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Steric and electronic effects in enantioselective hydrogenation of ketones on platinum modified by cinchonidine: Directing effect of the trifluoromethyl group

Angelo Vargas, Fatos Hoxha, Norberto Bonalumi, Tamas Mallat, Alfons Baiker *

Department of Chemistry and Applied Biosciences, ETH Zurich, CH-8093 Zurich, Switzerland

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Abstract

The directing effect of the CF_3 group on Pt/alumina modified by cinchonidine in the enantioselective hydrogenation of activated ketones was studied experimentally and theoretically using aliphatic α,α,α-trifluoromethyl ketones as model compounds. α,α,α-Trifluoromethyl ketones with varying steric hindrances of the groups on the two sides of the keto group (methyl-trifluoromethyl ketone **1a**, adamantyl-trifluoromethyl ketone **2a**, and *tert*-butyl-trifluoromethyl ketone **3a**) were examined. The catalytic results show that in weakly polar solvents, in which the interaction of the solvent with the substrate, modifier, and Pt is less important, the three alcohols **1b**, **2b**, and **3b** have the same absolute configuration (R). This indicates that enantioselectivity is guided by the trifluoromethyl substitution rather than by the relative bulkiness of the substituents at the two sides of the carbonyl group. The fluorinated substrate has a preferential interaction on the side of the α,α,α-trifluoromethyl group, as corroborated by the calculation of hydrogen–bonding interactions. When this interaction mode is calculated for the system alkaloid–trifluoroacetone, an energy difference between the Pro(R) and the Pro(S) configurations is found. Our findings suggest that electronic effects give a bias toward the formation of the (R)-enantiomer.

Keywords: Activated ketones; α,α,α-Trifluoromethyl ketones; Enantioselective hydrogenation; Pt/alumina; Cinchonidine; Steric and electronic effects

1. Introduction

Over the past two decades, the synthesis of enantiopure compounds by asymmetric catalysis has established its position as a frontier in chemical technology [1]. The most striking results have been obtained in homogeneous catalysis, but the intrinsic technical advantages of heterogeneous catalysis have also stimulated research in this field [2]. Promising results were achieved by chiral modification of metals, particularly using supported platinum modified with alkaloids of the cinchona series. Its remarkable versatility was shown by the asymmetric hydrogenation of various α-functionalized (activated) ketones, including α,α,α-trifluoromethyl ketones [3–12]. Several reviews offer a panorama of the state of the art in this field [13–17]. Nevertheless, a complete mechanistic insight has not yet been achieved, and several questions still puzzle researchers attempting to rationally design new catalysts based on this approach.

Reducing the debate to its basic issues, we can state that there is wide agreement that the alkaloid generates chiral sites by chemisorption on an otherwise achiral surface, and that enantiodiscrimination occurs through a 1:1 interaction between adsorbed substrate and modifier, whereas several proposals have been advanced concerning the interaction mode between substrate and modifier that leads to selectivity. We recently proposed [18] that on cinchona-modified Pt, adsorption of an α-ketoester on the *si*-side is directed by the position of the ester group, independent of the steric bulkiness on any side of the keto-carbonyl group. Some indications in this direction had already emerged in a previous study [19]. In other words, the activating function (an ester, carbonyl, acetal, or amido group) not only increases the reactivity of the ketone, but also directs its adsorption in the chiral environment generated by adsorption

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* Corresponding author.
E-mail address: baiker@chem.ethz.ch (A. Baiker).

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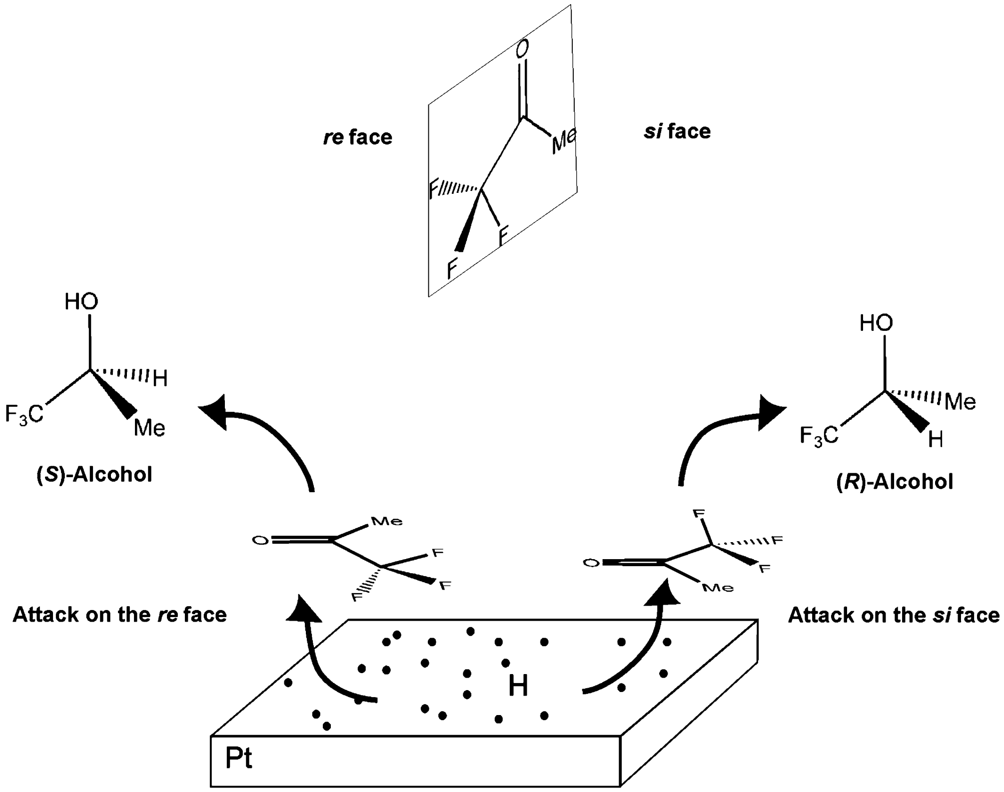

Scheme 1. Scheme of the hydrogen uptake by trifluoroacetone on a metal surface. Enantioselectivity occurs if one of the faces of the ketone is preferentially exposed to the adsorbed hydrogen.

of the alkaloid. In the present work, the enantioselective hydrogenation of aliphatic α,α,α-trifluoromethyl ketones is examined.

On hydrogenation, prochiral ketones generate either the (R)- or the (S)-alcohol according to the prochiral face that is attacked. In a racemic hydrogenation, addition at both the *re* and *si* faces occurs at equal amounts, and the racemate is obtained, but if the reaction is performed enantioselectively, then a chiral auxiliary is able to bias the hydrogenation selectively via a single face [20,21]. In reactions on metal surfaces, the activated hydrogen is added from the metal, and thus the selectivity occurs according to which face of the ketone is preferentially exposed to the surface. Scheme 1 shows the case of trifluoroacetone. When the metal is chirally modified, the chiral site generated can bias the hydrogen uptake selectively from one face. This can occur if the modifier interacts differently with the Pro(R) and the Pro(S) adsorbed ketones. In this work the nature of this interaction is investigated.

A widely accepted model for the enantioselective hydrogenation of activated ketones on cinchona-modified platinum is based on a hydrogen bonding interaction between the protonated alkaloid and the adsorbed substrate [15,22], which is supported by an in situ experimental evidence [23]. This 1:1 interaction model has been extensively described and discussed in the literature [13,15,17]; here we take only the basic assumption that a hydrogen bonding interaction is present in the chiral site and that the reaction at the molecular level is accelerated by the modifier (although this may not be reflected by the rate of hydrogen uptake, due to the coverage of a fraction of active sites by the modifier). Discrimination within a chiral site may occur because of the different steric requirements of the substituents at the two sides of the keto-carbonyl group. In this case the enantioselectivity would depend on the relative steric hindrance. The face of the prochiral ketone that better fits the chiral pocket is more stable and thus has a higher fractional coverage; furthermore, the best fit within the chiral space also determines a stronger hydrogen bond, and kinetic resolution can occur [24]. Note that in this case, only one attractive interaction occurs between the hydrogen donor and the ketone, whereas repulsive (steric) interactions determine the best fit in the chiral space.

On the other hand, enantiodiscrimination could also result from a guiding effect of the activating group of the ketone, due to a second interaction with the activating substituent. In this case, the relative interaction energy between the bifurcated bonds, involving two hydrogen acceptors, would determine the selectivity. Steric requirements also play a role in such an interaction, but these are restricted to the nonactivating substituent of the ketone. The most widely studied reaction on platinum is the hydrogenation of α-ketoesters, but this reaction is complicated by numerous side reactions [25–28]. To minimize this influence, we address enantioselection in the hydrogenation of α,α,α-trifluoromethyl ketones. In particular, we chose ketones for which the relative steric hindrance of the substituents is inverted but the (possible) directing effects due to the activating moiety are maintained. The analysis of the absolute configuration of the final products should then reveal which of the effects have driven enantioselection. The energies of the interaction