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Asymmetric Intermolecular Diels-Alder Reactions of Enantiopure Sulfinyl-Homo- and -Hetero-Dienes: Preliminary Results.

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Abstract: Reaction of (E)-(+)-(R)-2-*p*-tolylsulfinyl-1,3-pentadiene **1** with maleimide afforded **3** as a single, enantiomerically pure adduct under very mild conditions. **3** resulted from exclusive *endo* approach by a completely diastereofacialselective route.On the other hand, heterodiene (+)-(S)-3-*p*-tolylsulfinyl-3-buten-2-one **2** smoothly reacted with sensitive 2-methylenetetrahydrofuran yielding 1:1 diastereomeric dioxaspiroadducts **4a** and **4b**, readily separated by liquid chromatography.

Hetero- as well as homo-Diels-Alder reactions are widely used in the construction of cyclic molecules. Recent developments in enantio- and diastereo-selective [4+2] cycloaddition process have still increased researches in this area. Quite surprisingly, most of the reported works in this topic deal with chiral dienophiles or chiral Lewis acids catalysts and very few is known about chiral dienes.[1]

This is particularly striking when the chiral auxiliary is the sulfoxide group : although several 1-sulfinyldienes are known for sometime[2] we recently described[3] the first[4] synthesis of enantiopure 2-sulfinyldienes. Moreover, during this work we also synthesised the corresponding 3-sulfinyl-oxadienes.[3a]

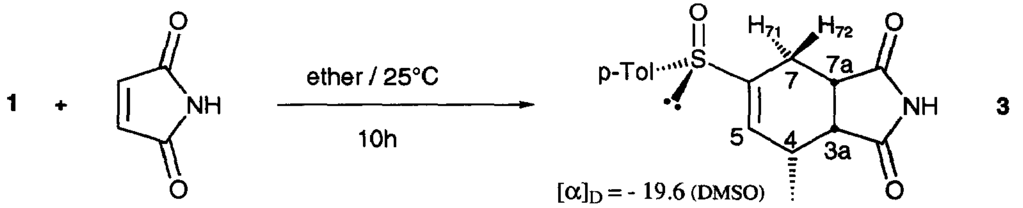
$[\alpha]_D = +117$ (ethanol) $[\alpha]_D = +299$ (acetone)

Scheme 1

We report here very interesting preliminary results concerning the reactivity of these dienes in uncatalyzed asymmetric homo- and hetero-Diels-Alder reactions.

In the case of homo-Diels-Alder reactions and in order to study both endo/exo- and diastereofacial selectivities, we examined the cycloaddition of (E)-(+)-(R)-2-p-tolylsulfinyl-1,3-pentadiene **1**[3b] (Scheme 1) with maleimide (*i.e.* direct electron demand reaction-type).

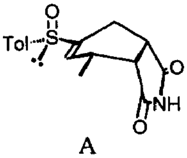
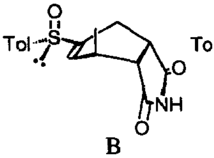
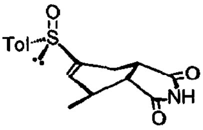
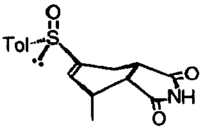
When diene **1** was reacted with maleimide (1 eq) in ether (1 mL/mmol) at room temperature, a white precipitate appeared within few hours and the reaction was complete after 10 hours (Scheme 2). ^{1}H, ^{13}C-NMR analysis as well as TLC of the evaporated crude product revealed *only one diastereoisomer* **3** which was recrystallized from CH_2Cl_2/Et_2O.[5]



Scheme 2

Spatial structure of this single adduct was deduced as follows : first, the four possible structures (A,B,C,D) were constructed and their geometries optimized by molecular mechanics.[6] Calculated vicinal coupling constants were then deduced by application of a Karplus type equation as modified by Bothner-By[7]: $^3J = 7 - \cos(\theta) + 5\cos(2\theta)$. The so obtained four sets of coupling constants were compared to the $^3J_{HH}$ constants measured in the 400 MHz ^1H-NMR spectrum of **3**. The results are presented in Table 1.

Table I. Observed and Calculated Vicinal Coupling Constants for Compound 3

Structure / J (Hz)	Observed	 A	 B	 C	 D
$J_{3a,4}$	6.8	5.5	2.1	12.1	7.6
$J_{3a,7a}$	9.1	11.0	11.0	11.0	11.0
$J_{4,5}$	4.3	3.0	8.6	3.3	9.7
$J_{71,7a}$	2.9	2.8	2.4	6.2	7.4
$J_{72,7a}$	8.0	6.0	7.0	12.2	11.1

Data collected in Table 1 show that a good agreement exists between structure A and compound **3**. This was further established by the nuclear Overhauser effects (nOes) : upon irradiation of the H_4 proton, a 4% enhancement was observed for the signal of H_{72} which fixed an axial orientation for these protons. Consequently, the methyl at C4 should be equatorial (structures A or C) . Furthermore, a strong effect (7%) between H_{3a} and H_4 indicated a syn geometry as in A (not C).

Finally, it has been possible to characterize **3** structurally by X-Ray diffraction analysis.[8] A Chem3D diagram of the molecular structure of **3** (Figure 1) confirmed the previously inferred structure A.

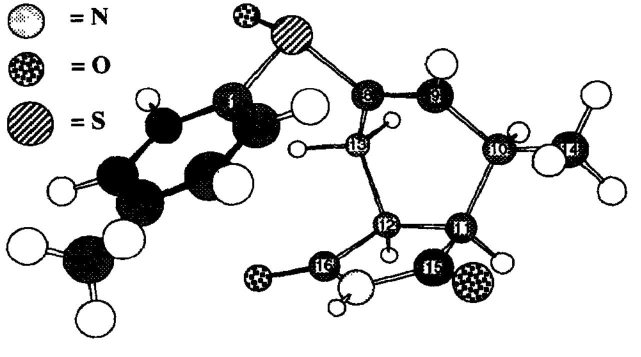
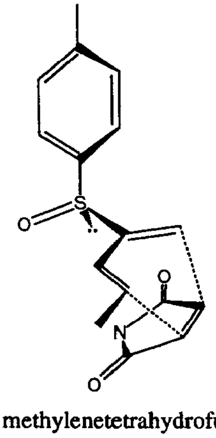


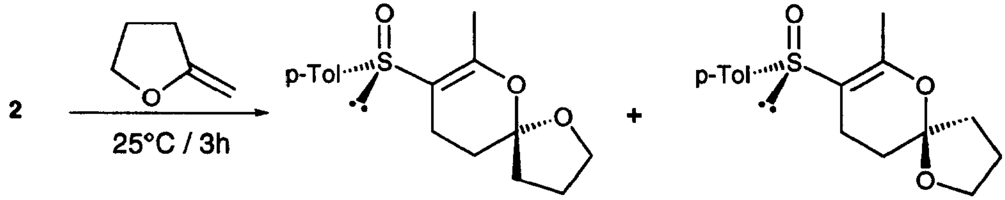
Figure 1: X-ray crystal structure of **3**. Selected values of bond distances (Å) and angles (deg): S-O = 1.498(2), S-C1 = 1.787(2), S-C8 = 1.7766(15), C8-C9 = 1.325(2), C1-S-C8 = 98.10 (7), C1-S-O = 106.21(8), C8-S-O = 106.49(9), S-C8-C9 = 119.56(13), C10-C11-C15 = 114.44(14), C13-C12-C16 = 108.95(14), C9-C10-C14 = 112.5(2).



Structure A for **3** results from exclusive *endo* approach by a completely diastereofacialselective route *i.e.* from the less hindered side of the diene (opposite to the p-tolyl group[9]) which is also the most nucleophilic (lone pair side[10]). This indicates a *s-trans* conformation of the S=O and C=C bonds in compound **1**, at least in the transition state.

This first cycloaddition of an enantiopure 2-sulfinylbutadiene[11] occurring with a complete asymmetric induction under mild conditions open the way of very promising further developments.

On the other hand, we also studied the hetero-Diels-Alder reaction of (+)-(S)-3-p-tolylsulfinyl-3-buten-2-one **2** with a vinyl ether (*i.e.* inverse electron demand case). In order to test the synthetic potential of this enantiopure oxabutadiene **2**, we chose 2-methylenetetrahydrofuran as dienophile, which would yield a spiroketal skeleton encountered in numerous biologically active natural products [12] (Scheme 3).



4a $[\alpha]_D = + 63$ (ethanol) **4b** $[\alpha]_D = - 83$ (ethanol)

Scheme 3

The reaction of methylenetetrahydrofuran (used as solvent) with **2** was complete after 3h stirring at room temperature. Unfortunately, the crude product resulting from evaporation of excess dienophile was shown by 400 MHz ^{1}H-NMR to be a 1:1 mixture of **4a**:**4b**. However these diastereomeric spiroketals **4** were completely separated by liquid chromatography on silica-gel (eluent : CH_2Cl_2 / 1‰ CH_3OH) with a 77% cumulated yield.[5,13] Only **4a** could be recrystallized from ether affording suitable crystals for X-Ray diffraction spectroscopy.[14] Crystal structure of **4a** is shown in Figure 2.

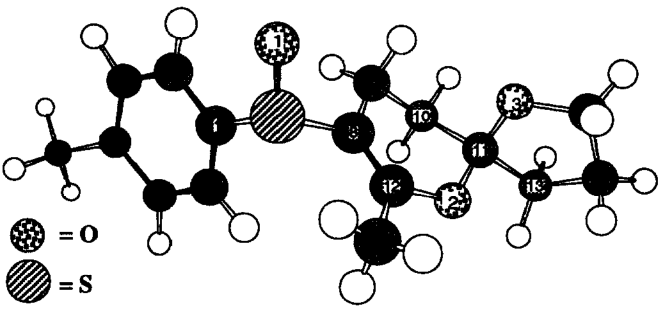


Figure 2: X-ray crystal structure of **4a**. Selected values of bond distances (Å) and angles (deg): S-O1 = 1.486(3), S-C1 = 1.798(3), S-C8 =1.773 (3), C8-C12 = 1.324(4), C11-O2 = 1.446(4), C11-O3 = 1.410(4), C1-S-C8 = 97.79(12), C1-S-O1 = 105.7(2), C8-S-O1 = 107.4 (2), S-C8-C12 = 119.7(2), O2-C11-O3 = 108.3 (2), C10-C11-C13 = 116.7 (3).

This constitutes the first example of an intermolecular hetero-Diels-Alder reaction using a chiral sulfinyloxadiene.[15] The outstanding reactivity of **2** allowed then the cycloaddition to proceed without heating nor catalyst. These very mild conditions made possible the use of α-methylenetetrahydrofuran as an interesting precursor of spiroketal derivatives.[16]

In summary, these first examples of intermolecular cycloadditions with simple enantiopure sulfinyl-diene and -heterodiene illustrate that both can be successfully employed in asymmetric synthesis under extremely mild conditions and can lead to unexpected new chemistry. Finally, it is worthy to note that the sulfinyl group exhibits an interesting "dual electron demand" effect as it seems activating in direct electron demand Diels-Alder reaction (*i.e.* 1→3), as well as in inverse electron demand (*i.e.* 2→4).

We are currently exploring additional aspects and synthetic applications of this chemistry.

Acknowledgment. The authors would like to thank Professor F. Huet for nOes NMR studies.

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