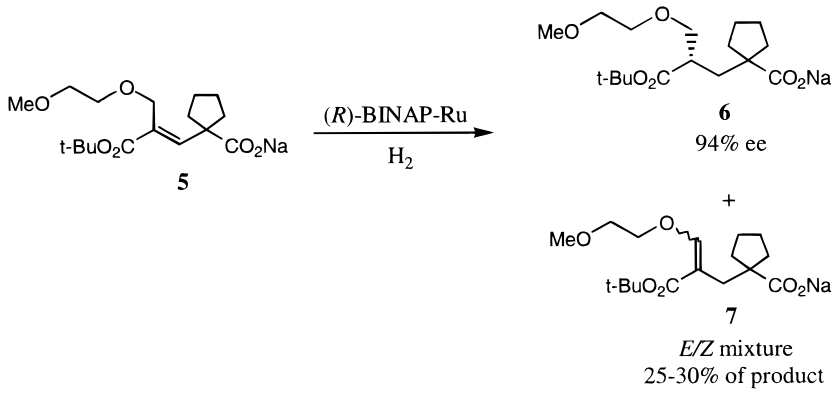
Scheme 1 . Asymmetric Hydrogenation of Carboxylate Salt 5 with Ru-BINAP Catalyst



and suggest a unique mechanistic pathway for this process. Details of these studies are expounded below.

Results and Discussion

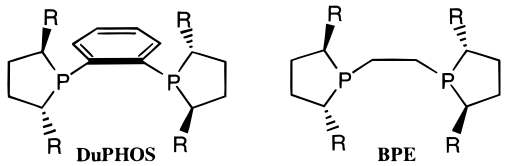
1. Catalyst Screening. Preliminary studies focused upon a general screen of commercially available chiral ligands and catalysts that might allow enantioselective hydrogenation of substrates of type **3**. An initial survey of catalysts, substrates, and conditions was conducted and revealed that the most appropriate substrates, in terms of hydrogenation rates, were the monocarboxylate salts of **3** and that the highest enantioselectivities were provided by a Ru catalyst containing the BINAP ligand.[6,7] One inceptive process that was considered for further development involved asymmetric catalytic hydrogenation of sodium carboxylate **5** (or the analogous cyclohexylammonium salt) using a catalyst precursor such as [(*p*-cymene)Ru((*R*)-BINAP)Cl_2] (S/C = 1000), which furnished the reduced product (i.e., **6**) in up to 94% enantiomeric excess (Scheme 1).

Unfortunately, in addition to hydrogenation, approximately 25−30% of the substrate **5** was isomerized during the reaction to an *E*/*Z* mixture of enol ethers **7**, which were unreactive under the hydrogenation conditions employed. Although the isomerized byproducts could be removed subsequently through a series of recrystallizations, substantial losses were incurred and the overall yield of the requisite material **2** was limited to 60−65%.[7]

The additional steps required to reprocess the BINAP-Ru-catalyzed hydrogenation product mixture and the resulting low overall yields of the essential compound **2** rendered this procedure ineffectual for production. Accordingly, an improved catalyst was sought. Previous work indicated that the sodium carboxylate substrate **5** would be most suitable for the present studies, which were aimed at development of a viable process for manufacturing.

We previously have found that cationic rhodium catalysts containing the DuPHOS and BPE ligands are uniquely capable of hydrogenating a diverse range of prochiral olefinic substrates with high reactivity and superior enantioselectivity.[5,8]

An important feature of the DuPHOS and BPE ligand systems is the ease with which the steric nature of the ligands may be altered systematically through variation of the R groups on the phospholane moieties. Moreover, since the ligand chirality is present within the phospholane rings, the influence of ligand backbone conformation may be examined through modification of the tethering unit between the two phosphorus atoms. Such a modular ligand design has provided an effective means for optimization of both rates and enantioselectivities in numerous catalytic reactions.[8]



Since substrates typified by **3** had not been examined previously in asymmetric catalytic hydrogenations using the DuPHOS/BPE-Rh catalysts, it was impossible to predict which DuPHOS or BPE ligand would provide paramount results in the case at hand. Our primary objective was to examine cationic Rh catalysts for the hydrogenation of **5** and to assess which DuPHOS or BPE ligand may be best suited for further optimization.

As noted above, substrate **5** has been found to isomerize readily to the stable enol ethers **7** under conditions that employ Ru-BINAP-type catalysts. This ineluctable isomerization activity, in fact, is the singular reason that the Ru-BINAP-catalyzed process is unavailing for the manufacture of candoxatril intermediate **2**. In previous investigations, we have found that cationic DuPHOS-Rh catalysts are rather ineffectual for olefin isomerization reactions, which constituted a possible advantage in the present case.

A series of cationic DuPHOS-Rh and BPE-Rh catalysts were screened for efficacy in the hydrogenation of carboxylate substrate **5**. These experiments were performed under a standard set of reaction conditions that were tailored to monitor enantioselectivity and isomerization activity. High catalyst loadings (1 mol %) were employed

(6) BINAP = 2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl. For a recent review covering industrial applications of BINAP-metal catalysts, see: Kumobayashi, H. *Recl. Trav. Chim. Pay-Bas* **1996**, *115*, 201.

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Table 1. Rhodium-Catalyzed Asymmetric Hydrogenation of 5[a]

entry	catalyst	ee[b] (%)	confgn	**6**:**7**[c]
1	[((*S*,*S*)-Me-BPE)Rh(COD)]BF_4	80	*R*	100:0
2	[((*S*,*S*)-Et-BPE)Rh(COD)]BF_4	97	*R*	100:0
3	[((*R*,*R*)-*i*-Pr−BPE)Rh(COD)]BF_4	92	*R*	100:0
4	[((*R*,*R*)-Me-DuPHOS)Rh(COD)]BF_4	>99	*S*	100:0
5	[((*S*,*S*)-Et-DuPHOS)Rh(COD)]BF_4	98	*R*	100:0
6	[(*R*)-BINAP(*p*-cymene)RuCl]Cl[d]	94	*S*	75:25
7	[((*S*)-BINAP)$_2$RuHCl][d]	82	*R*	92:8
8	[((*S*)-BINAP)Rh(COD)]Cl[d,e]	78	*S*	100:0
9	[((*S*,*S*)-BPPM)Rh(COD)]Cl[d,e]	22	*S*	100:0
10	[((+)-DIOP)Rh(COD)]Cl[d,e]	24	*R*	
11	[((*R*)-PROPHOS)Rh(COD)]Cl[d,e]	8	*S*	100:0

[a] Conditions: S/C = 100:1; 20 °C; 20 atm H_2; *c* = 0.2 M (MeOH); 3 h; scale, 1 mmol. [b] Enantioselectivities were determined by chiral HPLC as described in the Experimental Section. [c] Ratio of **6**:**7** was determined by comparison with ^{1}H NMR spectra of authentic samples. [d] Hydrogenation of substrate as cyclohexylammonium salt. See ref 7 for details. [e] Catalyst prepared in situ by addition of diphosphine to [(COD)RhCl]$_2$. See ref 7 for further details.

initially to ensure complete conversion to products. The results of the catalyst screening studies are shown in Table 1.

Substrate **5** is structurally similar to β,β-disubstituted enamides, which we have shown are most proficiently hydrogenated through use of the Me-BPE-Rh catalysts.[8a] Hence, we began by surveying a series of three sterically different BPE-Rh catalysts (Table 1, entries 1−3). As can be seen, smooth hydrogenation of **5** to **6** was observed in all cases over 3 h under 20 atm hydrogen pressure. No isomerized products **7** were detected in the product mixtures (analysis by ^{1}H NMR and HPLC, see Experimental Section). While the Me-BPE-Rh catalyst afforded the product **6** with modest enantioselectivity (80% ee), significantly higher selectivity was achieved with the Et-BPE-Rh catalyst (97% ee). The level of absolute stereocontrol diminished upon progressing to the more sterically demanding *i*-Pr-BPE ligand. We next progressed to the more conformationally rigid DuPHOS ligands and found that rhodium catalysts bearing these diphosphines appeared to be preferred (Table 1, entries 4 and 5). For example, the Et-DuPHOS-Rh catalyst provided **6** with 98% ee and no isomerization. The Me-DuPHOS-Rh catalyst was found to be paramount for this process, furnishing **6** with exceedingly high enantioselectivity (>99% ee, minor enantiomer was not detected) and high apparent rates, again with no isomerized substrate **7** observed.

Table 1 includes the results achieved in the initial catalyst screening studies for comparison.[7] As previously noted, the [(*R*)-BINAP(*p*-cymene)RuCl]Cl catalyst affords the desired product **6** in 94% ee, but with 25% isomerized products. A series of Rh catalysts bearing a range of known phosphines such as BINAP, BPPM, DIOP, and PROPHOS were examined and found inferior (Table 1, entries 8−11).[4]

As can be seen from the data in Table 1, the (*R*,*R*)-Me-DuPHOS-Rh catalyst afforded the product **6** with the desired *S* absolute configuration. Note that (*R*,*R*)-*i*-Pr-BPE-Rh provided (*R*)-**6**. This ostensible inconsistency arises from the change of Cahn−Ingold−Prelog designation associated with moving from a phospholane possessing 2,5-methyl groups to one bearing 2,5-*i*-Pr substituents. The two ligands actually possess an opposite sense of stereogenicity, despite the identical *R* descriptor.

Table 2. Pressure Effects in the Asymmetric Hydrogenation of 5[a]

entry	pressure (atm)	time[b] (min)	ee[c] (%)
1	5	60	>99
2	20	10	>99
3	40	10	>99

[a] Conditions: catalyst precursor = [((*R*,*R*)-Me-DuPHOS)Rh(COD)]BF_4; S/C = 2500; 20 °C; *c* = 0.6 M (MeOH); scale, 4 mmol. [b] Time allowed for complete conversion of **5**. [c] Enantioselectivities were determined by chiral HPLC as described in the Experimental Section.

For comparative purposes, we briefly have examined the effectiveness of neutral Rh catalysts generated in situ through the addition of Me-DuPHOS to the dimeric precursor [(COD)RhCl]$_2$. Thus, at S/C = 2000 and 20 atm hydrogen, only 94% conversion to **6** was observed over 1 h. Under identical conditions, complete conversion was observed within minutes when using the cationic Me-DuPHOS-Rh catalyst (vide infra). An increase in neutral catalyst loading (S/C = 100) allowed complete conversion to **6** over 2 h at 4 atm hydrogen. In both instances, the product **6** was obtained with enantioselectivities identical to those achieved with the cationic catalyst (>99% ee), and no isomerization to **7** was detected. These results suggest that the reaction is likely proceeding through the same catalytic intermediate, presumably a rhodium adduct bound through the carboxylate function of the substrate (vide infra), but that chloride may effectively compete with the carboxylate group of **5** as a ligand for the metal. Such competition presumably attenuates catalytic rates when the neutral complexes are employed, but once the substrate-catalyst intermediate is formed, tantamount enantioselectivities are achieved.

2. Reaction Parameters. The catalyst screening study outlined in the section above revealed [((*R*,*R*)-Me-DuPHOS)Rh(COD)]BF_4 as the most auspicious catalyst precursor for asymmetric catalytic hydrogenation of substrate **5**. Considering these results, as well as our established process for large-scale manufacture of the Me-DuPHOS ligand,[9] we viewed the (*R*,*R*)-Me-DuPHOS-Rh catalyst system as a suitable candidate for further process development. We next engaged in a program aimed at preliminary assessment of several reaction parameters associated with the Me-DuPHOS-Rh-catalyzed process.

2.1. Pressure Effects. In gas-consuming reactions, higher pressures generally provide higher concentrations of the dissolved gaseous reagent, and therefore, higher reaction rates are usually observed. In addition to its influence upon rates, hydrogen pressure also may have a substantial effect upon enantioselectivities achieved in asymmetric hydrogenation reactions, and many examples can be cited.[10] Thus, it was vital to examine the influence that hydrogen pressure may have upon both rates and enantioselectivity in the Me-DuPHOS-Rh-catalyzed hydrogenation of **5**. From the standpoint of process flexibility, hydrogenation reactions that perform effectively under the lowest possible pressures are desired.

Table 2 shows results obtained in the hydrogenation of **5** under different hydrogen pressures using the (*R*,*R*)-Me-DuPHOS-Rh catalyst at a S/C ratio of 2500/1. All hydrogenation reactions here and thoughout the remain-

(9) Burk, M. J. *Chemtracts: Org. Chem.* **1998**, *11*, 787.
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der of the manuscript were performed with 0.6 M solutions (0.2 g/mL) of the sodium carboxylate salt **5** in methanol; this concentration approaches that of a saturated solution of substrate.

Extent of reaction was estimated simply by monitoring hydrogen uptake. Subsequently, conversions were ascertained by NMR and HPLC analyses. As can be seen, the reaction rate was profoundly influenced by pressure; the reaction proceeded five to six times faster at 20 atm compared to 5 atm. Importantly, pressure was observed to exert no obvious influence upon enantioselectivity.

2.2. Temperature Effects. Temperature is an important parameter in any process, as it can greatly influence both reaction rates and selectivities. In asymmetric transformations, the corresponding enantioselectivity is a critical parameter that can be strongly dependent upon the reaction temperature. Evidence from previous studies suggested that the substrate **5** decomposes significantly (perhaps through decarboxylation) at temperatures exceeding 50 °C.[11] Hence, studies of temperature effects on the hydrogenation process were restricted, yet some information was gleaned. By performing the Me-DuPHOS-Rh-catalyzed hydrogenation of substrate **5** under 5 atm H_2 at S/C = 3500, complete conversion to **6** transpired within 30 min at 45 °C, while approximately 60 min were required at 18 °C. No loss of enantioselectivity (>99% ee) was observed over this temperature range. Thus, within certain constraints, temperature appears to be a feasible parameter to manipulate in order to increase reaction rates without compromising other factors.

2.3. Substrate-to-Catalyst Ratio. Due to the high cost of many asymmetric catalysts, the economic disposition of a manufacturing process can be greatly influenced by the substrate-to-catalyst (S/C) ratio. Optimization studies aim to define a catalytic system that performs the desired transformation and operates within process constraints at the highest possible rate and the highest possible S/C ratio. Importantly, however, a robust and reliable method is much more valuable than a capricious procedure. As the S/C ratio increases, catalytic processes often display lower stability and greater sensitivity to catalyst deactivation. Reaction rates necessarily will decrease in accord with increases in S/C ratio. A delicate balance between hydrogen pressure, temperature, and S/C ratio generally is required to provide the most economically attractive process.

The substrate-to-catalyst ratio (S/C) was first increased from 100:1 to 2500:1, and the reaction extent was monitored cursorily by hydrogen uptake (5 atm H_2). Under the selected conditions, the reaction was determined complete after 1 h, and the product **6** was isolated in greater than 90% yield with an enantiomeric excess of >99% (entry 1,Table 3).

On the basis of these encouraging results, the S/C ratio was gradually increased to 10000:1. The results of these preliminary studies are summarized in Table 3.

At S/C ratio of 3500:1, the reaction also was finished within 1 h (Table 3, entry 2). A reaction conducted with a S/C ratio of 5000:1 at 4 atm proceeded to 80% completion within 16 h (Table 3, entry 3). A further reduction of catalyst loading to a S/C ratio of 10000:1 diminished

Table 3. Effect of S/C Ratio on Rates of Conversion[a]

entry	S/C	pressure (atm)	time (h)	conversion (%)
1	2500:1	5	1	100
2	3500:1	5	1	100
3	5000:1	4	16	80
4	10000:1	4	20	60
5	10000:1	20	20	93

[a] Conditions: catalyst precursor = [((*R*,*R*)-Me-DuPHOS)Rh-(COD)]BF_4; 20 °C; *c* = 0.6 M (MeOH); scale, 4 mmol.

conversion of **5** to 60% over 20 h (Table 3, entry 4). The latter reaction proceeded to completion after the secondary addition of an equivalent amount of catalyst (i.e., total S/C = 5000). The turnover frequency of this reaction was quite high (approximately 4000 h^{-1}). Conducting the process at S/C = 10000 and 20 atm hydrogen led to an increase in rate as expected, and significantly higher conversion to product (93%) was observed over 20 h (Table 3, entry 5). In all cases, product **6** was obtained in >99% ee and no isomerization product **7** was detected.

From the above studies involving the Me-DuPHOS-Rh catalyst, it can be surmised that further optimization would allow very high S/C ratios (e.g., S/C > 10000) to be employed in this system. It is important to note that substrate purity can greatly influence the attainable S/C ratio. It is probable that greater attention to this detail, particularly with regard to which impurities may be limiting catalyst efficiency, could allow much higher S/C ratios to be realized in this reaction. Notwithstanding the importance of high S/C ratios in relation to overall production economics, the value of a robust and dependable process should not be underestimated. The assurance of consistently high conversion, and therefore simple recovery of pure product, likely will become a prominent factor once the S/C ratio has exceeded a certain level.

2.4. Substrates and Additives. The above studies were performed with the carboxylate salt **5**, and the results suggest that a critical feature of the catalysis is binding of the carboxylate moiety of **5** to the rhodium center of the catalyst. Consistent with this hypothesis, we have found that neither the methyl ester nor the corresponding free acid analogues of **5** appear to be suitable substrates in this reaction. Furthermore, in situ generated acid (by addition of 1.0 equiv of trifluoroacetic acid to **5**) gave <5% hydrogenation over 1.5 h under the standard conditions outlined above (S/C = 3500/1). Interestingly, addition of 0.8 equiv of triethylamine to the same mixture allowed complete conversion to product **6** within 2 h. Relative to the sodium salt **5**, the corresponding cyclohexylammonium salt of **5** was found to be less reactive and, therefore, was not further considered as a viable hydrogenation substrate. Finally, neither the sodium nor cyclohexylammonium salts of the isomerized enol ethers **7** were found to be hydrogenated by the cationic Me-DuPHOS-Rh catalyst.

Additives often may have a large influence on the overall activity and selectivities of a catalyst system.[4,12] In the present study, from the logical point of view, additives such as acid (in order to facilitate liberation of product from the rhodium catalyst) or alkylammonium salts (which may allow cation exchange with the sodium carboxylate and potentially enhance the nucleophilicity

(11) Decarboxylation of **5** occurs readily at temperatures >50 °C and is very dependent upon solvent. In DMSO, for example, decarboxylation occurs at room temperature.

(12) For examples of the effect of additives in many different catalytic processes, see the treatise: *Applied Homogeneous Catalysis with Organometallic Compounds*, Cornils, B., Herrmann, W. A., Eds.; VCH Publishers: Weinheim, 1996.

Table 4. Asymmetric Hydrogenation of Carboxylate Salt 5 with [(Me-DuPHOS)Rh(COD)]BF_4: Influence of Additives at S/C = 10000/1[a]

entry	additives	*p* (atm)	convn (%)	time (h)
1	none	20	93	20
2	AcOH (0.5 equiv)	20	33	16
3	Et_4NBF_4 (0.1 equiv)	4	7	7
4	AcOH (0.7 equiv), NEt_3 (0.5 equiv)	20	31	60

[a] Conditions: catalyst precursor = [((*R*,*R*)-Me-DuPHOS)Rh-(COD)]BF_4; 23 °C; *c* = 0.6 M (MeOH); scale, 4 mmol.

of the carboxylate) could have a positive influence on this system. In an effort to develop an improved process at high S/C ratios, we briefly examined the influence that certain additives had upon the Me-DuPHOS-Rh-catalyzed hydrogenation of **5** at S/C = 10000/1. At such high S/C ratios, any changes in the reaction profile would be more easily deciphered. The results of these studies are shown in Table 4.

Addition of 0.5 equiv of acetic acid reduced the conversion to 33%, from 93% without any additive (Table 4, entries 1 and 2). Addition of 0.1 equiv of tetraethylammonium tetrafluoroborate as "cation exchange catalyst" slowed the reaction remarkably (Table 4, entry 3). A combination of both acetic acid in slight excess and triethylamine, to form an ammonium salt and have slightly acid conditions, produced a severe depreciation of rate and conversion (Table 4, entry 4).

Summarily, on the basis of the above studies, it appears that the additive-free cationic Me-DuPHOS-Rh catalyst system was the ideal candidate for further development.

2.5. Process Validation. An efficacious procedure for the highly enantioselective hydrogenation of prochiral olefin **5** using the (*R*,*R*)-Me-DuPHOS-Rh catalyst system was identified. Additionally, we obtained valuable information in our laboratory-scale experiments concerning the potential utility of this method for large-scale production of the desired intermediate **2**. While catalytic hydrogenation reactions typically are well-behaved processes that are readily amenable to scale-up, converting a laboratory procedure into a manufacturing process can never be assumed and can present formidable challenges. The studies described thus far were limited to relatively small-scale reactions (1.4 g of substrate). Therefore, our next objective was to demonstrate the process on larger scales.

We first endeavored to demonstrate the process on a 1 kg scale in a 7 L vessel equipped with a gas flow meter. This would allow us to gain information concerning the reaction enthalpy, as well as more accurate rate data. To further examine catalyst tolerance, we employed lower quality methanol obtained directly from a 200 L drum. After the vessel was charged with **5** (1 kg) and methanol, the solution was degassed to remove oxygen (see below and Experimental Section for more details on degassing). The catalyst was then added as a degassed methanol solution at S/C = 3100, and the vessel was pressurized to 30 psi hydrogen. Rapid reaction commenced, and initial hydrogen uptake was determined to be ca. 3.3 L/min. Despite constant cooling (internal cooling coil) with water of 22.5 °C, the temperature rose from 23 to 28 °C within 15 min. Sampling the reaction mixture after 1.5 h revealed 86% conversion of **5**. Sampling after 6 h revealed complete conversion to the desired product **6** in >99% ee. Hydrogen consumption was essentially complete after 3 h reaction time. Standard reaction workup involving acidification and extraction with dichloromethane followed by treatment with cyclohexylamine afforded the requisite intermediate **2** in >95% yield.

Further validation of the present process was carried out in the pilot plant using 12.2 kg of substrate **5** in a 200 L pressure vessel. The substrate employed in this experiment had already been found suitable on a 250 g scale. Due to the equipment configuration, one major process operation was varied. Rather than adding the catalyst solution through an integrated charging chamber as in the 1 kg experiment above, the catalyst solution simply was added directly through the charging aperture of the reactor under a positive flow of nitrogen.

Our observations in the 1 kg run indicated that the reaction was already very fast at low hydrogen pressure. Hence, after addition of (*R*,*R*)-Me-DuPHOS-Rh catalyst (S/C = 3500) to a hydrogen presaturated solution of substrate **5**, the vessel was sealed and pressurized to 30 psi H_2. Hydrogen uptake began immediately and continued over 2 h, after which uptake waned. Sampling the reaction mixture after a total reaction time of 3 h revealed >95% conversion to the expected product **6**. The reaction was terminated after 5 h and processed through the standard workup protocol, which ultimately afforded product **2** as above.

3. Mechanistic Considerations. The results outlined above strongly imply that coordination of the basic carboxylate function of substrate **5** to the Rh center of the Me-DuPHOS-Rh catalyst may be an important event in the catalytic cycle. In contrast to the high rates and high enantioselectivities achieved in hydrogenation of the carboxylate substrate **5**, poor results were obtained with both the corresponding free acid and ester substrates. Moreover, identical enantioselectivities were observed with the neutral and cationic catalysts, albeit at different rates. This indicates that both reactions may be proceeding through a common intermediate.

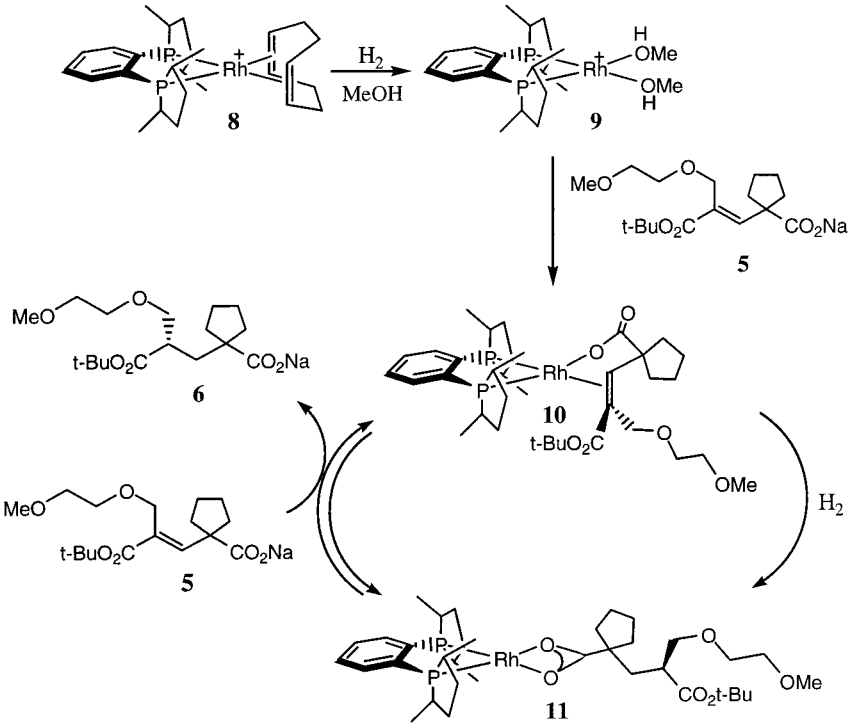
3.1. Mechanistic Proposal. On the basis of these data, as well as other information, we can propose a plausible mechanism for the Me-DuPHOS-Rh-catalyzed hydrogenation of substrate **5** (Scheme 2). We previously have shown that addition of hydrogen to the catalyst precursors $[(COD)Rh(DuPHOS)]^+X^-$ in coordinating solvents promotes reduction of the 1,5-cyclooctadiene (COD) group to cyclooctane and generates a solvated form of the catalytic species.[8f,14] For example, hydrogenation of the (*R*,*R*)-Me-DuPHOS-Rh catalyst precursor **8** in MeOH characteristically affords the bis(methanol) adduct **9** (^{31}P NMR: δ 102 ppm, J_{PRh} = 204 Hz), which is believed to serve as the general catalyst resting state in hydrogenation reactions.[13,14]

In the case at hand, reaction between **9** and the carboxylate substrate **5** may be expected to furnish a chelating intermediate such as **10**, whereby the carboxylate and olefin functionalities are both coordinated to the rhodium center. Substantial evidence supports the notion

(13) Armstrong, S. K.; Brown, J. M.; Burk, M. J. *Tetrahedron Lett.* **1993**, *34*, 879.

(14) (a) Halpern, J. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, Chapter 2. (b) Landis, C. R.; Halpern, J. *J. Am. Chem. Soc.* **1987**, *109*, 1746. (c) Nagel, U.; Rieger, B. *Organometallics* **1989**, *8*, 1534. (d) Brown, J. M.; Chaloner, P. A. *J. Chem. Soc., Chem. Commun.* **1980**, 344. (e) Brown, J. M.; Murrer, B. A. *J. Chem. Soc., Perkin Trans. 2* **1982**, 489. (f) Chan, A. S. C.; Pluth, J. J.; Halpern, J. *J. Am. Chem. Soc.* **1980**, *102*, 5952.

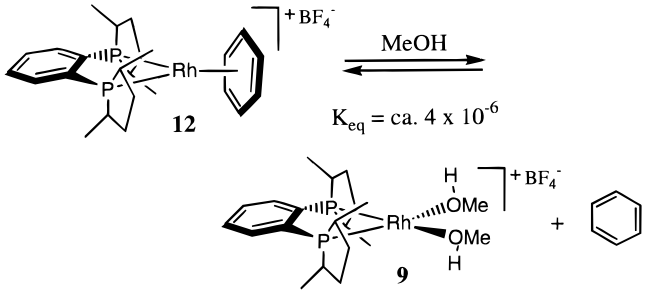
Scheme 2. Proposed Mechanism for Enantioselective Hydrogenation of 5 by (*R,R*)-Me-DuPHOS-Rh Catalyst (Note that BF_4^- Counterion Has Been Omitted for Clarity)



that secondary coordination of a substrate to the metal center of a catalyst is beneficial and may be responsible for the attainment of both high rates and high selectivities in catalysis.[4,13,14] Coordination of the *pro-R* face of the olefin moiety of **5** is indicated since transfer of hydrogen to this face is required to provide the observed product **6** with *S* absolute configuration. Analogous chelate complexes have been identified as intermediates in enamide hydrogenation reactions.[8f,13,14] Carboxylate−olefin chelates previously have been postulated as intermediates in enantioselective hydrogenation reactions, although little definitive spectroscopic data have been reported to date.[4,15]

Addition of hydrogen to intermediate **10** is anticipated to promote reduction of the olefinic group bound to Rh. Although details of the reduction steps are not known and are not depicted in Scheme 2, this process is expected to entail the typical sequence involving (i) oxidative addition of hydrogen to generate a dihydridorhodium intermediate, (ii) olefin insertion into a transient Rh−H bond to produce a Rh-alkyl species, and (iii) subsequent C−H reductive elimination to release the product.[16] However, given the propensity of carboxylate groups to chelate to transition metal centers,[17] it is tenable in the present case to postulate that the product **6** is not released from the metal immediately, but rather the stable η^2-carboxylate complex **11** forms as an intermediate in the catalytic cycle. Subsequent exchange between the carboxylate ligand of **11** and substrate **5** could then liberate the product **6** and regenerate the requisite intermediate **10** to complete the nexus of events that are necessary for enantioselective hydrogenation of **5**. Importantly, this mechanism suggests that the same intermediate **10** can be accessed either through the cationic catalyst as shown or via the neutral chloride-containing Rh catalysts through chloride displacement by carboxylate **5**.

3.2. Benzene Adduct 12. In an effort to corroborate these mechanistic postulates, we have endeavored to obtain spectroscopic evidence for the putative intermediates. To conduct these studies we employed the benzene adduct **12** (^{31}P NMR δ 100.5 ppm, $J_{PRh} = 202$ Hz; ^{1}H NMR δ 6.7 ppm; ^{13}C NMR δ 100.6, coordinated benzene), formed by hydrogenation of catalyst precursor **8** in benzene.[8f] In methanol, the benzene complex **12** reacts rapidly to form an equilibrium mixture with the intermediate bis(methanol) adduct **9**, as evinced by the



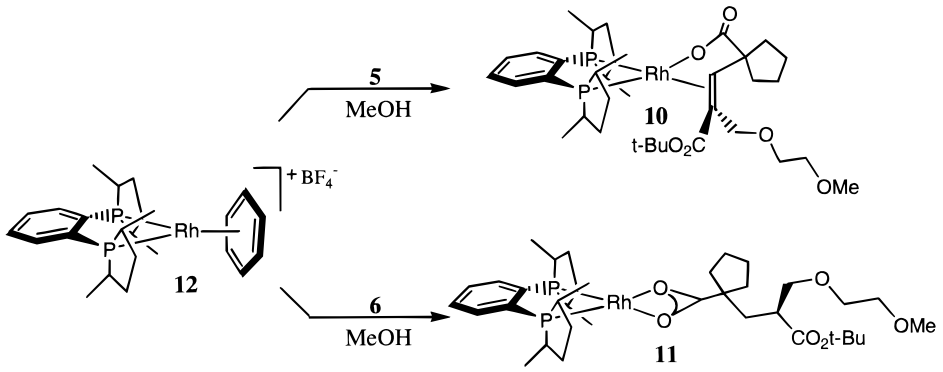
appearance of free benzene resonances in the ^{1}H NMR (δ 7.36 ppm) and ^{13}C NMR spectra (δ 129.3 ppm), and also by characteristic resonances for **9** in the ^{31}P NMR spectrum (δ 102 ppm, $J_{PRh} = 204$ Hz).[8f,13] The equilibrium

(15) (a) Christopfel, W. C.; Vineyard, B. D. *J. Am. Chem. Soc.* **1979**, *101*, 4406. (b) Ojima, I.; Kogure, T.; Yoda, N. *J. Org. Chem.* **1980**, *45*, 4728. (c) Takahashi, H.; Yamamoto, N.; Takeda, H.; Achiwa, K. *Chem. Lett.* **1989**, 559. (d) Kawano, H.; Ikariya, T.; Ishii, Y.; Saburi, M.; Yoshikawa, S.; Uchida, Y.; Kumobayashi, H. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1571.

(16) For a review of homogeneous catalytic hydrogenation mechanisms, see Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987; Chapter 10.

(17) (a) Mehrotra, R. C.; Bohra, R. *Metal Carboxylates*; Academic Press: New York, 1983. (b) Cotton, F. A.; Wilkinson, G. *Advanced Inorganic Chemistry*, 5th ed.; Wiley: New York, 1988.

Scheme 3. Independent Synthesis of Intermediates 10 and 11



mixture of **12** and **9** is established rapidly (within minutes) as approximately a 3:1 mixture *favoring* the benzene complex **12** (K_{eq} = ca. 4×10^{-6}) and does not vary over 18 h. Addition of benzene (10 molar equiv) to the mixture of **12** and **9** immediately shifts the equilibrium completely to the benzene complex **12** (^{31}P resonances for **9** not detected). For mechanistic studies, the benzene complex **12** serves as a very convenient source of the reactive intermediate bis(methanol) complex **9** without the complications often encountered through hydrogenation of catalyst precursors such as **8**.[8f,13]

3.3. Reaction Intermediates. We have independently synthesized a complex that may be assigned the structure of intermediate **10** through treatment of the benzene adduct **12** with carboxylate substrate **5** (Scheme 3). Rapid reaction transpired between the pale yellow complex **12** and **5** in methanol-d_4 to form a blood-red solution, and only a single new complex was observed by NMR spectroscopy. The newly formed compound displayed two new ^{31}P NMR signals at δ 84.8 (J_{PRh} = 164 Hz) and δ 83.5 (J_{PP} = 35.1 Hz, J_{PRh} = 170 Hz) consistent with two inequivalent phosphorus atoms situated trans to oxygen and olefinic ligands, respectively.[8f,13−15] Moreover, the ^{13}C NMR spectrum displayed two new olefinic resonances (δ 104.8 and 89.9 ppm) shifted far upfield from the corresponding resonances in the free substrate **5** (δ 169.2 and 131.6 ppm) due to coordination to the Rh center. In addition, the ^{13}C NMR resonance corresponding to the *t*-Bu ester carbonyl group shifted from δ 169.2 ppm in the substrate (α,β-unsaturated ester) to δ 175.8 ppm in the adduct **10**, as would would be expected from loss of conjugation due to coordination of the olefinic group to Rh (for comparison, see also resonances for saturated species **6** and **11** in Table 5).[16] Finally, IR spectroscopy in CD_3OD revealed further evidence advocating the suggested coordination mode for the substrate ligand in complex **10**.[18]

The fact that only a single complex (**10**) was detected by NMR suggests that high enantiofacial selectivity occurred in the binding of olefinic substrate **5** to the chiral Rh fragment. The specific diastereomer of **10** produced in this reaction has not yet been ascertained. Confirmation likely will rely upon crystallographic characterization of **10**, although attempts to obtain X-ray quality crystals thus far have been unsuccessful. In the present case, we assume that the face of **5** coordinated to Rh is the *pro-R* face to which hydrogen is transferred to afford the product (*S*)-**6**. However, the possibility remains, as in enamide hydrogenations, that transformation to the isolated hydrogenation product **6** proceeds through an inscrutable intermediate that is in rapid equilibrium with the major catalytic intermediate observed in solution.[14]

Table 5. Selected Spectroscopic Data for 5, 6, and Complexes 10−12[a]

compd	^{31}P data (δ)	^{13}C data (δ)	IR data, ν (cm^{-1})
5		155.7 (C=C)	1567 (CO_2^-)
		131.6 (C=C)	1691 (*t*-BuO_2C)
		183.2 (CO_2^-)	
		169.2 (*t*-BuO_2C)	
6		185.6 (CO_2^-)	1554 (CO_2^-)
		177.1 (*t*-BuO_2C)	1707 (*t*-BuO_2C)
10	84.8 (J_{PRh} = 164 Hz)	104.8 (C=C)	1578 (CO_2^-)
	83.5 (J_{PP} = 35.1 Hz,	89.9 (C=C)	1698 (*t*-BuO_2C)
	J_{PRh} = 170 Hz)	188.5 (CO_2^-)	
		175.8 (*t*-BuO_2C)	
11	101.2 (J_{PRh} = 196 Hz)	188 (br, CO_2^-)	
		176.6 (*t*-BuO_2C)	
12	100.5 (J_{PRh} = 202 Hz)	100.6 (η^6-C_6H_6)	

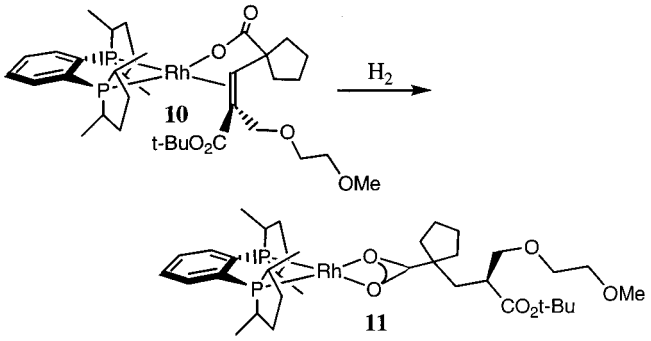
[a] All data were collected in CD_3OD at ambient temperature (20 °C). See the Experimental Section and Supporting Information for additional details.

In a similar fashion, we have independently prepared what we postulated as the initial product formed upon olefin hydrogenation, the η^2-carboxylate complex **11** containing reduced product, through reaction between the benzene adduct **12** and the prereduced material (*S*)-**6** in methanol (Scheme 3). This adduct displays a somewhat broadened ^{31}P doublet at δ 101.2 ppm (J_{PRh} = 196 Hz) and a broadened ^{13}C resonance at 188 ppm (η^2-carboxylate carbonyl), consistent with the structure assigned to **11** (see Table 5). Additional evidence underpinning the structure of **11** was obtained by formation of the analogous η^2-acetate complex through reaction between benzene adduct **12** and ^{13}C-labeled sodium acetate. This complex displayed a very similar ^{31}P doublet at δ 101.8 ppm (J_{PRh} = 201 Hz) and a somewhat broadened carbonyl ^{13}C resonance centered at δ 181 ppm (peak position confirmed by ^{13}C-label). Directly analogous bis(phosphine)Rh(η^2-acetate) complexes previously have been reported and display similar spectroscopic data.[19]

3.4. Interconversion of Intermediates. In further support of our mechanistic proposal, we have found that bubbling hydrogen through a preformed CD_3OD solution of **10** for 5 min promotes smooth transformation to the η^2-carboxylate adduct **11** as the only species detected in solution.

(18) Deacon, G. B.; Phillips, R. J. *Coord. Chem. Rev.* **1980**, *33*, 227.

(19) (a) Darensbourg, D. J.; Grötsch, G.; Wiegreffe, P.; Rheingold, A. L. *Inorg. Chem.* **1987**, *26*, 3827. (b) Werner, H.; Schäfer, M.; Nürnberg, O.; Wolf, J. *Chem. Ber.* **1994**, *127*, 27. (c) Kukla, F.; Werner, H. *Inorg. Chim. Acta* **1995**, *235*, 253.



The carboxylate complex **11** appears relatively stable under an atmosphere of hydrogen, and no products of hydrogen oxidative addition were detected spectroscopically. One interesting manifestation of this stability is that complex **11** does not release the reduced product **6** in the absence of a secondary carboxylate source that can displace **6** from the metal. Hence, treatment of the preformed carboxylate adduct **11** with 1 equiv of substrate **5** leads rapidly to an equilibrium mixture of **11** and the substrate complex **10**, with concomitant displacement of reduced product **6** (equilibrium position slightly favors of complex **10**; K_{eq} = ca. 1.2). Facile formation of the crucial intermediate **10** thus completes the catalytic cycle. These observations again are consistent with the mechanism proposed in Scheme 2 and also are concordant with the high hydrogenation rates that we observe for this process.

4. Summary and Conclusions

We have discovered and developed a vastly improved process for production of the glutarate derivative **2**, a key intermediate required for synthesis of Pfizer's drug candoxatril. The cationic (*R*,*R*)-Me-DuPHOS-Rh catalyst was found to be efficient (S/C = 3500, initial TOF = 6000 h^{-1}) for highly enantioselective hydrogenation of the unique carboxylate substrate **5** (>99% ee). Importantly, unlike many other catalysts, no isomerization of the starting olefin **5** was observed in this process. As a corollary to the high chemical purity of the crude hydrogenation product **6**, the desired intermediate **2** could be obtained in very high yields (>95%) using this new hydrogenation procedure. The robust nature of this practical process was revealed through successful pilot plant validation on 12 kg reaction scale.

Finally, a novel mechanism for the hydrogenation process has been proposed. Independent synthesis of the postulated intermediates **10** and **11** permitted the collection of detailed spectroscopic data that corroborate the hypothesis. These studies suggested highly diastereoselective formation of intermediate complex **10** upon chelation of substrate **5** to the Rh metal center through its carboxylate and olefin groups. Addition of hydrogen then promotes reduction of the olefinic functionality and affords the η^2-carboxylate complex **11** as a catalytic intermediate. In the absence of added substrate, this complex appears to be stable under the conditions. In the presence of substrate **5**, displacement of product **6** occurs to reform the requisite intermediate **10** and complete the catalytic cycle.

The mechanism and data presented above are rather specific and involve the unusual substrate **5**. However, the concepts put forth herein are likely to apply generally to many hydrogenation processes involving carboxylate substrates. It is conjectured that stable η^2-carboxylate intermediates (e.g., **11**) that form after hydrogenation of a pendant alkene may be rather common in these types of reactions (e.g., hydrogenation of itaconates). The notion that these η^2-carboxylate intermediates require displacement by additional carboxylate substrate in order to perpetuate the catalysis is also unique and is currently under investigation.

Experimental Section

General Procedures. All reactions and manipulations were performed using standard nitrogen-line or Schlenk-line techniques. Solvents were used as supplied and degassed by sparging with nitrogen or argon as described below. Chiral DuPHOS and BPE ligands and catalysts were prepared as previously described.[8,9] Hydrogen gas (99.999%) used for reactions up to 1 kg of substrate was purchased from Air Products and used as received directly from the cylinder. Hydrogen gas (99.99%) used for the 12 kg pilot plant procedure was purchased from BOC and also used as received. All other reagents were purchased from commercial suppliers and used as received. The substrate **5** was prepared at Pfizer as previously described.[7a]

HPLC separations were performed using an achiral Prodigy ODS(3) column (150 mm × 3.2 mm) with 5 μm particle size. Conditions employed were as follows: mobile phase, 70% H_2O (acidified to pH 2.5 with phosphoric acid) and 30% acetonitrile; flow rate, 1.0 mL/min; injection volume, 20 μL; detection, UV 210 nm. Typical retention times for **5** and **6** were 28.41 and 29.10 min, respectively. This method was employed to determine extent of conversion of **5** to **6** and also the extent of isomerization of olefin **5** to the enol ethers **7**. Chiral HPLC separations were accomplished using a Daicel Chiralpak AD column (250 mm × 4.6 mm) with 10 μm particle size. This method was employed to establish enantiomeric excesses in hydrogenation experiments and also provided further definitive data regarding extent of isomerization of substrate **5** to enol ethers **7**. The conditions employed were as follows: mobile phase, 97% heptane/3% ethanol; flow rate, 1.0 mL/min; injection volume, 20 μL; detection, UV 210 nm. This analysis was performed after acidic neutralization of the hydrogenation product mixture. Typical retention times for the acid form of **6** were as follows: *S* enantiomer, t_1= 9.1 min; *R* enantiomer, t_2 = 10.9 min.

Catalyst Oxygen Sensitivity. The orange-red crystalline complex [((*R*,*R*)-Me-DuPHOS)Rh(COD)]BF_4 was prepared as previously described.[5] This material is relatively stable to brief exposure to the atmosphere, thus allowing the catalyst to be weighed in air prior to being added to the reaction vessel. In solution, however, the catalyst is sensitive to atmospheric oxygen. Overall, oxygen appears to be the primary source for catalyst deactivation in this hydrogenation system, and the active catalyst reacts ostensibly in a stoichiometric fashion with O_2 to afford a catalytically inactive species. Reasonable care must be taken to degas solvents appropriately and to conduct these hydrogenation reactions under anaerobic conditions.

At high S/C ratios, the activity and longevity of the catalyst may be sensitive to parameters such as method/time of solvent deoxygenation and the method of adding catalyst to the vessel. Many procedures seem to be suitable. An effective procedure for degassing methanol that was employed in most of these studies simply involved bubbling nitrogen through the methanol solution (via pipet or gas dispersion tube) for 2 h under stirring at room temperature, prior to the addition of catalyst. For the pilot plant operation (12 kg substrate **5**), oxygen was satisfactorily removed by pressurizing the reactor with 20 atm nitrogen and agitating at 125 rpm for 10 min. This procedure was repeated four times.

Hydrogenation of Carboxylate Salt 5. A 50 mL Parr pressure vessel was charged with 1.4 g (4 mmol) of **5** and

purged carefully with nitrogen (five vacuum/nitrogen venting cycles). Methanol (6 mL, degassed as above) was added, and the reactor then was pressurized and vented four times with 5 atm hydrogen under stirring. After the pressure was released, a freshly prepared solution of 0.7 mg (0.12 μmol in MeOH) of [((*R,R*)-Me-DuPHOS)Rh(COD)]BF_4 was added as quickly as possible via syringe through an addition port. The vessel was sealed and pressurized with 75 psi hydrogen, and the mixture was allowed to stir at 18 °C for 80 min. After this time the hydrogen uptake was judged to have ceased. The reactor pressure then was released, the solution was transferred to a round-bottom flask, and the solvent was evaporated under reduced pressure. The residue was treated with 20 mL of 1 M aqueous hydrochloric acid, and the product was extracted into dichloromethane (3 × 10 mL). The combined organic layers were dried over sodium sulfate and filtered, the filter cake was washed three times with 5 mL of dichloromethane, and the solvent was evaporated under reduced pressure. The crude product (free carboxylic acid of **6**) was obtained as a pale yellow oil: yield 1.28 g (97%). The material thus obtained was subjected directly to full analytical characterization: $[\alpha]_D = +3.42°$, $[\alpha]_{365} = +13.21°$ (CH_3OH, 25 °C, l = 99.98 mm, c = 13.1 mg/mL); ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 9H), 1.45−1.57 (m, 2H), 1.65−1.68 (m, 4H), 1.80 (dd, 1H), 1.99 (dd, 1H), 2.09−2.16 (m, 2H), 2.57−2.66 (m, 1H), 3.36 (s, 3H), 3.40−3.61 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 24.54, 24.90, 27.93, 35.10, 36.61, 37.38, 44.56, 53.46, 58.91, 70.16, 71.81, 73.30, 80.56, 173.98, 183.41. Anal. Calcd for $C_{17}H_{30}O_6$: C, 61.80; H, 9.15. Found: C, 61.47; H, 9.30.

HPLC analysis was performed as outlined above and indicated that complete conversion of **5** to **6** had taken place and that no isomerization to enol ethers **7** had occurred. This assessment was corroborated by the NMR data listed above. Chiral HPLC indicated that the product **6** was formed in >99% ee (minor enantiomer could not be detected). Assignment of absolute configuration derived from comparison of HPLC elution order with that of an authentic sample of the acid form of configurationally defined (*S*)-**6** (provided by Pfizer). This indicated that the (*R,R*)-Me-DuPHOS-Rh catalyst provided the reduced product **6** with the desired (*S*)-absolute configuration.

Candoxatril substrate 5 (sodium salt): ^{1}H NMR (CD_3OD, 400.1 MHz) δ 1.50 (s, 9H), 1.70−1.58 (m, 6H), 2.38 (m, 2H), 3.36 (s, 3H), 3.54 (m, 2H), 3.62 (m, 2H), 4.28 (s, 2H), 7.05 (s, 1H); ^{13}C NMR (CD_3OD, 50.3 MHz) δ 183.2, 169.2, 155.7, 131.6, 81.9, 72.9, 70.9, 66.8, 59.3, 58.7, 40.6, 28.6, 24.5; ν_{max} (CD_3OD) 1691 (t-BuO_2C), 1567 (CO_2^-) cm^{-1}.

Hydrogenation Product 6 (Sodium Salt). The sodium salt **6** is the immediate product formed upon hydrogenation of substrate **5**. Isolation of **6** simply involved evaporation (in vacuo) of methanol solvent from a hydrogenation reaction, as described above, omitting the usual acidic workup: ^{1}H NMR (CD_3OD, 400.1 MHz) δ 3.68−3.44 (m, 5H), 3.47−3.38 (m, 1H), 3.36 (s, 3H), 2.65 (m, 1H), 2.16 (m, 1H), 2.04 (m, 1H), 1.85 (m, 2H), 1.60 (m, 3H), 1.51−1.30 (m, 3H) 1.46 (s, 9H); ^{13}C NMR (CD_3OD, 50.3 MHz) δ 185.6, 177.1, 81.6, 74.5, 72.8, 71.1, 59.3, 57.0, 46.6, 39.4, 38.5, 36.0, 28.5, 25.8; ν_{max} (CD_3OD) 1707 (t-BuO_2C), 1554 (CO_2^-) cm^{-1}.

[((*R,R*)-Me-DuPHOS)Rh(CD_3OD)$_2$]BF_4 (9). The bis(methanol) solvate **9** may be generated through hydrogenation of [(COD)Rh((*R,R*)-Me-DuPHOS)]BF_4 in methanol as described in refs 8f and 13. This species appears to be unstable in the absence of methanol and cannot be isolated. Hence, **9** (CD_3OD adduct) generally is formed in situ as a CD_3OD solution for NMR studies. Alternatively, equilibrium quantities of **9** may be generated through simple dissolution of **12** in CD_3OD, as described herein. The adduct **9** has the following ^{31}P spectral characteristics: ^{31}P NMR (CD_3OD, 162.0 MHz) δ 102.5 (d, J_{RhP} = 204.4 Hz); ^{31}P NMR (CD_3OD, 121.4 MHz) δ 99.2 (d, J_{RhP} = 204.4 Hz).

Substrate Adduct [((*R,R*)-Me-DuPHOS)Rh(5)] (10). The benzene adduct **12** (57 mg, 0.101 mmol) and substrate **5** (35 mg, 0.101 mmol) were placed in a small Schlenk tube under an atmosphere of argon. To the tube was added CD_3OD (1.0 mL, 99.8 atom %D) and the mixture placed in a warm (30−35 °C) water bath. Upon stirring for 15−20 min, the initial yellow heterogeneous mixture was converted to a blood-red homogeneous solution. Analytical studies were conducted on the solution thus obtained: ^{1}H NMR (CD_3OD, 400.1 MHz) δ 7.80 (m, 2H), 7.62 (m, 2H), 6.11 (br, 1H), 4.26 (m, 1H), 3.95 (m, 1H), 3.61 (m, 2H), 3.53 (m, 2H), 3.35 (s, 3H), 2.72 (m, 2H), 2.60−2.20 (m, 8H), 1.95−1.67 (m, 6H), 1.60−1.40 (m, 4H), 1.54 (s, 9H), 1.90−0.88 (m, 6H), 0.81 (m, 3H), 0.70 (m, 3H); ^{31}P NMR (CD_3OD, 162.0 MHz) δ 83.0 (dd, J_{PP} = 35.4 Hz, J_{RhP} = 172.7 Hz), 84.0 (dd, J_{RhP} = 158.8 Hz); ^{31}P NMR (CD_3OD, 121.4 MHz) δ 79.5 (dd, J_{PP} = 35.1 Hz, J_{RhP} = 172.3 Hz), 80.8 (dd, J_{RhP} = 156.2 Hz); ^{13}C NMR (CD_3OD, 50.3 MHz) δ 188.5, 175.8, 139 (br), 134−131 (m, br), 104.8 (br), 89.9, 82.9, 72.9, 71.0, 69.2, 59.9, 59.1, 44.2 (d, J = 22.6 Hz), 42.2 (br), 40.3, 37.8, 37.2, 36.5, 28.9, 26.7, 17.8, 14.0; ν_{max} (CD_3OD, cm^{-1}) 1698 (t-BuO_2C), 1578 (CO_2^-).

Carboxylate Adduct [((*R,R*)-Me-DuPHOS)Rh(6)] (11). In a fashion similar to that described above, the benzene adduct **12** (57 mg, 0.101 mmol) and carboxylate product **6** (35 mg, 0.101 mmol) were placed in a small Schlenk tube under an atmosphere of argon. To the tube was added CD_3OD (1.0 mL, 99.8 atom % D), and the mixture placed in a warm (30−35 °C) water bath. Upon stirring for 15−20 min, the initial yellow heterogeneous mixture was converted to a dark red homogeneous solution. Analytical studies were conducted on the solution thus obtained: ^{1}H NMR (CD_3OD, 400.1 MHz) δ 7.63 (m, 2H), 7.50 (m, 2H), 3.68−3.43 (m, 5H), 3.40−3.27 (m, 1H), 3.33 (s, 3H), 2.78 (m, 1H), 2,70 (m, 1H), 2.60 (m, 1H), 2.47 (m, 2H), 2.24 (m,4H), 2.20 (m,1H), 2.07 (m, 1H), 1.90−1.80 (m, 18H), 1.47 (s, 9H), 0.81 (m, 6H); ^{31}P NMR (CD_3OD, 162.0 MHz) δ 101.3 (d, J = 195.5 Hz); ^{31}P NMR (CD_3OD, 121.4 MHz) δ 98.1 (d, J = 198.0 Hz); ^{13}C NMR (CD_3OD, 50.3 MHz) δ 188 (v br), 176.6, 146.7 (dd, J = 33, 38 Hz), 131.9 (m), 131.0, 81.5, 74.4, 72.7, 71.1, 59.1, 57.0, 46.2, 39.4, 39.1 (d, J = 34.9 Hz), 38.5, 38.4 (d, J = 33.9 Hz), 37.1, 37.0, 35.7, 28.3, 25.8, 25.3, 19.1, 14.2.

[((*R,R*)-Me-DuPHOS)Rh(η^6-C_6H_6)]BF_4 (12). A Schlenk tube was charged with crystalline [((*R,R*)-Me-DuPHOS)Rh(COD)]BF_4 (2.15 g, 3.56 mmol), and a nitrogen atmosphere was established. The complex was dissolved in degassed dichloromethane (15 mL), and then benzene (2 mL, ~22.5 mmol) was added. The solution was transferred via syringe to a Parr pressure vessel that had already been purged with hydrogen. The Schlenk tube was rinsed with a further portion of dichloromethane (5 mL), which was also transferred to the pressure vessel. The vessel then was placed under hydrogen pressure (100 psi), and the reaction was allowed to stir at room temperature for 2 h. The solution was transferred via syringe to a Schlenk tube. Heptane (15 mL) was slowly added with rapid stirring to precipitate the product. The product was filtered under nitrogen and dried in vacuo to afford the benzene adduct **12** as a bright yellow powder (1.62 g, 79%): ^{1}H NMR (CD_2Cl_2, 200.1 MHz) δ 7.58 (m, 4H), 6.72 (s, 6H), 2.62−2.13 (m, 8H), 1.84−1.41 (m, 4H), 1.32−1.23 (m, 6H), 0.87−0.72 (m, 6H); ^{31}P NMR (CD_3OD, 162.0 MHz) δ 100.9 (d, J_{RhP} = 201.7 Hz; ^{31}P NMR (CD_3OD, 121.4 MHz) δ 97.6 (d, J_{RhP} = 201.5 Hz); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ 142.9 (d, J = 40 Hz), 131.5, 131.2 (d, J = 9.2 Hz), 100.6, 47.7 (d, J = 14.5 Hz), 47.4 (d, J = 14.6 Hz), 40.2 (d, J = 14.5 Hz), 39.9 (d, J = 14.8 Hz), 36.6, 36.0, 18.9, 13.5. Anal. Calcd for $C_{24}H_{34}P_2RhBF_4$: C, 50.20; H, 5.97. Found: C, 49.55; H, 5.96.

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Supporting Information Available: ^{13}C NMR and ^{31}P NMR spectra for compounds **5** and **6** as well as complexes **9**−**12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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