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Use of 9-anthrylcarbinol Derivatives as Chiral Auxiliaries in Asymmetric Diels-Alder Reaction

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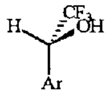
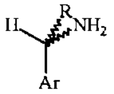
Abstract : The Diels-Alder reaction of the acrylates derived from 9-anthrylcarbinol, bearing various substituents, with cyclopentadiene, is studied under several conditions, in the absence or the presence of a Lewis acid. The ratio of cycloadducts depends on the reaction conditions and a satisfactory diastereomeric excess was obtained in the catalyzed reactions.

Introduction

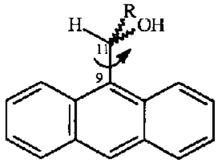
Arylcarbinols **1**[1] and some arylamines **2**[2] are widely used as Chiral Solvating Agent (CSA). They are known to render the NMR spectra of enantiomers nonequivalent. The 2,2,2-trifluoro-1-(9-anthryl)ethanol (Pirkle's alcohol) **1c** reveals a restricted rotation about the C_9-C_{11} bond and the free energy of activation for the rotation is 14.5 kcal/mole.[3] In our laboratory, other alkyl- or aryl-(9-anthryl)carbinols were synthesized, including the *tert*-butyl **3a** and the methyl **3b** derivatives.[4] The free energy of activation for bond rotation of these two compounds is respectively 21.7 kcal/mole and 11.0 kcal/mole.



R-(-)-**1a** Ar = Ph
1b Ar = 1-naphthyl
1c Ar = 9-anthryl



2
Ar = Ph, 1-naphthyl, 9-anthryl
R = Me, Ph



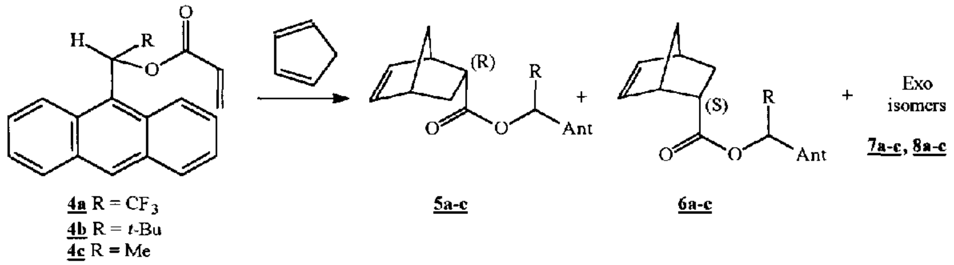
3a R = *t*-Bu
3b R = Me

In this paper, we report the results obtained for the Diels-Alder reaction of the acrylates of these alcohols with cyclopentadiene. To our knowledge, this is the first time that Pirkle's alcohol and derivatives have been used as chiral auxiliary in Diels-Alder reaction.The aim was to determine whether the asymmetric induction could be correlated, firstly with the large π-system (anthracene) and secondly with the rotational barrier of the $C_9(sp2)$-$C_{11}(sp3)$. These two points determine the conformation of the dienophile and the stereoselection of the Diels-Alder reaction.

Results and Discussion

The acrylates of 9-anthrylcarbinol **4** were readily obtained by reaction of the alcohol with acryloyl chloride. Enantiomerically pure 2,2,2-trifluoro-1-(9-anthryl)ethanol was of commercial grade and all the reactions were carried out with the (R)-enantiomer. The *tert*-butyl derivative prepared in the laboratory, was obtained enantiomerically pure by chromatographic separation on a chiral column using triacetatecellulose as chiral stationary phase or by diastereomeric derivation and later separation by standard chromatographic methods.[5] The acrylates were reacted with cyclopentadiene under several conditions. The results of the Diels-

Alder reactions were determined by comparison of the integration of the ^{1}H-NMR signals corresponding to ethylenic protons and that in the α-position of the carbonyl group of each diastereoisomer.



Scheme 1

The Diels-Alder reaction was carried out both in the absence and in the presence of a Lewis acid as a catalyst. In the thermal reaction, whatever the temperature, all four possible products **5-8** were obtained (scheme 1 and table 1). The overall *endo/exo* ratio is quite interesting, varying from 4/1 to 10/1, depending on the temperature and the substate; the best result being obtained with the *tert*-butyl acrylate **4b** at -20°C (entry 5). The *endo* cycloadducts ratio did not vary significantly (ca. 7:3).

Entry	Dienophile	T°C	Yield[a]	*endo/exo*	R/S
1	**4a**	-20	100	88/12	66/34
2	**4b**	120	100	80/20	68/32
3		25	100	84/16	69/31
4		-20	44	91/9	70/30
5	**4c**	25	100	82/18	72/28

Table 1 : Thermal Diels-Alder reaction with acrylate 4 and cyclopentadiene
[a] Yield based on dienophile

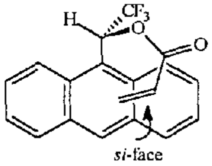
In the catalyzed reaction (table 2), the time required for completion of the cycloaddition was shortened considerably : in the case of **4a**, without a catalyst, all the dienophile was consumed after 12h at -20°C, and with $EtAlCl_2$ complete consumption was achieved after 1h at -70°C.

As excepted, compared to the non-catalyzed reaction, the use of Lewis acids generally led to a steep increase in *endo/exo* selectivity. We usually observed the formation of only *endo* products without any trace of *exo* adducts, except with $BF_3.OEt_2$ (entry 11 and 17), in these cases, the *endo/exo* ratio is about 9/1. With the acrylate of Pirkle's alcohol **4a** at -70°C in methylene chloride and with $ElAlCl_2$ (2 eq) as a catalyst (entry 10), the *endo* adducts **5a-6a** ratio is 85/15. The change of solvent, temperature or catalyst concentration decreased the selectivity of the reaction (entry 6-9).

As usually found, polymerization of the diene was a serious impediment to the reaction promoted by a Lewis acid, particularly with $TiCl_4$ as a catalyst, and in the cases of **4b** and **4c**. To avoid the polymerization, a methylene chloride/hexane mixture (1/1) was used as solvent,[6] but there was a drop in asymmetric induction or no reaction at all (entry 14, 16 and 18). The main diastereomer **5** is the same in the thermal and in the catalyzed reaction, whatever the substrate, the NMR spectrum of this diastereomer shows a characteristic shift of one ethylenic proton relative to the other, of 0.7 to 0.9 ppm. The anthryl group shields the *re*-face of the acrylate, directing the diene to the dienophile *si*-face. The two *endo* products **5** and **6** derived from both the s-*cis* and the s-*trans* conformation of the acrylate. Moreover, π–π orbital overlap between the anthryl group and the acrylate stabilizes the s-*trans* conformation, even in the absence of a catalyst.

Entry	Dienophile	Lewis acid (eq)	T°C	Solvent	Yield[a]	*endo/exo*	R/S
6	**4a**	$EtAlCl_2$ (0.5)	-70	CH_2Cl_2	100	100/0	70/30
7		$EtAlCl_2$ (0.5)	-30	CH_2Cl_2	100	100/0	65/35
8		$EtAlCl_2$ (0.5)	-30	$PhCH_3$	100	100/0	65/35
9		$EtAlCl_2$ (0.5)	-70	CH_2Cl_2/C_6H_{14}	100	100/0	63/37
10		$EtAlCl_2$ (2)	-70	CH_2Cl_2	100	100/0	85/15
11		$BF_3.OEt_2$ (0.5)	0	$PhCH_3$	40	87/13	62/38
12		$TiCl_4$ (1)	-70	CH_2Cl_2	45	92/8	55/45
13		$TiCl_4$ (0.75)	-70	$PhCH_3$	87	100/0	55/45
14		$TiCl_4$ (0.75)	-70	CH_2Cl_2/C_6H_{14}	-	-	-
15	**4b**	$EtAlCl_2$ (2)	-30	CH_2Cl_2	42	100/0	56/44
16		$EtAlCl_2$ (0.5)	-30	CH_2Cl_2/C_6H_{14}	85	100/0	43/57
17		$BF_3.OEt_2$ (1)	-30	CH_2Cl_2	100	90/10	63/37
18	**4c**	$EtAlCl_2$ (0.5)	-70	CH_2Cl_2/C_6H_{14}	38	100/0	43/57

Table 2 : Catalyzed Diels-Alder reaction with acrylate 4 and cyclopentadiene.
[a] Yield based on dienophile



Scheme 2

The absolute configuration of the main *endo* diastereomer was determined by reduction of the ester to primary alcohol and correlation to the appropriate enantiomer of 4-(hydroxymethyl)norbornene.[7] It displayed an optical rotation $[\alpha]^{25}_D = +35.0$ (c = 0.4, 95% EtOH) indicating that the 2-(R)-enantiomer was predominant. Almost identical results were obtained with acrylates **4b** and **4c**. This indicates that the steric effects of the substituents are not decisive. Moreover, no correlation was found between the rotational barrier of the bond C_9-C_{11} and the asymmetric induction. The best result was obtained with the acrylate **4a** derived from Pirkle's alcohol, which possesses an intermediate value for the free energy of activation. This result could be explained by stereoelectronic effect due to the presence of the trifluoromethyl group, but further studies are in progress.

Experimental:

Procedure for synthesis of acrylates : acryloyl chloride (0.29g, 3.2 mmol) was added at -40°C to a solution of **1c** (0.20g, 0.72 mmol) and triethylamine (0.26g, 2.5 mmol) in methylene chloride (12 ml). After stirring for 5h at room temperature, the reaction was quenched by addition of water, extracted with methylene chloride and dried (Na_2SO_4). The residue was purified by column chromatography on silica gel (hexane/methylene chloride, 1/1 v/v) to give the acrylate **4a** (0.16g, 67%) as an oil. ^{1}H-RMN ($CDCl_3$) : 5.95 (dd, J = 10.5, 1.0 Hz, 1H); 6.25 (dd, J = 17.4, 10.5 Hz, 1H); 6.54 (dd, J = 17.4, 1.0 Hz, 1H); 7.46-7.66 (m, 4H); 7.89 (q, J = 7.9 Hz, 1H); 8.00-8.04 (m, 2H); 8.39 (d, J = 9.0 Hz, 1H); 8.55 (s, 1H); 8.75 (d, J = 9.0 Hz, 1H). ^{13}C-RMN ($CDCl_3$) : 69.10; 122.84; 125.28; 126.43; 126.52; 126.67; 127.21; 128.91; 129.56; 131.59; 133.37; 164.07. $[\alpha]^{25}_D$ = +18.7 (c = 0.75, $CHCl_3$).

Procedure for catalyzed Diels-Alder reactions : a solution of acrylate **4a** (0.33g, 0.1 mmol) in methylene chloride (5 ml) was treated with ethylaluminium dichloride (0.2 ml of a 1M hexane solution) at -70°C under nitrogen. The mixture was stirred for 15 min and cyclopentadiene (0.075 ml) was added dropwise to the resulting yellow solution at the same temperature. After stirring for 1h, the reaction was quenched with a solution of ammonium chloride. Methylene chloride extraction, followed by drying (Na_2SO_4), evaporation and filtration through silica gel (hexane/methylene chloride, 1/1 v/v), gave adducts **5a** and **6a** (85/15).

5a : ^{1}H-RMN ($CDCl_3$) : 1.27 (d large, J = 8.9 Hz, 1H); 1.37 (dq, J = 8.5, 1.8 Hz, 1H); 1.45 (ddd, J = 11.8, 3.9, 2.6 Hz, 1H); 1.94 (ddd, J = 11.8, 9.2, 3.7 Hz, 1H); 2:86 (s broad, 1H); 3.17 (dt, J = 9.2, 3.9 Hz, 1H); 3.25 (s broad, 1H); 5.09 (dd, J = 5.8, 2.6 Hz, 1H); 5.95 (dd, J = 5.8, 3.1 Hz, 1H); 7.46-7.51 (m, 2H); 7.58-7.62 (m, 2H); 7.73 (q, J = 8.4 Hz, 1H); 8.02 (d, J = 8.4 Hz, 2H); 8.34 (d, J = 8.9 Hz, 1H); 8.54 (s, 1H); 8.81 (d, J = 9.2 Hz, 1H). ^{13}C-RMN ($CDCl_3$) : 29.22; 42.69; 43.33; 45.98; 49.73; 68.65; 122.72; 125.11; 127.79; 127:74; 129.59; 131.24; 137.92; 172.85. **6a** : ^{1}H- RMN ($CDCl_3$) : 1.32 (d broad, J = 8.9 Hz, 1H); 1.39-1.43 (m, 1H); 1.50 (dq, J = 8.7, 2.0 Hz, 1H); 1.84 (ddd, J = 12.1, 9.2, 3.6 Hz, 1H); 2:90 (s broad, 1H); 3.04 (dt, J = 9.2, 3.8 Hz, 1H); 3.45 (s broad, 1H); 6.01 (dd, J = 5.7, 3.1 Hz, 1H); 6.18 (dd, J = 5.7, 2.8 Hz, 1H); 7.46-7.50 (m, 2H); 7.57-7.62 (m, 2H); 7.75 (q, J = 8.4 Hz, 1H); 8.02 (d, J = 8.4 Hz, 2H); 8.34 (d, J = 8.9 Hz, 1H); 8.54 (s, 1H); 8.75-8.78 (m, 1H).

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