

Design of a New and Highly Effective Chiral Auxiliary for Diels–Alder Reaction of 1-Aminodiene

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Abstract: A theoretical investigation of the facial selectivity of optically active oxazolidin-2-one-substituted dienes has been realized. This analysis enabled the development of (*R*)-4-phenyloxazolidin-2-thione as a very effective chiral auxiliary for cycloaddition of 1-aminodiene.

The Diels–Alder reaction is one of the most widely investigated and versatile pericyclic reactions in organic synthesis.¹ Its concerted mechanism enables the creation of two σ bonds and up to four stereocenters in a single step, in a regio- and stereoselective manner. So, it is not surprising that the bulk of the investigations on asymmetric synthesis over the past 30 years has been devoted particularly to this reaction. To date, the vast majority of the approaches to asymmetric [4 + 2] cycloaddition to yield enantiomerically enriched six-membered ring compounds is based on chiral catalysts (dienophile activation by Lewis acids² or, more recently, by nonmetallic organocatalysts³) or on the use of optically pure dienophiles.⁴ Fewer examples of asymmetric induction utilizing chiral auxiliary modified dienes have been reported.^{4b,5} How-

ever, the literature dealing with cycloaddition of chiral aminodienes is currently growing^{6–9} (even if a few examples of asymmetric catalysis in the field of aminodienes were recently described¹⁰).

The first chiral aminodiene, developed by Smith, made use of pyroglutamic ester auxiliary.⁶ Although the asymmetric induction was good, there was no possibility of removing the lactam group while retaining the nitrogen functionality. Further investigations in the field of new auxiliaries led recently to the development of chiral oxazolidin-2-one substituted dienes.⁷ In the case of *N*-(butadienyl)-4-phenyloxazolidin-2-one, the auxiliary allowed further cleavage¹¹ on the cycloadducts (to provide the primary amine), but selectivities were moderate to good (see below). Here, we describe our effort in the optimization of the facial selectivity of this aminodiene by proper structural modification which led us to design a novel, very effective, chiral auxiliary for asymmetric Diels–Alder reaction of 1-aminodiene.

It was previously reported that absolute configuration of cyclohexenes obtained by Diels–Alder reaction of chiral oxazolidinone (or lactam) substituted dienes can be explained by the approach of the dienophile from the less hindered face of the cisoid diene presenting an *anti*¹² conformation around the C(diene)–N(heterocycle) bond.^{6a,d,7c} To guide us in optimizing the facial selectivity of the *N*-(butadienyl)-4-phenyloxazolidin-2-one, we have first searched to identify the factors determining this preferential cycloaddition of the diene in its *anti* conformation.¹³ Considering *N*-(butadienyl)oxazolidin-2-one

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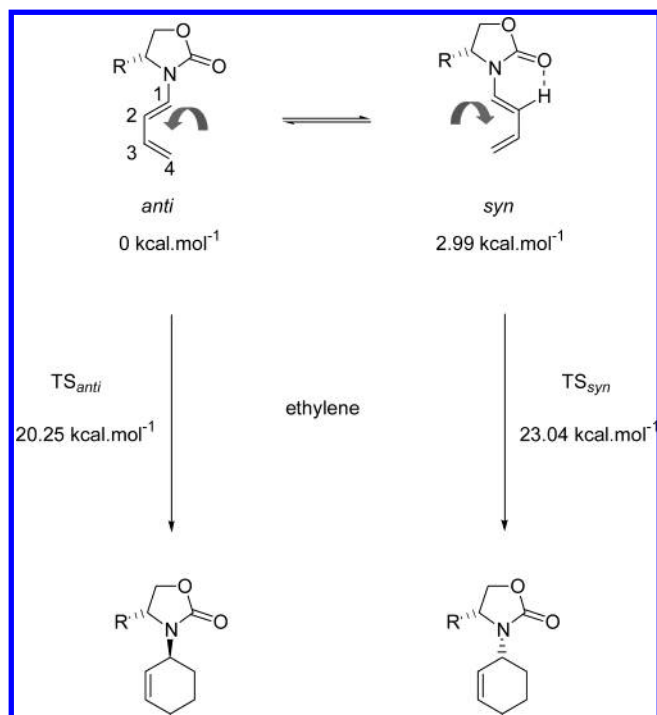


FIGURE 1. Relative energies (B3LYP/6-31**) of *anti* and *syn* conformers of the *N*-(butadienyl)oxazolidin-2-one ($R = H$) and the transition states of their reaction with ethylene (energy of both transition states is relative to the sum of the reactants energies considering the diene in its *anti* conformation).

($R = H$) as a model of the studied diene, we investigated the equilibrium between the two conformers *syn* and *anti* of the diene¹⁴ and the transition states of their reaction with ethylene by theoretical methods^{15,16} (Figures 1 and 2). This led to the identification of four factors influencing the discrimination between the two transition states.

The analysis of the two conformers of the diene indicated that the higher energy obtained for the *syn* structure could be explained by (i) a lower stabilization by electronic delocalization than in the *anti* conformer,¹⁷ (ii) a destabilizing interaction between the dipoles of the

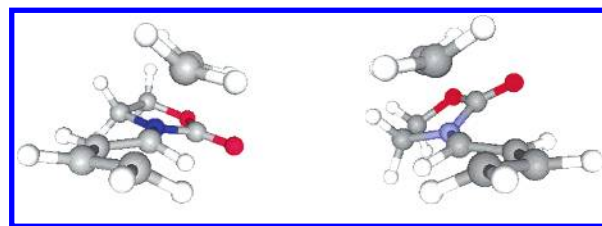


FIGURE 2. Structure and relative energy (B3LYP 6-31G**) of two relevant transition states for cycloaddition of ethylene and *N*-dienyloxazolidin-2-one: (left) TS_{anti} , 0 kcal·mol⁻¹, dihedral angle $C(=O)-N-C(1)-C(2) = 168.1^\circ$; (right) TS_{syn} , 2.79 kcal·mol⁻¹, dihedral angle $C(=O)-N-C(1)-C(2) = 39.5^\circ$. Key: gray, C; white, H; red, O; blue, N.

TABLE 1. Influence of the Exchange of the Carbonyl Oxygen by a Sulfur Atom on the Relative Energy (in kcal·mol⁻¹; B3LYP/6-31G**) and the Structure of the Two Conformers of the Diene

X = O	relative energy	0.00	2.99
	dipole of heterocycle	1.25 D	1.25 D
	$\theta^a_{C(=O)-N-C(1)-C(2)}$	175.0°	0.6°
X = S	relative energy	0.00	4.54
	dipole of heterocycle	1.42 D	1.58 D
	$\theta^a_{C(=S)-N-C(1)-C(2)}$	176.0°	6.5°

^a Dihedral angle.

dienyl and heterocyclic moieties in the *syn* structure, and this despite (iii) the emergence of a stabilizing interaction by hydrogen bond, between the oxygen of the carbonyl function and the hydrogen of the carbon 2 of the dienyl moiety, in the *syn* conformer.¹⁸ Moreover, the structure of the transition states revealed that their difference in energy can be attributed, in addition to these three factors, to (iv) a steric interaction rising in TS_{syn} between the dienophile and the hydrogen atom of the chiral center that induces a rotation of the heterocyclic moiety and then reduces over again the possibility of stabilization by electronic delocalization.

This analysis drove us to imagine the substitution of the exocyclic oxygen of the oxazolidinone auxiliary by a

(13) We presume that formation of other diastereoisomers is due to cycloaddition of the diene in its *syn* conformation and not to the approach of the dienophile from the most hindered face of the diene in its *anti* conformation.

(14) The Diels–Alder reaction occurs from the conformer presenting a *cisoid* conformation of the dienyl moiety; all the considered structures of dienes in this publication will present a *cisoid* conformation.

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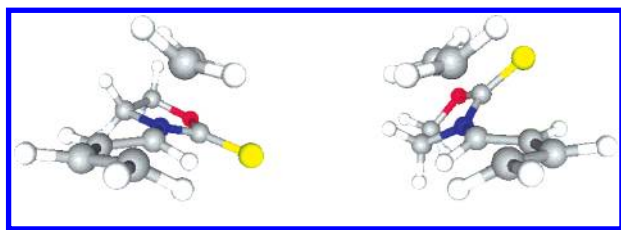
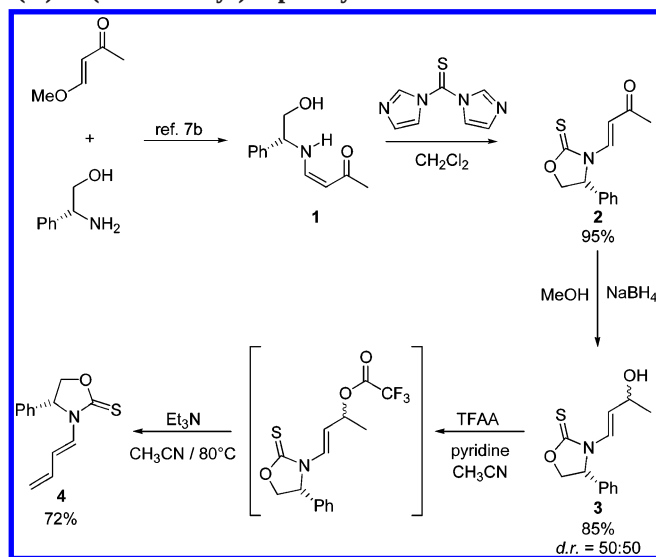


FIGURE 3. Structure and relative energy (B3LYP 6-31G**) of two relevant transition states for cycloaddition of ethylene and *N*-dienyloxazolidin-2-thione: (left) TS_{anti}, 0 kcal·mol⁻¹, dihedral angle C(=S)–N–C(1)–C(2) = 164.2°; (right) TS_{syn}, 4.60 kcal·mol⁻¹, dihedral angle C(=S)–N–C(1)–C(2) = 44.6°. Key: gray, C; white, H; red, O; blue, N; yellow, S.

SCHEME 1. Synthesis of (R)-N-(Butadienyl)-4-phenyloxazolidine-2-thione



sulfur atom to improve the facial selectivity. We anticipated indeed that this modification would decrease the hydrogen bond interaction between the (thio)carbonyl and the hydrogen fixed on the carbon 2 of the dienyli moiety and hence increase the energetic discrimination between the two transition states. To assess our hypothesis, we carried on with computational studies.

Optimization of the two considered conformers of *N*-(butadienyl)oxazolidin-2-thione revealed, as expected, that oxygen substitution by a sulfur induces an increase in the destabilization of the *syn* conformer of the diene (Table 1). Analysis of the diene structures indicated that this increase in the relative energy between the two considered conformers with substitution (X = O or S) can be attributed to a weaker stabilizing effect by hydrogen bond¹⁹ in the *syn* conformer and a higher dipole moment of the heterocycle, in the case of the oxazolidin-2-thione substituted diene (X = S). Investigations of the transition states of the Diels–Alder reaction of the respective conformers with ethylene confirmed this higher relative energy between the *anti* and *syn* structures in the case of sulfur derivatives (Figure 3). The use of 4-phenylox-

TABLE 2. Diels–Alder Reaction of *N*-(Butadienyl)-4-phenyloxazolidin-2-one and -thione with Representative Dienophiles A=B

dienophile	X	time	conv. ^a	endo:exo ^{b,c}	d.e. ^{b,d}
	O	48h	89%	85:15	56%
	S	48h	83%	95:5	96%
	O	15h	80% ^e	84:16	80%
	S	15h	100%	84:16	>99%
	O	15h	100%	/	66% ^f
	S	15h	100%	/	90%
	O	15h	100%	100:0	86%
	S	15h	100%	100:0	>99%
	O	3h	99%	/	24%
	S	3h	100%	/	50%
	O	24h	99%	59:41	51%
	S	24h	94%	81:19	76%

^a Conversion measured by GC with phenanthrene as internal reference. ^b Diastereoisomeric ratios were determined by GC on the crude mixtures. ^c Relative configurations were assigned by ¹H NMR. ^d Diastereoisomeric excess of C(1). ^e Isolated yield. ^f Diastereoisomeric ratio was determined in ¹H NMR by integration of OCH₃ signal.

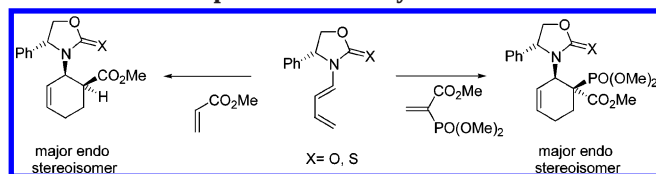
azolidin-2-thione as chiral auxiliary instead of the oxazolidin-2-one analogue would then improve significantly the facial selectivity of the diene in Diels–Alder reaction. Having this prediction in hand, we validated our concept by experimental means.

To experimentally examine the incidence of the designed structural modification of the diene on the facial selectivity, we synthesized and cyclized both oxygen and sulfur derivatives. Optically pure (*R*)-*N*-(butadienyl)-4-phenyloxazolidin-2-one was obtained from (*R*)-phenylglycinol by a previously described method.^{7b} Application of a similar strategy to the synthesis of the novel oxazolidin-2-thione analogue provided the desired diene in good overall yield (Scheme 1).²⁰ Chiral oxazolidin-2-one- and -thione-substituted dienes were then subjected

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(20) See the Supporting Information for experimental details and structural assignments.

SCHEME 2. Representative Cycloadducts



to a series of cycloadditions with representative electron-deficient dienophiles (Table 2).²⁰ All reactions were conducted in refluxing acetonitrile, as previously described in nonchiral series.^{7d,21} In the case of unsymmetrical dienophiles, one regioisomer was formed in agreement with the “ortho rule” of the Diels–Alder cycloaddition (Scheme 2).^{6d,7d} Four diastereoisomers (but usually less than four) could be detected by GC analysis of the crude mixtures (see the Supporting Information); the selectivities of Table 2 were calculated from their respective ratios. Structural assignments resulted from NMR analysis of pure samples of the major endo diastereoisomers, and mixtures of known composition of the minor isomers, isolated by liquid chromatography.

A number of conclusions can be drawn from the collected data. First, the reactivity of the diene is not drastically affected by the structural modification. Second, the chiral 4-phenyloxazolidin-2-thione auxiliary provides systematically better experimental facial selectivities as compared to those obtained with the oxazolidin-2-one analogue. This is in complete agreement with

our theoretical predictions. Interestingly, a significant increase in the *endo/exo* selectivity is also observed in some cases. This can be explained, in our opinion, by steric hindrance between the sulfur atom and the substituent in *exo* position in TS_{anti} (see Figure 3). In the case of symmetrically *trans*-disubstituted dienophiles (DEAD and dimethyl fumarate), even if the selectivities are significantly improved by the use of oxazolidin-2-thione auxiliary, results remain however moderate.

In conclusion, we have documented a theoretical analysis of the facial selectivity of optically active oxazolidin-2-one-substituted dienes that has further enabled the development of the most effective chiral auxiliary for cycloaddition of 1-aminodiene thus far, namely 4-phenyloxazolidin-2-thione. The strategy of carbonyl oxygen substitution by a sulfur atom in chiral oxazolidin-2-one auxiliaries, to influence conformational equilibrium and so improve the facial selectivity, could be extended to other systems.

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Supporting Information Available: Description of methodological approach and of the dipole calculation. Cartesian coordinates, total energies at the B3LYP 6-31G(d,p) level, and number of imaginary frequencies of the considered dienes and transition states. Experimental procedures and structural analyses for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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