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Diastereoselectivity in the Aza-Diels-Alder Reaction of a Sulfonyl Imino Acetate with Danishefsky's Diene.

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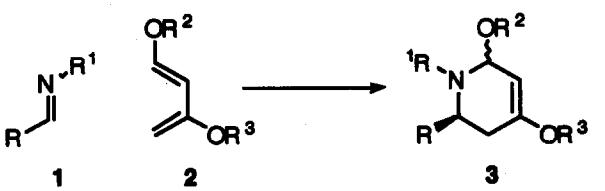
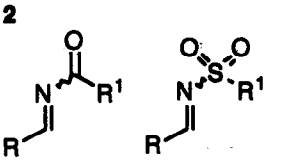
Abstract: N-(1*R*)-Camphorsulfonyl imine **8**, generated *in situ* from the corresponding brominated glycine derivative, reacted with Danishefsky's diene under thermal conditions at room temperature, to give a high yield of a 2.04 : 1 ratio of diastereomeric Diels-Alder adducts after acid hydrolysis. The observed diastereoselectivity was reversed when catalytic amounts of certain Lewis-acids were used, but was unaltered with others. The highest diastereoselectivity was 2.30 : 1 with titanium tetraisopropoxide at -78 °C.

As part of a programme aimed at synthesising certain biologically important natural products which contain either a poly-hydroxylated piperidine[1] or a poly-hydroxylated indolizidine[2] skeleton, we became interested in the aza-Diels-Alder reaction[3] of an imine of type **1** with an oxgenated diene **2** to rapidly build up a tetrahydropyridine building block **3** (**Equation 1**). Imines are relatively unreactive dienophiles[3] unless the formal cycloaddition is catalysed either by protonation of the imine[4] or when the imine is complexed by a Lewis-acid[5].

Equation 1.



1 **2** **3**

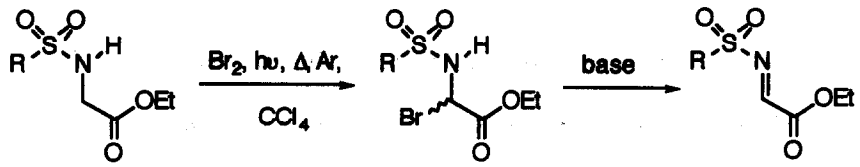


4 **5**

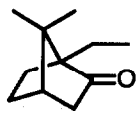
Alternatives to imines **1**, in the cycloaddition reaction, are the more reactive acyl imines **4**[6] or sulfonyl imines **5**[7]. Prato[7c] and Holmes[7e] have independently reported the use of chiral auxiliaries on the ester moiety of imines **5** (R = R*O$_2$C), ensuing diastereoselectivities varying from 53 : 47[7c] to 88 : 12[7e]. We report in this communication our preliminary results on the use of a readily available camphor based chiral auxiliary on the nitrogen of the imine, i.e. using sulfonyl imine **8**.

Imine **8** was prepared *in situ* using the method reported by Prato[7c], i.e. by bromination[8] of the corresponding glycinate **6**[9], affording quantitative conversion to the highly moisture sensitive bromide **7** (as a 1:1 mixture of diastereoisomers), followed by elimination under basic conditions (**Scheme 1**).

Scheme 1.

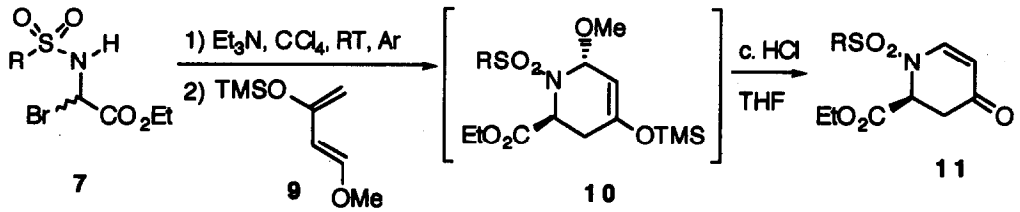


For **6**, **7**, and **8**, R =



A trial reaction of imine **8**, generated by triethylamine mediated elimination of HBr from **7**, followed by the addition of Danishefsky's diene **9** afforded a mixture of only two diastereomeric Diels-Alder adducts (by crude nmr[10]) after 8 hours at room temperature in carbon tetrachloride, possibly possessing the relative stereochemistry shown in structure **10**, which would result from the two possible diastereomeric *exo*-transition states[10] (**Equation 2**). The two adducts **10** could not be directly isolated due to hydrolytic instability and were hydrolysed *in situ* with c. HCl in tetrahydrofuran to give a 58 % yield of the pure tetrahydropyridines **11** as an inseparable 65 : 35 mixture of diastereoisomers[11] after silica gel chromatography.

Equation 2.



With the knowledge that the cycloaddition of the camphorsulfonyl imine **8** generated by this route occurred readily with Danishefsky's diene, we examined the reactions of imine **8**, generated by two different methods, both thermally and under Lewis-acid catalysed conditions. The results of this study are summarised in **Table 1**. From these results several points are worthy of note. Firstly, the diastereomeric induction is highest for the thermal reactions in the least polar solvents, the best ratio is 67:33 for the reaction carried out in carbon tetrachloride at -15 °C. Secondly, the sense of induction is reversed when using diethylaluminium chloride, though the induction is only 41:59. By contrast, other Lewis acids give the same sense of induction as the thermal reactions and the highest diastereoselection being obtained using titanium tetraisopropoxide, though the reaction is slow and only 25 % complete after 6 hours.

Finally, all the catalysed reactions are most efficient only when a catalytic amount of Lewis acid is used. With larger quantities, the reaction becomes sluggish or halted altogether and only hydrolysis products can be isolated after work up.

Table 1.

Entry	Base	Solvent	Lewis acid (mol. equiv.)	Temp. °C	Time h	Diastereomeric ratio[a]	Yield (crude[b]) %
1	Et_3N	CCl_4	none	20	8	65 : 35	58 (100)
2	"	Et_2O	"	"	"	60 : 40	- (90)
3	"	CH_2Cl_2	"	"	"	54 : 46	- (100)
4	"	MeCN	"	"	"	58 : 42	- (")
5	"	CCl_4	"	-15	"	67 : 33	- (")
6	n-BuLi	toluene	"	20	"	57 : 43	- (")
7	"	"	Et_2AlCl (0.25)	-75	6	50 : 50	- (70)
8	"	"	" (0.50)	"	"	41 : 59	45 (")
9	"	"	" (0.75)	"	"	41 : 59	- (60)
10	"	"	" (1.00)	"	"	n/a	- (0[c])
11	"	"	$TiCl_4$ (0.25)	"	"	57 : 43	- (70)
12	"	"	$ZnCl_2$ (0.25)	"	"	n/a	- (0[c])
13	"	"	$Ti(O^iPr)_4$ (0.25)	"	"	70 : 30	- (25)
14	"	"	" (1.00)	"	"	67 : 33	- (25)
15	"	"	$BF_3.Et_2O$ (0.25)	"	"	64 : 36	- (60)
16	"	"	" (0.50)	"	"	56 : 44	- (50)
17	"	"	Cp_2TiCl_2 (0.10)	"	"	65 : 35	- (40)

a; See reference 11. b; Estimated using the weight of crude product recoverd after aqueous workup by ^1H nmr (at 300 or 400 MHz). c; No Diels-Alder adduct was obeerved in the crude product.

In conclusion, we have demonstrated that the N-camphorsulfonyl auxiliary on an imino acetate derivative can be used to give moderate diastereoselectivity in the reaction of imine **8** with diene **9**, and it is at least as efficient as previously reported[7] carboxylate substituted auxiliaries. We are currently engaged in following up these results to fully explain and confirm the stereochemical outcome of the reactions, both thermal and catalysed. We shall report on our further studies and the absolute stereochemistry of adducts **11** in due course.

Acknowledgements.

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8. Bromination of glycinate **6** was carried as briefly described[8], i.e. 1 molar equivalent of Br_2 in dry CCl_4 at reflux under Ar for 2h, with UV irradiation from a Hanovia 125W medium pressure lamp (4781). Conversion was quantitative and the bromide was used directly without purification.
9. (1*R*)-Camphor substituted glycinate **6** was prepared in analytically pure form in 65 % yield after silica gel chromatography, from ethyl glycinate hydrochloride, (1*R*)-(-)-camphorsulfonyl chloride, Et_3N (2 molar equivalents) in CH_2Cl_2 for 8h.
10. The assignment of the *exo*-relative stereochemistry to the mixture of diastereomeric adducts **10** has yet to confirmed. It is concievable that the two diastereoisomers are both *endo*-adducts, but on the basis of our current evidence [a) the crude Diels-Alder products **10** display only two methoxy peaks at δ 3.66 and 3.70; b) the corresponding Diels-Alder reaction of the N-phenylsulfonamide dienophile with Danishefsky's diene provides a single diastereoisomer, as shown by a single methoxy resonance in the crude nmr spectrum at δ 3.40; and c) the only products obtained when cyclopentadiene was employed, either with the N-camphorsulfonyl or the N-phenylsulfonyl groups, were the *exo*-adducts], we believe that the *exo*-mode of addition is more likely. Similar results have been reported in the literature[7c,7e].
11. The diastereomeric ratio of adducts **11** was estimated by the ratio of the two olefinic signals at δ 7.71-7.73 and 7.59-7.62 (each 1H, m) respectively for each diastereoisomer, (400 MHz ^{1}H nmr). All other analytical data was as expected for the assigned structures: υ_{max} (film) *inter alia* 1746 (ester C=O), 1674 (sat. ketone C=O), and 1601(unsat. ketone C=O) cm^{-1}; λ_{max} (EtOH) 280 (ε 10,920) nm; m/z (f.a.b., *m*-nba matrix) 384 $(M+H)^+$, 215 $(M-C_8H_{10}O_3S)^+$, 170 (base peak, $M-C_{10}H_{12}O_3S)^+$; Analysis, $C_{18}H_{25}NO_6S$ requires C, 56.4; H, 6.6; N, 3.7, found C, 56.1; H, 6.5; N, 3.6 %.

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