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LETTERS

Vinyl-allenes as dienes in the Lewis acid-mediated hetero Diels–Alder reaction with aldehydes

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Abstract

The Lewis acid-mediated, hetero Diels–Alder reaction of a vinyl-allene system with aldehydes as heterodienophiles has been carried out. In the cases studied, only two cycloadducts have been obtained, which correspond to the *endo* (major compound) and *exo* (minor compound) approach of the aldehyde through the less hindered face of the dienic system. © 2000 Elsevier Science Ltd. All rights reserved.

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Compounds containing the vinyl-allene moiety have been used in several types of pericyclic reactions, including hydrogen sigmatropic shifts,[1] electrocyclization[2] and inter-[3] and intramolecular[4] Diels–Alder reactions. In several instances, the presence of the allene resulted in a facilitated reaction compared with the non-allenic case.[5]

Pursuing our interest in the synthetic uses of the hetero Diels–Alder reaction,[6] we decided to try to find general conditions for this reaction with vinyl-allenes as the diene and aldehydes as the heterodienophile. We have not been able to find examples of this reaction in the literature, and we feel that it could be of great interest, both theoretically and synthetically, since the allene part of the molecule can be prepared in enantiomerically pure form.

For non-allenic dienes reacting with aldehydes in the hetero Diels–Alder reaction, some activation is required, usually through the use of highly oxygenated dienes and high pressures or Lewis acid catalysis.[7] In order to test whether the presence of the allene lowered those requirements, we started by preparing compounds **4** and **5** (Scheme 1), in which the sole activation is due to the presence of alkyl groups on the diene.

Compounds **4** and **5** were prepared in good yield by S_N2' displacement with EtMgBr/CuBr·Me_2S[8] of the benzoates derived from the propargylic alcohols (**2** or **3**), obtained by addition of the lithium acetylide derived from 1-ethynylcyclohexene to the corresponding aldehyde.

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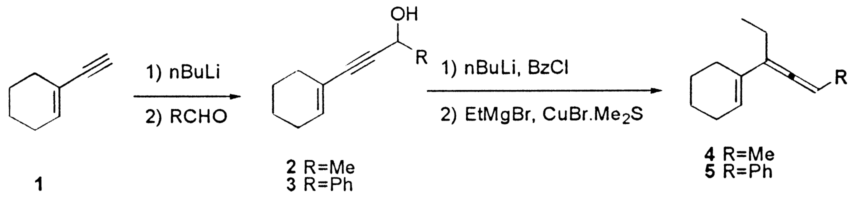
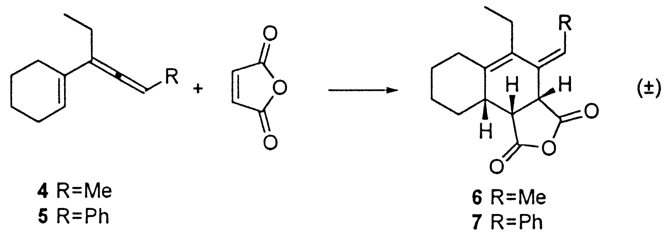


Scheme 1.

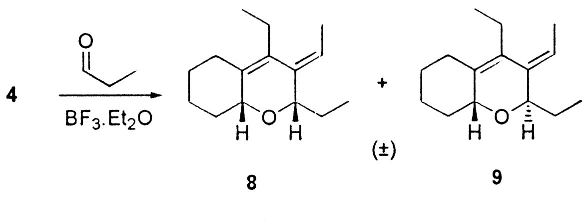
To test the overall reactivity of these vinyl-allenes, we decided to carry out the Diels–Alder reaction of **4** and **5** with maleic anhydride, since this reaction has been reported recently with other vinyl-allenes[3] and the published results can be used for comparison. Both compounds **4** and **5** reacted easily at room temperature in toluene, yielding after 24 h only one isomer in greater than 90% yield. The compound obtained in each reaction was identified as the isomer resulting from the *endo* approach of the dienophile through the less hindered face of the diene, i.e. the one opposite to the substituent on the allene terminus (Scheme 2).



Scheme 2.

These results indicate a high reactivity for **4** and **5** in those pericyclic reactions, since for the similar reaction reported with other vinyl-allenes,[3] the reaction times were much longer, typically 4–7 days, and, in some cases, at a higher temperature.

Encouraged by these results, we submitted compound **4** to the reaction with propionaldehyde and boron trifluoride etherate, under the same conditions used previously by us in hetero Diels–Alder reactions with monoactivated dienes.[6] A typical experimental procedure is as follows: the vinyl-allene was added to a mixture of aldehyde (1.5 equiv.) and boron trifluoride etherate (1.1 equiv.) in diethyl ether at 0°C. After stirring for 24 h at room temperature, the reaction was quenched by addition of triethylamine and ice-water. The crude extract was fractionated first by column chromatography, and then purified by HPLC in order to isolate and characterize each compound. Two major compounds were isolated and identified by NMR spectroscopy[9] as cycloadducts (Scheme 3) with regiochemistry consistent with the ethyl group acting as the activating group on the diene. The relative stereochemistry was established by NOE studies, the major

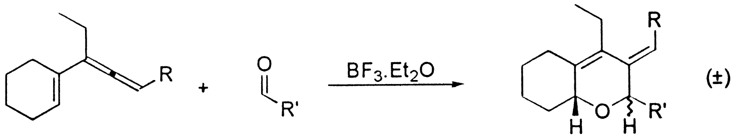


Scheme 3.

compound (**8**) being assigned the *cis* stereochemistry, consistent with an *endo* approach of the heterodienophile to the dienic portion of the molecule. The minor compound (**9**) was assigned the *trans* stereochemistry, which indicated an *exo* approach of the aldehyde. The configuration of the exocyclic double bond in both adducts indicates that the reaction takes place through the less hindered face of the system, i.e. the one opposite to the methyl group on the allene terminus.

Vinyl-allene **5** also reacted with propionaldehyde to give only two isomers, which were also the *endo* and *exo* adducts. In order to make an initial test of the importance of steric and electronic factors, **4** and **5** were subjected to the same reaction conditions using isobutyraldehyde and benzaldehyde as heterodienophiles. The results of those reactions are presented in Table 1.

Table 1



4 R=Me
5 R=Ph

R	R'	Yield[a] (cis:trans)[b]
Me	Et	70 (70:30)
Me	^{i}Pr	60 (74:26)
Me	Ph	62 (64:36)
Ph	Et	54 (73:27)
Ph	^{i}Pr	36 (66:34)
Ph	Ph	40 (75:25)

[a] Yields corresponding to the mixture of adducts after column chromatography.

[b] Ratios calculated by NMR or GC integration on the crude reaction mixture.

It can be observed that the best yields are obtained with the simpler non-branched propionaldehyde, and that the presence of the phenyl group on the vinyl-allene seems to lower the yield of cycloadducts. It has to be pointed out, however, that in most cases the yield is affected during the purification, since those compounds appear to be quite acid sensitive, especially the major *cis* adducts. For that reason, the ratios were estimated on the crude reaction mixtures.

In conclusion, we have prepared a vinyl-allene system highly reactive towards a dienophile such as maleic anhydride, which also reacts with aldehydes to give hetero Diels–Alder adducts with high regio- and diastereofacial selectivity and moderate *endo*/*exo* selectivity. To our knowledge, this is the first example of such a reaction, which gives synthetically useful yields of substituted oxanes.

The feasibility of obtaining the allene moiety in enantiomerically pure form from homochiral propargyl alcohols allows us to envision the application of this reaction to the enantioselective synthesis of natural products of interest.

Acknowledgements

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9. All compounds exhibit spectroscopic data consistent with the proposed structures, including low- and high-resolution mass spectrometry. For most compounds the structure and stereochemistry were assigned by a combination of ^{1}H NMR, COSY, ROESY, HSQC, HMBC, ^{13}C NMR and DEPT experiments.