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ASYMMETRIC DIELS-ALDER REACTIONS OF 1,3-DISILOXYCYCLOHEXADIENE WITH CHIRAL ACRYLAMIDES

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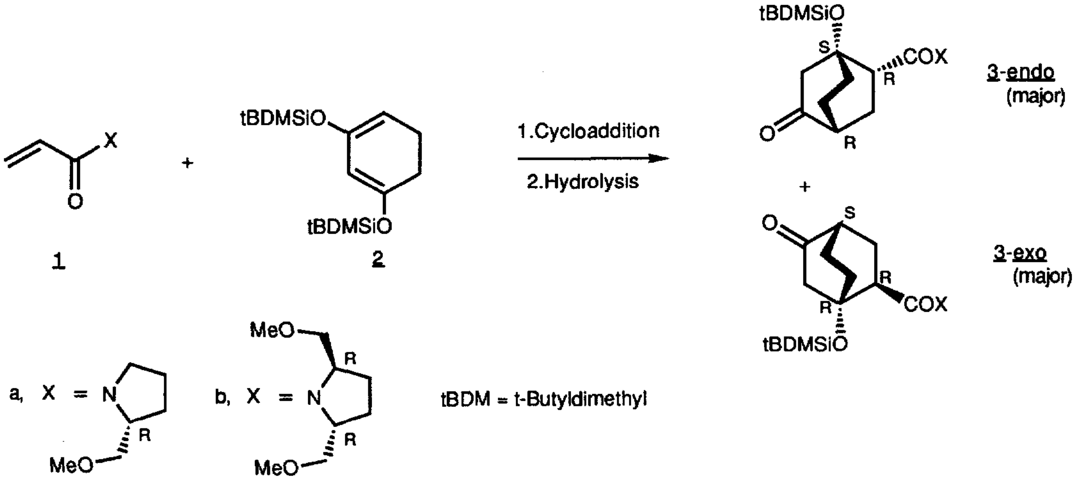
Abstract : Diels-Alder reactions of 1,3-disiloxycyclohexadiene 2 with acrylamide 1b, derived from a chiral pyrrolidine possessing C_2 symmetry, occur with high endo : exo and diastereofacial selectivities. The endo : exo ratio is controlled by the choice of the catalyst.

In the preceding communication[1], we showed that the endo-exo stereoselectivity of Diels-Alder reactions of acrylamides with cyclic 1,3-disiloxydienes could be efficiently controlled by an appropriate selection of the Lewis acid catalyst. As a natural outgrowth of these studies, we were stimulated to examine the reaction of these highly functionalized dienes with acrylamides derived from chiral amines. Several recent publications have indeed shown that asymmetric Diels-Alder reactions between chiral α,β-unsaturated amides or iminium salts and cyclopentadiene take place with excellent diastereofacial selectivity[2]. In this communication, we describe our preliminary contribution to this exciting field.

The chiral acrylamides 1a and 1b evaluated during the course of this study are derived from (2R)-methoxymethyl-pyrrolidine[3] and (2R, 5R)-trans-bis(methoxymethyl)-2,5-pyrrolidine[4] which possesses C_2 symmetry. They were readily prepared by known methods.

1,3-Disiloxydiene 2 was reacted with acrylamides 1a and 1b under conditions described in Table 1. Mild hydrolysis (H_2O or HCl 0.25 M) of the primary adducts smoothly regenerated the carbonyl function to yield bicyclic ketones 3a and 3b[5] (Scheme 1).

Endo : exo ratios and diastereofacial selectivities were easily determined by capillary gas-liquid chromatography on the crude hydrolysis mixtures. Diastereoisomers were separated by flash chromatography and their stereochemistry was assigned on the basis of ^1H NMR analyses[6].



- Scheme 1 -

The following conclusions can be drawn from the examination of Table 1 :

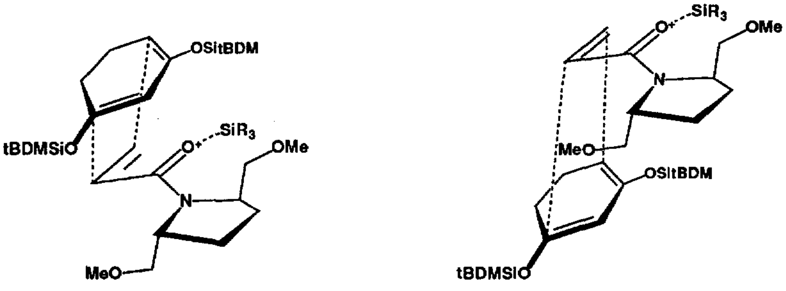
(1) *endo : exo ratios* : as previously observed with N,N-dimethyl acrylamide, the reactions of 1a and 1b with 2 showed high endo : exo ratios favouring the *endo isomer when t-butyldimethylsilyl triflate was used as catalyst* (entries A,D,E and F) and the *exo isomer when Eu(fod)$_3$ was the catalyst* (entries B and G). The thermal reaction which was run at 170°C was less selective but also gave the exo isomer as major product (entry C).

Table 1 : Reactions of diene 2 with acrylamides 1a and 1b

Entry	Dieno-phile	Catalyst (10 % molar)	Solvent	T(°C)	Time	Yield$^{(a)}$ (%)	Endo : Exo	% de of ENDO	% de of EXO
A	1a	^{t}BuMe$_2$SiOTf	CH$_2$Cl$_2$	- 60°	30 min	87	84 : 16	77	96
B	1a	Eu(fod)$_3$	Toluene	80°	24 hrs	90	0 : 100	-	25
C	1b	no	Toluene	170°$^{(b)}$	64 hrs	66	23 : 77	13	74
D	1b	^{t}BuMe$_2$SiOTf	Toluene	20°	40 min	75	70 : 30	> 98	98
E	1b	^{t}BuMe$_2$SiOTf	Toluene	-60°	3 hrs	60	87 : 13	> 98	> 98
F	1b	^{t}BuMe$_2$SiOTf	CH$_2$Cl$_2$	-60°	30 min	96	88 : 12	> 98	> 98
G	1b	Eu(fod)$_3$	Toluene	80°	66 hrs	98	0 : 100	-	90

$^{(a)}$ Total isolated yield after flash chromatography; $^{(b)}$ Reaction performed in a sealed tube

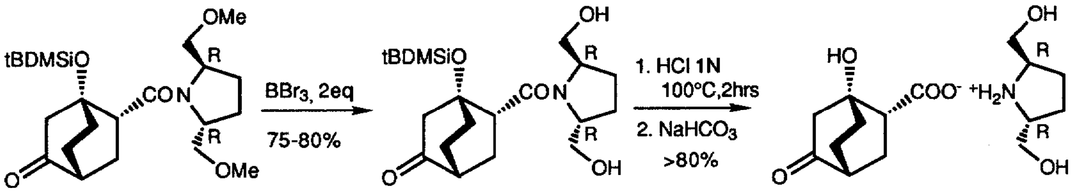
(2) *diastereofacial selectivities :* with acrylamide 1a, diastereoselectivity was modest for the endo portion in the reaction catalysed by t-butyldimethylsilyl triflate (entry A) and poor for the exo isomer resulting from the $Eu(fod)_3$ catalysed reaction (entry B). This could be the result of the presence of two reacting conformations around the C-N bond. With 1b, this problem is suppressed since the chiral auxiliary possesses axial symmetry. *High diastereoselectivities are indeed observed* in all catalysed reactions *on both endo and exo isomers 3b* (entries D to G). Only the uncatalysed reaction gave a poor diastereoselectivity as a result of the high temperature (entry C). The diastereofacial selectivity can be rationalized by considering transition states 4 and 5 (Scheme 2). In transition state 4, the diene approaches in an endo fashion from the less hindered side of the s-cis conformer[7] of acrylamide 1b. Transition state 4 is clearly lower in energy than transition state 5 and leads to the adduct 3b-endo with the R configuration α to the amide group. The absolute configuration of the 3b-endo diastereoisomer was experimentally confirmed by an X-ray diffraction analysis[8] by reference to the known configuration of the asymmetric carbon atoms of the chiral auxiliary.



4 5

- Scheme 2 -

The control of the endo : exo ratio, the excellent diastereoselectivity and the high chemical yield associated with these cycloadditions are promising . However the synthetic usefulness of these findings relies upon the possibility of removing the chiral auxiliary under mild conditions. Direct hydrolysis of the amide group requires acidic or basic conditions which are uncompatible with many functional groups and could lead to epimerization. On the other hand, mild hydrolysis conditions could be expected for the pyrrolidine amides in which the ether functions have been transformed into the corresponding alcohols[9]. In preliminary experiments, it was indeed found that the ether functions of 3b-endo were readily cleaved by BBr_3 (Scheme 3). The resulting diol 6-endo was smoothly hydrolysed to the ammonium carboxylate 7-endo. Identical results were observed for the 3b-exo epimer. In both cases, the configuration α to the amide group was maintained throughout the sequence.



3b-endo 6-endo 7-endo

- Scheme 3 -

Further examples of asymmetric Diels-Alder reactions of chiral α,β-unsaturated amides with activated dienes will be the subject of future reports.

Acknowledgements

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References and Notes

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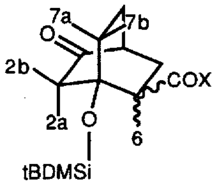
5. Pure products were characterized by IR, ^{1}H NMR and ^{13}C NMR.
6. For example :



3b-exo diastereoisomers
major : δ 2a = 2,35 ppm δ 7b = 2.62 ppm $^4J_{6\text{-}2b}$ = 0Hz $^4J_{6\text{-}7a}$ = 1,8Hz
minor : δ 2a = 2,31 ppm δ 7b = 3.24 ppm $^4J_{6\text{-}2b}$ = 0Hz $^4J_{6\text{-}7a}$ = 1,7Hz
3b-endo diastereoisomers
major : δ 2a = 3,42 ppm δ 7b = < 2.0 ppm $^4J_{6\text{-}2b}$ = 1,6Hz $^4J_{6\text{-}7a}$ = 0Hz
minor : δ 2a = 4.03 ppm δ 7b = < 2.1 ppm $^4J_{6\text{-}2b}$ = 1,6Hz $^4J_{6\text{-}7a}$ = 0Hz

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