ASYMMETRIC DIELS-ALDER REACTION OF OPTICALLY ACTIVE 3-(3,3,3-TRIFLUOROPROPENYLSULFONYL)OXAZOLIDINE: SYNTHESIS OF (8*R*)-8-TRIFLUOROMETHYL-2-OXA-6-THIA-5-AZATRICYCLO[5.2.2.0^{1,5}]-UNDECANE-6,6-DIOXIDE

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Abstract- Asymmetric Diels-Alder reaction of optically active 3-(3,3,3-trifluoropropenylsulfonyl)-1,3-oxazolidine (**1**) with several dienes gave adducts regio- and stereoselectively in 69 - 78 % *de*. Acetalization of 2-methoxybutadiene adduct with catechol gave tricyclic sultam-oxazolidine (**15**), which could be readily deprotonated and gave bridgehead sulfide (**16**).

Recently, we reported the asymmetric Diels-Alder reactions of optically active 1-(3,3,3-trifluoropropenylsulfonyl)pyrrolidine with high diastereomer excess (*de*).[1] The C_2-symmetry of the pyrrolidine (pyrrolidino[3,2-*d*:4,5-*d*']bisdioxane), which was prepared from D-mannitol through a relatively long synthetic steps,[2,3] was important for the diastereofacial selection. As a readily available chiral auxiliary, we designed spirocyclic 1,3-oxazolidine[4] sulfonamide prepared from L-alanol and cyclohexanone. Whereas this new asymmetric induction system is different from the original pyrrolidine sulfonamide system in lack of the C_2-symmetry, it still keeps the same mechanism for the diastereofacial selection which is dominated by the stable conformation of α,β-unsaturated amide substrates.[2,5] We report here preparation of spirocyclic 3-(3,3,3-trifluoropropenylsulfonyl)-1,3-oxazolidine (**1**) and the asymmetric Diels-Alder reaction with several dienes. Derivatization of [4 + 2] adduct with 2-methoxybutadiene was also examined and we obtained trifluoromethylated bicyclo[2.2.2]octane-sultam system.

Scheme 1

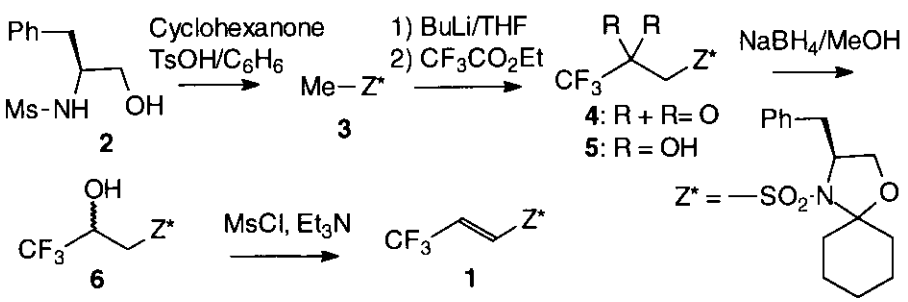
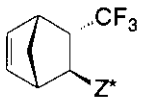
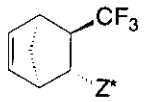
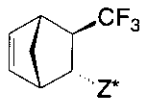
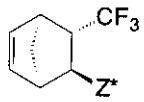
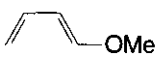
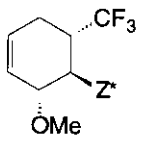
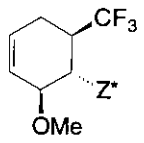
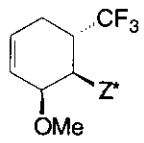
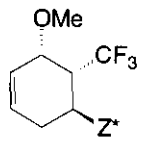
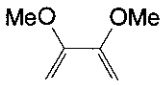
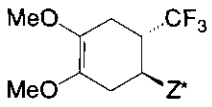
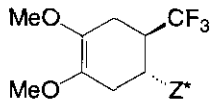
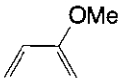
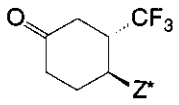
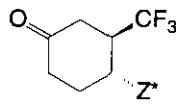


Table 1. High Pressure (1.0 GPa) Diels-Alder Reaction of Oxazolidine (**1**) with Some Dienes.

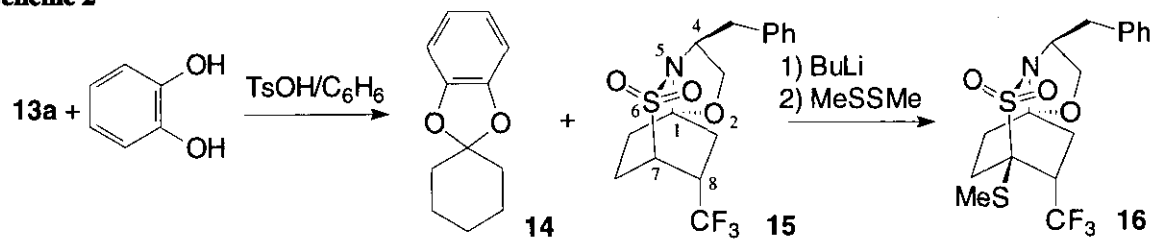
Dienes	Temperature (°C)	Products (% ratio)	Yields (%)
	50	 **7a** (73)  **7b** (9)  **8a** (16)  **8b** (2)	94
	50	 **9a** (71)  **9b** (13)  **10** (12)  **11** (4)	83
	100	 **12a** (85)  **12b** (15)	76
	100 [a]	 **13a** (86)  **13b** (14)	58

[a] After Dields-Alder reaction, the reaction mixture was treated with 2M HCl/THF solution at room temperature.

Optically active sulfonamide dienophile (**1**) was prepared from *N*-mesyl-L-alanol (**2**) starting from acid-catalyzed acetalization with cyclohexanone to yield oxazolidine (**3**).[6] Mesyl group of **3** was deprotonated with BuLi and treated with ethyl trifluoroacetate to give a mixture of trifluoromethyl ketone (**4**) and its hydrate (**5**) after aqueous workup. This mixture was reduced to the corresponding alcohol (**6**) with $NaBH_4$ in methanol. Dehydration of (**6**) was achieved with *in situ* generation of *O*-mesylate and elimination to give unsaturated sulfonamide (**1**) in 73 % overall yield from oxazolidine (**3**). *E*-Stereochemistry of **1** was confirmed by the ^1H NMR spectrum ($J_{H_\alpha\text{-}H_\beta}$ = 15 Hz) (Scheme 1).

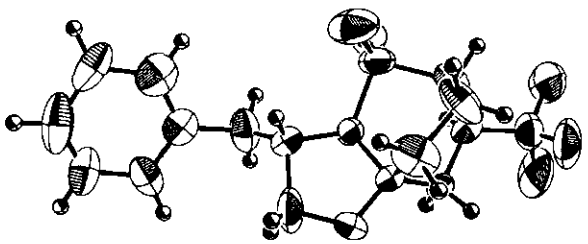
Diels-Alder reaction of **1** with several dienes is summarized in Table 1. The reaction of **1** with cyclopentadiene was firstly examined in a sealed tube containing toluene solution at 140 °C for 15 h. Although the adducts were observed in the reaction mixture, the reaction was incomplete. We already reported the slower reaction of unsaturated sulfonamide with dienes, and to complete the reaction we had employed the high pressure conditions.[1] High pressure (1.0 GPa) reaction of **1** with cyclopentadiene at 50 °C gave an adducts mixture of **7a** which was isolated after column chromatography, **7b** (SO_2-*exo* stereoisomers), and **8a**,**b** (SO_2-*endo* stereoisomers) in totally 94 % yield. The product distribution was indicated by the ^1H NMR spectrum as 73:9:16:2. Stereochemistry of the products was determined on the basis of the long-range ^1H NMR coupling between the *endo* protons and the bridge protons. The major products were the SO_2-*exo*

Scheme 2

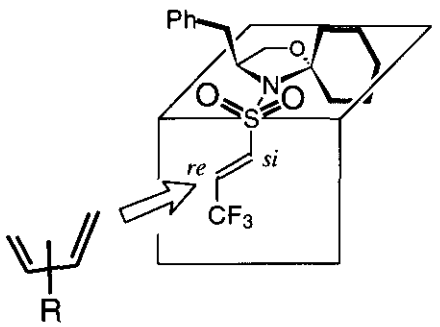


stereoisomers (**7a**) and (**7b**) (78 % *de*) as similar as the previous result.[1] *High pressure reaction of* **1** *with* 1-methoxybutadiene (50 °C, 1.0 GPa) gave a 71:13:12:4 mixture in 83 % yield, and the structures were determined based on the ^{1}H NMR spectrum and the cyclohexene conformation as **9a**, **9b**, **10**, and regioisomer (**11**), respectively (69 % *de* for **9a**/**9b**). Chromatographic treatment separated this mixture into the two fractions containing **9a**, **b** and **10**, **11**. Epimeric counterparts of **10** and **11** should be small content and they could not identified in the ^{1}H NMR spectra. Since dienes with electron-donating substituents on C2- and/or C3-position are less reactive than C1- and/or C4-substituted dienes, dienophile (**1**) reacted with 2,3-dimethoxybutadiene at higher temperature (100 °C, 1.0 GPa). Diastereomer mixture of **12a** and **12b** was obtained in 76 % yield (70 % *de*). 2-Methoxybutadiene which would lead to the synthetically useful cyclohexanones also reacted with **1** at higher temperature (100 °C, 1.0 GPa) followed by treatment with THF/*aq* 2M HCl for the hydrolysis of resulting enol ether adducts to afford diastereomers of 3-trifluoromethylcyclohexanone derivatives (**13a**; 50 %), (**13b**; 8 %) regioselectively. Major isomer of 2-methoxybutadiene adduct (**13a**) is the starting material for the optically active 3-trifluoromethylcyclohexanone derivatives. Thus, we examined the acetalization of the ketone with catechol in refluxing benzene with *p*-TsOH catalyst. However, the obtained products were cyclohexanone phenylene acetal (**14**) and tricyclic sultam oxazolidine (**15**), which were given by the transacetalization of **13a** and catechol in 64 and 75 % yields, respectively (Scheme 2). Since single crystals of **15** were obtained, the absolute configuration of **15** was confirmed as 4*S* and 8*R* by X-Ray crystallography (Figure 1). Accordingly, in the asymmetric Diels-Alder reaction of **1**, the major approach of dienes on the *si-re* face

Figure 1. ORTEP-Drawing of compound **15**



Scheme 3. The Favorable Approach of Dienes on the *si-re* Face of a Stable Conformer of Dienophile (**1**)



of the most stable conformer of dienophile (**1**) is established (Scheme 3).[7] The diastereofacial selectivity (*de*) of **1** is lower (69 - 78 % *de*) than that of the previously used dienophile with C_2-symmetrical pyrrolidine chiral auxiliary (100 % *de*).[1] Oxazolidine is a rather flexible ring system compared to the C_2-symmetrical pyrrolidino[3,2-*d*:4,5-*d'*]bisdioxane system. This flexibility would make the other conformers leading to the minor *Re-Si* face approach more stable, and it caused decrease in stereoselectivity of Diels-Alder reaction of **1**.

Noteworthy of the structure of **15** is suitable for the deprotonation to bridgehead carbanion because the orientation of the two S=O bonds satisfies the requirement for stabilization of neighboring *p*-orbital[8,9] unlike the corresponding bridged lactams in which bridgehead enolates are prohibited by the C=C bond distortion. Thus, sultam (**15**) was readily deprotonated with BuLi at -78 °C in THF and the following addition of dimethyl disulfide gave bridgehead sulfide (**16**) in 89 % yield (Scheme 2). Such bridgehead derivatization is important for the application of the optically active Diels-Alder adducts to the chirally trifluoromethylated synthetic building blocks.

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