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Surprising fenchone induced cyclization: synthesis of the new chiral diol biphenyl-2,2′-sulfone-3,3′-bisfenchol (BISFOL)

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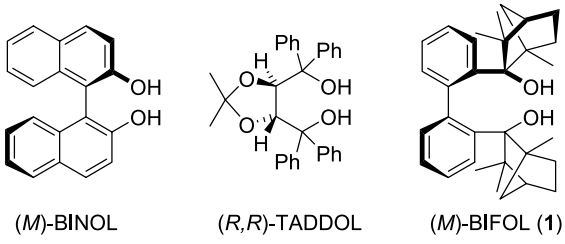
Abstract—The new chiral diol BISFOL (biphenyl-2,2′-sulfone-3,3′-bisfenchol) is surprisingly formed by cyclization of diphenylsulfone after treatment with *n*-buthyllithium at −78 °C and subsequent addition of (−)-fenchone. Formation of fenchyl alcohol as byproduct points to a Meisenheimer intermediate as primary cyclization product, which transfers lithium hydride yielding the cyclic sulfone. As a chiral and chelating ligand, BISFOL catalyzes enantioselective diorganozinc additions to aldehydes and forms with dimethylzinc an unprecedented, macrocyclic, dimeric methylzinc complex.

1. Introduction

Additions of organolithium reagents to chiral ketones are fundamental synthetic methods for syntheses of chiral diols.[1] Chelating diols such as BINOLs[2] and TADDOLs[3] play as chiral ligands an eminent role in enantioselective synthesis. We recently reported the synthesis and the X-ray crystal structure of (*M*)-BIFOL (**1** biphenyl-2,2′-bisfenchol, Scheme 1), which exhibits, as BINOLs, a flexible, chiral biaryl axis with minus (*M*) conformation induced by the hydrogen bonded fenchol moieties, and sterically crowded aliphatic alcohol functions, as TADDOLs.[4]



(*M*)-BINOL (*R,R*)-TADDOL (*M*)-BIFOL (**1**)

Scheme 1. BIFOL (biphenyl-2,2′-bisfenchol) with minus (*M*)-biaryl conformation.

Modular chiral chelating fenchols (Scheme 2), accessible via short synthetic routes, were applied recently as catalysts in enantioselective additions of organozincs to aldehydes,[5] in enantiopure organolithiums reagents,[6] and in fenchyl phosphinites for Pd-catalyzed allylic alkylations.[7] Herein, we present the surprising formation of the new fenchyl alcohol BISFOL (**2**, biphenyl-2,2′-sulfone-3,3′-bisfenchol; Scheme 2) via an unprecedented fenchone induced cyclization.

2. Results and discussion

ortho-Lithiation[8] of diphenylsulfone (**3**) with *n*-butyllithium in diethylether–tetrahydrofuran (1:1) at −78 °C followed by reaction with (−)-fenchone, hydrolytic work up and recrystallization from ethanol/dichloromethane afforded colorless crystals of BISFOL (**2**) in 20% yield. However, the expected open bisfenchol sulfone **4** could not be detected. Besides BISFOL, fenchol, the reduction product of fenchone, was detected (Scheme 3).

The structure of BISFOL (**2**) was confirmed by single-crystal X-ray diffraction (Fig. 1). BISFOL exhibits intramolecular hydrogen bonds between the hydroxy groups of the fenchyl moieties and the oxygen atoms of the sulfone group (O1–H1–O2: 2.17 Å, O1–O2: 2.69 Å, O3–H2–O4: 2.24 Å, O3–O4: 2.72 Å, Fig. 1).

To explore this unexpected fenchone induced cyclization, several carbonyl compounds were employed as electrophiles besides fenchone (Table 1, Scheme 3). Treatment of dilithiodiphenylsulfone with benzophenone or fluorenone gave, after hydrolytic work up, exclusively the non-cyclized, open products (Table 1). Reductions of benzophenone and fluorenone to the corresponding alcohols were not observed,

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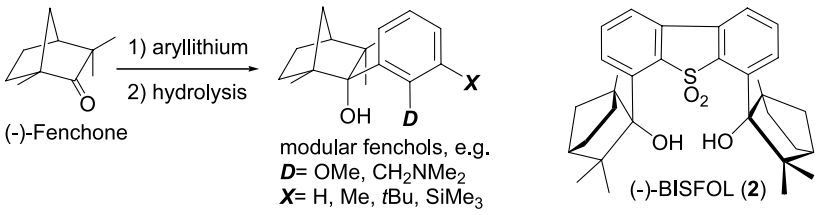
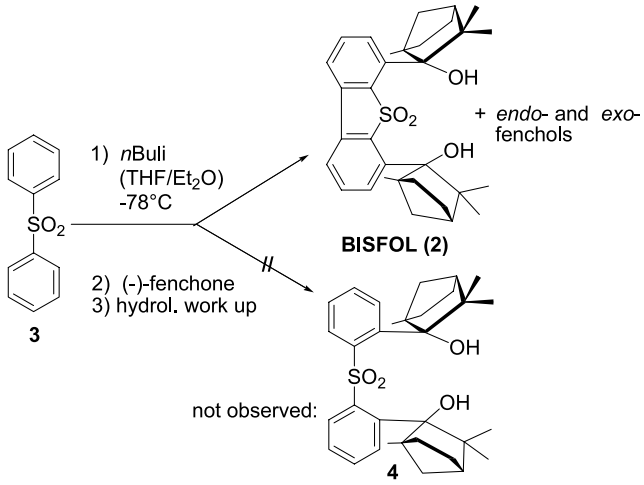


Scheme 2. From fenchone, modular fenchols are efficiently accessible.



Scheme 3. Surprising formation of BISFOL (**2**) via attempted synthesis of the open bisfenchol sulfone **4**.

yet an other difference to the reaction with fenchone. Camphor or benzaldehyde gave under the same reaction conditions neither cyclic nor acyclic products, enolization or reduction were dominating (Table 1). Hence, among the employed carbonyl compounds, only fenchone yields the cyclized diol **2**. The isolation of *endo*- and *exo*-fenchols as byproducts point to the formation of lithium hydride during the reaction. This supports, as a possible mechanistic

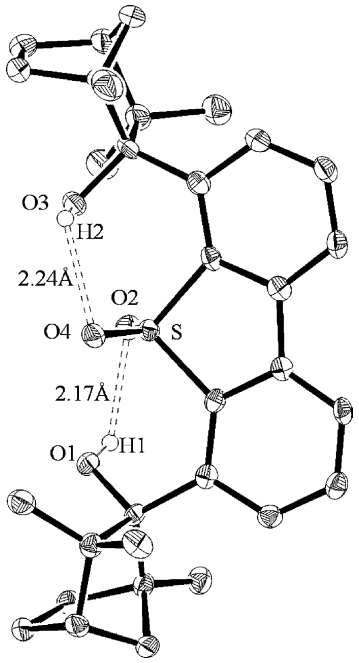
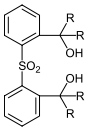
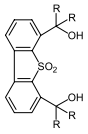
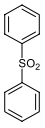


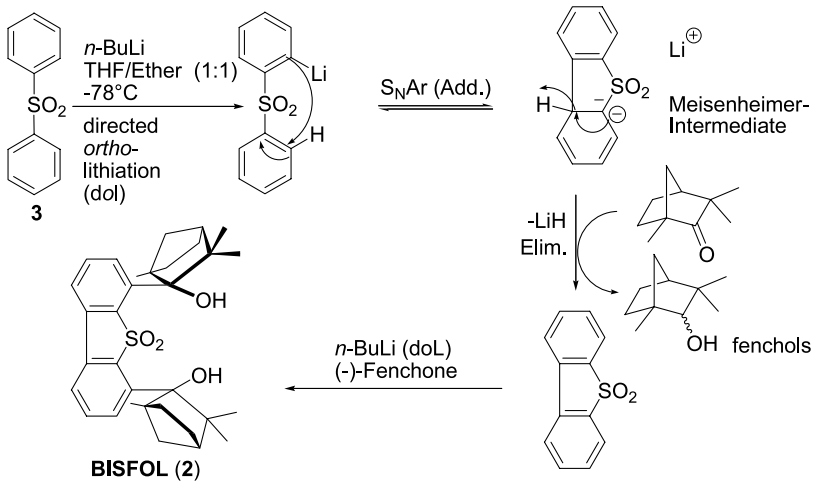
Figure 1. X-ray crystal structure of BISFOL (**2**).

scenario, a cyclization through nucleophilic aromatic substitution of the lithiated diphenylsulfone (**3**) via an addition–elimination sequence (Scheme 4).

Table 1. Treatment of dilithiodiphenylsulfone with different carbonyl compounds (cf. Scheme 3) yielding open or cyclic products

Product[a]					
Carbonyl-compound	Open (%)[b]	Cyclic (%)[c]	Byproduct (%)[d]	Educt (%)[e]	Educt (%)[e]
	27	—	—	70	67
	6	—	—	55	38
	—	—	–	64	30
	—	20	*endo*/*exo* fenchol[f]	60	60
	—	—	23	42	17

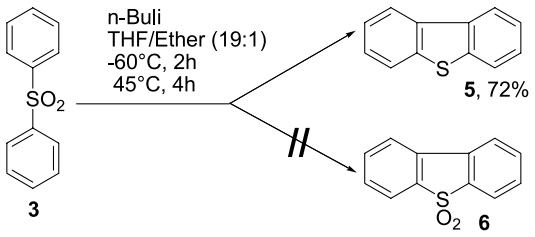
[a] 'R' represents the substituent of the carbonyl group.
[b] No cyclization.
[c] Cyclization.
[d] Reduction product of the employed carbonyl compound during the reaction.
[e] Recovered educt.
[f] The alcohols were identified by gas-chromatography by comparing with the authentic material.



Scheme 4. Proposed reaction mechanism via nucleophilic aromatic substitution.

According to this suggested sequence, *ortho*-lithiation of diphenylsulfone (**3**) yields an aryllithium unit, which adds to the second phenyl group forming a Meisenheimer intermediate being stabilized by the sulfone group. The aryl unit is rearomatized by elimination of lithium hydride, which reduces fenchone to the *endo*- and *exo*- fenchol byproducts (Scheme 4, Table 1). Indeed, Brinon et al. postulated a similar elimination of lithium hydride during an analogue cyclization of diphenylsulfone with *n*-buthyllithium, yielding dibenzothiophene **5**, while no cyclic sulfone **6** was observed (Scheme 5).[9]

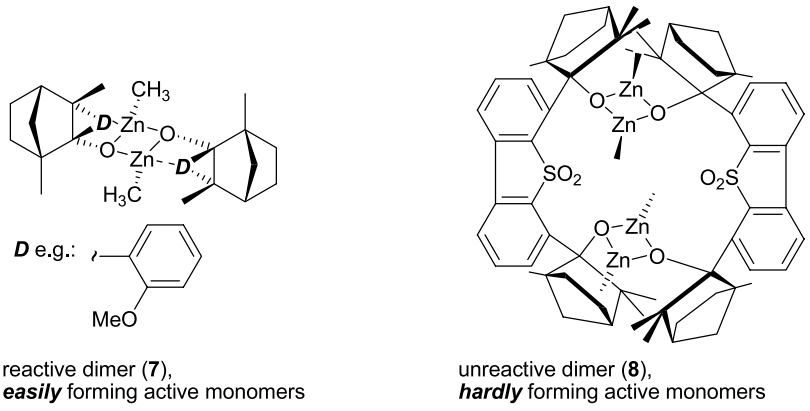
Fenchone seems to be particularly suitable for hydride transfer due to steric reasons, as it was demonstrated by Reetz et al. in the reduction of fenchone with potassium hydride.[10] Hellwinkel et al. have reported unexpected formations of heterocyclic systems from sulfonamides due to rearrangement by the reaction with organolithium compounds.[11] Due to its rigid chiral structure, BISFOL **2** is a promising ligand for enantioselective transformations, for example, catalyzed diorganozinc additions to aldehydes.[12] However, only up to 19% ee were achieved with 3 mol% of **2** in diethylzinc additions to benzaldehyde to give 1-phenylpropanol. The low enantioselectivity and especially the low reactivity of **2** as pre-catalyst in diethylzinc additions might arise from formation of rather stable dimeric and hence passive catalysts.[5] Indeed, reaction of dimethylzinc with a toluene solution of **2** at 0 °C and recrystallization from toluene yields a macrocyclic C_2-symmetrical dimer with two, rather than only one, four-membered, dimer-building Zn_2O_2 rings (Scheme 6, Fig. 2).



Scheme 5. Brinon's cyclization via lithiation of **3** yielding dibenzothiophene **5**.

3. Conclusions

The surprising, fenchone induced cyclization of *ortho*-lithiated bisphenylsulfone can be explained by a nucleophilic aromatic substitution sequence. Besides the new chiral BISFOL fenchole is formed via lithium hydride elimination. The unique propensity of fenchone to support



Scheme 6. Homochiral methylzinc dimers based on fencholes. While reactive dimmers (**7**) easily dissociate into active monomeric catalysts, the macrocycle in **8** inhibits active catalyst formation.

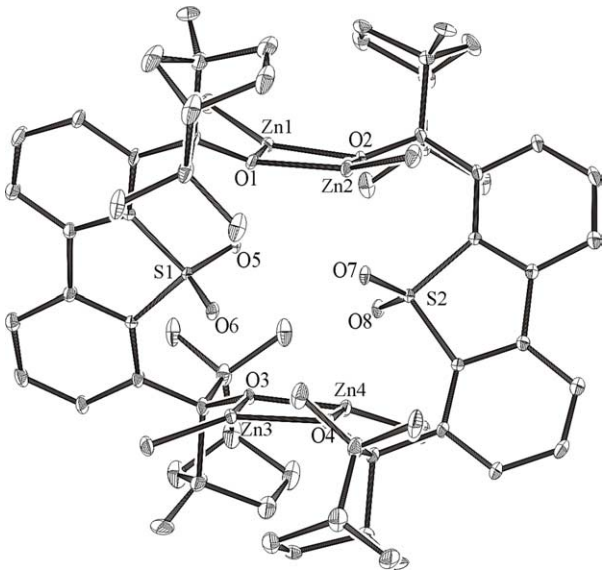


Figure 2. X-ray crystal structure of **8**, the dimeric, macrocyclic zincmethyl complex of BISFOL. Hydrogen atoms are omitted for clarity.

this cyclization is evident from comparisons with other carbonyl compounds. The low reactivity and enantioselectivity of BISFOL in diorganozinc additions to benzaldehyde is explained by the high stability of the macrocyclic alkylzinc complex. Anyhow, as rigid, chelating and C_2-symmetric diol, BISFOL has promising potentials as building block in enantioselective reagents and catalysts.

4. Experimental

All reactions were carried out under argon atmosphere using Schlenk-tube techniques. Solvents were dried by standard methods and distilled under argon prior to use.

4.1. Synthesis of biphenyl-2,2′-sulfone-3,3′-bisfenchol (BISFOL 2)

To a stirred solution of 6.55 g diphenylsulfone (30 mmol) in 45 ml THF and 45 ml Et_2O, which was cooled on a dry ice/alcohol bath (−78 °C), was added 39 ml (1.6 M, 60 mmol) of a solution of *n*-butyllithium in hexane. After the addition was complete, the solution was stirred 10 h by −78 °C. After stirring the solution at room temperature, 9.72 ml (60 mmol) (−)-fenchone were added to the mixture at −78 °C. Hydrolysis was performed with 200 ml H_2O. After separation of the ether layer, the water layer was extracted with 100 ml Et_2O. The combined organic layers were dried over anhydrous Na_2SO_4. Filtration and distillation of the solvents left a yellow oil, to which 100 ml pentane was added. Cooling at −78 °C during 2 h in a dry ice/alcohol bath resulted in the precipitation of a solid, which was isolated by filtration of the mixture. This procedure was repeated, giving a total yield of compound **2** of 1.31 g (20%). After recrystallization from dichloromethane/ethanol the decomposition point was 283 °C.

Analytic and spectroscopic data of **2**. Mp: >283 °C (decomposition); calcd: C 73.81, H 7.74, found C 73.64, H 7.74; ^{1}H NMR ($CDCl_3$, 300 MHz) 0.58 (3H, s), 1.08 (3H, s), 1.26 (3H, s), 1.43–2.38 (6H, m), 3.05 (1H, s), 5.31 (1H, s), 7.52 (1H, t), 7.70 (2H, d); ^{13}C NMR ($CDCl_3$, 75 MHz) 145.87, 137.76, 132.87, 132.38, 131.13, 119.49, 86.42, 54.86, 49.24, 48.12, 43.10, 34.01, 29.94, 24.33, 21.60, 18.01; $[\alpha]_D^{20}$ −253 (*c* 0.3, toluene); EI-MS: 520 (M^+), 504 (M^+-O), 502 (M^+-H_2O); IR KBr, cm^{-1}) 3556 (OH, s), 2989–2800 (C_{alkyl}–H, m), 1300 (C–SO_2, s), 1140 (C–SO_2, s). X-ray crystal data of **2**: $C_{32}H_{40}O_4S$; M=520.70; space group $P2_12_12_1$; a=11.4739(4) Å, b=14.8690(5) Å, c=16.2201(3) Å, V=2767.24(1) Å^3; Z=4; T=100(2) K; μ=0.152 mm^{-1}; reflections total: 22,011, unique: 6037, observed: 4905 ($I>2\sigma$ (I)); parameters refined: 494; $R1$=0.0347, $wR2$=0.0623; GOF=1.026.

4.2. Synthesis and X-ray analysis of Me_2Zn–BISFOL 8

A solution of dimethylzinc (0.5 mmol, 2 M, 0.25 ml) in toluene was added at room temperature to a solution of 0.5 mmol (260 mg) of **2** in 1 ml of toluene. The mixture was stirred for 30 min. After cooling the solution to −78 °C and thawing three times, the precipitate formed was dissolved in hot toluene. Slow cooling to room temperature yielded the homochiral dimer as colorless crystals. X-ray crystal data of **8**: $C_{34}H_{44}O_4SZn_2$; M=679.49; space group $I222$; a=10.848(1) Å, b=17.585(1) Å, c=18.632(1) Å, V=3554.3(4) Å^3; Z=4; T=293(2) K; μ=1.441 mm^{-1}; reflections total: 10,367, unique: 3847, observed: 2359 ($I>2\sigma$ (I)); parameters refined: 189; $R1$=0.0817, $wR2$=0.2013; GOF=1.064.

4.3. Catalytic $ZnEt_2$-additions to benzaldehyde

0.12 mmol (3 mol% with respect to benzaldehyde) of **2** was treated with 4.52 ml (4.07 mmol, 0.9 M) of diethylzinc in hexane at 0 °C for 15 min. Benzaldehyde (0.40 ml, 3.84 mmol) was added and this mixture was kept for 24 h at −30 °C. After quenching with water and hydrolyzing with hydrochloric acid, the organic layer was separated, neutralized ($NaHCO_3$) and dried (Na_2SO_4). The enantiomeric excess was analyzed by GC (Chiraldex G-TA column).

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