Tetrahedron Letters, Vol. 33, No. 41, pp. 6147-6150, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

Diastereofacial Selectivity in Diels-Alder Reactions of Chiral 2-substituted-1,3-dienes.

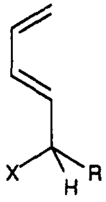
Robert Bloch* and Nathalie Chaptal-Gradoz.

Laboratoire des Carbocycles, associé au CNRS, Institut de Chimie Moléculaire d'Orsay,
Bât. 420, Université de Paris-Sud, 91405 Orsay (France)

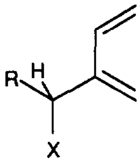
***Key Words** : Cycloaddition, regioselectivity, π-facial selectivity, chloroprene.*

***Abstract** : Starting from chloroprene, an improved synthesis of alkyl and aryl (1,3-butadien-2-yl) methanols 1 is described. Thermal Diels-Alder reactions between these dienols or their ethers 3 and various dienophiles give rise with fair to good regio- and diastereoselectivity to monocyclic "para" adducts. In contrast a total regioselectivity and an excellent π-facial selectivity is observed when the Diels-Alder cycloadditions of the dienic ethers 3 are conducted in the presence of a Lewis acid.*

The Diels-Alder cycloaddition is an important and useful process in organic synthesis owing to the simultaneous creation of four contiguous chiral centers [1]. In the recent years, the effect of an adjacent chiral center on the diastereoselectivity of these reactions has received considerable attention. In particular, if several reports have shown the influence of heteroatom substitution at the allylic position of 1-substituted-1,3-dienes A [2], very few investigations have been made concerning 2-substituted-1,3-dienes **B**. This lack of interest may be due to the poor regioselectivity [3] and diastereoselectivity [4] usually observed in Diels-Alder reactions of such dienes.



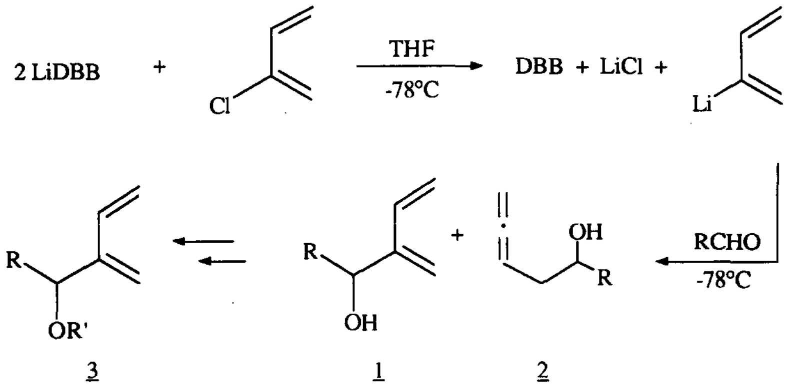
A



B

We wish to report in this letter the excellent regio- and π-facial selectivity obtained in Lewis acid catalyzed Diels-Alder reactions of chiral 2-substituted-1,3-butadienes of type **B** with α,β-unsaturated aldehydes and ketones, opening a new way to the enantioselective synthesis of polyfunctionalized cyclohexanes [5].

The starting dienols **1** are usually synthesized by reaction of aldehydes with 2-lithio-1,3-butadiene obtained from chloroprene via 2-tributylstannyl-1,3-butadiene [6]. In the case of aromatic and α,β-ethylenic aldehydes, small amounts of the allenic alcohols **2** are also formed. We have improved this synthesis by direct generation of 2-lithio-1,3-butadiene from chloroprene and 4,4'-di-tert-butylbiphenyl lithium (LiDBB) [7]. In these conditions, compounds **1** can be obtained in a one pot process with better yields and similar diene/allene ratios.

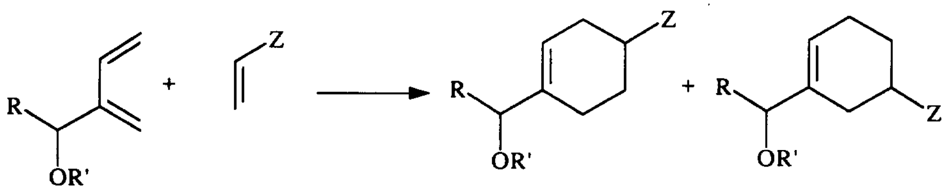


The hydroxyl moiety of dienols **1** has been protected following standard methods to give the corresponding ethers **3**.

Table 1 lists the results of thermal Diels-Alder reactions of **1** and **3** with some unsymmetrical dienophiles. As could be predicted by considering the frontier orbitals contributions [8] and as already reported for others 2-substituted-1,3-dienes [9], the regioselectivity in favour of the "para" adducts is not very high and is almost independent of the nature of R and R'. In contrast, the diastereoselectivity seems to be directly connected to the presence of a free hydroxyl group : the good selectivity observed in this case (entries 1 to 6) practically disappears for dienes containing a protected hydroxyl group (entries 7, 8 and 9). This observation suggests that hydrogen bonds between the diene and the dienophile might play an important part [10]. Then, we focused our attention on the catalytic process and found that the regioselectity as well as the stereoselectivity are considerably increased if the cycloaddition is conducted in the presence of a Lewis acid. Representative results of Lewis acid-catalyzed reactions of acrolein and methylvinylketone with the dienes **3** are collected in table 2. In all cases, a totally regioselective cycloaddition giving rise to the "para" isomer is observed. Furthermore, an excellent diastereoselectivity, slightly dependent of the steric bulk of the protective group R' and of the substituent R, is promoted by the Lewis acid. The very high regioselectivity can be well explained both by the increased polarisation of the LUMO of the C=C double bond [11] and by the severe steric interaction , in the more stable endo transition state [12] leading to the "meta" isomer, between the substituent of the diene and the boron ligands of the complexed dienophile. It is important to note that the major stereoisomers obtained in these catalyzed reactions have the configuration of the minor stereoisomers obtained by thermal reactions so that the stereoselectivity of the reaction is entirely reversed.

The determination of the relative configurations of the different stereoisomers obtained in the thermal or the catalyzed Diels-Alder cycloadditions and the rationalization of their formation are currently under investigation.

Acknowledgments *: The authors gratefully thank the Rhône-Poulenc Company and the C.N.R.S. for a grant to N. Chaptal-Gradoz.*



1 (R'=H) or 3 4 (para) 5 (meta)

***Table 1** : Thermal Diels-Alder reactions of 1 and 3* [a)]

Entry	Diene	Dienophile	Ratio 4/5 b)	Stereoselectivity c)	Yield % d)
1	R = Ph, R' = H	Z = CO_2Me	70 / 30	80 / 20	72
2	R = Ph, R' = H	Z = COMe	77 / 23	80 / 20	92
3	R = p-$MeOC_6H_4$, R' = H	Z = COMe	80 / 20	80 / 20	76
4	R = C_6H_{13}, R' = H	Z = CO_2Me	67 / 33	80 / 20	83
5	R = C_6H_{13}, R' = H	Z = COMe	78 / 22	80 / 20	82
6	R = C_6H_{13}, R' = H	Z = $CONMe_2$	70 / 30	80 / 20	69
7	R = C_6H_{13}, R' = TBDMS	Z = CO_2Me	70 / 30	55 / 45	87
8	R = C_6H_{13}, R' = TBDMS	Z = COMe	70 / 30	55 / 45	77
9	R = C_6H_{13}, R' = Ac	Z = CO_2Me	60 / 40	60 / 40	78

a) The reactions have been carried out in refluxing benzene for 48 h.

b) The ratios 4 / 5 have been determined by GLC after MnO_2 oxydation of the hydroxyl group. The "para" structure of the major regioisomers has been proved in the case of entry 1, after MnO_2 oxydation, by ^1H NMR in the presence of the shift reagent $Eu(fod)_3$.

c) Determined by GLC.

d) Yields are given for products isolated by column chromatography.

***Table 2** : Lewis acid catalyzed Diels-Alder reactions of 3* [a)]

Entry	Diene	Dienophile	Lewis acid	Ratio 4/5 b)	Stereoselectivity c)	Yield %d)
1	R = Ph, R' = TBDMS	Z = COMe	$AlCl_3$	100 / 0	0 / 100	67
2	R = Ph, R' = TBDMS	Z = COMe	$BF_3{\cdot}Et_2O$	100 / 0	0 / 100	62
3	R = Ph, R' = TMS	Z = COMe	$BF_3{\cdot}Et_2O$	100 / 0	< 5 / 95	78
4	R = Ph, R' = CH_3	Z = COMe	$BF_3{\cdot}Et_2O$	100 / 0	< 5 / 95	88
5	R = C_6H_{13}, R' = TBDMS	Z = COMe	$AlCl_3$	100 / 0	12 / 88	66
6	R = C_6H_{13}, R' = TMS	Z = COMe	$BF_3{\cdot}Et_2O$	100 / 0	19 / 81	61
7	R = iPr, R' = TMS	Z = COMe	$BF_3{\cdot}Et_2O$	100 / 0	< 5 / 95	56
8	R = Ph, R' = TBDMS	Z = CHO	$BF_3{\cdot}Et_2O$	100 / 0	0 / 100	40
9	R = Ph, R' = TMS	Z = CHO	$BF_3{\cdot}Et_2O$	100 / 0	6 / 94	75

a) The reactions have been conducted under argon at -78°C in methylene chloride and quenched by addition of triethylamine.

b)The ratios 4 / 5 have been determined, after deprotection and MnO_2 oxydation of the hydroxyl group, by comparison between the ^{13}C NMR spectra of the thermal and catalytic processes.

c) Determined by ^1H NMR of the crude products.

d) Yields of products isolated by column chromatography.

References and Notes

1) For recent reviews see : a) Helmchen G.; Karge, R.; Weetman, J. in "*Modern Synthetic Methods*", Scheffold, R. Ed., Springer Verlag, New York, **1986**, p. 261 ; b) Paquette, L.A. in "*Asymmetric Synthesis*", Morrison J.D. Ed., Academic Press, New York, **1984**, vol. 3, p. 455.

2) Experimental : a) Tripathy, R.; Franck, R.W.; Onan, K.D. *J. Am. Chem. Soc.*, **1988**, *110*, 3257-3262 and references therein ; b) Fisher, M.J.; Helre, W.J.; Kahn, S.D.; Overman, L.E. *J. Am. Chem. Soc.* **1988**, *110*, 4625-4633 ; c) Kozikowski, A. P.; Jung, S.H.; Springer, J.P. *J. Chem. Soc. Chem. Commun.* **1988**, 167-169 ; d) Mc Dougal, P.G.; Jump, J.M.; Rojas, C.; Rico, J.G. *Tetrahedron Lett.* **1989**, *30*, 3897-3900; e) Trost, B.M.; Lee, D.C. *J. Org. Chem.* **1989**, *54*, 2274-2275 ; f) Fleming, I.; Sarkar, A.K.; Doyle, M.J.; Raithby, P.R. *J. Chem. Soc. Perkin Trans I* **1989**, 2023-2030 ; g) Datta, S.C.; Franck, R.W.; Tripathy, R.; Quigley, G.J.; Huang, L.; Chen, S.; Sihaed, A. *J. Am. Chem. Soc.* **1990**, *112*, 8472-8478 ; h) Burnouf, C.; Cristobal-Lopez, J.; Calvo-Flores, F.G.; de Los Angeles Laborde, M.; Olesker, A.; Lukacs, G. *J. Chem. Soc. Chem. Commun.* **1990**, 823-825 ; i) Barluenga, J.; Gonzalez, F.J.; Fustero, S.; Garcia-Granda, S.; Perez-Carreno, E. *J. Org. Chem.* **1991**, *56*, 4459-4463.

Theoretical : a) Kahn, S.D.; Hehre, W.J. *J. Am. Chem. Soc.* **1987**, *109*, 663-666 ; b) Kaila, N.; Franck, R.W.; Dannenberg, J.J. *J. Org. Chem.* **1989**, *54*, 4206-4212.

3) a) Tsuge, O.; Wada, E.; Kanemasa, S.; Sakoh, H. *Chemistry Lett.* **1984**, 469-472 ; b) Hosomi, A.; Masunari, T.; Tominaga, Y.; Hojo, M. *Bull. Chem. Soc. Jpn* **1991**, *64*, 1051-1053.

4) Brown, P.A.; Bonnert, R.V.; Jenkins, P.R.; Lawrence, N.J.; Selim, M.R. *J. Chem. Soc. Perkin Trans I* **1991**, 1893-1900.

5) The synthesis of optically pure hydroxydienes of type **B** has been very recently described : a) Ref. 4 ; b) Hatakeyama, S.; Sugawara, K.; Kawamura, M.; Takano, S. *Tetrahedron Lett.* **1991**, *32*, 4509-4512.

6) Wada, E.; Kanemasa, S.; Fujiwara, I.; Tsuge, O. *Bull. Chem. Soc. Jpn* **1985**, *58*, 1942-1945.
2-Lithio-1,3-butadiene has also been generated from methylvinylketone by the Shapiro reaction : Brown, P.A.; Jenkins, P.R. *Tetrahedron Lett.* **1982**, *23*, 3733-3734.

7) Rawson, D.J.; Meyers, A.I. *Tetrahedron Lett.* **1991**, *32*, 2095-2098 and references therein.

8) Fleming, I. in "*Frontier Orbitals and Organic chemical reactions*", John Wiley and sons, New York, **1978**, p. 132.

9) see for example Hosomi, A.; Saito, M.; Sakurai, H. *Tetrahedron Lett.* **1980**, *21*, 355-358.

10) Tripathy, R.; Carroll, P.J.; Thornton, E.R. *J. Am. Chem. Soc.* **1990**, *112*, 6743-6744.

11) Ref. 8, p. 163.

12) It has been recently reported that for Lewis acid catalyzed Diels-Alder reaction between acrolein and butadiene, the endo transition state involving the diene and the anti complex of s-cis acrolein is the more stable : Birney, D.M.; Houk, K.N. *J. Am. Chem. Soc.* **1990**, *112*, 4127-4133.

(Received in France 19 May 1992)