Journal of Catalysis 280 (2011) 104–115

Contents lists available at ScienceDirect

Journal of Catalysis

journal homepage: www.elsevier.com/locate/jcat

Multiple cycle reaction mechanism in the enantioselective hydrogenation of α,α,α-trifluoromethyl ketones

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ARTICLE INFO

Article history:
Received 2 February 2011
Revised 8 March 2011
Accepted 9 March 2011
Available online 13 April 2011

Keywords:
Enantioselective
Diastereoselective
Hydrogenation
Platinum
Cinchona alkaloid
NMR
Trifluoromethyl ketone
Trifluoromethyl alcohol

ABSTRACT

The enantioselective hydrogenation of 2,2,2-trifluoroacetophenone (**1**) on cinchona-modified Pt, combined with the diastereoselective hydrogenation of cinchonidine and NMR analysis of the modifier–substrate–product interactions, revealed the key role of the product (*S*)-1-phenyl-2,2,2-trifluoroethanol (**2**) in enantioselection. We propose a multiple cycle mechanism including a racemic route (a) on the unmodified sites and three enantioselective routes. In the enantioselective cycles, there is an N–H–O type interaction between the quinuclidine N and the carbonyl O-atom of the substrate. At low conversion, the alkaloid alone is the source of chiral information (route *b*). With increasing conversion, the weakly acidic minor product (*S*)-**2** forms an adduct with the alkaloid and this complex controls the enantioselection (route *c*, lower ee). The frequently applied strong acid additive TFA replaces (*S*)-**2** and the alkaloid–TFA complex gives the highest ee (route *d*). The diastereoselective hydrogenation of cinchonidine disproves a former mechanistic model proposed in the literature.

1. Introduction

Early after discovering the enantioselective hydrogenation of α-ketoesters by Orito's group [1], it was generally considered that the Pt–cinchona system is highly specific to the transformation of the 1,2-dicarbonyl compounds α-ketoesters, α-ketoacids, and α-diketones [2,3]. The successful hydrogenation of 2,2,2-trifluoroacetophenone (**1**) to (*R*)-1-phenyl-2,2,2-trifluoroethanol (**2**, Scheme 1) with cinchonidine (CD)-modified Pt/alumina was the first evidence that the real structural requirement the substrate has to fulfill is the presence of an activating function in α–position to the carbonyl group [4]. In the past years, the research in the hydrogenation of α,α,α-trifluoroketones has revealed unique characteristics of this reaction class, compared with those of the mostly investigated transformation, the hydrogenation of α-ketoesters.

From a synthetic point of view, the most important deviation is the unusual substrate specificity of the Pt–cinchona system: Hydrogenation of **1** [5] and alkyl-4,4,4-trifluoroacetoacetates [6] afforded up to 96% ee, while the reaction is poorly selective with some aryl-substituted aromatic, benzylic, and particularly with aliphatic trifluoromethyl ketones [7–10].

From a mechanistic point of view, the differences fill a long list. In the hydrogenation of α-ketoesters, blocking the basic quinuclidine N atom of the alkaloid by alkylation or arylation eliminates the enantioselection, while *O*-methylation (to MeOCD) has only a minor effect on the ee [11,12]. This difference has been commonly interpreted as evidence for the involvement of the quinuclidine N in the activated complex leading to enantioselection and for the minor importance of the OH function [13–18]. *N*-methylation of CD leads to a loss of ee also in the hydrogenation of **1** and ethyl-4,4,4-trifluoroacetoacetate [19]. The influence of *O*-methylation is more complicated. In the hydrogenation of five different aryl-substituted 2,2,2-trifluoroacetophenones, the ee was almost completely lost or even the opposite enantiomer, the (*S*)-alcohol formed in small excess (4–11%), when CD was replaced with MeO-CD [5]. On the contrary, replacement of CD by MeOCD enhanced the ee from 70% to 90% in the hydrogenation of ethyl 4,4,4-trifluoroacetoacetate [20]. In some other cases, the effect of *O*-methylation depended also on the substituents in the substrate and on the solvent [8,19].

There are several more examples on the crucial role of the alcoholic OH function in enantioselection. In the hydrogenation of trifluoromethyl cyclohexyl ketone, replacement of toluene by EtOH inverted the ee with both CD and CN [21]. In two other instances, in the hydrogenation of adamantyl trifluoromethyl ketone and *tert*-butyl-trifluoromethyl ketone, the major product was inverted upon addition of 2-propanol [10]. Formation of the corresponding

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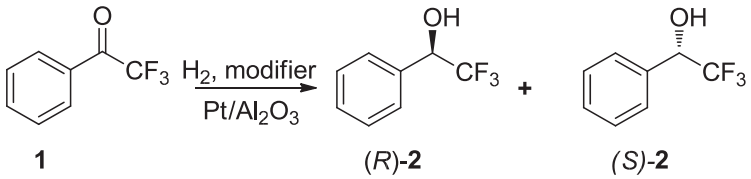
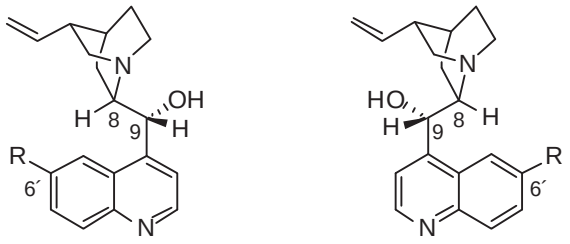
doi:10.1016/j.jcat.2011.03.009





8 (*S*), 9 (*R*)		R	8 (*R*), 9 (*S*)		R
Cinchonidine	(CD)	H	Cinchonine	(CN)	H
Quinine	(QN)	OMe	Quinidine	(QD)	OMe

Scheme 1. Hydrogenation of 2,2,2-trifluoroacetophenone (**1**) on cinchona-modified Pt/Al_2O_3.

hemiketal with the solvent can diminish the ee at high conversion but cannot cause inversion of the major enantiomer [22]. NMR analysis also proved that no hemiketal was formed with the product α,α,α,-trifluoromethyl alcohol, as expected in the presence of the CF_3 group.

A thoroughly investigated phenomenon is the unpredictable effect of acid additives and solvents in this reaction class. In the hydrogenation of ethyl-4,4,4-trifluoroacetoacetate, replacement of the solvent toluene with AcOH doubled the ee and addition of TFA increased it further. In case of the 4′-CF_3 derivative of **1**, however, carboxylic acids diminished the ee. For comparison, in the hydrogenation of **1** and its aryl-substituted derivatives, replacement of CD with CD·HCl increased the ee under all conditions applied [5]. Obviously, the effect of carboxylic acids cannot simply be attributed to protonation of the quinuclidine N of CD, but rather H-bonding interactions have to be taken into account, as indicated by IR measurements [23,24].

Recently, Bartók's group reported numerous striking examples on the inversion of the major enantiomer by the addition of the strong acid TFA to the reaction mixture [10,25–28]. According to their interpretation of the unexpected inversion, a "nucleophilic intermediate complex" (N → C=O type interaction) between the alkaloid and ketone would be formed in the absence of TFA but even in the presence of AcOH. In contrast, in the presence of TFA, the protonated quinuclidine N of the alkaloid modifier would interact with the carbonyl O-atom of the substrate via an N–H–O type interaction. This assumption is rather astonishing, since an NMR study proved the complete protonation of the quinuclidine N of CD by 24 equivalents of AcOH [29]. The only additional effect of TFA was the protonation of the quinoline N, the transformation of which was negligible in AcOH. Bartók's concept focusing on the protonation of the quinuclidine N of the alkaloid by TFA also cannot rationalize the unexpected inversions in alcohols [10,21], whose solvents do not protonate CD.

Our opinion is fundamentally different. On the basis of DFT calculations [30,31] and in situ spectroscopic measurements [32,33], we assume an N–H–O type interaction between the quinuclidine N and the carbonyl O-atom even in a non-acidic medium. We attribute the frequently unpredictable behavior of the Pt–cinchona system in the hydrogenation of α,α,α-trifluoromethyl ketones to additional H-bonding interactions. This concept can rationalize the special effect of carboxylic acids [6,24]. Here, we present our novel observations on the role of the product in the hydrogenation of **1** and the evolution of competing enantioselective cycles during reaction.

2. Experimental section

2.1. Materials

2,2,2-Trifluoroacetophenone (**1**, 99%, Aldrich) was carefully distilled in vacuum before use. (±)-1-Phenyl-2,2,2-trifluoroethanol (**2**, >98%, Fluka), (*R*)-**2**, (⩾99.0%, Fluka), (*S*)-**2**, (⩾99.0%, Fluka), cinchonidine (CD, 98% NT, Fluka), cinchonine (CN, ⩾98% NT, Fluka), quinine (QN, 99%, Fluka), quinidine (QD, >99%, Acros), toluene (⩾99.7%, Fluka), trifluoroacetic acid (TFA, 99%, Acros), toluene D_8 (99.94%, Cambridge Isotop Lab., INC.), and chloroform D (99.8%, Armar Chemicals) were used as received. The 5 wt.% Pt/Al_2O_3 catalyst was purchased from Engelhard (Engelhard 4759).

2.2. Catalytic hydrogenations

The 5 wt.% Pt/Al_2O_3 catalyst was reduced at elevated temperature in a fixed-bed reactor prior to use. According to the standard procedure, the catalyst was heated under flowing nitrogen up to 400 °C in 30 min, followed by a reduction in flowing hydrogen for 60 min at the same temperature, and finally cooled down to