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# Enantiopure *p,p'*-Disubstituted 1,2-Diphenylethane-1,2-diols as Chiral Inducers in the Ti-mediated Oxidation of Sulfides: a Case of Reversal of Asymmetric Induction by Fluorine Substitution

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**Abstract:** In the asymmetric oxidation of methyl *p*-tolyl sulfide, (**2a**), and benzyl phenyl sulfide (**2b**) by TBHP, mediated by a titanium complex with enantiopure (*R,R*)-*p,p'*-disubstituted-1,2-diphenylethane-1,2-diols, both the unsubstituted diol (*R,R*)-**1a** and the *p*-OMe substituted diol (*R,R*)-**1b** lead to sulfoxides of *S* configuration, with ee up to 99%. On the contrary the *p*-$CF_3$ substituted ligand (*R,R*)-**1c** leads to significantly lower ee and in the case of **2a** a reversal of asymmetric induction is observed. 

The introduction of fluorine atoms into chiral organic compounds leads to new substances often endowed with unique biological or physical properties, therefore enantiopure organofluorine compounds are acquiring particular interest in biorganic[1] and material chemistry.[2] Fluorine atoms can induce strong electronic perturbation[1c,d] and they are able to coordinate metal atoms more strongly than oxygen.[3] The influence of fluorine substitution is known also in asymmetric synthesis[4] and recently, employing oppositely configurated 3,4-difluoro and 3,4-dihydroxypyrrolidines[5] as Ti-ligands in the Sharpless asymmetric epoxidation, it was observed that the former affords higher ee than the latter and induces opposite chirality thus demonstrating that "*the modes of binding of the hydroxy and fluoro catalyst had important features in common*". Prompted by this novel and important report, we show herein that the introduction of fluorine substituents on a chiral ligand causes a reversal[6] of the absolute configuration induced in the products even if the absolute configuration of the ligand is the same. We have recently set up a new method[7] (Scheme) for the asymmetric oxidation[8] of aryl sulfides by TBHP, based on a catalytic precursor formed *in situ* by reacting (*R,R*)-1,2-diphenylethane-1,2-diol (**1a**), Ti(*i*-PrO)$_4$ and water (ratio 0.1/0.05/1): alkyl aryl and aryl benzyl sulfoxides are obtained in 60-80% chemical yield with ee up to 99%.

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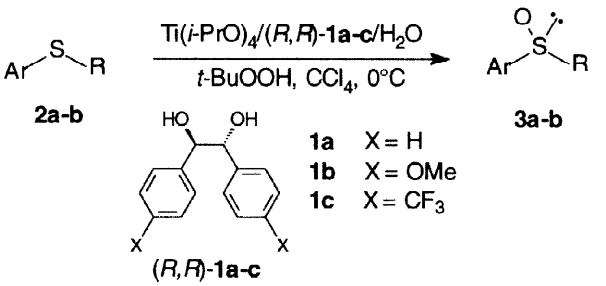
**Scheme**




Since many different enantiopure 1,2-diarylethane-1,2-diols can be easily prepared *via* asymmetric dihydroxylation[9] of (*E*)-1,2-diarylethenes, the effect of the aryl substituents on the chemical and stereochemical outcomes of this reaction can be studied. We then prepared[10] the enantiopure diols (*R,R*)-**1b** and (*R,R*)-**1c** by quinidine mediated asymmetric *syn*-dihydroxylation of the corresponding *p,p'*-disubstituted (*E*)-1,2-diarylethenes.[11,12] The (*R,R*) absolute configuration was assigned to (+)-**1b** by comparison of its $[\alpha]_D$ with literature values[12] and to (+)-**1c** on the basis of the Sharpless stereochemical rule[9,13] and by the analysis of the CD spectrum of its 2,2-dimethyl-1,3-dioxolane.[14] Once the ee and the absolute configuration of (*R,R*)-(+)-**1b** and (*R,R*)-(+)-**1c** were established with certainty they were tested as chiral ligands in the Ti-catalyzed asymmetric oxidation of methyl *p*-tolyl sulfide (**2a**) and benzyl phenyl sulfide (**2b**), and the results compared (Table) with those given by the unsubstituted diol (*R,R*)-**1a**.

**Table. Enantioselective oxidations employing diols (*R,R*)-1a-c as ligands**[a]

| entry | diol | sulfide | sulfoxide (%)[b] | ee (%) | Abs. conf.[c] |
|---|---|---|---|---|---|
| 1 | **1a** | **2a** | 62 | 80[d] | *S* |
| 2 | **1a** | **2b** | 73 | 99[e] | *S* |
| 3 | **1b** | **2a** | 60 | 48[d] | *S* |
| 4 | **1b** | **2b** | 65 | 92[e] | *S* |
| 5 | **1c** | **2a** | 70 | 26[d] | ***R*** |
| 6 | **1c** | **2b** | 80 | 18[e] | *S* |

[a] Conditions: sulfide/(*R,R*)-**1**/Ti(*i*-PrO)$_4$/$H_2O$ = 1.0/0.1/0.05/1.0 in $CCl_4$ at 0°C under $N_2$ atmosphere, reaction time 2 h, 2 equivalents of 70% TBHP in water as oxidant. [b] Isolated yields, amount of sulfone < 10%. [c] Determined by comparison of $[\alpha]_D$ with literature values, see ref. 15 [d] Determined by HPLC on a Daicel Chiralcel OB column. [e] Determined by HPLC on a Daicel Chiralcel OJ column.

The above results reveal that whilst the chemical yields obtained with the three diols are similar (60-80%), the presence of a substituent in the *para* position of the benzene ring heavily affects the ee of the products. The higher ee's with both the sulfides **2a** and **2b** were in fact obtained with the unsubstituted diol (*R,R*)-**1a** (entries 1 and 2) **2b** resulting a particularly good substrate. The presence of a OMe group in *para* position in (*R,R*)-**1b** led to a decrease in the enantioselectivity of the reaction (entries 3 and 4) especially with **2a** which

afforded a 48% ee. The use of the *p*-$CF_3$ substituted diol (*R*,*R*)-**1c** dramatically decreased the ee (18%) obtained with the good substrate **2b** and, unexpectedly, afforded the *p*-tolyl methyl sulfoxide (**3a**) with opposite stereochemistry (*R*) with respect to those obtained with the other diols. In summary, for the series (*R*,*R*)-**1a**, (*R*,*R*)-**1b**, (*R*,*R*)-**1c** we have not only a reduction of the absolute value of the ee but even a reversal of the asymmetric induction: diols with the same chiral backbone induce different enantioselectivity depending on their substituents onto the phenyl ring. A detailed mechanistic rationale of this effect cannot be presently formulated, the only possible comments being as follows: the presence of both the OMe and $CF_3$ group, i.e. coordinating moieties, can lead to the formation of new Ti complexes (different from those resulting from the interaction between a titanium atom and the unsubstituted ligand (*R*,*R*)-**1a**) having different structure, therefore different reactivity and, possibily, opposite stereoselectivity. As a consequence, competing mechanisms may take place, leading to an overall reduction of stereoselectivity (entry 1 vs 3, 2 vs 4). The strong reduction of ee and the reversal of asymmetric induction observed with the fluorine substituted diol (*R*,*R*)-**1c** (entries 6 and 5) could be interpreted as determined by a relevant intervention of the second mechanism (i.e. the mechanism mediated by the species derived from the coordination of the *para* substituents to the titanium) which becomes prevailing in the case of worse substrate **2a**. The hypothesis of the intervention of a F-Ti bond which affects the asymmetric induction in this reaction is in keeping with the observation[5] of Marson and Melling. In conclusion, we have described herein the first example in which the introduction of fluorine substituents onto a chiral ligand causes a reversal of the enantioselectivity. Although the reason of such stereochemical switch is currently unclear, this finding affords a further information about the important role of fluorine substituted ligands in asymmetric synthesis.

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6. It has to be noticed that a reversal of asymmetric induction in the stoichiometric Ti-mediated oxidation of sulfides has been already observed using (*R,R*)-1,2-bis(4-methoxyphenyl)ethane-1,2-diol and (*R,R*)-1,2-bis(2-methoxyphenyl)ethane-1,2-diol as chiral inducer [Yamamoto, K.; Ando, H.; Shuetake, T.; Chikamatsu, H. *J. Chem. Soc., Chem. Comm.* **1989**, 754]. Furthermore (*R*)-(+)-2,2'-dihydroxy-1,1'-binaphthyl and (*R*)-(-)-2,2'-dihydroxy-5,5',6,6',7,7',8,8'-octahydro-3,3'-dinitro-1,1'-binaphthyl used as catalyst in the same reaction induce, respectively, the formation of (*R*) and (*S*) *p*-tolyl methyl sulfoxide [Reetz, M. T.; Merk, C.; Naberfeld, G.; Rudolph, J.; Griebenow, N.; Goddard, R. *Tetrahedron Lett.* **1997**, *38*, 5273]. However in neither the above cases organofluorine ligands are involved.

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10. All new compounds gave satisfactory spectral data ($^1$H NMR, $^{13}$C NMR and mass spectra) and elemental analysis. The ee's (≥98%) were determined directly upon the diols using c.s.p. Chiralcel OJ and hexane/2-propanol mixtures as eluent. Selected data for **1c**: $[\alpha]_D$= + 76.7° (*c* 0.95, $CHCl_3$); ee > 99%; mp = 132 °C; $^1$H NMR (300 MHz, $CDCl_3$) δ 1.58 (s, 2H), 4.77 (s, 2H), 7.25 (d, *J* 9.1 Hz, 4H), 7.52 (d, *J* 9.1 Hz, 4H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 78.39, 125.13, 125.20, 127.28, 130.68, 143.32.

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14. The CD spectrum (acetonitrile) of the 2,2-dimethyl-1,3-dioxolane of (+)-**1c** shows Cotton effects in correspondence of the $^1L_b$, $^1L_a$ and $^1B$ transition of the substituted benzene chromophores [Michl, J.; Thulstrup, E. W. "Spectroscopy with polarized light" VCH Publisher Inc., New York, 1986]. These Cotton effects strictly resemble (in position, sign, sequence and intensity) to those of the structurally related dioxolane of (*R,R*)-(+)-**1a** and (*R,R*)-(+)-**1b**. In addition, the positive $^1L_a$ and $^1B$ exciton couplets can be only related to a (*R,R*) configurated 2,2-dimethyl-1,3-dioxolane. [see Rosini, C.; Spada, G. P.; Proni, G.; Masiero, S.; Scamuzzi, S. *J. Am. Chem. Soc.* **1997**, *119*, 506]. A complete description and a detailed analysis of the CD spectra of these and other structurally related dioxolanes will be presented elsewhere.

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