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(S)-(+)-3-p-Tolylsulfinylbut-3-en-2-one : A Spectacular Oxabutadiene for Asymmetric Cycloaddition of Styrenic Compounds

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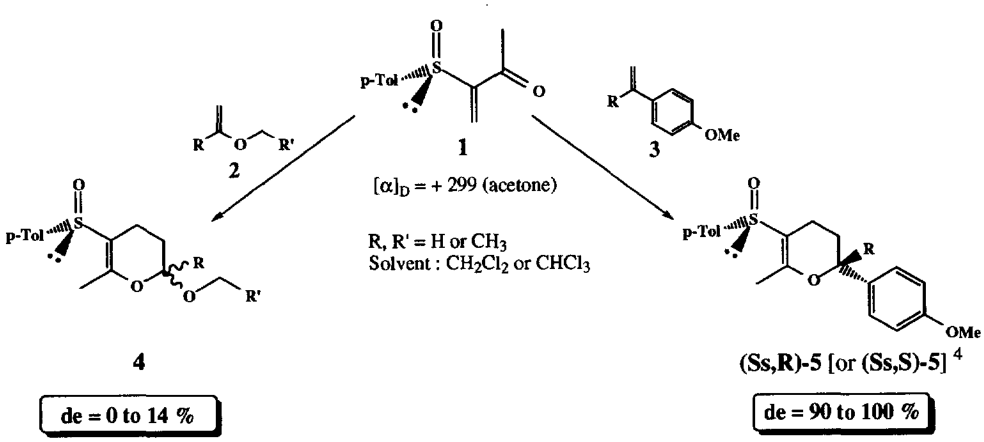
Abstract : Heterocycloaddition of optically active (S)-(+)-3-p-tolylsulfinylbut-3-en-2-one **1** was successfully achieved with various electron-rich dienophiles in extremely mild and non-catalytic conditions. Nature of the dienophile (enol ether **2** v.s. styrene **3**) proved to play a critical role in the stereochemical outcome of the reaction : less than 14% de with **2**, more than 94% de with **3**.

The interest of unsatured sulfoxides in Diels-Alder reaction is obvious[1] and any studies contributing to the development of new sulfoxide intermediates and their reactivities remain of the upmost importance.

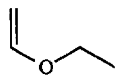
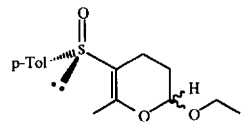
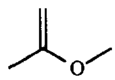
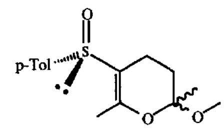
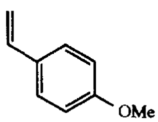
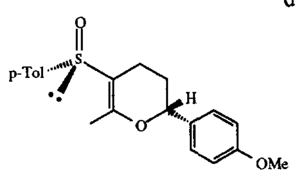
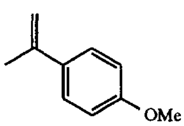
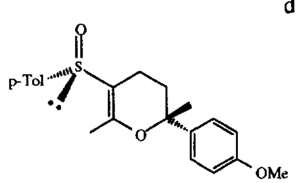
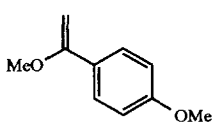
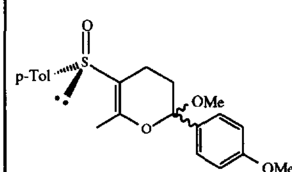
In a previous report[2] was described the first example of intermolecular heterocycloaddition of (S)-(+)-3-p-tolylsulfinylbut-3-en-2-one **1** in inverse electronic demand giving dioxaspiroadduct very easily but with low selectivity from sensitive 2-methylenetetrahydrofuran. The high degree of reactivity of oxabutadiene **1** lead us to extend cycloadditions studies towards : on the first hand acyclic enol ethers **2**, and on the other hand styrenic derivatives **3** of lower dienophilicity.

Results reported here[3] confirm high reactivity of compound **1** in all cases and show a dramatic influence of the nature of its counterpart on the level of stereoselectivity.



Scheme

Cycloaddition[3] of (S)-(+)-3-p-tolylsulfinylbut-3-en-2-one **1** with dienophiles **2**, **3** and **6**.

Entry	Dienophile	Solvent	Time[a] (h)	T (°C)	Yield[b] (%)	de[c] (%)	Adducts
1	 **2a**	CH_2Cl_2	8	20	92	14	 **4a** [d]
2		H_2O	2	20	90	36	
3		$CHCl_3$	8	20	78	12	
4	 **2b**	CH_2Cl_2	5	20	54	0	 **4b** [e]
5		H_2O	3	20	21	8	
6		$CHCl_3$	5	20	88	4	
7	 **3a**	CH_2Cl_2	168	40	50	94	 **(Ss,R)-5a** [or **(Ss,S)-5a**] [d]
8		H_2O	144	20	66	90	
9		$CHCl_3$	24	61	80	94	
10	 **3c**	CH_2Cl_2	50	40	80	>99	 **(Ss,R)-5b** [or **(Ss,S)-5b**] [d]
11		H_2O	36	20	64	>99	
12		$CHCl_3$	15	61	67	>99	
13	 **6**	CH_2Cl_2	10	20	78	18	 **7** [e]
14		H_2O	8	20	48	12	
15		$CHCl_3$	2	61	89	8	

(a)- Monitored by T.L.C. (Eluent : Ether), (b)- Purified product by chromatography, (c)- Determined by ^{1}H-NMR, 400MHz, (d)- Diastereomerically pure after chromatography, (e)- Diastereomeric mixture after chromatography.

Table

In this systematic study, all reactions were performed without catalyst[5] and tested in dichloromethane, chloroform and water.

Cycloaddition of ethyl vinyl ether **2a** with **1** (Table : entries 1-3) readily occured (at room temperature, in a few hours) with very low selectivity in halogenated solvents; a small enhancement of diastereomeric excess is observed in water together with high yield. Diastereomeric separation of adducts **4a** is easily performed by chromatography. Similar results are obtained with 2-methoxypropen **2b** in chloroform (entry 6). With this enol ether, aqueous medium seems to cause a significant hydrolysis of adduct **4b** into 1,5 diketone **8** [6] (entry 5).

Although less reactive, 4-vinylanisole **3** reacts satisfactorily with **1** by refluxing over an extended time. No degradation product is observed under these modified conditions. Thus, after 24 hours of reflux in chloroform, cycloadduct **5a**[3] is obtained in a high diastereoselective manner (de : 94%) and is easily purified as a sole optically pure diastereomer in 80% yield (entry 9).

This amazing level of selectivity in this series was confirmed with 4-isopropenylanisole **3c** (entries 10-12) which leads to the desired adduct **5b** with a total diastereoselectivity (de > 99%).

Contrast beetween the different selectivity observed makes attractive the borderline case of 4-(1-methoxyvinyl)anisole **6**. Results (entries 13-15) demonstrated unambiguously the dominant effect of methoxy substituent as directing group in the transition state : the low degree of selectivity observed agrees with those obtained with other enol ethers **2a-b**. So, high stereochemical control in the formation of adducts would specifically occur when the aromatic moiety of dienophile acts as stereodirecting group.[4]

To conclude, we have found that styrenic compounds can undergo high stereoselective heterocycloaddition with powerful oxabutadiene **1**. Litterature contains very few examples of such cycloaddition type[7-9] : so far, satisfactory yields required high pressure[10] or a suitable heterodiene-catalyst system[11]. Morever, asymmetric version has been related only in one example and gives modest facial selectivity.[10] So, the powerful stereocontrolled process described suggests extended studies with other styrenic dienophiles and applications in asymmetric synthesis will be reported in due course.

References and Notes

1. (a) Carreño, M.C. *Chem. Rev.*, **1995**, *95*, 1717-1760 ; (b) Drabowicz, J. ; Kielbasinski, P. ; Mikolajezyk, M. Synthesis of sulfoxides in *"The Chemistry of Sulfones and Sulfoxides"* Patai, S.; Rappoport, Z. and Stirling, C. Eds., John Wiley & Sons Inc.; Colchester, Essex, Great Britain (**1988**), Chapter 8.
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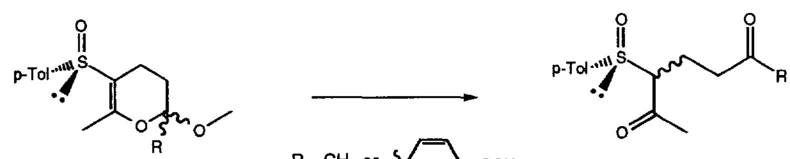
3. All structures were confirmed by ^{1}H-NMR, ^{13}C-NMR, infrared and mass spectroscopy. Acceptable combustion analyses (± 0.3%) or high resolution mass spectra were obtained for all samples.

   Representative data and typical procedure for selected compounds : a mixture of (S)-(+)-3-p-tolylsulfinylbut-3-en-2-one **1** (104 mg ; 0.5 mmol) and 4-vinylanisole **3b** (200μL ; 1.5 mmol) in dry chloroform (3 mL) was refluxed for 24 hours. After concentration under vacuo, the crude product was purified by chromatography on silica gel (eluent : cyclohexane/ethyl acetate, 8/2) to give the optically pure adduct **5a** (138 mg ; 80% yield) as a white solid which was recrystallized in ether / petroleum ether : **5a** : $[\alpha]_D$ + 93 (c 0.66, acetone); mp 72-75°C; ^{1}H-NMR ($CDCl_3$) δ 1.54-1.64 (m, 1H), 1.5-1.62 (m, 1H), 1.85-2.07 (m, 1H), 2.32 (s, 1H, CH_3C=C), 2.41 (s, 3H, CH_3Ar), 2.49 (dd, J=16, 5 Hz, 1H), 3.79 (s, 3H, CH_3O), 4.66 (dd, J=11 Hz, 1H, CHO), 6.88-7.22

(AB system, J=8 Hz, $4H_{arom}$). ^{13}C-NMR ($CDCl_3$) δ 15.5, 17.8, 21.3, 29.4, 55.3, 78.4, 113.5, 114.0, 124.5, 127.4, 129.6, 140.0, 140.2, 159.5, 159.6. **4a** : $[\alpha]_D$ + 114 (c 0.5, acetone); mp 72-75°C (petroleum ether); ^1H-RMN (CD_3COCD_3) δ 1.17 (t, J=7 Hz, 3H, CH_3-CH_2), 1.56-1.91 (m, 4H), 2.27 (s, 3H, CH_3C=C) 2.39 (s, 3H, CH_3Ar), 3.55 (dq, J=9, 7 Hz, 1H, CH_2O), 3.85 (dq, J=9, 7 Hz, 1H, CH_2O), 5.08 (t, J=2.5 Hz, 1H, CHO), 7.2-7.38 (AB system, J=8 Hz, $4H_{arom}$);^{13}C-RMN (CD_3COCD_3) δ 10.9, 15.2, 15.5, 21.2, 26.2, 63.9, 97.3, 113.9, 124.5, 129.6, 140.1, 140.2, 156.1. $[\alpha]_D$ - 232 (c 0.95, acetone); mp 82-85°C (ether); ^1H-RMN (CD_3COCD_3) δ 1.23 (t, J=7 Hz, 3H, CH_3-CH_2), 1.52-1.91 (m, 4H), 2.28 (s, 3H, CH_3C=C) ; 2.40 (s, 3H, CH_3Ar), 3.64 (dq, J=9, 7 Hz, 1H, CH_2O), 3.73 (dq, J=9, 7 Hz, 1H, CH_2O), 4.93 (dd, J=5, 2.5 Hz, 1H, CHO), 7.28-7.42 (AB system, , J=8 Hz, $4H_{arom}$);^{13}C-RMN (CD_3COCD_3) δ 12.8, 15.0, 17.6, 21.2, 26.6, 64.4, 98.6, 112.2, 124.9, 130.0, 140.3, 142.7, 156.6. **4b** : ^1H-RMN δ 1.36/1.42 (2s, 3H, CH_3-C-O), 1.41-1.70 (m, 2H), 1.88-1.95 (m, 1H), 2.34 (s, 3H, CH_3C=C), 2.39 /2.40 (2s, 3H, CH_3Ar), 2.41-2.52 (m, 1H), 3.24-3.31 (2s, 3H, CH_3-O), 7.27-7.41 (4d, AA'BB' system, J=8 Hz, $4H_{arom}$); ^{13}C-RMN δ 11.9/13.4, 17.4/17.7, 21.3, 22.4, 30.9/31.7, 49.1/51.7, 99.1/99.8, 114.1/114.4, 124.3/124.4, 129.6, 139.7/140.0, 140.2/140.5. **5b** : $[\alpha]_D$ + 156 (c 0.85, acetone); mp 120-121°C (ether/petroleum ether); ^1H-RMN δ 1.39 (s, 3H, CH_3), 1.47-1.58 (m, 1H), 1.78 (dt, J=12, 6 Hz, 1H), 1.98-2.24 (m, 2H), 2.37 (s, 1H, CH_3C=C), 2.40 (s, 3H, CH_3Ar), 6.85-7.22 (AB system, J=8.8 Hz, $4H_{arom}$), 7.28-7.40 (AB system, J=8.1 Hz, $4H_{arom}$); ^{13}C-RMN δ 13.5, 18.2, 21.3, 26.6, 33.1, 55.3, 79.2, 112.7, 113.8, 124.3, 125.5, 129.6, 137.11, 140.1, 140.4, 157.5, 158.7. **7** :^1H-RMN δ 1.43-2.57 (m, 4H), 2.32/2.37 (s, 3H, CH_3C=C), 2.37/2.38 (s, 3H, CH_3Ar), 3/3.06 (s, 3H, CH_3O), 3.77 (s, 3H, CH_3O), 6.28 -7.39 (m, 8H, H_{arom}); ^{13}C-RMN δ 12.5/13.8, 17.4/17.6, 21.3/21.4, 33.7/34.4, 50.1/50.4, 55.3, 100.8/101.5, 113.7/113.8, 115.1/115.2, 124.3/124.4, 127.3, 129.6, 131.7/132.0, 139.5, 140.2, 155.5/155.8, 159.6.

4. The determination of absolute configuration of adducts **5** is under progress by X-Ray crystallography and by chemical correlation to known enantiopure lactones and will be published in a full paper.
5. Use of catalyst (Et_2AlCl, $Eu(fod)_3$ for example) has been unsuccessfully carried out in the case of ethyl vinyl ether.
6. Epimeric mixtures of 1,5 diketones **8** are observed (ratio **4b/8** : 1/1) and characterized by infrared spectroscopy υ_{max} : 1710 (C=O), 1031 (S=O) cm^{-1} .



4b, 7 **8**

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