Enantioselective hydrogenation of trifluoromethylcyclohexyl ketone on cinchona alkaloid modified Pt-alumina catalyst

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The enantioselective heterogeneous catalytic hydrogenation of trifluoromethylcyclohexyl ketone (**2**), on Pt-alumina (E4759) modified by different chiral compounds in toluene and ethanol solution with and without trifluoroacetic (TFA) has been investigated. The effects of the type of modifiers and their concentration (0–10 mmol/l), hydrogen pressure (1–100 bar), temperature (273–301 K) and conversion on the reaction rate and the enantioselectivity (ee) were studied. The achieved ee was 48% in the case of CD. Depending on solvents the inversion of enantioselectivity was observed. The available information suggests that the compounds responsible for chiral induction are different intermediates, the structure of which depends mostly on the acidic or non-acidic nature of the hydrogenation medium.

KEY WORDS: hydrogenation; enantioselective; platinum-alumina; fluoroketones; cinchona alkaloids; intermediate complexes.

1. Introduction

Optically active compounds containing fluorine are valuable materials for both the pharmaceutical and the agrochemical industry [1–3]; some have even been successfully utilized as precursors of liquid crystalline compounds. Trifluoromethyl alcohols are widely used as chiral synthons: their enantiomers can be prepared by resolving racemates [4], chiral reagents [5], microbiological methods [6] and reduction using homogeneous chiral transition metal complexes [7,8]. Pt-alumina catalysts modified with cinchona alkaloids have proven to be efficiently applicable to the enantioselective hydrogenation of the so-called activated ketones (including trifluoromethyl ketones). The significance of this field is well demonstrated by the high number of pertinent reviews, the most recent of which was published in 2003 [9].

First time the heterogeneous cinchona-modified Pt-alumina catalyst system was applied for the preparation of chiral trifluoromethyl alcohols was the enantioselective hydrogenation of 2,2,2-trifluoroacetophenone (**1**); the corresponding alcohol was obtained in an enantiomeric excess (ee) of 50–60% [10–12]. Later the optimization of experimental conditions enabled the achievement of 74% [13] and 92% ee [14] (scheme 1). The past few years have seen significant progress in the realization and interpretation of the heterogeneous catalytic enantioselective hydrogenation of compounds carrying trifluoromethyl groups [15–21].

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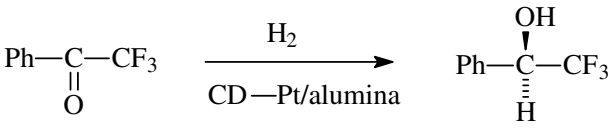

Scheme 1.

According to our present knowledge, the Pt-alumina-cinchona alkaloid system is the most efficient enantioselective catalytic hydrogenation system, which allows the realization of 97–98% ee in the hydrogenation of ethyl pyruvate (EtPy) [22,23]. These high ee values have stimulated extensive studies to elucidate the details of the reaction mechanism; however, more and more unanswered questions arise concerning the stereochemistry of the reaction and, in this context, the interpretation of chiral induction.

The objective of the experiments described in this work was to supply new evidence regarding the role of stereochemical factors by analyzing the enantioselective heterogeneous catalytic hydrogenation of activated ketones containing trifluoromethyl groups. Comparison of the results of the hydrogenation, under identical conditions, of 2,2,2-trifluoroacetophenone (**1**), a compound studied earlier, and trifluoromethylcyclohexyl ketone (**2**) (figure 1), one never studied before should theoretically yield such new results. One might ask how the ee achieved for **1**, a compound containing a phenyl group will be affected by the cyclohexyl group present in **2**. Thus, the present manuscript discusses the hydrogenation of **2** and a comparison is made with the hydrogenation results of **1**.

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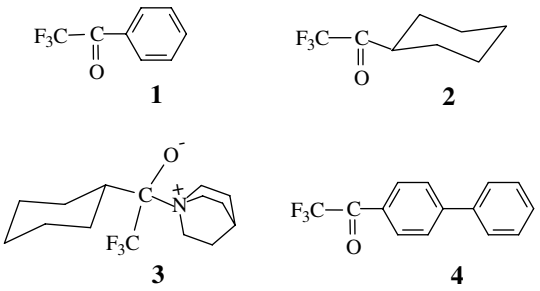

Figure 1. Compounds including in the text (**1**: trifluoroacetophenone, **2**: trifluoromethylcyclohexyl ketone, **3**: zwitterion, **4**: 4(trifluoroacetyl)biphenyl).

2. Experimental

2.1. Materials

AcOH, toluene, ethanol, tetrahydrofurane (THF), trifluoroacetic acid (TFA), cinchonidine (CD), cinchonine (CN), brucine (BN), dextrokarbinol base (DB), ephedrine (E), α,α-diphenyl-L-prolinol (DP) (figure 2) were purchased from Fluka, quinuclidine, 1,4-diazabicyclo[2.2.2]octane (Dabco) were Aldrich products. The substrate **2** was synthesized by Grignard reaction with 60% yield, according to literature [24]. After successive distillation on Vigreaux column at 50 Hgmm, the purity of synthesized **2** was ~90%. The purity of **2** after distillation of Fischer-Spaltrohr-System was 99% by GC/MS (HP5890/HP5970).

Pretreated (100 min. in hydrogen atmosphere at 673 K according to Refs. [25,26]) 5% (ww) Engelhard platinum alumina catalyst (E4759) was used.

2.2. Hydrogenation

Hydrogenation was performed in a 10 mL atmospheric batch reactor and in a Berghof Bar 45 autoclave. The catalytic system including the catalyst and 1–5 mL of solvent was purged 3–5 times with hydrogen after prehydrogenated (30 min) of the catalyst. The calculated amount of modifier and 0.1–2 mmol of substrate were introduced and stirred (1000–1200 rpm) in the presence of hydrogen for the required reaction time. Standard conditions were: 25–30 mg E4759, 1 mmol substrate and 2 mL toluene (at 1 bar H_2 pressure), 42–45 mg E4759 and 5 mL toluene (at H_2 pressure >1 bar), 293–298 K, 0.5 mmol/L CD, 1 bar H_2 pressure, 1000–1200 min^{-1} rpm, 1 mmol or 2 mmol substrate.

2.3. Analysis

The conversion and ee were calculated using GC data. The identification of product and the enantiomeric excess [ee% = ([*R*]−[*S*]) × 100/([*R*]+[*S*])] were monitored by gas chromatography (HP 5890 GC-FID), using 30 m long Cyclodex-B capillary column, uncertainty ±2%). The major enantiomer was determined by measurement of the optical rotation of the reaction product (*R*-enantiomer $[\alpha]_D^{25} = +17.7$ (c 7.9, $CHCl_3$) [27]).

2.4. NMR measurements

Brucer Avance DRX500 NMR spectrometer was used in all experiments operating at 11.7 T magnetic field strength (500.13 MHz ^{1}H-NMR and 125.77 MHz ^{13}C-NMR frequency). Samples of approximately 20 mg of the **2** were prepared in 0.6 mL acetone (d_6) or $CDCl_3$ solution and the quinuclidine was added in a five times higher molar excess [28], then the solution was transferred to a 5 mm NMR tube. J-modulated ^{13}C-NMR spectra were recorded at room temperature in approximately 12 h long experiments.

3. Results and discussion

Our objective was to study the enantioselective hydrogenation of **2** under mild experimental conditions, assuming that careful optimization would allow high ee to be attained. Knowing how **1** behaved under similar conditions [21], we also aimed at examining the effect of substrate structure on ee, in order to study the stereochemical conditions of hydrogenation. The effects of

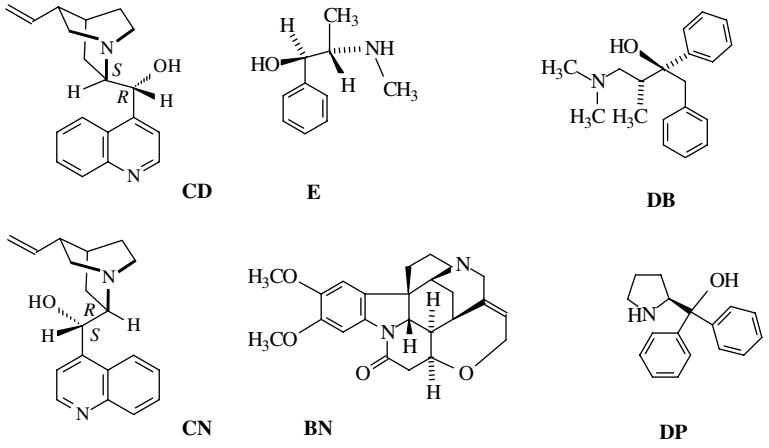

Figure 2. Structure of modifiers.

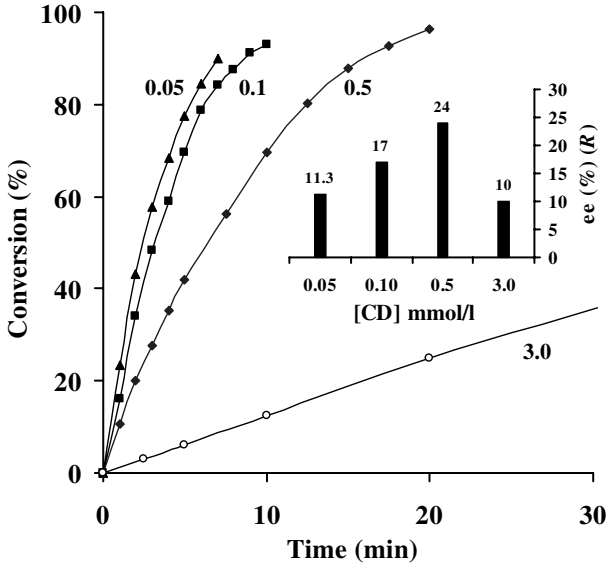

Figure 3. Enantioselective hydrogenation of trifluoromethylcyclohexyl ketone (**2**): the effect of CD concentration (0.05–3.0 mmol/L) on conversion and ee (standard conditions, 1 bar hydrogen pressure, 1 mmol **2**).

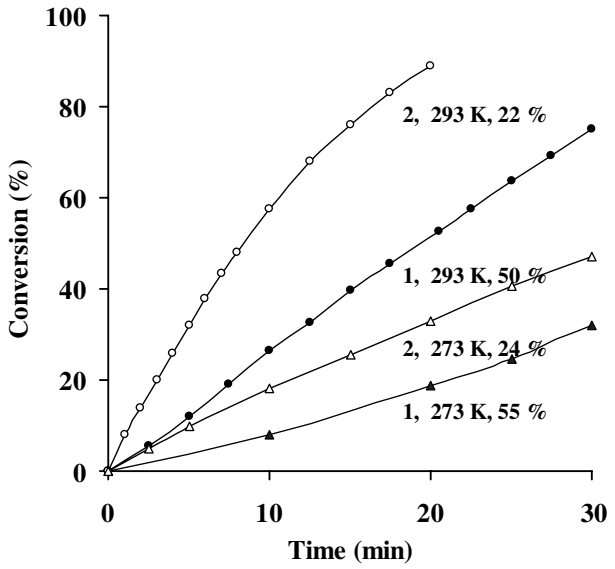

Figure 4. Enantioselective hydrogenation of **1** and **2**: the effect of temperature on conversion and ee (*R*) (standard conditions, 1 bar hydrogen pressure, 1 mmol **1** or **2**).

other chiral modifiers were also examined (figure 2). Experimental observations on the effects of acids of different strengths, obtained in the course of studying EtPy hydrogenation [29] were also made use of.

*3.1. Enantioselective hydrogenation of trifluoromethylcyclohexyl ketone (**2**)*

The results of the experiments carried out at a hydrogen pressure of 1 bar are summarized in figures 3–5. Of the two solvents that had been found to be the best for the enantioselective hydrogenation of EtPy

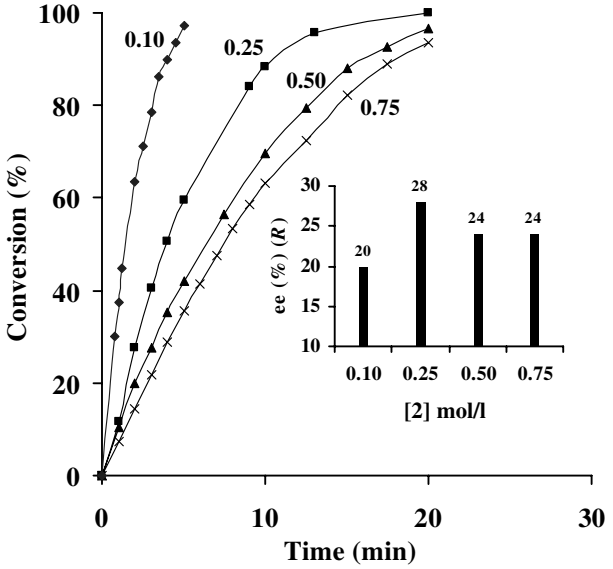

Figure 5. Enantioselective hydrogenation of trifluoromethylcyclohexyl ketone (**2**): the effect concentration of **2** (25 mg E4759, 0.5 mmol CD, 1 ml toluene, 1 bar hydrogen pressure, 273 K).

(AcOH, toluene), the majority of the experiments presented here were conducted in toluene, because AcOH had been shown to be unsuitable for the hydrogenation of **1** [21] and the same had been found in previous experiments with **2**. As shown in figure 3, a moderate CD concentration (0.5 mmol/L) was advantageous for ee, similarly to **1** but unlike EtPy hydrogenation, in the case of which an ee of about 90% was attainable at CD concentrations as low as 0.1 mmol/L in toluene and 0.01 mmol/L in AcOH, under similarly mild experimental conditions [26,30].

The ee achieved in the enantioselective hydrogenation of **2** was significantly lower that achieved in the case of **1** (22–28% for **2** and 50–55% for **1**). The low ee is probably a consequence of the dissimilar stereoelectronic factors determined by the structure of the **2**. It could be presumed that, in the case of **2**, relatively low CD concentrations would be sufficient for the achievement of high enantioselectivities, based on the differences in behavior (i.e. competition with other components) between **1** and **2** during adsorption. This presumption, however, was not confirmed by the experiments. According to figure 3, reaction rate decreases with increasing CD concentrations, while the curve of ee has a maximum. This is contrary to the observations made with **1** in that case, lower rates were associated with lower ee values (at any given temperature). In other words, the **2**-CD-Pt/alumina system does not follow the rule of "increasing rate – increasing ee", recognized in studies on the enantioselective hydrogenation of EtPy [31].

The data in figure 4 demonstrate how strictly hydrogenation rate is dependent on temperature, while ee does not change significantly. It is also revealed that, under identical conditions, the rate of the hydrogenation of **2** is

higher than that of **1**. Thus, this is another case which – similarly to other exceptions [32–35] – indicates "that ligand acceleration [31] is a welcome effect but not a necessary prerequisite for achieving high enantioselectivity" [33]".

Enantioselectivity was only slightly improved by the optimization of reaction conditions (figure 5). Ee was somewhat increased by increasing the concentration of the substrate, while hydrogenation was also accelerated. Increasing hydrogen pressure did not have an advantageous effect on enantioselectivity.

Table 1
Enantioselective hydrogenation of trifluoromethylcyclohexyl ketone (**2**) over cinchona alkaloid modified Pt-alumina [a]

Entry	Modifier (mmol/L)	Solvent	Time (min)	Conversion (%)	ee (%)
1	0.5 CD	T	30	70	22 (*R*)
2	0.5 CD	T	20	89	22 (*R*)
3	0.5 CN	T	60	25	8 (*S*)
4	1.5 CN	T	45	47	10 (*S*)
5	2.0 CN	T	30	36	7 (*S*)
6	0.5 CD	EtOH	60	28	8 (*S*)
7[b]	0.5 CD	EtOH	120	31	16 (*S*)
8[b]	5.0 CD	EtOH	135	27	13 (*S*)
9	0.5 CN	EtOH	30	40	13 (*R*)

[a]Experimental conditions: 25 mg E4759, 2 mL solvent, H_2 pressure: 1 bar, 293 K, 1 mmol substrate.
[b]273 K, T = toluene.

Table 2
Enantioselective hydrogenation of trifluoromethylcyclohexyl ketone (**2**) over modified Pt-alumina [a]

Entry	Modifier	Solvent	TFA (μL)	Conversion (%)	ee (%)
1	CD	T	5	16	33 *R*
2	MeODHCD	THF	5	87	26 *R*
3[b]	CD	T	20	25	44 *R*
4[b]	CD	T	100	10	25 *R*
5[b]	CD	T	50	32	41 *R*
6[c,d]	CD	AcOH	20	26	13 *R*
7[c,d]	CD	AcOH	20	100	13 *R*
8[d]	CD	T	20	100	44 *R*
9	DB	T	0	100	0
10	DB	T	20	0.3	0
11	BN	T	0	48	0
12	DP	T	0	100	14 *S*
13	DP	T	20	6	3 *S*
14	E	T	0	90	11 *S*
15[e]	CD	T	20	28	47 *R*
16	CN	T	20	13	32 *S*

[a]Experimental conditions: 42–46 mg E4759, 5 mL solvent, 6.8 μmol (1.36 mmol/L) modifier, H_2 pressure: 20 bar, 1 h, 273 K, 1 mmol of **2**, T = toluene.
[b]2 mmol of **2.**
[c]283 K.
[d]100 bar H_2 pressure.
[e]fresh TFA.

In order to increase ee, solvents other than toluene as well as various modifiers and TFA were also tested. The data in tables 1–2 illustrate the dependence of enantioselectivity on TFA concentration, the pressure of hydrogen and the chemical nature of the modifier and the solvent.

Studies on the solvent dependence of hydrogenation yielded interesting results: in EtOH as solvent, the enantiomer opposite to the one expected was obtained in excess. Although the excess is small (7–22%), the effect is still remarkable. In addition to trifluoromethyl ketones [20], a similar phenomenon of solvent polarity has also been observed in the hydrogenation of EtPy [36] and ketopantolactone [37] on chirally modified Pt. The highest hydrogenation rate was observed in the CD-toluene system, which also produces the highest ee. CN increases reaction rate to a smaller extent than does CD, both in toluene and AcOH.

As shown by the data in table 2, the highest ee was achieved in the toluene-CD-TFA system, just like in the case of **1** [21]. To compensate for the decrease in reaction rate due to the presence of TFA, hydrogen concentration was increased by raising the hydrogen pressure to 20 bar. Pressures above 20 bar were not advantageous for the level of ee. The best result (ee = 47%) was obtained with fresh TFA at 273 K. Several chiral modifiers were tested without any improvement in enantioselectivity. The results in solvent mixtures of THF-TFA and AcOH-TFA fall behind that obtained in the toluene-TFA system.

3.2. NMR measurements

The formation of the ionic species in the solution was studied by ^{13}C-NMR spectroscopy. **2** was used as a strong electrophile agent and the complex was created by the addition of excess tertiary amine quinuclidine (**2**:quinuclidine = 1:5). The adduct was studied in two different solvent systems, deuterated chloroform and acetone; however, the formation of the zwitterionic species was observed only in the acetone system. The carbonyl signal of **2** resonates at 195.0 ppm and the signal has a quartet fine structure as a result of the scalar coupling to three fluorine atoms in the trifluoromethyl group. The addition of the nucleophile to **2** results in a significant chemical shift decrease (Δ = 101 ppm) of the carbonyl signal to 94.0 ppm. However, the complex formation is not complete even at the high nucleophile molar excess as was compared to **1** [21], because both the free carbonyl species and the zwitterionic form can be identified in the ^{13}C-NMR spectrum.

4. Interpretation and conclusion of the results

After a detailed analysis of the results of the enantioselective hydrogenation of **1** and 4-(trifluoro-acetyl)

biphenyl (**4**) under the conditions used for the studies on **2**, hypothetic structures were formulated for the adsorption complexes responsible for enantioselection, based on the so-called adsorption model [21]. In agreement with the interpretation and conclusion given in ref. [21], the results obtained with **2** can also be explained by the formation of intermediates of similar structures (in order to avoid repetition, the details are not described here). It is, however, important to mention certain differences (a lower ee in the case of **2**; the solvent-dependent change in the sense of enantioselection) and certain experimental observations reported in this year.

There is a significant difference between the structures of surface complexes responsible for chiral induction in the presence and absence of TFA in the reaction mixture (see ref. [21]). The structure of the intermediate complex in the presence of TFA is shown in figure 6 (**a**), drawn in accordance with the reaction mechanism proposed in ref. [15]. Possible surface complexes for the interpretation of hydrogenation in toluene in the absence of TFA are **b** and **c** (figure 6). The reaction in ethanol yielding a product of opposite configuration could be explained by the formation of a surface complex with structure **d**. The formation of intermediates **c** and **d** could be envisaged in the way proposed earlier [21,36]: the nucleophilic N of the quinuclidine skeleton of CD interacts with the electrophilic carbon atom of the carbonyl groups of trifluoromethyl ketone. The formation of complexes of this type may be experimentally verified by recording the NMR spectra of zwitterionic adducts (figures 1, 3). On the other hand, the reality of mechanisms of this type has also been confirmed by DFT calculations [38]. The formation of adsorption complexes **c** and **d** may be connected with the different solvatation of **2** in the two solvents of different polarities (ethanol, toluene) [39]. Solvatation probably affects not only **2** but also the modifier and, consequently, the structure of the intermediate as well as the adsorption–desorption processes.

As regards the lower ee observed for **2** as compared to **1**, it is probably due not only to the steric bulk of the substrate, but also to the higher surface mobility of **2** as compared to the phenyl-containing **1**, because **1** is also attached to the surface via the π-electron sextet. The occurrence of any enantioselection at all in the case of **2** may be due to the interaction of fluorine atoms with the surface.

The steric bulk of the substrate is discussed in a most recent publication [40] saying: "We consider that the steric bulk of the alkyl substituent could have an important role in defining the interaction of the reactant with the cinchona modifier on the surface of the platinum nanocrystals." This conclusion was formulated in the course of studies on the subsequent hydrogenation of methyl pyruvate and EtPy and might explain the large difference between values of ee observed in the enantioselective hydrogenation of **1** and **2**. Various circumstances, however, contradict this possibility. On the one hand, when the experiments described in ref. [40] were repeated under the mild conditions applied in our work (1 bar hydrogen pressure), the results were not reproduced. On the other hand, earlier we found [41] that in the case of the hydrogenation of pyruvates, enantioselectivity was hardly affected at all by the steric bulk of the ester group.

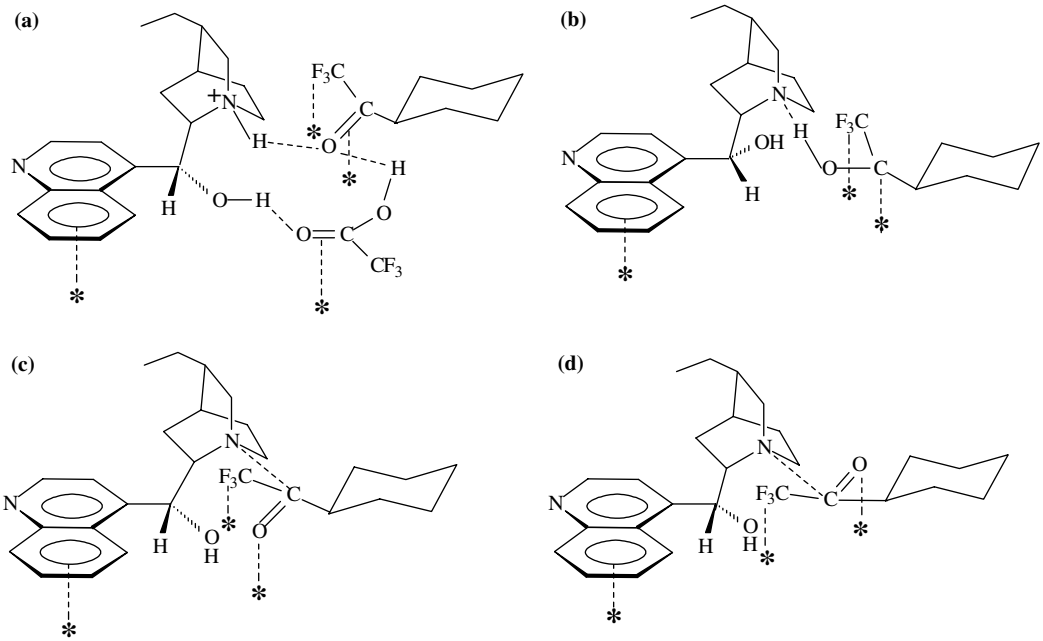

Figure 6. Proposed adsorbed adduct complexes between dihydrocinchonidine and **2** with TFA additive (**a**) and without TFA in toluene (**b** or **c**) or ethanol (**d**).

Acknowledgments

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