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Research Note

Enantioselective hydrogenation of aromatic ketones: structural effects

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Abstract

Enantioselective hydrogenation of acetophenone derivatives demonstrates the potential of the Pt–cinchona system in the synthesis of chiral alcohols that possess no functional group in the α-position to the CH–OH group. Electron-withdrawing functional groups in the aromatic ring increased the reaction rate and enantiomeric excess (ee), and the position of the group (*o*-, *m*-, or *p*-) was also important. 60% ee was obtained in the hydrogenation of 3,5-di(trifluoromethyl)acetophenone under ambient conditions, though the special role of reaction parameters has not been investigated yet. Addition of cinchonidine slowed down all hydrogenation reactions—an unprecedented behaviour for chirally modified Pt.
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Keywords: Enantioselective hydrogenation; Cinchonidine; Platinum/alumina; Acetophenone derivatives

1. Introduction

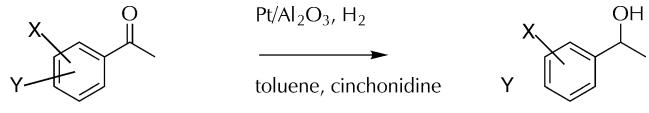
Two types of chirally modified metal catalysts are effective in the enantioselective hydrogenation of ketones: the Ni–tartaric acid system for β-functionalized and unfunctionalized aliphatic ketones [1–4] and the Pt–cinchona alkaloid system for α-functionalized (activated) ketones [5–9]. The Pt–cinchonidine system has been successfully applied also for the hydrogenation of activated aromatic ketones, such as 1-phenyl-2,3-propanedione [10,11], 2-(trifluoroacetyl)pyrrole [12], and 1,1,1-trifluoroacetophenone [13–16]. In the latter reaction up to 91% enantiomeric excess (ee) was achieved under optimized conditions [17]. In contrast, the ee is 20% or less in the hydrogenation of the corresponding simple aromatic ketone, acetophenone [18,19]. Apparently, the presence of an electron-withdrawing functional group in the α-position to the carbonyl group is critical for obtaining high enantioselectivity with cinchona-modified Pt.

Other catalyst systems have also been tested. Hydrogenation of 3-coumaranone over Pt/SiO_2 modified by chiral binaphthalene derivatives afforded only 18% ee [20]. In the hydrogenation of acetophenone with (*S*)-proline-modified Pd/C the best ee was 22% at 78% yield [21]. A mechanistic study revealed that proline formed an adduct with acetophenone, and 1-phenylethanol was produced in a diastereoselective reaction via hydrogenolysis of the C–N bond of the adduct [22].

Here, we report the enantioselective hydrogenation of acetophenone derivatives over cinchonidine-modified Pt/Al_2O_3. Acetophenones possessing various electron-withdrawing and releasing functional groups at 2-, 3-, and 4-positions were selected (Scheme 1) to reveal the role of electronic and steric effects on the reaction rate and enantioselectivity.

2. Experimental

All reactants and CD were used as received. A 5 wt% Pt/Al_2O_3 catalyst (Engelhard 4759) was prereduced before use in a fixed-bed reactor by flushing with N_2 at 400 °C for 30 min, followed by a reductive treatment in H_2 for 90 min at the same temperature. After being cooled to



X, Y = H, F, CF_3, COOEt, OCH_3, CH_3

Scheme 1. Hydrogenation of substituted acetophenones to phenylethanols over cinchonidine-modified 5 wt% Pt/Al_2O_3.

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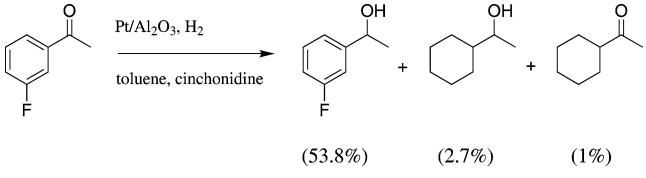
room temperature in hydrogen, the catalyst was immediately transferred to the reactor. Platinum dispersion after heat treatment was 0.27 (determined by TEM).

Hydrogenations were carried out in a parallel pressure reactor system Endeavor, with eight mechanically stirred 15-ml stainless steel reactors equipped with glass liners. Control experiments using different amounts of catalyst and varying the stirring frequency did not indicate significant external mass transport limitation for the reactions studied. Intraparticle diffusion effects can not be ruled out completely, but are unlikely due to the small catalyst particle size (50–100 μm) and the relatively low reaction rates compared to the corresponding racemic hydrogenations (Table 1). Under standard conditions 42 ± 2 mg of catalyst, 1.84 mmol of substrate, 2 mg (6.8 μmol) of cinchonidine, and 5 ml of solvent were stirred (500 rpm) at 10 bar and room temperature (23–25 °C) for 2 h.

Conversion and ee were determined by an HP 6890 gas chromatograph equipped with a chiral capillary column (WCOT fused silica 25 m × 0.25 mm, coating CP-Chirasil-Dex CB, Chrompack). Enantioselectivity is expressed as ee $(\%) = 100 \times |(R-S)|/(R+S)$. The products were identified by GC/MS. Reproducibility of ee was within ±0.5%.

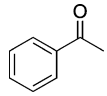
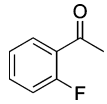
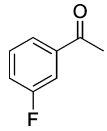
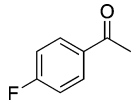
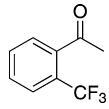
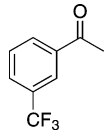
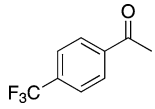
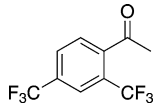
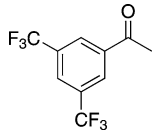
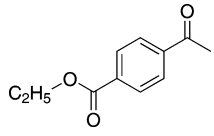
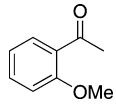
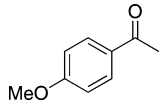
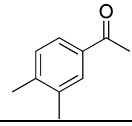
3. Results

Hydrogenation of acetophenones possessing one or two substituents in the aromatic ring has been carried out under identical conditions in toluene. The enantioselectivities and reaction rates, characterized by the yields achieved in 2 h, are collected in Table 1. The chemoselectivity in these reactions was 99% or higher, except for the hydrogenation of fluoroacetophenones **2**–**4**. In these reactions defluorination and saturation of the aromatic ring system was significant. Scheme 2 illustrates these side reactions after prolonged reaction time (16 h), on the example of 3-fluoroacetophenone. It is assumed that the basic quinuclidine N atom of cinchonidine ($pK_a = 10.0$ [23]) facilitates dehalogenation. Under standard conditions in 2 h the amount of defluorinated products was small; nevertheless, formation of HF as coproduct might lead to considerable catalyst deactivation. Defluorination is likely responsible for the relatively low yields in the hydrogenation of **2**–**4** and it may also distort the enantioselectivities. Defluorination was even more pronounced in the case of pentafluoroacetophenone; the results with this reactant are not shown in Table 1.



Scheme 2. Typical side reactions in the hydrogenation of fluoroacetophenones over cinchonidine-modified 5 wt% Pt/Al_2O_3. Standard conditions, 16 h, yields in brackets.

Table 1
Hydrogenation of substituted acetophenones with and without cinchonidine under standard conditions (2 h)

	Substrate	σ	Yield (%)	ee (%)[a]	Rel. rate[b]
1		0	4.7	17	0.16
2		–	4.8	2	0.20
3		0.34	7.8	29	0.29
4		0.15	9.4	14	0.46
5		–	0.3	52	0.50
6		0.46	12	44	0.35
7		0.53	16	14	0.27
8		–	3.1	29	0.21
9		–	21	37	0.27
10		0.44	24.5	24	0.53
11		–	2.2	5.5	0.079
12		−0.27	3.3	10.5	0.14
13		–	1.7	17	0.075

[a] On the basis of retention times in GC analysis, always the (*S*)-enantiomer formed in excess, except for the hydrogenation of **9** and **11**.

[b] Relative rate over CD-modified Pt, related to the rate over unmodified Pt.

The ee to (*S*)-phenylethanol (17%, Table 1), achieved in the hydrogenation of the reference compound acetophenone (**1**), is close to the highest value (20%) published in the literature [18,19]. For aryl-substituted acetophenones the ee varied in the range 2–52%. Estimated on the basis of elution order during GC analysis, cinchonidine-modified Pt provided always the (*S*)-enantiomer in excess, except for **9** and **11**. Inversion of enantioselectivity in the latter two reactions could not be confirmed yet by an independent method. For comparison, under similar conditions cinchonidine-modified Pt produced the (*R*)-enantiomers in excess in the hydrogenation of 2,2,2-trifluoroacetophenone and its aryl-substituted derivatives [17].

The chemical nature of the substituent and its position relative to the carbonyl group strongly influenced the enantioselectivity (Table 1). The role of position of the functional group is clearly seen by comparing the ee's obtained with fluoroacetophenones (**2**–**4**), trifluoromethylacetophenones (**5**–**9**), and methoxyacetophenones (**11**, **12**). Steric effects due to substitution in the 2-position are indicated also by the low reaction rates; the most striking example is the hydrogenation of **5**. When considering only the *m*- and *p*-substituted acetophenones, there is good qualitative agreement between the ee and the Hammett parameters (σ). With some exceptions (**4**, **7**, and **13**), electron-withdrawing substituents (F, CF_3, and ester groups: $\sigma > 0$) increased the ee, and electron-releasing substituents (MeO group: $\sigma < 0$) decreased the enantioselectivity, compared to the hydrogenation of acetophenone.

In all known enantioselective hydrogenation reactions of α-functionalized (activated) ketones, hydrogenation in the presence of a cinchona alkaloid is faster than the corresponding reaction catalyzed by unmodified Pt. This correlation is not valid here in the hydrogenation of acetophenone derivatives that do not possess an electron-withdrawing functional group in the α-position. For all reactants **1**–**13** lower rates were observed in the presence of cinchonidine as illustrated by the relative rates in Table 1.

The conditions in Table 1 are not optimized for achieving high enantioselectivity. For example, hydrogenation of **9** under standard conditions but at 1 bar instead of 10 bar afforded 25% conversion and 60% ee after 8 h. Hence, the two electron-withdrawing groups in *m*-positions tripled the enantioselectivity, compared to the best ee reported for the hydrogenation of the reference compound acetophenone [18,19]. A detailed study of the influence of various reaction parameters on the rate and ee is presently carried out in our laboratory.

4. Discussion

It was proposed earlier [24] that the efficient enantioselective hydrogenation over cinchona-modified Pt is limited to *trans*-α-dicarbonyl compounds such as α-ketoesters or α-diketones. The successful hydrogenation of 2,2,2-trifluoroacetophenone [14] was the first evidence against this postulate, indicating that the real requirement for the reactant is the presence of an electron-withdrawing (activating) group in the α-position. The results shown here allow further refinement of the scope of the Pt–cinchona system. Apparently, the key requirement is the activation of the carbonyl group and the position of the activating functional group is of secondary importance. The presence of electron-withdrawing functional group(s) in the aromatic ring of acetophenone far from the carbonyl group was sufficient to achieve up to 60% ee.

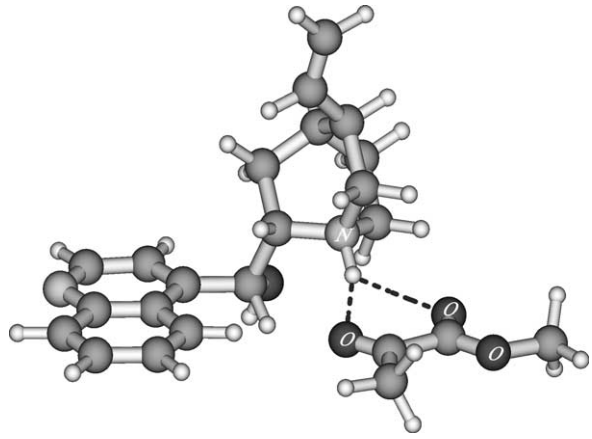


Fig. 1. Optimised structure of the complex between protonated cinchonidine and *s*-*cis*-methyl pyruvate, leading to (*R*)- lactate upon hydrogenation [25].

Theoretical calculations [25] indicated that a possible role of the electron-rich functional group in the α-position to the ketocarbonyl group is the stabilization of the hydrogen bond interaction between the reactant and the alkaloid on the Pt surface. The formation of a bifurcated hydrogen bond between the quinuclidine N atom of cinchonidine and the two carbonyl O atoms of *s*-*cis*-methyl pyruvate is shown in Fig. 1 as an illustration. Interestingly, among the trifluoromethyl-substituted acetophenones the substitution at the 2-position—i.e., closest to the carbonyl group—afforded the highest ee (**5**–**7**, Table 1). This behaviour may indicate the involvement of a fluorine atom in the reactant-modifier interaction during hydrogenation of **5**.

A common feature of enantioselective hydrogenations over cinchona-modified Pt is the rate acceleration induced by the chiral modifier [6,7]. This is not the case for acetophenone derivatives. For all tested reactants a rate deceleration between a factor of 2 and 13 was measured (compare relative rates in Table 1). A closer inspection of the relative rates reveals that these values are always higher in the presence of electron-withdrawing substituents (F, CF_3, and ester groups: $\sigma > 0$) and lower with electron-releasing substituents (Me and MeO groups: $\sigma < 0$), compared to the relative rate in the hydrogenation of acetophenone. This relationship is conform with the well-known and recently interpreted [26] rate acceleration effect induced by interaction of the cinchona alkaloid with the activated carbonyl group on the Pt surface. Note that van Bekkum

et al. [27] showed many years ago that hydrogenation of acetophenones on Pd/C is accelerated by electron-withdrawing and retarded by electron-donating substituents.

As concerns the apparent rate acceleration induced by the chiral modifier, the frequently used term "ligand-accelerated" reaction [28] is misleading in heterogeneous catalysis. Addition of a cinchona alkaloid to the reaction mixture has a double effect on the reaction rate. It adsorbs strongly on the metal surface and diminishes the number of active sites available for the hydrogenation reaction ("poisoning effect"). Besides, its interaction with the reactant in the enantio-discriminating step may enhance the intrinsic reaction rate related to the number of active sites (TOF). If the second effect is smaller than the poisoning effect, the overall (observed) reaction rate is lower on the modified catalyst, even if the reaction mechanism is the same and there is an intrinsic rate acceleration with the modifier. Unfortunately, a reliable determination of the number of active sites available for the hydrogenation reaction in the presence of a modifier is not yet possible.

5. Conclusions

The enantioselective hydrogenation of acetophenone derivatives to the corresponding aromatic alcohols is the first example in which the Pt–cinchona system is efficient in the hydrogenation of ketones possessing no functional group in the α-position. Variation of the chemical nature and position of the functional groups resulted in remarkable changes in reaction rate and enantioselectivity, indicating the importance of both electronic and steric effects. Clarification of the synthetic potential of the method requires further research.

Acknowledgments

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