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Research Note

Asymmetric hydrogenation of racemic 2-fluorocyclohexanone over cinchona modified Pt/Al_2O_3 catalyst

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Abstract

The first example of enantioselective heterogeneous catalytic hydrogenation of an α-fluoro ketone is reported. The hydrogenation of racemic 2-fluorocyclohexanone over cinchonidine- or methoxycinchonidine-modified Pt/Al_2O_3 resulted in diastereoselective and enantioselective formation of the *cis*-(1*R*,2*S*)-2-fluorocyclohexanol. Due to the preferential hydrogenation of the *S* enantiomer, the kinetic resolution of the substrate was possible; the unreacted *R* enantiomer was accumulated in the reaction mixture. Under our experimental conditions, high diastereoselectivities (up to 85%) and good enantioselectivities (up to 59%) were obtained, demonstrating that activation of a ketone by a single α fluorine atom is efficient for obtaining enantiodiscrimination in this heterogeneous catalytic system.

Keywords: Heterogeneous hydrogenation; Enantioselectivity; Cinchona alkaloid; Platinum catalyst; Kinetic resolution; Fluoroketone

1. Introduction

The preparation of chiral fluorinated compounds has received much attention recently because of their unique chemical and pharmacologic properties [1]. The optically pure fluoro alcohols are very useful chiral building blocks. The extensive effort devoted to finding new methods for their synthesis has resulted in the development of several asymmetric catalytic methods for this purpose [2–5]. Enantioselective hydrogenation of fluorinated prochiral carbonyl compounds is among the most convenient procedures [2]. Several noble metal complexes bearing chiral ligands have been successfully used in the enantioselective hydrogenation of fluorinated ketones [6–8]. Due to the well-known advantages of heterogeneous catalysts compared with the chiral complexes that are soluble in the reaction medium, recent efforts have focused on finding such catalytic systems for the enantioselective hydrogenation of fluorinated ketones. One of the most promising of these is the cinchona alkaloid-modified supported platinum catalyst used initially by Orito and co-workers for the hydrogenation of α-keto esters [9]. The scope of this method has been continuously extended to other activated ketones [10], and these catalysts have been found to be suitable for the enantioselective hydrogenation of aromatic trifluoromethyl ketones [11–15]. Furthermore, high enantioselectivies were also obtained in the hydrogenation of trifluoroacetoacetates and some trifluoro-β-diketones [16–18].

We recently reported the hydrogenation of racemic ethyl 2-fluoroacetoacetate (EFA) over cinchona-modified Pt catalyst that resulted in up to 82% enantiomeric excess (ee) along with >95% diastereomeric excess (de) [19]. During hydrogenation, the dynamic kinetic resolution of the substrate occurred through spontaneous racemization of the stereochemically labile unreacted enantiomer. Thus, activation of the keto group by one fluorine atom in the α position in this β-keto ester was sufficient for the enantioselective hydrogenation of this compound. However, the effect of activation by one α fluorine atom of ketones on their asymmetric hydrogenation over cinchona-modified Pt catalyst remains an open question. Based on the good enantioselectivities reported for the hydrogenation of α-keto ethers and α-hydroxy ketones bearing carbonyl groups activated by alkoxy or hydroxyl groups [20–23], we expected to find a similar effect of the α fluorine atom. Racemic

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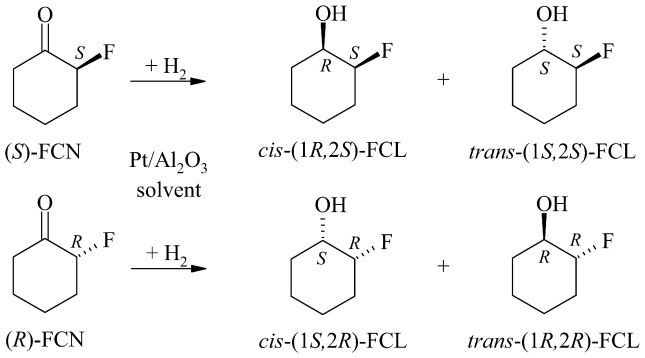


Scheme 1. General scheme of hydrogenation of 2-fluorocyclohexanone.

2-methoxycyclohexanone was kinetically resolved by hydrogenation over 10,11-dihydrocinchonidine-modified Pt/Al_2O_3; the *S* enantiomer reacted much faster than the *R*, leading to high optical purity of the hydrogenated product [20]. Encouraged by these results, we chose to study the hydrogenation of racemic 2-fluorocyclohexanone (FCN) over cinchona alkaloid-modified Pt/Al_2O_3 for testing the asymmetric hydrogenation of ketones activated by one α fluorine atom. The possible isomers of the hydrogenated product 2-fluorocyclohexanol (FCL) are shown in Scheme 1.

2. Experimental

Commercial alumina-supported Pt catalyst, 5% Pt/Al_2O_3 (Engelhard 4759), was used as received. Cinchonidine (CD, ⩾98%, Fluka) was used without purification. Cinchonidine hydrochloride (CD × HCl), O-methylcinchonidine (OMeCD), and N-methylcinchonidinium chloride (NMeCD) were prepared as described previously [24,25]. Tetrahydrofurane (THF, ⩾99.5%, Fluka) was dehydrated using $LiAlH_4$ and distilled before use; toluene (⩾99.5%) and acetic acid (AcOH, ⩾99.5%) were used as received.

2-Fluorocyclohexanone (FCN) was prepared by ring-opening of cyclohexene oxide using KHF_2 [26] and Jones oxidation of the resulting *trans* 2-fluorocyclohexanol (*trans*-FCL) [27] in 40% overall yield after distillation under reduced pressure, as shown in Scheme 2. The purity of FCN identified by GC-MS (Agilent Techn. 6890N GC-5973 MSD) and ^{1}H NMR (Bruker AVANCE DRX-500 spectrometer) analysis was >99% as determined by gas chromatography (using an HP 5890 II equipped with a flame ionization detector).

The hydrogenations were carried out in a conventional glass hydrogenation apparatus or a stainless steel autoclave equipped with a glass liner. First, 50 mg of catalyst, 3 ml of solvent, and 5 mg of modifier were loaded into the reactor. After flushing for 15 min and stirring for 5 min under H_2 atmosphere, 0.1 ml of FCN was added. The hydrogen uptake was followed; samples were withdrawn at prespecified reaction times and analyzed. The compounds FCN and *cis*- and *trans*-FCL found in the reaction mixture were identified by GC-MS and ^{1}H NMR analysis. Conversions and selectivities were determined by GC analysis using a Cyclosil-B (30 m × 0.2 mm, J&W Scientific) chiral capillary column.

Table 1
Hydrogenation of FCN over CD modified Pt/Al_2O_3[a]

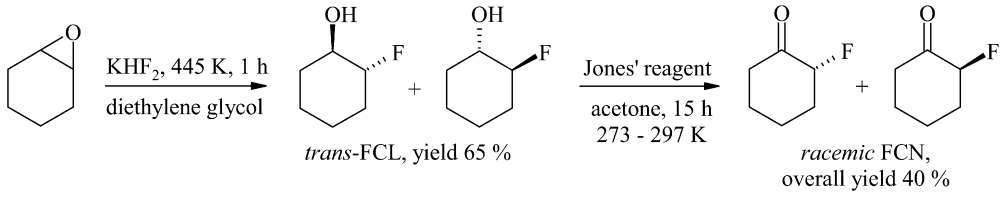
Solvent	Reaction time (min)	Conversion (%)	ee_{FCN}[b] (%)	de[c] (%)	ee_{cis}[d] (%)	ee_{trans}[d] (%)
Toluene[e]	80	96	–	39	–	–
Toluene	10	52	14	74	17	5
	25	92	62	75	9	14
THF	50	42	15	81	26	9
	80	60	29	82	25	21
	140	88	62	82	15	26
AcOH	15	37	18	79	52	22
	30	53	39	76	46	26
	120	82	73	74	31	40
	5[f]	67	44	79	35	35
SM 1/1[g]	10	34	22	81	55	26
	20	52	40	81	50	30
	120	88	90	77	27	42
	30[h]	39	28	85	55	26
	120[h]	77	81	83	36	46

[a] Reaction conditions: see Section 2, 0.1 MPa H_2, 296 ± 2 K.
[b] The (*R*)-FCN enantiomer was in excess.
[c] The *cis*-FCL isomers were formed in excess.
[d] The *cis*-(1*R*,2*S*)-FCL and the *trans*-(1*R*,2*R*)-FCL enantiomers were formed in excess.
[e] Reaction without modifier.
[f] Reaction under 4 MPa H_2 pressure.
[g] Solvent mixture: AcOH/THF 1/1.
[h] Reaction carried out at 273 K.

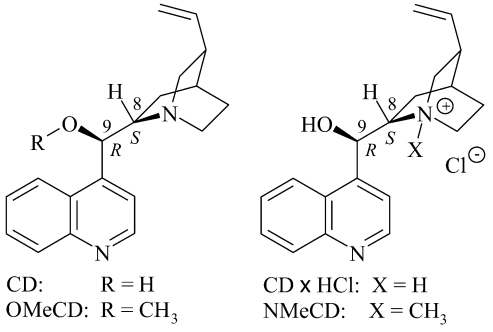
The ee of the unreacted FCN (ee_{FCN}) and the de and ee of the *cis*- and *trans*-hydrogenated products (ee_{cis} and ee_{trans}) were calculated by the following formulas: $de(\%) = |[cis\text{-FCL}] - [trans\text{-FCL}]| \times 100/([cis\text{-FCL}] + [trans\text{-FCL}])$; $ee_{FCN}(\%) = |[R\text{-FCN}] - [S\text{-FCN}]| \times 100/([R\text{-FCN}] + [S\text{-FCN}])$; $ee_{cis}(\%) = |[1R,2S\text{-FCL}] - [1S,2R\text{-FCL}]| \times 100/([1R,2S\text{-FCL}] + [1S,2R\text{-FCL}])$; and $ee_{trans}(\%) = |[1R,2R\text{-FCL}] - [1S,2S\text{-FCL}]| \times 100/([1R,2R\text{-FCL}] + [1S,2S\text{-FCL}])$. The absolute configuration of the FCN enantiomer accumulated in the reaction mixture was determined by measuring the optical rotation (Polamat A polarimeter, $c = 1$, benzene) of the unreacted FCN isolated by column chromatography (silica gel, eluent: hexane/dichloromethane 1/2) and comparison with published optical rotation data [28].

3. Results and discussion

Results obtained in the hydrogenation of FCN over CD-modified Pt/Al_2O_3 in different solvents are presented in Table 1. In the absence of the chiral modifier, the hydrogenation of FCN results in the selective formation of the *cis*-FCL (39% de in toluene). However, in the presence of CD the de increased, with >80% obtained in THF. In the presence of CD, one of the two enantiomers of the starting material accumulated, and the ee of the unreacted FCN increased with reaction time. Thus, kinetic resolution of the racemic FCN occurred, (*S*)-FCN was hydrogenated at a higher rate, and (*R*)-FCN accumulated in the reaction mixture, as determined by optical rotation measurement of the purified compound. A clear sign of the kinetic resolution was the much higher hydrogenation rates obtained



Scheme 2. Preparation of racemic 2-fluorocyclohexanone.



Scheme 3. Structure of cinchona alkaloids used as modifier.

up to about 50% conversion, as demonstrated by the samples obtained during the reactions. In the recently reported hydrogenation of EFA [19], the substrate was stereochemically more labile due to the rapid equilibration between the keto and enol species. During hydrogenation of FCN, the unreacted and accumulated enantiomer was not racemized, due to the faster hydrogenation of FCN compared with its transformation to the enol species.

In the presence of CD, both *cis*- and *trans*-FCL were formed enantioselectively. The highest ee values were obtained in AcOH; however, the de was slightly lower than in THF. When a mixture of these two solvents was used, good de and ee_{cis} were observed. As in the samples obtained at low conversions, no racemization of the excess (*R*)-FCN was observed, and the ratio of the *cis*-/*trans*-FCL was >90/10, it follows that from the two *cis*-FCL enantiomers, (1*R*,2*S*)-FCL was formed in excess. A stereochemical balance also showed that from the *trans*-enantiomers, the (1*R*,2*R*)-FCL was in excess. Thus, both FCN enantiomers were hydrogenated preferentially to the FCL isomers having the *R* configuration of the newly formed chiral center. Increased H_2 pressure in AcOH over CD-modified catalyst led to high hydrogenation rates without any significant effect on the ee values, compared with the results under atmospheric H_2 pressure. The most significant effect of decreasing the reaction temperature (to 273 K) in AcOH/THF 1/1 was an increase in the de of the reaction, whereas the ee's were close to expected values based on the conversion.

The effect of the modifier structure (see Scheme 3) was studied in THF, AcOH, and the 1/1 mixture of these solvents. Selected results are given in Table 2.

Using the hydrochloride CD × HCl gave similar results as the free base, whereas the N-methyl salt of cinchonidine (NMeCD) resulted in racemic products, similar to most of the studied activated ketones [14,29]. The only exception was the hydrogenation of keto-pantolactone, in which inversion of the enantioselectivity was reported [30]. Thus, in the hydrogenation

Table 2
Effect of the modifier structure on the hydrogenation of FCN over Pt/Al_2O_3[a]

Solvent	Modifier	Reaction time (min)	Conversion (%)	ee_{FCN}[b] (%)	de[c] (%)	ee_{cis}[d] (%)	ee_{trans}[d] (%)
THF	CD × HCl	40	43	17	74	25	10
		90	78	49	76	19	20
		150	92	81	76	11	28
	NMeCD	180	36	0	60	1	0
	OMeCD	15	43	4	72	7	0
		30	72	12	72	6	2
		60	97	48	71	2	5
AcOH	OMeCD	15	33	22	76	59	4
		60	59	50	74	52	15
		180	80	80	73	37	30
SM 1/1[e]	OMeCD	30	37	28	79	57	15
		70	59	61	79	54	18
		120	72	78	79	46	28

[a] Reaction conditions: see Section 2, 0.1 MPa H_2, 296 ± 2 K.
[b] The (*R*)-FCN enantiomer was in excess.
[c] The *cis*-FCL isomers were formed in excess.
[d] The *cis*-(1*R*,2*S*)-FCL and the *trans*-(1*R*,2*R*)-FCL enantiomers were formed in excess.
[e] Reaction at 273 K in solvent mixture AcOH/THF 1/1.

of FCN, the quinuclidine N plays an essential role in binding the substrate in the enantiodiscriminating step. Using MeOCD as the modifier resulted in low ee's in THF, similar to the hydrogenation of trifluoroacetophenones [13] and opposite to that of trifluoro-β-diketones [17] in toluene. However, in AcOH or AcOH/THF, MeOCD led to a moderate increase in ee compared with CD. In the hydrogenation of trifuoro-β-ketoesters [31] and trifluoro-β-diketones [17], the same change in the modifier structure in acidic solvents led to a pronounced increase in ee. The observed modifier effect resembled that reported for the hydrogenation of EFA [19], except the unreacted enantiomer of the latter substrate was racemized during hydrogenation. To verify whether the racemization of FCN occurred during hydrogenation in acidic solvent, the composition of the reaction mixture was followed over time in the absence and presence of MeOCD modifier (Fig. 1).

In contrast with 2-methoxycyclohexanone [20], with FCN in the presence of modifier, the differences between the hydrogenation rates of the two enantiomers are much smaller. The hydrogenation of both FCN enantiomers was accelerated by the presence of the chiral modifier. In the presence of MeOCD, the *S* enantiomer reacted at a ca. 2.5 times higher initial rate than the *R* enantiomer; this decreased to a factor of 1.5 at 80% conversion. These rate differences resulted in kinetic resolution of FCN. Furthermore, according to the data presented in Fig. 1b, the racemization of the accumulated enantiomer oc-

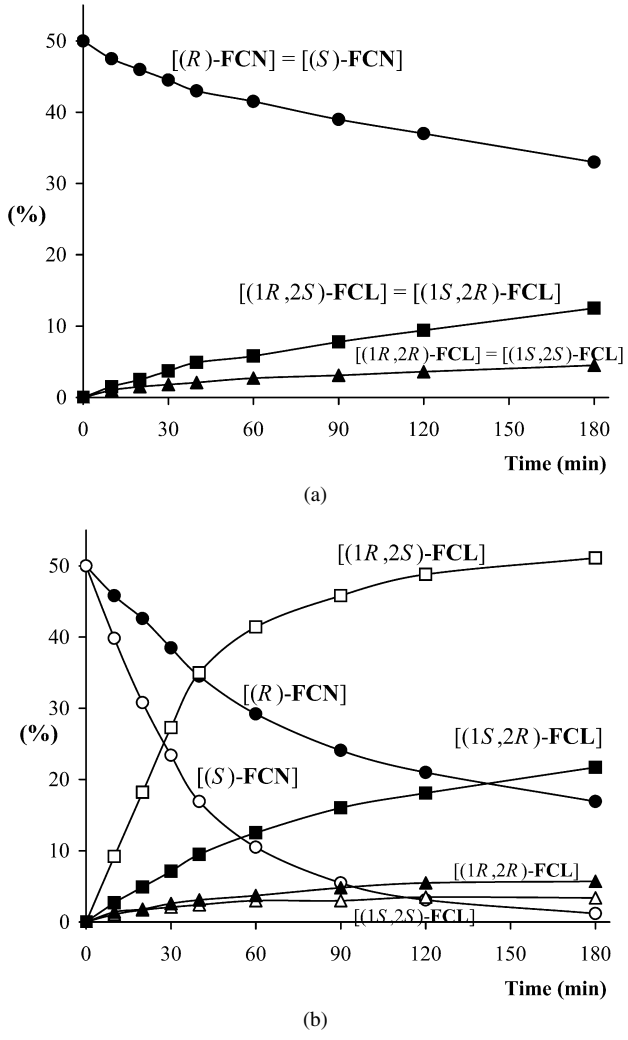
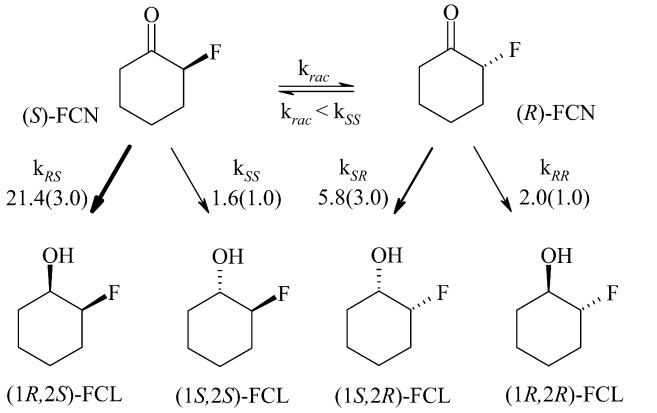


Fig. 1. Product distribution in the hydrogenation of racemic FCN over 5% Pt/Al_2O_3. Reaction conditions: 50 mg catalyst, 3 ml AcOH/THF 1/1, 0.1 ml FCN, 0.1 MPa H_2, 273 K, without modifier (a) and using 5 mg MeOCD (b); (FCN = 2-fluorocyclohexanone, FCL = 2-fluorocyclohexanol).

curred at a much lower rate compared with the hydrogenation. Thus, the sum of the concentration of the compounds having the 2*S* configuration ([*S*-FCN] + [1*R*,2*S*-FCL] + [1*S*,2*S*-FCL]) had about the same value as that having the 2*R* configuration ([*R*-FCN] + [1*S*,2*R*-FCL] + [1*R*,2*R*-FCL]) at low reaction times, and their ratio changed gradually up to 55/45 in favor of the compounds with the 2*S* configuration after 3 h reaction. The racemization probably occurs by the well-known equilibrium process between the keto species and the corresponding enol species. Although this equilibrium is shifted toward the enol by the presence of fluorine in the α position due to the formation of an intramolecular hydrogen bond [17], in protic polar solvents the shift to the keto form was favored by intermolecular hydrogen bonds [32]. This resulted in a low racemization rate of FCN and a lack of dynamic kinetic resolution, in contrast to the hydrogenation of EFA.

Accordingly, the reaction pathways for the hydrogenation of FCN over cinchona alkaloid-modified Pt catalyst are presented in Scheme 4, highlighting the preferred reaction routes. The stereoselectivities of the hydrogenation of the FCN enantiomers



Scheme 4. Reaction pathways for the hydrogenation of racemic 2-fluorocyclohexanone over OMeCD-modified Pt/Al_2O_3. Pseudo first order rate constants (h^{-1}/g catalyst) are shown near the arrows; values in parenthesis are the pseudo first order rate constants for the reaction in absence of modifier, reaction conditions see Fig. 1.

are well illustrated by the pseudo–first-order rate constants included in Scheme 4, calculated according to the method and equations used in the case of 2-methoxycyclohexanone [20].

Finally, we stress that our present study is the first to report the enantioselective hydrogenation over chirally modified heterogeneous catalyst of a ketone activated solely by one α fluorine atom. Although, the high de's were accompanied by moderate ee's, up to 59%, our study demonstrates that the enantioselective hydrogenation over cinchona-modified supported Pt catalyst of fluoroketones may become a viable alterative for the production of optically enriched fluoroalcohols. The kinetic resolution of the substrate was observed during its hydrogenation; however, due to the low racemization rate of the accumulated enantiomer, the dynamic kinetic resolution of the substrate did not occur. Our findings broaden the scope of this extensively studied heterogeneous catalytic system.

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