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Asymmetric Diels–Alder reactions of optically active oxazolidinone-derived vinylsulfonamides

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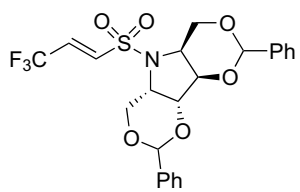
Abstract—Chiral vinylsulfonamides bearing an oxazolidin-2-one moiety derived from (*R*)-2-phenylglycinol and (1*R*,2*S*)-norephedrine have been employed as dienophiles in asymmetric Diels–Alder reactions at normal pressure affording d.e.s of up to 99% when $EtAlCl_2$ or Et_2AlCl were employed as Lewis acids. Theoretical calculations justify the observed enantio- and diastereoselectivity. © 2001 Published by Elsevier Science Ltd.

1. Introduction

The Diels–Alder reaction can be considered as one of the most powerful transformations in synthetic organic chemistry. The stereospecific creation of up to four stereogenic centers in a single step makes this cycloaddition suitable for application to complex molecules.[1] The development of asymmetric variants of the Diels–Alder reaction has attracted a great deal of interest and both the use of chiral auxiliaries, mainly chiral dienophiles, and optically active Lewis acids have been widely investigated.[2]

On the other hand, vinyl sulfonamides are well established peptidomimetics[3] and inhibitors of cysteine proteases.[4] Different methods for their preparation have been reported,[5] the most recent being the cleavage of 1,2-thiazetidine 1,1-dioxides[6] and the condensation of *N*-Boc-methanesulfonamides with aldehydes.[7] Vinylsulfonamides have being utilized in various reactions such as aziridine formation[8] and 1,3-dipolar cycloadditions,[9] and are also excellent Michael acceptors.[10] Some examples have also been reported on the use of vinyl sulfonyl amides as dienophiles in Diels–Alder cycloaddition reactions. Thus, vinylsulfonamides have been used in cycloaddition reactions to hexachlorocyclopentadiene and diphenylisobenzofuran,[11] and related cyclic systems such as isothiazolin-3-one 1,1-dioxide have also been employed as dienophiles in the search for potential anxiolytic agents.[12] In addition, vinylsulfonamides bearing 1,3-diene moieties[13] or a furan ring[14] have been employed for the synthesis of sultams by intramolecular Diels–Alder reactions.

However, reports on the use of chiral α,β-unsaturated sulfonamides as dienophiles in asymmetric Diels–Alder reactions are scarce. Thus, only trifluoromethylated vinyl sulfonamides such as **1**,[15] bearing a C_2-symmetric pyrrolidine chiral auxiliary and **2**,[16] bearing a 1,3-oxazolidine auxiliary, have recently been employed. However, high-pressure conditions are required and the use of Lewis acid catalysis afforded decomposition products due to the presence of labile moieties.



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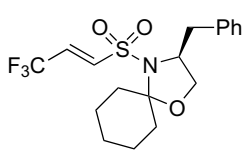

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In this context, we envisaged that the presence of a carbonyl group close to the sulfonylamide moiety would add an additional coordination point for a Lewis acid, thus preventing rotation through the S–N bond and therefore allowing for asymmetric induction. We report the preparation of enantiomerically pure oxazolidinone-derived vinylsulfonamides and their use as chi-

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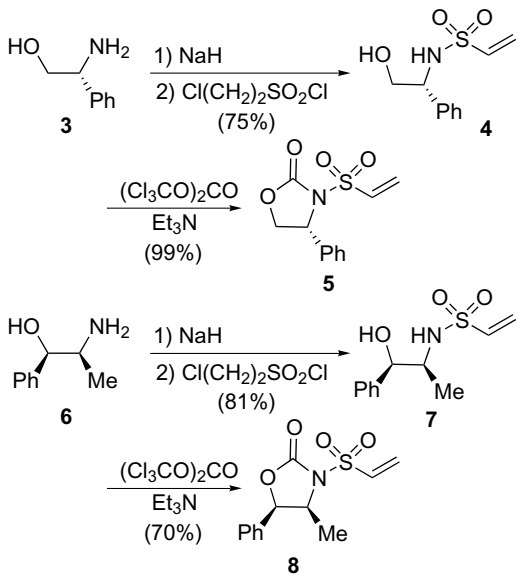
ral dienophiles in asymmetric Diels–Alder cycloaddition reactions.

2. Results and discussion

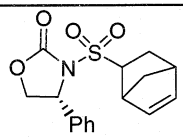
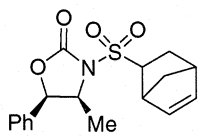
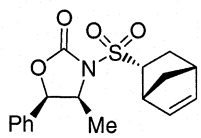
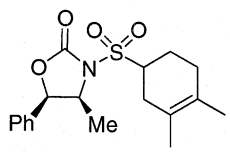
Starting from 3-(vinylsulfonyl)oxazolidin-2-one, **5** was prepared by deprotonation of (*R*)-2-phenylglycinol **3** with 1.5 equiv of NaH followed by reaction with 2-chloroethanesulfonyl chloride, which gave vinylsulfonamide **4** in 75% yield after in situ elimination of hydrogen chloride (Scheme 1). Subsequent reaction with triphosgene afforded **5** in quantitative yield. Chiral vinylsulfonamide **8** was obtained in 57% overall yield from (1*R*,2*S*)-norephedrine following a similar procedure (Scheme 1).

The chiral α,β-unsaturated sulfonamides **5** and **8** were employed as dienophiles in asymmetric Diels–Alder cycloaddition reactions. Thus, reaction of phenylglycinol-derived chiral vinylsulfonamide **5** with cyclopentadiene at rt afforded the cycloadduct **9** in 1.8/1 *endo*/*exo* ratio, each of these diastereoisomers in low d.e. (Table 1, entry 1). When the reaction was performed at −40°C in the presence of a Lewis acid such as $EtAlCl_2$ the observed d.e.s improved significantly (Table 1, entry 2), but remained unchanged on performing the reaction at a lower temperature (Table 1, entry 3).



Scheme 1. Preparation of starting chiral vinylsulfonamides.

Table 1. Diels–Alder reactions of chiral vinylsulfonamides **5** and **8**

Entry	Diene	Conditions	Product	No.	*endo*/*exo*[a]	Yield (%)[b]	d.e. *(endo)* (%)[d]	d.e. *(exo)* (%)[d]
1		CH_2Cl_2, rt, 1d		**9**	1.8/1	98	12	8
2		$EtAlCl_2$, CH_2Cl_2, -40°C, 4 h		**9**	1.8/1	98	30	36
3		$EtAlCl_2$, CH_2Cl_2, -78°C, 4 h		**9**	1.8/1	30	30	36
4		CH_2Cl_2, rt, 1d		**10**	2.3/1	98	0	0
5		$EtAlCl_2$, CH_2Cl_2, -40°C, 5 h		**10a**	1/0	51[c]	>99	
6		Et_2AlCl, CH_2Cl_2, -40°C, 5 h		**10a**	1/0	50[c]	>99	
7		$EtAlCl_2$, CH_2Cl_2, 0°C, 12 h		**11**		32[c]	80	

[a] Measured by ^1H NMR (300 MHz).

[b] Isolated crude yield.

[c] After flash chromatography.

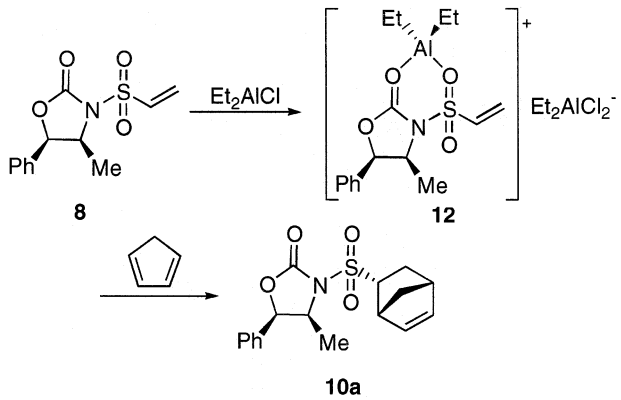
[d] Measured by ^1H NMR (300 MHz)

The use of norephedrine-derived vinylsulfonamide **8** in the cycloaddition reaction with cyclopentadiene at rt afforded a slightly higher *endo*/*exo* ratio than previously, but no asymmetric induction was observed for any of these diastereomers **10** (Table 1, entry 4). However, the addition of $EtAlCl_2$ or Et_2AlCl_2 at −40°C had a dramatic effect in this case, both on the *endo*/*exo* stereoselectivity and asymmetric induction (Table 1, entries 5 and 6).[17] Thus, only one diastereomer **10a**[18] was detected in the crude product, its *endo* stereochemistry being determined by ^1H NMR experiments. The X-ray diffraction analysis[19] of **10a** confirmed this assignment and allowed us to determine unequivocally the absolute configuration in all of the new stereocenters (Fig. 1), resulting from attack of the diene to the *Re* π-face of the dienophile. When vinylsulfonamide **8** reacted with 2,3-dimethylbuta-1,3-diene in the presence of $EtAlCl_2$, the reaction was very slow at −40°C and was performed instead at 0°C, affording 80% d.e. (Table 1, entry 7).

The observed enhancement of the asymmetric induction and *endo*/*exo* ratio by addition of $EtAlCl_2$ or Et_2AlCl to **8** could be justified as a result of the formation of a cationic Lewis-acid–dienophile complex such as **12** (Scheme 2). Similar species have been proposed to account for the high stereoselectivity in the asymmetric Diels–Alder reactions with chiral α,β-unsaturated *N*-acyloxazolidinones.[20]

Semi-empirical (PM3) calculations[21] performed on a cationic Lewis acid–dienophile complex formed between $EtAlCl_2$ and **8** showed a preferred conformation with the *Si*-face of the vinyl system shielded mainly for the methyl group of the oxazolidinone ring. Attack of the cyclopentadiene to the *Re* π-face would lead to **10a** (Fig. 2).

In order to get further insight into the preferred *endo* selectivity of this cycloaddition, we performed ab initio transition state searches[22] for *endo* and *exo* transition structures in the reaction between cyclopentadiene and



Scheme 2. Activation of vinylsulfonamide **8** by Et_2AlCl and cycloaddition reaction with cyclopentadiene.

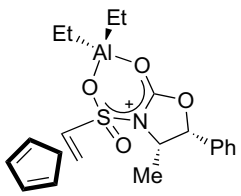


Figure 2. Approximation of the cyclopentadiene to Et_2AlCl-activated **8**.

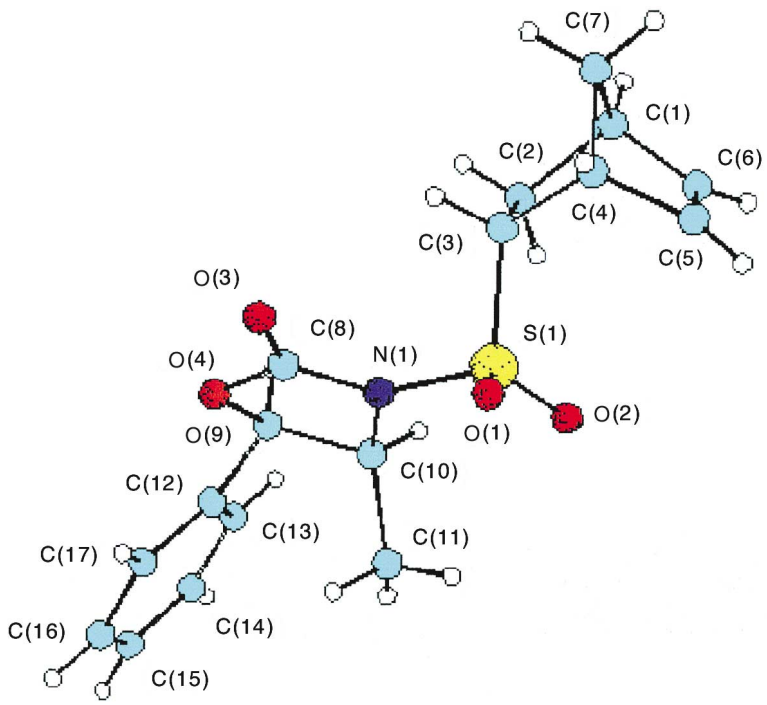


Figure 1. X-Ray diffraction structure of cycloadduct **10a**.

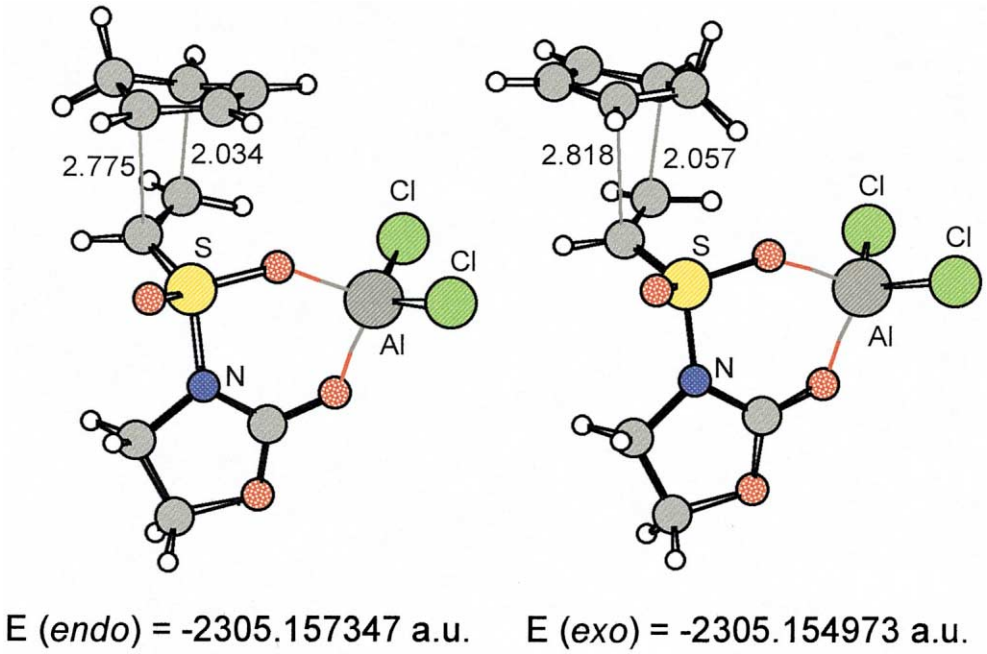


Figure 3. *Endo* and *exo* transition structures [B3LYP/6-31G(d,p)//HF/3-21G]. Distances are expressed in angstroms.

a cationic species formed by a Lewis-acid activated vinylsulfonamide analogous to **8** but deprived of the phenyl and methyl groups due to computational limitations. The HF/3-21G level of theory was applied and the located *endo* and *exo* transition structures were characterized by frequency calculations. The structures showed a high degree of asynchronicity with significant zwitterionic character (Fig. 3), as is known in Lewis acid-catalyzed Diels–Alder reactions.[23] Subsequent single point DFT calculations performed at the B3LYP/6-31G(d,p) level showed a difference in energies of 1.5 kcal/mol favoring the *endo* transition state.[24]

3. Conclusion

We conclude that a Lewis acid-activated vinylsulfonamide bearing a chiral norephedrine-derived oxazolidin-2-one moiety can act, similarly to α,β-unsaturated *N*-acyloxazolidinones, as an effective asymmetry-inducing dienophile in Diels–Alder cycloaddition reactions.

Acknowledgements

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17. The following synthesis of cycloadduct **10a** is representative: To a solution of **8** (100 mg, 0.3 mmol) in CH_2Cl_2 (5 mL) under nitrogen was added $EtAlCl_2$ (1 M solution in hexanes, 0.3 mL, 0.3 mmol) and freshly distilled cyclopentadiene (247 μL, 3 mmol). The mixture was stirred at −40°C for 5 h and to the resulting solution was added aqueous HCl (1 M, 15 mL). The mixture was extracted with CH_2Cl_2 (3×20 mL) and the organics were dried (Na_2SO_4) and evaporated (15 Torr), affording a residue which was purified by flash chromatography (silica gel, hexane/AcOEt gradients) affording adduct **10a**.
18. Compound **10a**: White solid, mp 154–155°C. $[\alpha]_D^{25} = -13.4$ (*c* 1.2, $CHCl_3$). IR (KBr) *v* 3063, 3032, 1771, 1337, 1145, 1021, 972, 830, 764, 704. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.04 (d, $J = 6.7$ Hz, 3H), 1.40 (d, $J = 9$ Hz, 1H), 1.59 (d, $J = 9$ Hz, 1H), 1.64 (ddd, $J = 12.2$, 4.9, 2.7 Hz, 1H), 2.25 (ddd, $J = 12.2$, 9.5, 3.7 Hz, 1H), 3.07 (m, 1H), 3.42 (m, 1H), 4.44 (ddd, $J = 9.5$, 4.9, 3.2 Hz, 1H), 4.60 (quint., $J = 6.7$ Hz, 1H), 5.72 (d, $J = 7.3$ Hz, 1H), 6.13 (dd, $J = 5.5$, 2.9 Hz, 1H), 6.34 (dd, $J = 5.5$, 3 Hz, 1H), 7.27–7.46 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 16.7, 29.8, 42.8, 45.3, 49.8, 57.7, 63.3, 80.1, 125.7, 128.8, 129.1, 131.4, 132.8, 138.0, 152.5. Anal calcd for $C_{17}H_{19}NO_4S$: C, 61.24; H, 5.75; N, 4.20; S, 9.60. Found: C, 60.98; H, 5.71; N, 4.12; S, 9.40%.
19. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 166268. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
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