Selectivity Enhancement for the *Jacobsen – Katsuki* Epoxidation in Fluorinated Solvents

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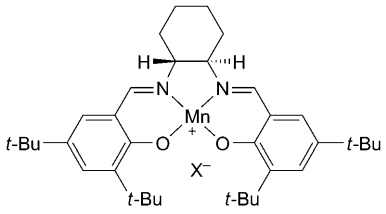
In 1,1,1,2,3,4,4,5,5,5-Decafluoropentane using 2-phenylpyridine *N*-oxide as donor ligand, the enantioselectivity of the *Jacobsen – Katsuki* epoxidation is improved up to 10% ee as compared to established protocols.

1. Introduction. – The asymmetric olefin epoxidation is one of the most useful methods for the synthesis of enantiomerically enriched compounds [1]. Chiral Mn(salen) catalysts for the epoxidation of unfunctionalized olefins have been developed by *Jacobsen* and co-workers [2], and by *Katsuki* and co-workers [3] starting in 1990. While the enantioselectivities are good-to-excellent for a broad range of olefin substrates, the method still suffers from limitations (*e.g.*, with terminal olefins), making further improvements desirable.

With the catalyst structure (*Fig.*), optimized and more or less fixed, major improvements were achieved by refining the reaction conditions [4]. Typical reaction conditions using the *Jacobsen* catalyst **1a** include use of NMO (*N*-methylmorpholine *N*-oxide) as promoter (5 equiv. based on substrate) and *m*-CPBA (*meta*-chloroperbenzoic acid) or NaOCl as oxidant in CH_2Cl_2 at 0° [5].

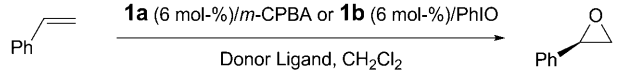


(*R*,*R*)-**1a** X = Cl
(*R*,*R*)-**1b** X = BF_4

Figure. *The* Jacobsen *catalyst*

2. Results and Discussion. – The first step in our optimization of the reaction conditions was the search for a more effective promoter ligand (*Table 1*). Styrene was chosen as an example for a 'difficult' substrate for *Jacobsen* conditions (terminal olefin, 46% ee with (*R*,*R*)-**1a**/*m*-CPBA and NMO at 0°). The combination of (*R*,*R*)-**1a** and

Table 1. *Epoxidation of Styrene under Different Reaction Conditions*



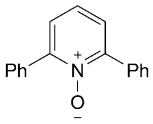
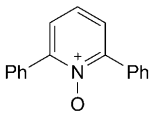
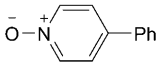
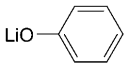
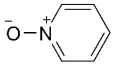
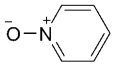
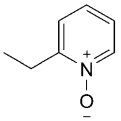
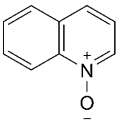
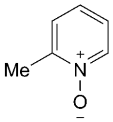
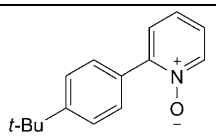
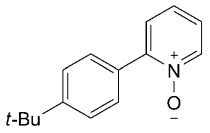
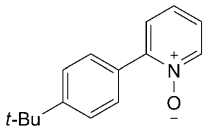
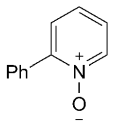
Entry	Donor ligand[a])	Catalytic system	Temp. [°]	Yield [%][b])	ee [%][c])
1	–	(*R*,*R*)-**1a**/*m*-CPBA	0	23	0
2	*t*-BuOK	(*R*,*R*)-**1b**/PhIO	r.t.	91	13
3 [4b]	–	(*R*,*R*)-**1a**/PhIO	r.t.	17	19
4	–	(*R*,*R*)-**1b**/PhIO	r.t.	36	23
5	–	(*R*,*R*)-**1b**/PhIO	−5	21	36
6		(*R*,*R*)-**1b**/PhIO	−5	30	34
7		(*R*,*R*)-**1a**/*m*-CPBA	−5	2	40
8	$(Me_2N)_3P{=}O$	(*R*,*R*)-**1b**/PhIO	r.t.	19	36
9	$Et_3P{=}O$	(*R*,*R*)-**1b**/PhIO	r.t.	37	40
10		(*R*,*R*)-**1a**/*m*-CPBA	−5	78	40
11[d])		(*R*,*R*)-**1b**/PhIO	r.t.	66	41
12		(*R*,*R*)-**1a**/*m*-CPBA	−5	52	42
13		(*R*,*R*)-**1b**/PhIO	−5	71	45
14	NMO	(*R*,*R*)-**1a**/*m*-CPBA	0	97	46
15		(*R*,*R*)-**1a**/*m*-CPBA	−5	90	47
16		(*R*,*R*)-**1b**/PhIO	−5	65	48
17		(*R*,*R*)-**1a**/*m*-CPBA	−5	95	48

Table 1 (cont.)

Entry	Donor ligand[a])	Catalytic system	Temp. [°]	Yield [%][b])	ee [%][c])
18		(*R*,*R*)-**1b**/PhIO	– 5	73	49
19		(*R*,*R*)-**1a**/*m*-CPBA	– 5	91	50
20		(*R*,*R*)-**1b**/PhIO	– 5	78	51
21		(*R*,*R*)-**1b**/PhIO	– 40	68	53

[a]) Styrene/*m*-CPBA/donor ligand 1 : 2 : 2.5 for **1a**/*m*-CPBA, styrene/PhIO/donor ligand 1 : 2 : 0.12 for **1b**/PhIO. [b]) Determined by capillary GC integration against mesitylene as internal standard. [c]) Determined by capillary GC on a *Hydrodex-β-TBDAc* chiral column. [d]) Prepared *in situ* by addition of excess BuLi to phenol.

PhIO [6] (or *m*-CPBA) without promoter gives poor yields and selectivities (*Table 1*, *Entry 3*). Iodosobenzene is obviously not able to replace the strongly coordinating Cl^- ligand [7a]. However, addition of donor ligands results in medium-to-good yields of epoxide (see, *e.g.*, *Table 1*, *Entries 10* and *13*). *tert*-Butoxide gave very poor enantioselectivies, in contrast to phenolate (*Table 1*, *Entries 2* and *11*). Addition of sterically demanding ligands (*Table 1*, *Entries 6* and *7*), phosphine oxide, or HMPT (hexamethylphosphoric triamide; *Table 1*, *Entries 8* and *9*) led to similar results as did reactions without any donor ligand (*Table 1*, *Entries 4* and *5*). The best results with regard to yield and enantioselectivity were obtained with substituted pyridine *N*-oxides (*Table 1*, *Entries 12–21*). Addition of 2-phenylpyridine *N*-oxide as donor ligand (*Table 1*, *Entries 20* and *21*) gave the best enantioselectivities overall. Analysis of *Table 1* confirms our mechanistic view that nonplanar conformations of the active catalyst will be effected by an interplay between binding strength and steric demand of the axial ligand [7b][7c].

Catalyst **1b** has a distinct advantage over the original protocol employing catalyst **1a** together with 5 equiv. of NMO (based on substrate) [5]. Studies with **1a**/*m*-CPBA had shown that adddition of donor ligand below 2.5 equiv. (based on substrate) results in much lower enantioselectivies than those listed in *Table 1*. With the use of the non-coordinating BF_4^- anion, PhIO and the *N*-oxide do not have to compete with the anion

for the axial position; thus, the amount of promoter can be reduced to 2 equiv. based on **1b**, *i.e.*, only 0.12 equiv. based on substrate!

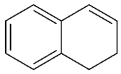
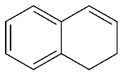
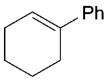
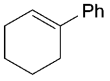
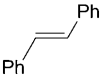
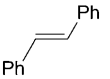
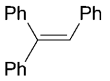
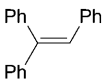
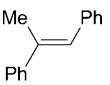
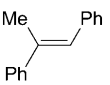
Compared to catalyst re-design or introduction of new promoters, an even less demanding option to improve selectivities is the change of solvent. Solvent effects have so far not been studied systematically for the *Jacobsen–Katsuki* epoxidation [8]. Our new epoxidation protocol (*Table 1, Entries 20* and *21*) was applied in a variety of solvents with differing polarities (*Table 2*). 1,1,1,2,3,4,4,5,5,5-Decafluoropentane, which is reasonably priced, gave by far the best enantioselectivities in styrene epoxidation with the (*R*,*R*)-**1b**/PhIO catalytic system at room temperature, considerably better than established epoxidation methods in 'conventional' solvents [1a][4a][5]. From the results in *Table 2*, no direct correlation of the catalyst efficiency with the polarity of the solvent is evident, nor can the enantioselectivities be explained by some 'magic' fluorine effect. In fact, reactions in fully perfluorated solvents give very poor yields and selectivities. While the reason for this surprising solvent effect remains unresolved at the moment, this effect can be observed with a variety of olefins[1]). For the substrates shown in *Table 3* (only a limited number of comparative data with catalyst **1a** is available), enantioselectivities achieved with (*R*,*R*)-**1b**/PhIO and 2-phenylpyridine *N*-oxide as promoter in 1,1,1,2,3,4,4,5,5,5-decafluoropentane are as good as literature reference or better, up to 10% ee for styrene. With the same general conditions (room temperature, stoichiometry) applied to all substrates, there is a clear trend for improved enantioselectivities, especially in the case of difficult substrates such as styrene. Optimization of the reaction conditions for individual substrates leaves further room for improvements.

Table 2. *Styrene Epoxidation in Different Solvents*

Solvent	Yield [%]	ee [%]
Perfluoroheptane	7	21
THF	2	36
CCl_4	78	38
Benzene	84	39
CH_2Br_2	84	45
CH_2Cl_2	67	46
$CHCl_3$	56	47
1,2,3-Trichloropropane	73	47
1,2-Dichloroethane	73	48
1,3-Dichloropropane	80	48
1,1,2,2-Tetrachloroethane	73	49
1,1-Dichloroethane	80	51
1,1,2,2,3,3,4,4,5,5,6,6-Dodecafluorohexane	82	52
1,1,1,2,3,4,4,5,5,5-Decafluoropentane	98	56

[1]) One of the referees suggested that match/mismatch combinations of diastereoisomeric 1,1,1,2,3,4,4,5,5,5-decafluoropentane molecules with the reagents involved might play a role in the observed selectivities. 1,1,1,2,3,4,4,5,5,5-Decafluoropentane used in our experiments was purchased from different suppliers (*ABCR*, *Alfa Aesar*) and always gave reproducible selectivities. It remains to be tested whether or not the use of stereochemically pure 1,1,1,2,3,4,4,5,5,5-decafluoropentane would give different results.

Table 3. *Epoxidation of Different Substrates with Catalyst (*R,R*)-***1b*** (6 mol-%), *PhIO* (2 equiv.), *2-Phenylpyridine* N*-Oxide* (12 mol-%) *in 1,1,1,2,3,4,4,5,5-Decafluoropentane for 24 h*

Entry	Substrate	Catalytic System	Temp. [°]	Yield [%][a])	ee [%][b])
1 [5]		(*R*,*R*)-**1a**/*m*-CPBA	0	97	46 (*R*)
2		(*R*,*R*)-**1b**/PhIO	r.t.	98[c])	56 (*R*)
3 [1a]		(*R*,*R*)-**1a**/NaOCl$_{(aq)}$	0	67	86 (1*S*,2*R*)
4		(*R*,*R*)-**1b**/PhIO	r.t.	57	90 (1*S*,2*R*)
5 [4a]		(*R*,*R*)-**1a**/NaOCl$_{(aq)}$	0	69	93 (1*S*,2*S*)
6		(*R*,*R*)-**1b**/PhIO	r.t.	54	93 (1*S*,2*S*)
7 [4a]		(*S*,*S*)-**1a/**NaOCl$_{(aq)}$	4	–[d])	25 (1*R*,2*S*)
8		(*R*,*R*)-**1b**/PhIO	r.t.	51	31[e]) (1*S*,2*R*)
9 [4a]		(*R*,*R*)-**1a**/NaOCl$_{(aq)}$	0	97	92 (*S*)
10		(*R*,*R*)-**1b**/PhIO	r.t.	61	91[e]) (*S*)
11 [4a]		(*R*,*R*)-**1a**/NaOCl$_{(aq)}$	0	87	88 (1*S*,2*S*)
12		(*R*,*R*)-**1b**/PhIO	r.t.	70	93 (1*S*,2*S*)

[a]) Isolated, not optimized yields except for styrene oxide. [b]) Determined by capillary GC on a *Hydrodex-β-TBDAc* chiral column except for (*E*)-stilbene oxide and triphenylethylene oxide. [c]) Determined by capillary GC integration against mesitylene as internal standard. [d]) Yield is not given in [4a]. [e]) Determined by chiral HPLC (method for *Entries 8* and *10:* heptane/IPA 90 : 10, 260 nm, 1 ml/min).

Experimental Part

General. Jacobsen catalyst **1a**, solvents (*Table 2*), and substrates (*Table 3*) were purchased from *ABCR*, *Sigma-Aldrich*, *Fluka*, *Alfa Aesar*, and *Acros.* THF and benzene were dried over Na. Fluorinated and chlorinated solvents (*Table 2*) were freshly distilled and collected under Ar prior to use. TLC: *Silica gel 60 F_{254} 25* aluminium sheets 20 × 20 cm from *Merck KGaA Co.*, D-Darmstadt. Chiral HPLC: *Merck HITACHI* UV detector: *L-7400*, pump: *Merck HITACHI* pump *L-7100*, chiral column type: *Chiralpak*

AD-H 0.46 cm ∅ × *25 cm* from *Daicel*. Chiral GC: *Agilent Technologies 6890N Network GC* system, chiral GC column: *Hydrodex-β-TBDAc*. GC/MS: GC *Varian 3400*, achiral GC column: *Macherey-Nagel optima 5 MS* 30 m × 0.25 mm, 0.25 μm film). ^{1}H- and ^{13}C-NMR spectra: *Varian 300* and *Bruker 500* spectrometer. MS: *Thermo TSQ 700.*

General Procedure for Olefin Epoxidation. [Mn^{III}(salen)X] (0.058 mmol, 0.06 equiv.) and the donor ligand are dissolved at r.t. in 10 ml of freshly distilled solvent under Ar. In the case of oxidation with *m*-CPBA, 2.40 mmol (2.5 equiv.) of donor ligand were added; in the case of PhIO oxidation, 0.115 mmol (0.12 equiv.) of donor ligand were used. With stirring, the substrate olefin (0.96 mmol, 1 equiv.) was added to the soln., and 2 equiv. (1.92 mmol) of either PhIO or *m*-CPBA was added slowly (*ca*. 5 min). The reaction mixture was then stirred at r.t. for 5 h (*m*-CPBA) or 24 h (PhIO). Workup: If the oxidant was *m*-CPBA, the reaction mixture was washed two times with 5% Na_2CO_3, and the org. phase was dried (Na_2SO_4). The org. phase was filtered through a short SiO_2 column and eluted with AcOEt/cyclohexane. If the oxidant was PhIO, the crude mixture could be filtered directly through a SiO_2 column and eluted with AcOEt/cyclohexane. The absolute configurations of the major epoxide products (except for styrene oxide) were not determined but assigned according to the literature.

Preparation of N-*Oxide Ligands.* The *N*-oxides used as promoters were prepared by *m*-CPBA oxidation from their respective pyridine or quinoline precursors according to [9] and [10]. The spectroscopic data of the *N*-oxides thus obtained are in agreement with those given in the literature.

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