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Highly Enantioselective Oxidation of Ferrocenyl Sulfides

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Abstract:

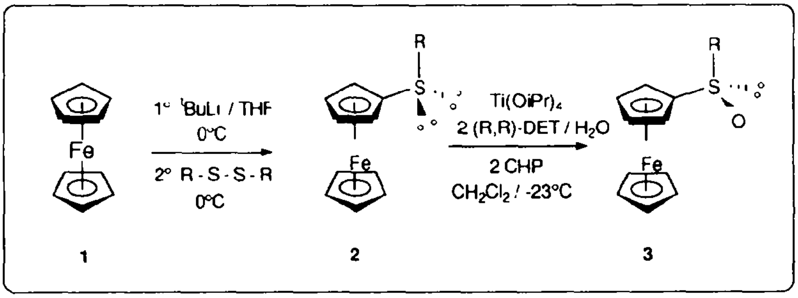
Oxidation of aryl or alkyl ferrocenyl sulfides by cumene hydroperoxide was investigated in presence of chiral titanium complexes. It was found that the preparation of the combination $Ti(O^iPr)_4$ / DET / H_2O = 1 : 2 : 1 is very sensitive to time and temperature. In suitable conditions some aryl ferrocenyl sulfoxides almost enantiomerically pure (> 99% ee) could be produced.

Introduction

Asymmetric oxidation of sulfides can be performed by various ways.[2] One of the most efficient approaches is the oxidation by an hydroperoxide in presence of a stoichiometric or catalytic amount of a chiral titanium complex. We described the use of the combination $Ti(O^iPr)_4$ / (R,R)-diethyl tartrate (DET) / H_2O = 1: 2: 1[3,4] sometimes called the Kagan reagent.[5] Another modification (the Modena reagent) has been also used, it is based on the combination $Ti(O^iPr)_4$ / diethyl tartrate = 1 : 4 . The Kagan reagent has been successfully applied to many cases (for example see refs 7-9), the Modena reagent was also useful.[5,10]. It seems that according to the substrate one or the other reagent is the more appropriate. Because of our interest in the area of chiral ferrocenes[11,12] we wished to prepare various ferrocenyl sulfoxides of high ee's. We wanted to explore the asymmetric oxidation of ferrocenyl sulfides as a potential route to chiral ferrocenyl sulfoxides. We present here the results obtained by using cumene hydroperoxide (CHP) in the presence of chiral titanium complexes.

Results

The first attempts were performed under the conditions previously described by us for aryl sulfides[4]. The sulfoxides were isolated by flash chromatography on silica gel, avoiding misinterpretation of ee's because of enantiomeric fractionation in the chromatography.[13] The ee's were rather low, some are described in ref. 13 for example.



Scheme 1

In order to accelerate the formation of sulfoxides in the oxidation of sulfides **2** (scheme 1, the oxidation is quite slow), 2 equivalents of cumene hydroperoxide were used instead of 1.1 as usual. Moreover it was suspected that the preparation of the chiral titanium complex (Kagan reagent) could be an important parameter if there are several titanium complexes simultaneously generated. We discovered that the time and the temperature at which is realized the mixing of $Ti(OiPr)_4$ and DET can be a very important parameter, according to the structure of the sulfide to oxidize. We devised two procedures (methods A and B) for the preparation of the titanium complex (Kagan reagent). The best procedure (method A) involves the addition of $Ti(OiPr)_4$ on DET, followed by addition of 1 equivalent of water after t_1 = 3-4 minutes. The whole process is performed at 27°C. Subsequently the mixture is kept at the same temperature for a time t_2 = 20-25 minutes. Then the temperature is decreased to -23°C, the sulfide is added and finally the reaction starts after the slow addition of a cooled solution (at -23°C) of cumene hydroperoxide (2 equiv). Representative results are indicated in Table 1. When the complex is prepared at 20°C (method B) there is a significant decrease of the enantioselectivity for oxidation of aryl ferrocenyl sulfides (the two first entries in table 1), but not for the other sulfides (Table 1). The Modena reagent (anhydrous conditions) was prepared with 3 or 4 equivalents of DET (methods C and D), the enantioselectivity decreases significantly (Table 1) respective to method A.

Table 1

Asymmetric oxidation of ferrocenyl aryl and ferrocenyl alkyl sulfides Fc-S-R by the Kagan and Modena reagents using different methods of the Ti-complex preparation (see also text)

	Method A [a]		Method B [b]		Method C [c]		Method D [d]	
R	ee (%)[e]	yield[f], time	ee (%)[c]	yield[f], time	ee (%)[e]	yield[f], time	ee (%)[c]	yield[f], time
Ph	>99	86%, 62h	77	73%, 96h	74	80%, 48h	77	65%, 64h
p-Tol	>99	78%, 65h	64	60%, 120h	/		79	70%, 65h
t-Bu	95	81%, 69h	94	55%,120h	90	40%,120h	/	
n-Bu	31	63%, 13h	/		/		8-9	52%, 14h
Me	92	72%, 16h	90	81%, 18h	/		/	
i-Pr	78	61%, 15h	84	63%, 22h	/		/	

a : $DET/Ti(OiPr)_4/H_2O/CHP$: 2/1/1/2, at 27°C, t_1>3 min, reaction at -23°C
b : $DET/Ti(OiPr)_4/H_2O/CHP$: 2/1/1/2, at 20°C, $t_1$2-3 min, reaction at -23°C
c : $DET/Ti(OiPr)_4/H_2O/CHP$ 4/1/0/2, at 27°C, t_1>30 min, reaction at -23°C
d : $DET/Ti(OiPr)_4/H_2O/CHP$: 3/1/0/2, at 27°C, t_1>30 min, reaction at -23°C
e Measured by HPLC on Chiralcel OD-H
f Isolated yield

In a further step the potential of method A was investigated for the oxidation of a range of ferrocenyl sulfides (Table 2). Very high ee's were obtained (at least 99 %) for the oxidation of phenyl and p-tolyl ferrocene sulfides (entries 1 and 2, table 2). A strong decrease is observed for p-chlorophenyl sulfoxide (43 % ee), such an electronic effect had already been noticed in the asymmetric oxidation of aryl methyl sulfides.[3] Excellent enantioselectivities were also achieved for the synthesis of t-butyl or methyl ferrocenyl sulfoxides. Less hindered alkyl groups, especially linear alkyls are detrimental to the enantioselectivity, the same trend has been found in the oxidation of alkyl sulfides.[3,4] Sterically hindered ferrocenyl aryl sulfides (such as 1-naphthyl and mesityl) could not be oxidized in satisfactory yields even at higher temperatures and for longer reaction times.

Table 2

Asymmetric oxidation of selected ferrocenyl aryl and ferrocenyl alkyl sulfides Fc-S-R by the Kagan reagent using methods A and B (see text)

n°	R-S(O)-Fc	Reaction time , hr	e.e.(%) [a]	Yield (%) [b]	[α]D [c]
1	*p*-Tol [c]	65	>99	78	- 305 (R)[d]
2	Ph [e]	62	>99	86	-182 (R)[d]
3	*p*-Cl Ph [c]	66	45	92	/
4	*t*-Bu [c]	69	95	81	- 339 (R)
5	Me [e]	16	92	72	-184 (R)[d]
6	*i*-Pr [f]	22	84	62	-362 (R)[d]
7	*n*-Bu [e]	13	31	63	/
8	*n*-Octyl [f]	18	2-3	55	/

a : Measured by HPLC on Chiralcel OD-H
b : Isolated yield
c : (c = 0.5; $CHCl_3$), for the enantiomerically pure sulfoxide after recristallisation,
d : Absolute configuration based on the model in ref. 14
e : $DET/Ti(OiPr)_4/H_2O/CHP$: 2/1/1/2, at 27°C, $t_1>3$ min, reaction at -23°C
f : $DET/Ti(OiPr)_4/H_2O/CHP$: 2/1/1/2, at 20°C, $t_1=2\text{-}3$ min, reaction at -23°C

As an example the asymmetric synthesis of ferrocenyl p-tolyl sulfoxide is described below:

6 mL of tert-butyl lithium (1.7M, 10 mmol) were added to a solution of ferrocene (2.2g, 12 mmol) in THF (10 mL) at 0°C. The reaction mixture was stirred for 2 h, and gave 7 mmol of ferrocenyl lithium.[15] The p-tolyl disulfide (3.2 g, 13 mmol) were added at room temperature. After 3 h, the mixture was poured in 50 mL of NaOH (2M) and extracted with Et_2O (3x50 mL). The combined organic layers were dried and the solvent was evaporated under vacuum. The residue was loaded to a silica gel column and eluted with cyclohexane. The flash chromatography afforded 2.74 g (8.9 mmol, 74%) of cristallised sulfide which are used in the following oxidation (method A) :

Titanium tetra-isopropoxide (1 mL, 3.4 mmol) was added to a solution of (R,R) diethyl tartrate (1.2 mL, 6.8 mmol) in dichloromethane at 27°C. The mixture was stirred for t_1 = 3 min (or more), then one equivalent of water (62 µL, 3.4 mmol) was added with a microliter syringe and after 20 min (t_2) the mixture was cooled at -23°C under argon. Ferrocenyl p-tolyl sulfide (1.05 g, 3.4 mmol) was added and stirring was continued for an additional 20 min. Then, cumene hydroperoxide (1.3 mL, 7 mmol) in 3 mL of dichloromethane (precooled at -23°C) was added dropwise and the whole system was kept 65 h at - 23°C (unstirred). The mixture was added to a solution of ferrous sulfate heptahydrate (9 g, 30 mmol), citric acid (3 g, 14 mmol), water (100 mL), dioxane (50 mL) and ether (50 mL). The two-phase mixture was stirred for 25 min and then transferred to a separatory funnel and extracted with Et_2O (3 x 50 mL). The combined organic layers were treated with NaOH (2M, 50 mL). The two-phase mixture was stirred vigorously for 60 min to remove DET. After the separation, the organic layers were dried over $MgSO_4$ and concentrated to give the crude product. A flash chromatography with ethyl acetate / cyclohexane : 1/1 gave the sulfoxide with 78% yield (0.86g, 2.65 mmol) and >99% e.e.

The new procedure for the asymmetric oxidation of aryl ferrocenyl sulfides allows to reach an *almost complete enantioselectivity* (≥ 99 %) in the corresponding sulfoxides when the aryl group is devoid of electron-withdrawing groups.[16] This observation substantially enlarges the scope of asymmetric oxidation as a way to prepare enantiopure sulfoxides and demonstrate the importance of the initial step (i.e. the preparation of the titanium reagent). This gives hope to enhance the enantioselectivity in many other cases of asymmetric oxidation of sulfides.

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(16) The procedure A does not improve the ee's already described for asymmetric oxidation of aryl methyl sulfides.[4] The structure of the class of compounds is key for finding the suitable titanium reagent, as already noticed in another case [17].

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