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Disulfonamides derived from camphor: A new ligand for the titanium alkoxide-promoted addition of diethylzinc to benzaldehyde

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With biographical summary

Abstract: The preparation of several disulfonamides **3** and **4** derived from camphor are described, as well as their use in the titanium tetraisopropoxide-promoted enantioselective addition of diethylzinc to benzaldehyde, the enantiomeric ratio being up to 82.0:18.0.

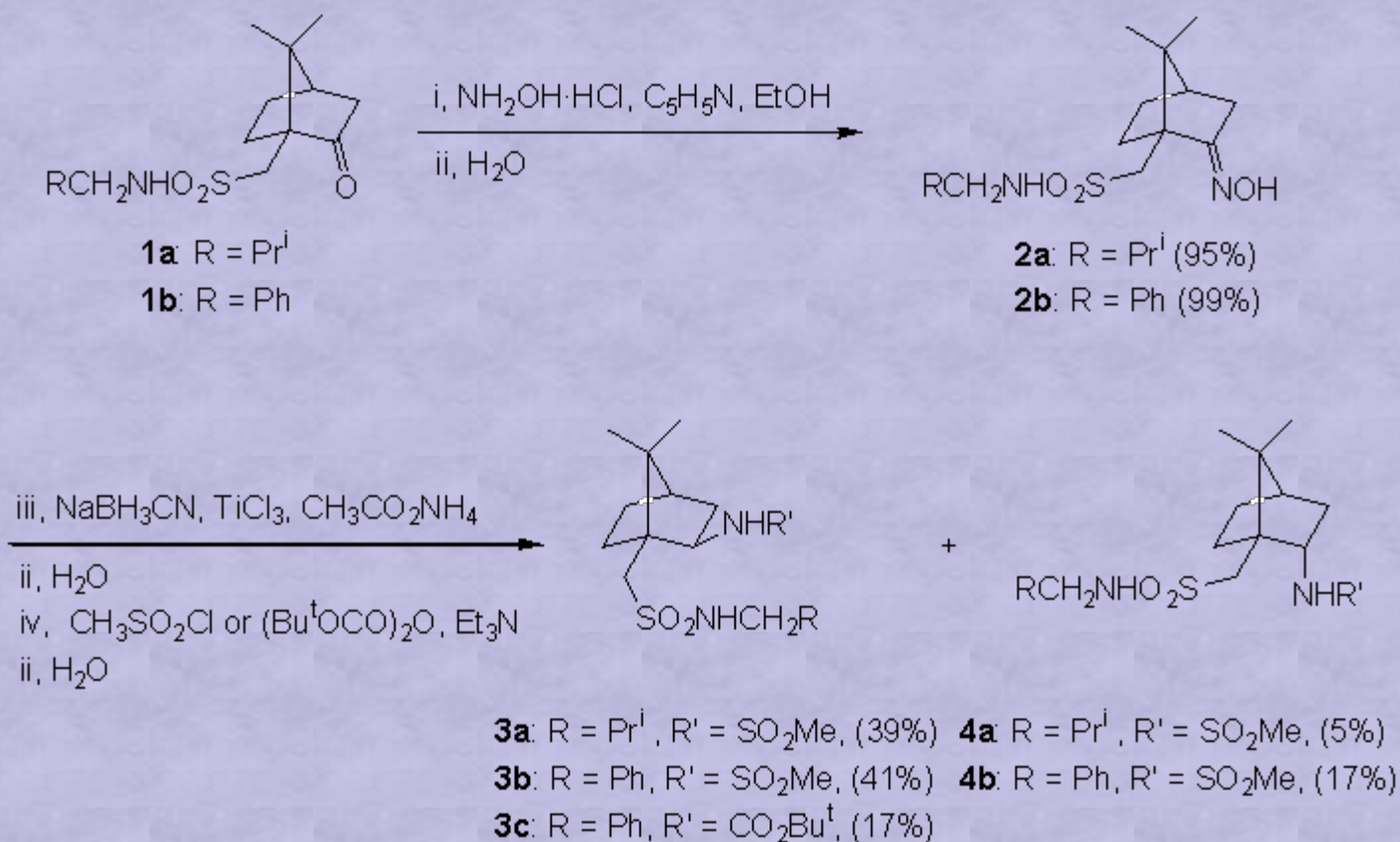**Keywords:** Titanium, dialkylzinc, enantioselective addition.

Introduction

The difference in biological activity between two enantiomers, the necessity of homochiral compounds for the total synthesis of natural products and the questions of regulatory agencies about data of fate and effects of both enantiomers of a chiral pharmaceutical compound, in the course of registration, focused the interest of organic chemistry on enantioselective reactions. Among them, the nucleophilic addition to carbonyl compounds is of paramount importance in synthetic organic chemistry, as a useful tool for enantioselective carbon-carbon bond formation. Concerning this subject, the addition of diethylzinc to benzaldehyde has become a prototype in the evaluation of new chiral ligands. The use of Ti(IV) alkoxides [1] as a Lewis acid in the promotion of the above mentioned reaction has been quite popular and perhaps the most popular class of ligand has been the disulfonamide derived from chiral 1,2-diamines [2] and 1,5-diamines [3]. This fact, together with the unusual properties of hydroxycamphorsulfonamide derivatives as ligands makes these ligands able to promote the classical enantioselective addition of dialkylzinc to aldehydes in the presence of titanium(IV) alkoxide [4], as well as the new enantioselective addition of dialkylzinc to prostereogenic ketones in the presence of titanium(IV) alkoxide [5]. In this communication, we study the preparation of camphor disulfonamides derivatives and their use as ligand in the titanium-promoted addition of dialkylzinc to carbonylic compounds.
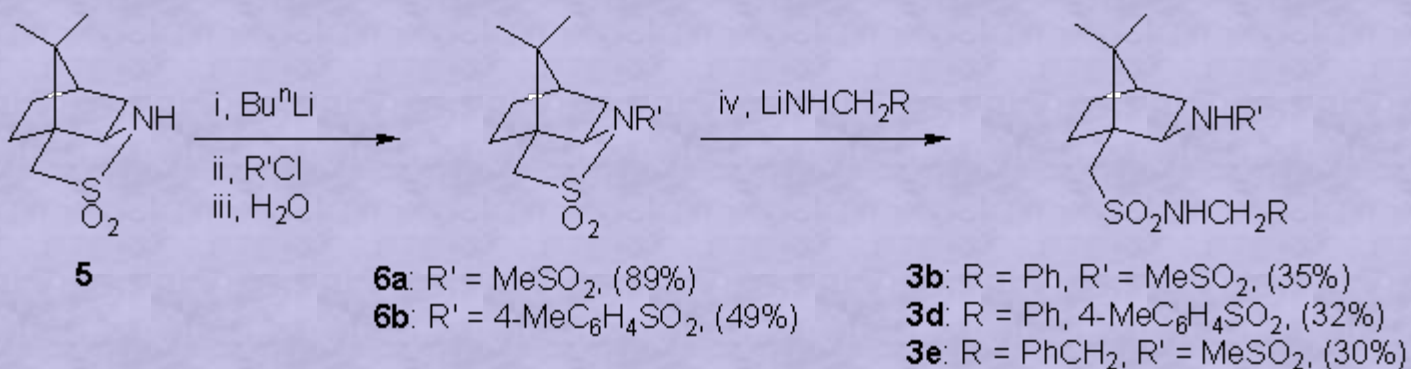
Results and Discussion

The preparation of disulfonamide ligands was performed by a three step sequence from the corresponding *N*-alkyl camphorsulfonamide **1**; its condensation with hydroxylamine [6] gave the expected oxyme **2** with excellent yields. The reduction of oxyme using sodium cyanoborhydride, titanium trichloride and ammonium acetate [7] afforded the corresponding amine as a *exo/endo* mixture. The further reaction with mesyl chloride or di-*tert*-butyl dicarbonate gave the expected *exo/endo*-amide mixture, which was easily isolated by flash column chromatography (mesyl derivatives) or by crystallization (*N*-Boc derivative) (Scheme 1).

Scheme 1

i, NH$_2$OH·HCl, C$_5$H$_5$N, EtOH

ii, H$_2$O

1a: R = Pr^i
1b: R = Ph

2a: R = Pr^i (95%)
2b: R = Ph (99%)

iii, NaBH$_3$CN, TiCl$_3$, CH$_3$CO$_2$NH$_4$

ii, H$_2$O
iv, CH$_3$SO$_2$Cl or (Bu^{t}OCO)$_2$O, Et$_3$N
ii, H$_2$O

3a: R = Pr^i, R' = SO$_2$Me, (39%) **4a**: R = Pr^i, R' = SO$_2$Me, (5%)
3b: R = Ph, R' = SO$_2$Me, (41%) **4b**: R = Ph, R' = SO$_2$Me, (17%)
3c: R = Ph, R' = CO$_2$Bu^t, (17%)

Different problems in the reproducibility and in the scale-up of the reduction made us turn to another pathway to prepare these ligands. The starting material was the Oppolzer camphorsultam (**5**), prepared in its turn from the corresponding camphorsulfonyl chloride according to the literature [8]. Deprotonation with butyllithium of compound **5** followed by reaction with the corresponding sulfonyl chloride gave the expected heterocyclic compound **6**, which was opened by reaction with an excess of the corresponding lithium amide to yield the expected ligands **3** (Scheme 2).
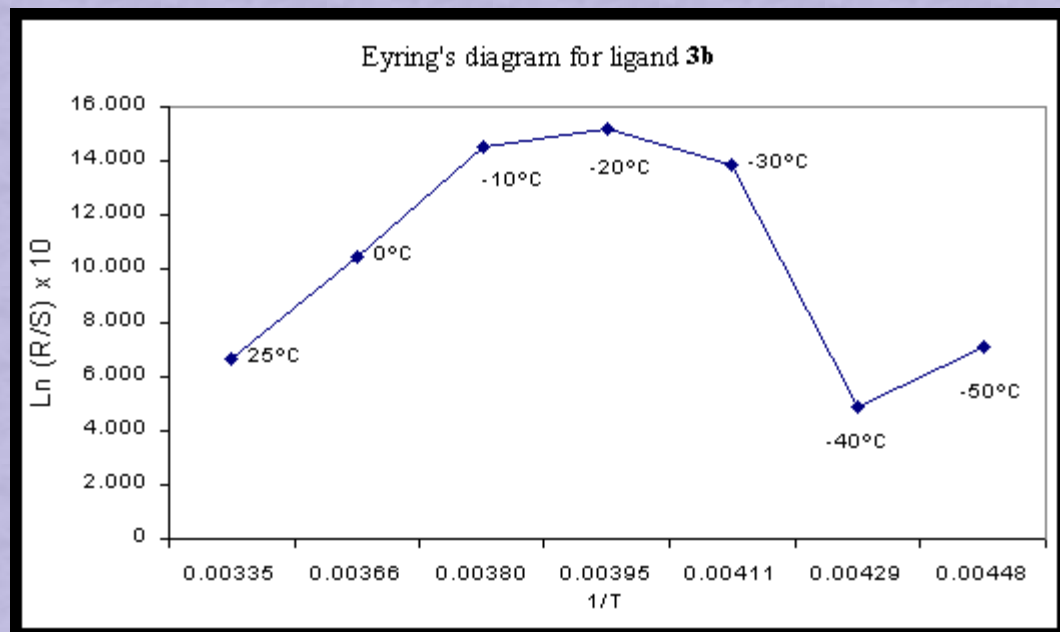
Scheme 2

i, Bu^{n}Li

ii, R'Cl
iii, H$_2$O

iv, LiNHCH$_2$R

5

6a: R' = MeSO$_2$, (89%)
6b: R' = 4-MeC$_6$H$_4$SO$_2$, (49%)

3b: R = Ph, R' = MeSO$_2$, (35%)
3d: R = Ph, 4-MeC$_6$H$_4$SO$_2$, (32%)
3e: R = PhCH$_2$, R' = MeSO$_2$, (30%)

Once the ligands were obtained, they were submitted to the classical titanium tetraisopropoxide-promoted enantioselective addition of diethylzinc to benzaldehyde in toluene. The influence of temperature on the enantioselection was study for the ligand **3b**. The maximum enantiomeric ratio was found at −20deg.C.

Figure 1 indicates probably the existence of several reaction mechanisms in competition.

Figure 1

Eyring's diagram for ligand **3b**

Other ligands were tested at −20deg.C (see Scheme 3), the following remarks being worthy to note: a) Usually, the main enantiomer in the enantioselective addition is *R* (in the case of using the corresponding hydroxysulfonamide the main enantiomer was *S* [4]); b) The role of the R group in the ligand in very important, the best e.r. being given by the aromatic one (compare ligands **3a** and **3b**); c) The nature of the R' group is also important: in the case of carboxamide derivatives the secondary alcohol **7** was nearly racemic (compare ligands **3b** and **3c**); d) The *exo/endo* position of the amide group is quite important: the best result is obtained with the *exo*-derivative (compare ligands **3b** and **4b**; the same result was found in the case of hydroxysulfonamides [4]).

Scheme 3
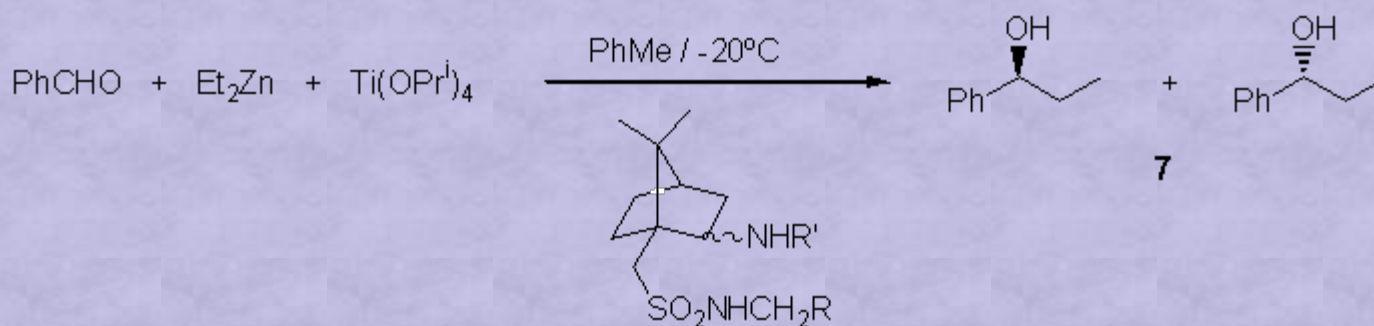
3a: R = Pr^i, R' = MeSO$_2$, *exo*; r.e. **7** (*R:S*) = 70:30
3b: R = Ph, R' = MeSO$_2$, *exo*; r.e. **7** (*R:S*) = 82:18
3c: R = Ph, R' = Bu^{t}OCO, *exo*; r.e. **7** (*R:S*) = 44:56
4b: R = Ph, R' = MeSO$_2$, *endo*; r.e. **7** (*R:S*) = 44:56

Work is in progress to develop better ligands and to improve the reaction conditions for this classical

enantioselective addition, as well as to expand to the enantioselective addition of dialkylzinc reagents to prostereogenic ketones.

Conclusion

The here described disulfonamides derived from camphor are efficient ligands in the titanium alkoxide-promoted enantioselective addition of diethylzinc to benzaldehyde. The obtained results are in agreement with those obtained by us with the corresponding hydroxycamphorsulfonamide derivatives. However, the main enantiomer is the oppositein both cases in spite of the absolute configuration in the ligand stereocenters is the same. The influence of substituents in these ligands is larger than in the case of hydroxysulfonamide derivatives.

Acknowledgements

Experimental Part

For general information, see reference [4] .

Preparation of (1S,2S,4S)-N- methanesulfonylcamphorsultam (**6a**). Typical Procedure.

To a solution of camphorsultam (**5,** 3.4g, 15.7mmol) in THF (30ml) was slowly added (ca. 10 min) a solution of n-butyllithium in hexane (12.8ml, 20.4mmol) at -78deg.C. Stirring was continued for 30 min at 0deg.C and then, the resulting solution was cooled down to -78deg.C. Methanesulfonyl chloride (1.6ml, 20.4mmol) was added to the solution and the mixture was stirred during 18 hr allowing the temperature to rise to 20deg.C. The reaction mixture was hydrolyzed with a saturated solution of ammonium chloride (15ml) and extracted with ethyl acetate (3x10ml). The organic layer was dried over anhydrous sodium sulfate and evaporated (15Torr), yielding the pure title compound (5.6g, 89%).

1H-NMR (CDCl$_3$): 0.97 (s, 3H), 1.23 (s, 3H), 1.30-2.05 (m, 7H), 3.18 (s, 3H), 3.45, 3.47 (2d, 2H), 3.65-3.70 (m, 1H).

Preparation of (1S,2S,4S)-N-benzyl-2-methanesulfonylamino-7,7-dimethylbicyclo[2.2.1]hept-1-ylmethanesulfonamide (**3b**). Typical Procedure.

To a solution of benzylamine (3.0ml, 44mmol) in THF (30ml) was added a solution of n-butyllithium in hexane (19.3ml, 31mmol) at -78deg.C. After 0.5 hr a solution of compound **6a** (2.82g, 7.0mmol) in THF (30ml) was added to the above solution. The resulting mixture was stirred overnigth, allowing the temperature to rise to 20deg.C. The resulting mixture was then hydrolyzed with a saturated solution of ammonium chloride (15ml) and extracted with ethyl acetate (3x10ml). The organic layer was dried over anhydrous sodium sulfate and evaporated (15Torr) to give a residue, which was purified by column chromatography (silica gel, hexane/EtOAc) affording the pure title compound (0.98g, 35%).

[a]$^{25}_D$: -34.44 (c = 2, CHCl$_3$)

IR (melted): 3297 (NH), 3031 (HC=C).

1H-NMR (CDCl$_3$): 0.74 (s, 3H), 0.92 (s, 3H), 1.10-1.20, 1.55-2.20 (2m, 7H), 2.71, 3.19 (2d, 2H), 3.16 (s, 3H), 3.55-3.65 (m, 1H), 4.30-4.35 (m, 2H), 5.08 (d, 1H), 5.18 (t, 1H), 7.30-7.40 (m, 5H).

13C-NMR (CDCl$_3$): 20.15, 20.4, 27.05, 32.65, 39.2, 39.25, 44.6, 46.15, 49.5, 52.5, 59.2, 128.05, 128.25, 128.9, 136.9.

MS (EI): 281 (M$^+$-119, <1%), 139 (12), 111 (31), 101 (13), 95 (13), 86 (100), 84 (69), 83 (18), 82 (26), 58 (23), 56 (14), 54 (34), 53 (11), 44 (36), 42 (23), 41 (12).

Enantioselective addition of diethylzinc to benzaldehyde. Typical Procedure.

To a solution of ligand **3b** (0.4g, 1mmol) in toluene (10ml) was added a solution of diethylzinc in toluene (6ml, 12mmol) at -20deg.C. After 10 min, titanium tetraisopropoxide (1.9ml, 6.5mmol) was added. Then, benzaldehyde (0.5ml, 5mmol) was added. The resulting solution was stirrred at the same temperature for 2 h. The reaction was then quenched with a saturated solution of ammonium chloride (10ml), filtered off through celite and extracted with ethyl acetate (3x10ml). The organic layer was dried over anhydrous sodium sulfate and evaporated (15Torr). The residue was destilled bulb to bulb to yield the alcohol **7** (0.66g 98%). The chiral ligand can be recovered by flash column chromatography.

References and Notes

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