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Priority Communication

1-Naphthyl-1,2-ethanediol as a new chiral modifier of platinum in the enantioselective hydrogenation of activated ketones

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Abstract

1-Naphthyl-1,2-ethanediol (NED) is shown to be a useful modifier in the hydrogenation of ketopantolactone and ethyl-4,4,4-trifluoroacetoacetate under mild conditions. It represents the first effective chiral nonamine-type modifier of Pt for the enantioselective hydrogenation of activated ketones. The enantio-differentiation is attributed to substrate–modifier interactions involving hydrogen bonding between the keto-carbonyl O atom and one or two OH groups of NED. Prominent nonlinear behavior was observed when mixtures of (*S*)-NED and (*R*)-2-(1-pyrrolidinyl)-1-(1-naphthyl)ethanol {(*R*)-PNE} were applied as chiral modifiers. The phenomenon is traced to stronger adsorption of PNE on the metal surface, despite the identical "anchoring moiety" (naphthalene ring) of the two modifiers.

Keywords: Asymmetric; Enantioselective; Hydrogenation; Pt/Al_2O_3; 1-Naphthyl-1,2-ethanediol; 2-(1-Pyrrolidinyl)-1-(1-naphthyl)ethanol; Ketopantolactone; Ethyl-4,4,4-trifluoroacetoacetate

1. Introduction

The application of a metal hydrogenation catalyst together with a strongly adsorbing chiral molecule ("chiral modifier") is a simple and powerful method for the heterogeneous enantioselective hydrogenation of prochiral substrates. Among the known catalyst systems, supported Pt modified by small amounts of a cinchonaalkaloid (discovered by Orito et al. [1]) is the best choice for the enantioselective hydrogenation of activated ketones [2–5]. A systematic variation of the structure of cinchonidine [6] and some other chiral amine modifiers [7–9] revealed that the crucial structural parts of the modifier, beside the stereogenic center(s), are the flat aromatic ring system for anchoring onto the Pt surface and the basic aliphatic nitrogen function for interacting with the substrate.

Meanwhile, several other chiral amines have been synthesized and tested in the hydrogenation of activated ketones, mainly of ethyl or methyl pyruvate. The useful modifiers of Pt include 2-(1-pyrrolidinyl)-(1-naphthyl)ethanol [10] and other similar chiral 1,2-aminoalcohols [9,11], 1-(1-naphthyl)ethylamine and their derivatives [8,12], anthryl- and phenanthryl-ethylamines [13], vinca alkaloid derivatives [14], L-triptophane derivatives [15], and isocinchona alkaloids [16]. All these modifiers fulfill the requirements for an effective chiral modifier of Pt, extracted from studies of cinchona derivatives as noted above. In other words, all of them may be considered as analogous to the cinchona alkaloids and not as truly new types of chiral modifiers of Pt. This conclusion is supported by recent theoretical calculations of the interaction of ethyl pyruvate with some modifiers [17].

Interestingly, there is a report on 3% enantiomeric excess (ee) achieved in pyruvate hydrogenation with quaternized codeine (methylcodeinium iodide) [18] and 2% ee with *N*-benzylcinchonidium chloride [19]. However, other authors obtained reproducibly a racemic product with the latter cinchona derivative [20], and this observation is now commonly accepted as a strong experimental evidence for the crucial role of the basic N atom of cinchona alkaloids in the reactant–modifier interaction(s).

Here we report the enantioselective hydrogenation of activated ketones over Pt/Al_2O_3 modified by 1-naphthyl-1,2-ethanediol (NED, Scheme 1). To our knowledge, this is the first example of an effective nonamine-type chiral modifier of Pt and this unexpected finding may generate new opportu-

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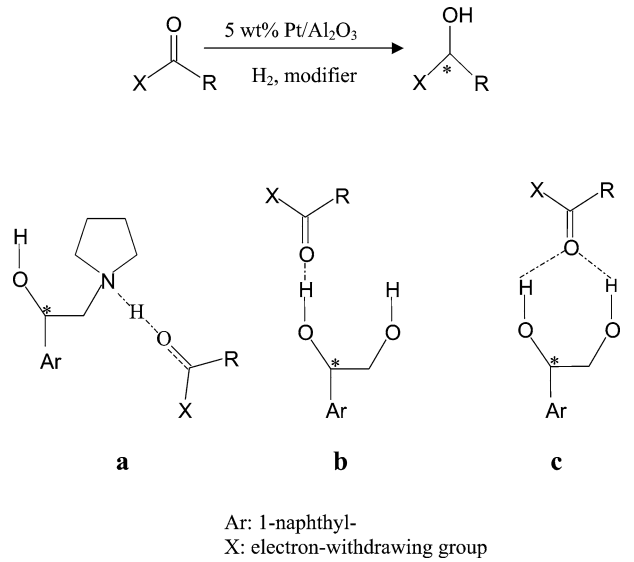

Scheme 1. Enantioselective hydrogenation of activated ketones over Pt/Al_2O_3 modified by 1-naphthyl-1,2-ethanediol. Models for interactions between activated ketones and NED or PNE. For description of **a**, **b**, and **c** see text.

nities in the search for suitable chiral modifiers for platinum metals.

2. Experimental

2.1. Chemicals

4,4-Dimethyldihydrofuran-2,3-dione (ketopantolactone, Hoffmann-La-Roche, $>99\%$), ethyl-4,4,4-trifluoroacetoacetate (Fluka, $>98\%$), 2,2,2-trifluoroacetophenone (Fluka, $>98\%$), acetic acid (Fluka, $>99\%$), toluene (J.T. Baker, $>99\%$), and 1,2-dichlorobenzene (Fluka, $>99\%$) were used as received. Ethyl pyruvate (Fluka, $>97\%$) was carefully distilled in vacuum before use.

(*R*)- and (*S*)-1-naphthyl-1,2-ethanediol and (*R*)-2-(1-pyrrolidinyl)-1-(1-naphthyl)ethanol (PNE) were synthesized from 1-vinylnaphthalene according to the method developed in Pfaltz's group [7,10]. 1-Vinylnaphthalene was freshly synthesized from 1-naphthaldehyde (Acros, 95%) via a Wittig reaction, because of its high tendency to polymerize. The final products were purified by flash column chromatography and then recrystallized several times in an ether/hexane (1/1) mixture until clean ^1H NMR spectra were obtained. ^1H NMR ($CDCl_3$, 500 MHz): NED 8.04 (m, 1H), 7.87 (m, 1H), 7.79 (d, 1H), 7.68 (d, 1H), 7.48 (m, 3H), 5.61 (dd, 1H), 3.96 (dd, 1H), 3.78 (dd, 1H), 2.88 (d, 1H, OH), 2.45 (m, 1H, OH); PNE 8.05 (d, 1H), 7.87 (m, 1H), 7.77 (m, 2H), 7.47 (m, 3H), 5.53 (dd, 1H), 4.75–3.50 (br s, 1H, OH), 2.80 (m, 4H), 2.62 (m, 2H), 1.85 (m, 4H). The measured $[\alpha]_D$ values at 20 °C in $CHCl_3$ and calculated ee values (in brackets) are $-116°$ ($>99\%$ ee), $-91°$ ($>98\%$ ee) and $+90°$ ($>97\%$ ee) for (*R*)-2-(1-pyrrolidinyl)-1-(1-naphthyl)ethanol (PNE) and (*R*)- and (*S*)-1-naphthyl-1,2-ethanediol (NED), respectively. Calculation of ee's in the modifiers was made on the basis of the $[\alpha]_D$ values and ee's reported in Refs. [7,10,21].

2.2. Catalytic hydrogenations

A 5% Pt/Al_2O_3 catalyst (Engelhard 4759) was prereduced in flowing H_2 for 90 min at 400 °C. The Pt dispersion after heat treatment was 0.27 as determined by TEM measurements.

The hydrogenation reactions were carried out in a 100-mL stainless-steel autoclave equipped with a 50-mL glass liner and PTFE cover. Pressure was held constant during reaction with a Büchi BPC 9901 system. Under standard conditions, 20 mg prereduced catalyst, 1.84 mmol substrate, 12.7 μmol modifier (corresponding to a substrate/modifier molar ratio of 144), and 10 mL solvent (toluene) were used. Unless otherwise stated, the reactions were carried out at room temperature.

Conversion and enantiomeric excess were determined using an HP 6890 gas chromatograph (GC) and a Chirasil-DEX CB (ChromPack) capillary column.

3. Results and discussion

The new modifier 1-naphthyl-1,2-ethanediol was first tested in the enantioselective hydrogenation of ketopantolactone, an intermediate in the synthesis of pantothenic acid (vitamin B_5). In Fig. 1 the performance of NED is compared to that of (*R*)-2-(1-pyrrolidinyl)-1-(1-naphthyl)ethanol {(*R*)-PNE [10]}, the modifier of which possesses a similar structure but one of the OH functions is replaced by a 1-pyrrolidinyl group. The ee to (*R*)-pantolactone decreased at higher pressures with both modifiers. The same correlation was observed with (*R*)-PNE in the enantioselective hydrogenation of ethyl pyruvate [10]. The loss of enantioselectivity to (*R*)-lactate at high surface hydrogen concentration was explained by the hydrogenation of the naphthyl ring of PNE and the

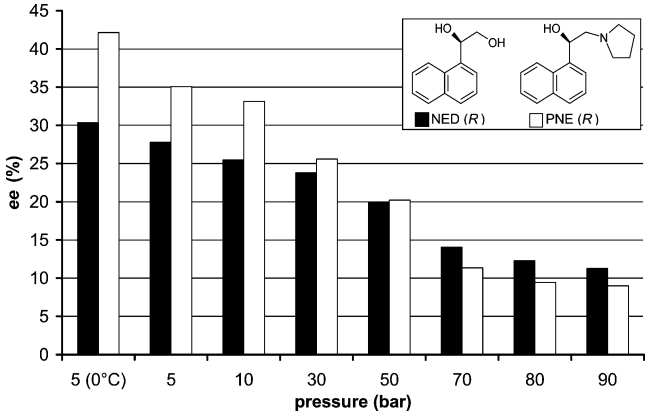

Fig. 1. Pressure dependence of enantioselectivity in the hydrogenation of ketopantolactone on 5% Pt/Al_2O_3 modified by NED and PNE under standard conditions.

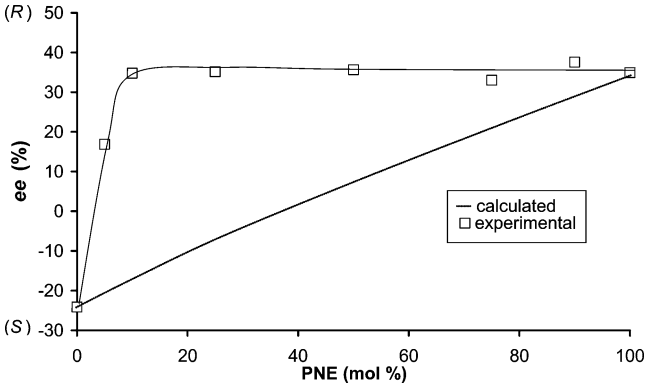

Fig. 2. Nonlinear behavior of mixtures of (*R*)-PNE and (*S*)-NED in the enantioselective hydrogenation of ketopantolactone on 5% Pt/Al_2O_3; standard conditions, 10 bar.

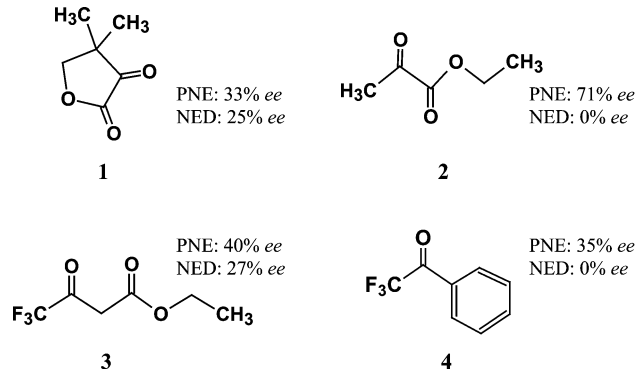

Fig. 3. Hydrogenation of various activated ketones on Pt/Al_2O_3 modified by either PNE or NED. The ee's are compared at 100% conversion. Standard reaction conditions, 10 mL toluene (dichlorobenzene for **3**), 20 mg catalyst (40 mg for **3** and **4**), and 10 bar. The reaction time necessary to achieve full conversion varied in the range 0.3–1.5 h.

weaker adsorption of the (partially) saturated modifier. Note that saturation of the quinoline ring of cinchonidine during enantioselective hydrogenation is a well-documented side reaction [22,23]. Hence, we assume that the better efficiency of NED at high pressures is due to the slower hydrogenation of the naphthalene ring of NED, compared to that of PNE.

The initial TOF values at 10 bar were 2.4, 2.9, and 3.6 s^{-1} in the absence of modifier, in the presence of NED {either (*R*) or (*S*)}, and (*R*)-PNE, respectively. Thus both NED and PNE induce a small rate acceleration compared to the unmodified reaction.

The results in Fig. 1 indicate that the adsorption strength of NED and PNE on Pt may be a critical parameter in determining their efficiency. To clarify this point, the nonlinear behavior of mixtures of the two modifiers was studied in the hydrogenation of ketopantolactone (Fig. 2). This method has been shown to be a useful tool for in situ investigation of modifier adsorption on Pt and Pd [24–26]. The calculated ee in Fig. 2 corresponds to an ideal case in which both modifiers adsorb on the metal surface with the same adsorption free energy, they do not interact with each other in solution or on the metal surface, and catalyze the enantioselective hydrogenation of ketopantolactone with the same rate and ee that are characteristic for each modifier when used alone [27].

The experimental values in Fig. 2 demonstrate that PNE governs the enantioselection when using mixtures of (*R*)-PNE and (*S*)-NED as modifiers. Even when Pt was modified by a 10 mol% PNE–90 mol% NED mixture, the ee was the same as obtained for pure PNE. The remarkable nonlinear behavior is attributed mainly to the stronger adsorption of PNE on Pt. This conclusion may be astonishing at first sight, as both modifiers possess the same anchoring moiety: a naphthalene ring. We assume that the stronger adsorption of PNE on Pt is due to the presence of the basic N atom. Ranade et al. [28,29] have shown recently that an amino function is a much better directing group in diastereoselective hydrogenation of aromatic compounds than a hydroxyl function, due to the stronger electronic attraction of the amino group to the metal surface. The same conclusion may be drawn when considering the soft acid character of Pt-group metals and the different basicities of the amino and alcoholic OH functions.

The stronger adsorption of PNE on Pt leads to surface enrichment of PNE in PNE–NED mixtures, the effect of which seems to be responsible for the nonlinear behavior in Fig. 2, and presumably also for the faster hydrogenation of the aromatic ring of PNE and its lower efficiency at high pressures (Fig. 1).

Beside the different adsorption strength of NED and PNE, the various electronic and steric effects among the adsorbed species may also contribute to the nonlinear behavior of their mixture but these effects are largely unknown.

The two chiral modifiers NED and PNE have been tested in the hydrogenation of some other activated ketones, such as ethyl pyruvate (**2**), ethyl-4,4,4-trifluoroacetoacetate (**3**), and 2,2,2-trifluoroacetophenone (**4**) (Fig. 3). Though the conditions are not optimized for any of the reactions, we can conclude that PNE is effective in all four reactions as a chiral modifier of Pt, whereas NED can only be used for **3** and ketopantolactone (**1**). The reason for this unusual structural effect is yet unclear. Besides, the ee's obtained with PNE are always higher than those achieved with NED.

An intriguing question is the nature of substrate–modifier interactions on the Pt surface resulting in enantioselection. The model suggested for PNE in the hydrogenation of ethyl pyruvate [17] is depicted in Scheme 1a. The attractive interaction, represented by the N–H–O-type hydrogen bond, is completed by a repulsion exerted by the aromatic ring of the modifier (not shown in Scheme 1).

We propose two possible structures for the attractive interaction between NED and the activated ketone substrate, involving hydrogen bonding between the oxygen atom of the keto-carbonyl group of the substrate and one or two hydroxyl groups of the modifier (Schemes 1b and 1c). Using ab initio calculations, Klein [30] found two analogous structures as the most stable interactions between *vic*-diols (ethane-1,2-diol, propane-1,2-diol, or butane-2,3-diol) and water. Middleton et al. [31] described structures similar to Scheme 1c for fluorinated *gem*-diols with hydrogen-bond

acceptors. The presence of fluorine bonded directly to the α-carbon atom confers a strongly acidic character to the hydroxyl groups and an unusually high stability to the complex. In our case the double interaction cannot be so strong due to the weak acidity of the diol ($pk_a = 13.4$ [32]). On the other hand, the single O–H–O-type interaction in Scheme 1b is expected to be considerably weaker than the N–H–O interaction in Scheme 1a.

An attempt to confirm the structures in Scheme 1b or 1c by NMR failed. Note that there is no NMR evidence yet for the N–H–O-type hydrogen bond between the known chiral modifiers and any of the activated ketones. However, very recently this hydrogen bonding type could be evidenced for the cinchonidine–ketopantolactone interaction using ATR infrared concentration modulation spectroscopy [33].

4. Conclusions

A new chiral modifier of Pt, 1-naphthyl-1,2-ethanediol (NED) has been found for the enantioselective hydrogenation of activated ketones. At best, the NED–Pt/Al_2O_3 catalyst system afforded 30% ee to (*R*)-(−)-pantolactone in the hydrogenation of ketopantolactone at 5 bar and 0 °C. A remarkable nonlinear effect was observed when mixtures of (*S*)-NED and (*R*)-2-(1-pyrrolidinyl)-1-(1-naphthyl)ethanol ((*R*)-PNE) were applied as modifiers. This behavior is traced to the stronger adsorption of PNE on Pt, likely due to the stronger electronic attraction of the amino group to the Pt surface. Two feasible models have been proposed for the NED–substrate interaction involving O–H–O-type hydrogen bonds.

Until now it was generally believed [2,4] that a crucial feature of an effective chiral modifier of Pt is a basic, aliphatic nitrogen atom for interacting with the activated ketone substrate. Here we provide strong experimental evidence against this hypothesis. Understanding the functioning of the Pt–NED catalyst system may initiate new approaches for tailor-made modifiers and broaden the scope of heterogeneous asymmetric catalysis.

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