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Origins of Enantioselectivity in Reductions of Ketones on Cinchona Alkaloid Modified Platinum

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Abstract: A model to explain the stereoselectivities of reductions of activated ketones on cinchona alkaloid modified platinum is proposed and is supported by calculations by density functional and force field methods. The model involves nucleophilic catalysis by the cinchona alkaloid. The zwitterionic adduct between a cinchona alkaloid and ketone is adsorbed on Pt through the quinoline ring and two heteroatoms and is subsequently reduced with inversion. The model rationalizes the observed stereoselectivities for hydrogenation of carbonyl compounds.

The asymmetric reduction of α-ketoesters and related ketones on Pt modified with cinchona alkaloids[1] (Figure 1), first described by Orito in 1979,[2] is a useful method for the large-scale production of pharmaceutical intermediates. Numerous investigations during the last decade were devoted to understanding the mechanism and origins of enantioselectivity. No proposal explains all the experimental evidence. The most prominent mechanism, proposed by Baiker, explains the enantioselectivity as arising from reduction of a hydrogen-bonded complex between the alkaloid and ester.[3,4] Baiker's group has proposed that a protonated cinchona alkaloid and the ketone assemble on a Pt surface complexed by a bifurcated hydrogen bond. Figure 2a demonstrates this model for cinchonidine and methyl pyruvate. The cinchonidine–pyruvate adduct adsorbs on the Pt surface via the quinoline unit, and hydrogenation takes place from the metal surface side. Because the lower energy diastereomeric s-cis complexes between cinchonidine and pyruvate are almost identical in energy, it was assumed that the s-trans conformers are more reactive or complex better with the platinum surface.[4b]

Margitfalvi invoked a supramolecular complex that is stereoselectively reduced.[5] The ketone and cinchona alkaloid form a complex in which one side of ketone is shielded by the aromatic ring of the cinchona alkaloid, leaving the other side
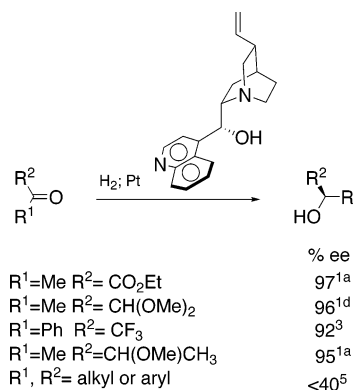
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	% ee
R^1=Me R^2= CO_2Et	97[1a]
R^1=Me R^2= $CH(OMe)_2$	96[1d]
R^1=Ph R^2= CF_3	92[3]
R^1=Me R^2=$CH(OMe)CH_3$	95[1a]
R^1, R^2= alkyl or aryl	<40[5]

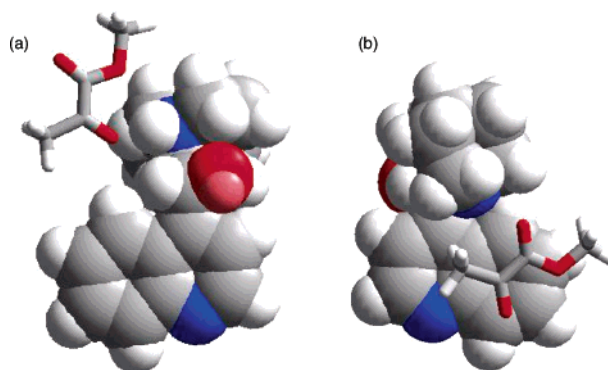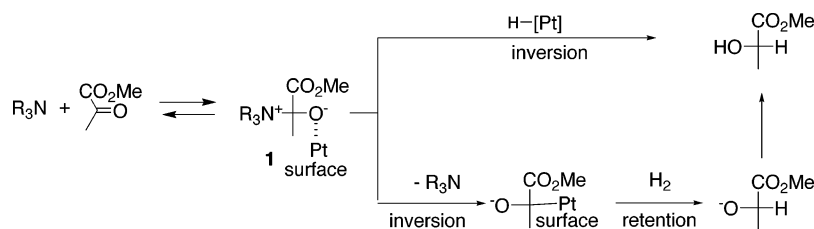***Figure 1.*** Asymmetric ketone reduction on cinchonidine-modified Pt.

Figure 2. (a) Baiker's model of the hydrogen-bonding interaction between the protonated cinchonidine and s-trans conformation of pyruvate. The quinoline is attached to the Pt surface (omitted in the picture). The hydrogenation takes place from the platinum (front) side. The cinchonidine is shown in a CPK representation, and the pyruvate is shown in a polytube model. (b) The model of supramolecular complex proposed by Margitfalvi. Hydrogen attacks from the unshielded (front) side of pyruvate.

open for hydrogenation. Figure 2b shows this for cinchonidine and pyruvate. This model requires the cinchona alkaloid to complex in its "closed form" (see below), a conformation in

Figure 3. Postulated mechanisms for reduction of methyl pyruvate catalyzed by cinchonidine-modified Pt (R_3N = cinchonidine). Besides the C–Pt covalent bond shown there is an interaction between the oxygens and the quinoline of cinchonidine with the Pt surface.

which the quinuclidine nitrogen points toward the quinoline aromatic ring, opposite to the "open form" conformation in which the quinuclidine nitrogen points away from the quinoline aromatic ring. However, rigid cinchona alkaloids that can only exist in the "open" form induce enantioselectivity similar to that of usual cinchona alkaloids.[6] Numerous observations suggest that the "closed" form does not play an important role in the enantioselectivity.[6c,d]

A third model proposes nucleophilic catalysis involving the nitrogen of the chiral modifier and the ketone carbonyl;[7] this mechanism has largely been overlooked in current literature that favors the hydrogen bond model. One exception is the recent work by Bartok et al., where the alteration of the sense of enantioselectivity induced by changing the reaction solvent from toluene to acetic acid was explained by proposing a switch in the mechanism from nucleophilic attack in toluene to hydrogen bonding in acetic acid.[8]

We have studied the mechanism of enantioselective reduction of methyl pyruvate on cinchonidine modified platinum using a variety of computational techniques. An alternative mechanism is proposed based upon reduction of an intermediate involving covalent bond formation between the ketone and the nucleophilic cinchona modifier. We suggest that the initial step is the formation of zwitterionic adduct **1** between cinchonidine and pyruvate on the platinum surface; this adduct is likely to be stabilized by hydrogen bonding in acidic media. Subsequently, the C–N bond between pyruvate and cinchonidine undergoes hydrogenolysis with overall inversion of configuration as schematically shown in Figure 3. One possible mechanism of hydrogenation is nucleophilic replacement of cinchonidinium by the Pt surface with inversion of stereochemistry, followed by hydrogenolysis of Pt–C bond with retention of stereochemistry.

Catalytic hydrogenolysis of ammonium salts of structure similar to complex **1** proceeds under mild conditions with inversion of configuration.[9] (Figure 4a) Although examples of hydrogenation of quaternary ammonium salts on platinum are scarce, activated quaternary ammonium salts undergo facile hydrogenations[10] (Figure 4b). There is no evidence for rapid reductions of nonactivated quaternary ammonium salts on platinum. Nonetheless, the cleavage of the C–N$^+$ bond in
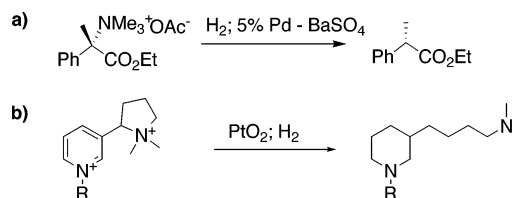

Figure 4. Examples of (a) Pd- and (b) Pt-catalyzed hydrogenolysis of ammonium salts.

zwitterionic intermediates should be significantly accelerated, compared to regular salts.

The plausibility of formation of a zwitterionic adduct is supported by the formation of zwitterions in reactions between trifluoroacetophenone and tertiary amines such as triethylamine and quinuclidine in acetonitrile.[11] Such intermediates are also likely in the reactions of ketones with primary or secondary amines, dimerization of ketenes[12] and opening of anhydrides[13] catalyzed by cinchona alkaloids. The additional stabilization of the zwitterion comes from the interaction of O$^-$ with platinum.

In acidic media, the zwitterionic adduct, which has higher basicity than the amine in nonpolar solvents, may obtain additional stabilization from hydrogen bonding. This can explain why the rate and ee are increased by addition of weak acid[14] and why the best ee's are obtained when acetic acid is used as the solvent for the reaction. On the other hand, the observed reduction of both ee and rate in the presence of strong acid[15] such as TFA agrees with the fact that amine addition to ketones is slowed in strongly acidic media by conversion of amine to ammonium cation.[16]

Figure 1 lists known examples of highly enantioselective heterogeneous reductions of ketones, excluding β-dicarbonyls. The energetics of the reaction of quinuclidinium, a model for a protonated cinchona alkaloid, with different ketones were computed at the B3LYP/6-31G*[17] level of theory, using the Gaussian98[18] program package. Because of difficulties with computing a reaction of these complexes on a metal surface, protonation was used as a model to assess the stabilities of tetrahedral adducts of amines with ketones. The results are summarized in Figure 5. The compounds that yield high ee (methyl pyruvate, 3-methoxy-2-butanone and 1,1-dimethoxy-2-propanone) react exothermically with quinuclidinium, whereas

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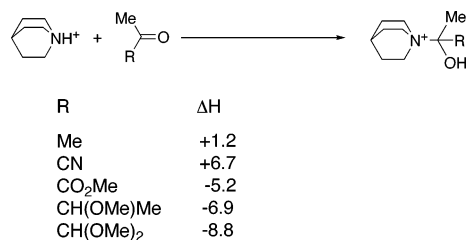
R	ΔH
Me	+1.2
CN	+6.7
CO₂Me	-5.2
CH(OMe)Me	-6.9
CH(OMe)₂	-8.8

Figure 5. B3LYP/6-31G* gas-phase enthalpies (kcal/mol) of reactions of quinuclidinium with ketones.
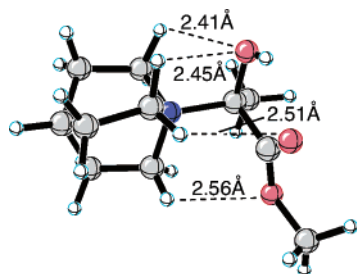

Figure 6. Hydrogen bonding in quinuclidine−methyl pyruvate adduct.

less activated ketones do not. The preference for reactions of ketones having oxygens or fluorines attached to the α-carbon is reinforced by formation of internal hydrogen bond O−H···X (when the protonated pyruvate−cinchona alkaloid complex is considered) and electrostatic attraction (CH···X hydrogen-bonding) in the adduct as shown in Figure 6 for methyl pyruvate. Interactions of the oxygens of the adduct with the Pt surface are also expected to stabilize the tetrahedral adduct.

The first step toward understanding of the enantioselectivity of the reaction was to perform conformational analysis of 10,11-dihydrocinchonidine (DHCd), to which cinchonidine is quickly converted under the reaction conditions, and its proto-nated adduct with pyruvate. The relative energies of the different conformers of the diastereomeric adducts of 10,11-dihydrocin-chonidinium with pyruvate were scanned, utilizing the AMBER* force field[19] as implemented in MacroModel 6.0.[20] Then the low energy structures were reoptimized by B3LYP hybrid density functional. The reliability of the force field was tested by comparing the relative energies of four low energy confor-mations of cinchonidine obtained by AMBER* optimization with the values reported earlier by Bürgi and Baiker using quantum mechanical calculations.[21] The low energy conforma-tions and their energies are shown in Figure 7. The "Open 3"[22] conformer is sterically less hindered and leaves the quinuclidine

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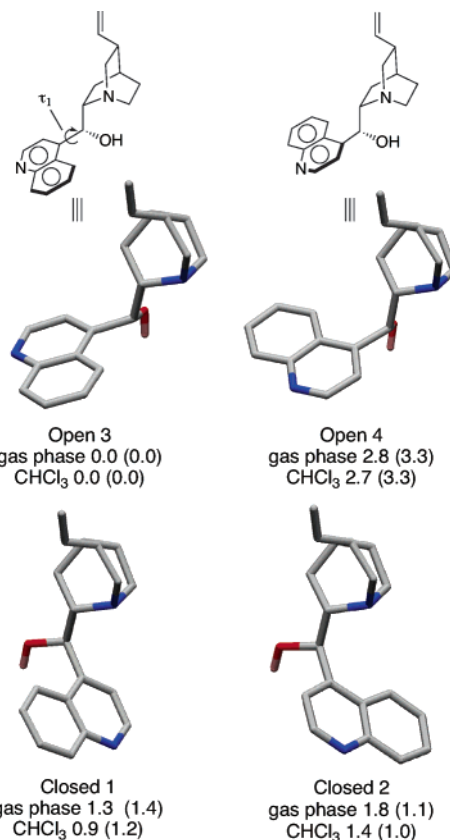(21) Bürgi. T.; Baiker, A. *J. Am. Chem. Soc.* **1998**, *120*, 12920−6.

Figure 7. Structures and relative energies (kcal/mol) of low energy cinchonidine conformations B3LYP/6-31+G*/PCM (AMBER*/GB/SA [CHCl₃]). Hydrogens on carbons are omitted.

nitrogen sterically accessible for reaction as a nucleophile. The average and maximum deviations between AMBER* and B3LYP calculated energies are 0.4 and 0.7 kcal/mol, respec-tively.

The conformational analysis of the diastereomeric adducts, **2a** and **2b**, from the reaction of the des-ethyl DHCd with ethyl pyruvate was performed with AMBER. Monte Carlo confor-mational searches[23] were employed to find the lowest energy conformations. Two low energy conformers were found for each diastereomer. The two conformers of each diastereomer differ from each other by a 180° rotation of the ester group. Their structures are shown in two perspectives, along with the relative DFT and AMBER energies in Figure 8.

In both adducts **2a** and **2b**, the cinchonidine part of the molecule adopts the "Open 3" conformation. This is likely to be the dominant conformation of cinchonidine in any tetrahedral adduct, since "Closed" conformations experience large repul-sions between the quinoline ring of cinchonidine and the activated carbonyl compound−pyruvate in the reaction discussed here, attached to the ammonium center. When cinchonidine acts as base, the quinoline group of a "Closed" conformation is likely to overlap with the molecule being deprotonated. The "Open 4" conformation is high in energy in the free base and remains unfavorable in the adduct.

The tetrahedral intermediate formed by attack of the "Open 3" conformation on methyl pyruvate has methyl, hydroxy and

(22) The nomenclature used to describe the conformers is that proposed by Bürgi and Baiker.[19]

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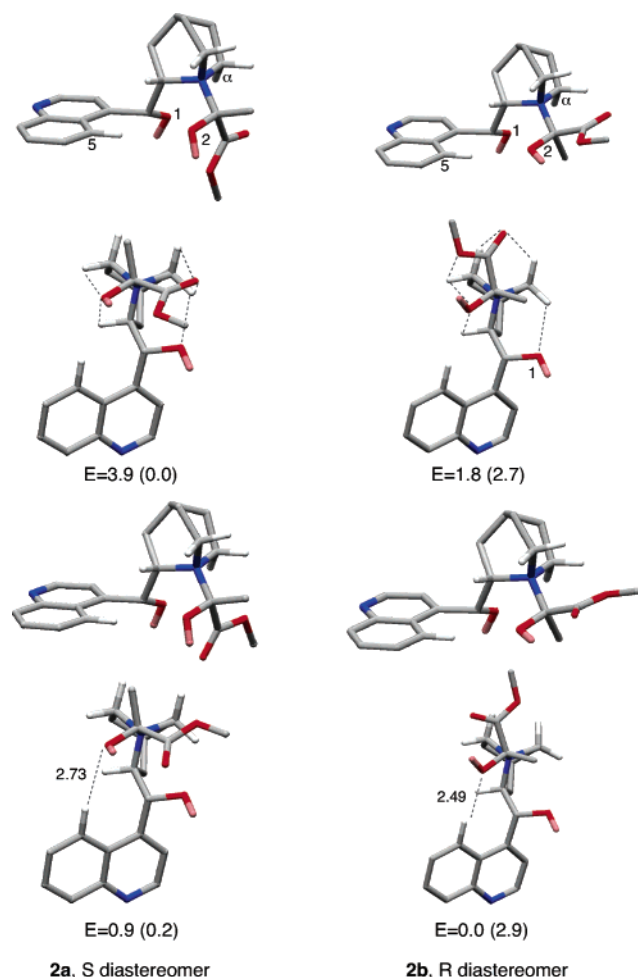
Figure 8. Two views of the lowest energy conformations of **2a** and **2b**. Relative energies, kcal/mol, are computed at B3LYP/6-31G* level (AMBER* values are in parentheses). Some CH···O contacts with H···O distances below 2.7 Å are shown by dashed lines. Structures at the top and bottom differ only by ~180° rotation of the carboxylic acid.

ester groups on the newly formed stereogenic center. The two intermediates are labeled as (*S*) and (*R*), respectively, according to the configuration at the new chiral center. Note that the configuration of this stereogenic center is opposite to the configuration of the final product, since hydrogenation occurs with inversion.

The low energy conformers have different relative energies by AMBER and DFT, which may be due to the lack of precision in the AMBER energy estimation of charged/strained structures. Nonetheless, both force field and DFT produce the two lowest energy conformers of both the (*S*) and (*R*) diastereomers with the same feature: they have the hydroxy-O^2H of the lactate moiety near the quinoline C^5-H group. This is the most crowded sector, and the steric demands dictate the necessity of placing the smallest substituent there to minimize the repulsion with the C^5-H hydrogen of quinuclidine. It also allows a favorable CH···O interaction. The methyl and ester groups then can go into either of the two remaining staggered positions, as shown in Figure 8. All structures have relatively positive C^5-*H* and C^α-*H* hydrogens at a distance of 2.6 ± 0.2 Å from the O^2 and O^1 oxygens, respectively, and at the angles that allow CH···O hydrogen bond formation.[24]

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For further understanding of the hydrogenation process, it is useful to discuss some of the facts known about the mechanism of reduction on cinchona modified platinum: first, it is known that the cinchona alkaloids adsorb strongly on the platinum surface, with the aromatic moiety lying flat or slightly tilted.[25] The interaction between a Pt surface and an oxygen can also be significant: water adsorption on a Pt surface is worth 12 kcal/mol,[26] and pyruvate is preferably bound to a platinum surface through the lone pairs of oxygen rather than the π-system.[27] Thus, the cinchona−ketone complex should be bound to platinum with both oxygens and the aromatic ring interacting with platinum.

The model presented here postulates that enantioselectivity arises from differences between the stabilities of the diastereomers of the intermediate platinum bound zwitterion **1**, and that the platinum−bound complex formed in greatest abundance leads to the major reduction product. Sometimes the least stable intermediate in a catalytic cycle is more rapidly transformed to product, as shown in classic work on the Knowles reduction by Halpern.[28] However, such situations are expected to be accompanied by a selectivity trend that is characterized by a decrease in enantioselectivity with decreasing temperature and/ or increasing hydrogen pressure of a reaction. This is not observed for the cinchona catalyzed hydrogenation of pyruvates.[29,30]

Low energy conformers of the (*S*) intermediate zwitterion can be adsorbed on the platinum surface with quinoline and two oxygens attached to the surface as can be seen in Figure 9a.[31] The low energy conformer of the R adduct adsorbed on the surface is shown in Figure 9b. After full B3LYP/6-31G* optimizations of structures shown in Figure 9, with protonation of the alkoxide instead of coordination to the Pt surface, the *S* diastereomer was found to be 3.8 kcal/mol lower in energy than the *R*.

Upon reduction with inversion, the *S* intermediate **2a** will give the *R* alcohol product. Assuming the intermediates are both converted to products with inversion, the product ratio based on the relative energies of the two conformers of **2a** and **2b** predicts that *S*-methyl lactate will be formed in 99.6% ee at 25 °C. This agrees reasonably well with the mid 90% ee values obtained experimentally.[32,1a]

To ensure that the ethyl group in DHCd has no significant influence on the relative energies of various conformations, the relative energies of the DHCd−pyruvate complexes, involving

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(30) Bartok, M.; Balazsik, K.; Szollosi, Gy.; Bartok, T. *J. Catal.* **2002**, *205*, 168.
(31) The geometries shown in Figure 9 were obtained with MacroModel. Pt atoms were frozen during all calculations, with a Pt−Pt distance of 2.775 Å. Pt−O distances were constrained to 2.1 Å. Everything else was allowed to relax. The resulting structures automatically converge to geometries shown in Figure 9.
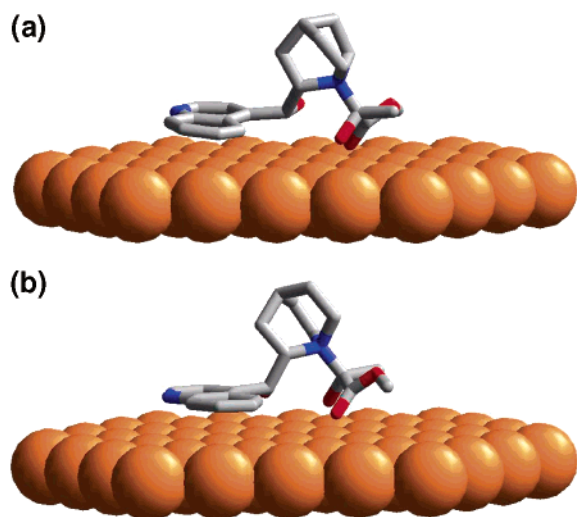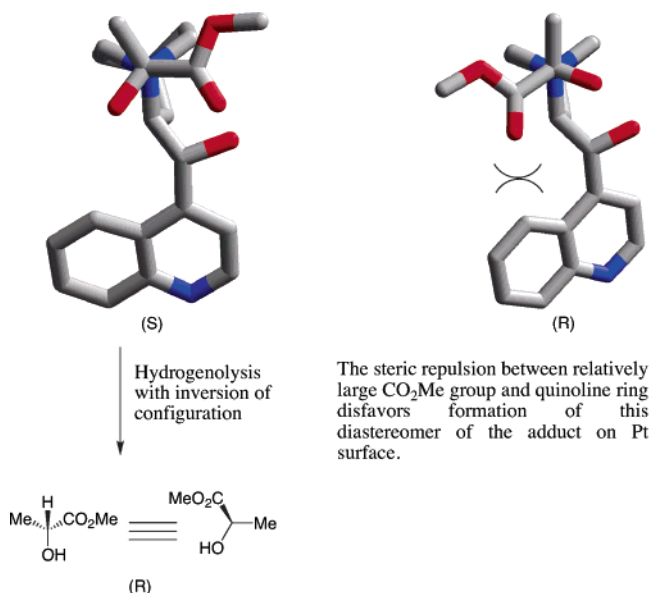(32) LeBlond, C.; Wang, J.; Liu, J.; Andrews, A. T.; Sun Y.-K. *J. Am. Chem. Soc.* **1999**, *121*, 4920−1.

Figure 9. (a) Proposed model of the (*S*)-zwitterion on platinum surface. (b) Proposed model of the (*R*)-zwitterion on platinum surface.

Figure 10. Models for zwitterion bound to Pt surface. The (*S*)-zwitterion on the left is favored because of the CO$_2$Me−quinoline repulsion in the (*R*)-zwitterion (on the right). Hydrogenolysis of the (*S*)-zwitterion leads to the (*R*)-alcohol product.

the substitution of an ethyl group to the des-ethyl counterparts, were assessed utilizing AMBER*. The introduction of an ethyl group changes the relative energies of various conformers by 0.1 kcal/mol or less.

Figure 10 shows the front view of the (*S*) des-ethyl DHCd−pyruvate adduct as it is adsorbed on the Pt surface. The Pt surface (displaced in front of the adduct) is not shown. The cinchona alkaloid adds to the ketone on the Pt surface forming a zwitterionic adduct with quinoline, O⁻, and an α-heteroatom bonded to platinum. This means that in the adduct the heteroatom containing groups of the ketone point toward the quinoline and the alkyl group points away from the quinoline. The (*R*) zwitterion is sterically disfavored as indicated in the structure on the right of Figure 10. The preferred diastereomer has the smallest group (O⁻) placed next to quinoline group. This favored diastereomer is then hydrogenated with inversion of configuration. This model can be applied to any α-activated ketone; the activating group (CF$_3$, CR$_2$OR, CR(OR)$_2$, etc.) is larger than O⁻ in all cases. Other α-ketoesters, for example, ethyl-2-oxo-4-phenylbutyrate also react according to the rule. Figure 1 shows experimental results for a variety of α-activated ketones, whose enantioselectivities follow this rule in every case.

This model rationalizes the enantioselectivity of known hydrogenation reactions and is consistent with the available experimental data. The enantioselectivity is determined by coordination of three points of the cinchona alkaloid activated

ketone tetrahedral adduct to the Pt surface and the repulsion between activating group and quinoline in the pro-S reactive intermediate bound to the Pt surface. In the Baiker (Figure 2a) and Margitfalvi (Figure 2b) models, stereoselectivity is determined by the preferred orientation of the s-trans conformation of pyruvate in the complex with the cinchona alkaloid. The analogous coordination by the other molecules shown in Figure 1 is required to explain the stereoselectivity with these models.

Evidence has been presented that the mechanism of hydrogenation of activated ketones on cinchona alkaloid modified platinum occurs through nucleophilic addition of a cinchona alkaloid to the ketone to form a zwitterionic adduct, which is then hydrogenolyzed with inversion of configuration. The enantioselectivity of the reaction is determined by the relative stabilities of the diastereomeric adducts adsorbed on platinum.