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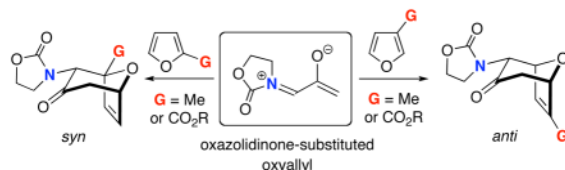
Regioselectivities of (4+3) Cycloadditions Between Furans and Oxazolidinone-Substituted Oxyallyls

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Abstract



The (4+3) cycloadditions of oxazolidinone-substituted oxyallyls and unsymmetrically-substituted furans lead to *syn* regioselectivity when the furan has a 2-Me or 2-COOR substituent, while *anti* regioselectivity is obtained with a 3-Me or 3-COOR group. DFT calculations are performed to explain the selectivities. The reactivities and regioselectivities are consistent with the ambiphilic reactivity of amino-oxyallyls with furans.

The (4+3) cycloaddition of oxyallyls with dienes (Scheme 1) is a useful route to seven-membered carbocycles.¹ Theoretical studies have examined the mechanisms of these cycloadditions,² which may be either stepwise or concerted depending on the groups X and M in **1**. The use of a heteroatom-stabilized oxyallyl, in particular an oxygen-, nitrogen-, or sulfur-derivative, in conjunction with an unsymmetrical diene has often been reported to provide high levels of regioselectivity (*2-syn* vs *2-anti*).^{1,3} However, there have to date been few systematic studies of how the regioselectivity for a given class of oxyallyl is influenced by the substituents on the diene.

We have previously reported a method for (4+3) cycloadditions that commences with the oxazolidinone-containing allenamide **3** (Scheme 2).⁴ Oxidation of **3** by dimethyldioxirane (DMDO) in the presence of a furan furnishes selectively the *endo*⁵ cycloadduct **4**, and can be performed successfully with either electron-rich (Me) or electron-poor (COOR) groups on the furan. The cycloaddition is believed to involve the oxyallyl **5**, and is promoted by a Lewis acid (ZnCl₂). We recently studied the electronic structures of the oxyallyls by density functional theory calculations on **6**.⁶ They are zwitterions (unlike the parent oxyallyl, which is a diradical⁷), and there is substantial electron delocalization from the nitrogen onto the

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 Supporting Information Available: Experimental procedures, NMR spectra and characterizations for all new compounds, B3LYP geometries and energies are available free of charge via the Internet at <http://pubs.acs.org>.

allyl group, consistent with an iminium enolate structure. The (4+3) cycloadditions of **5** and **6** with furan are calculated to be concerted processes. Only the $E_{C=N}$ isomer of the oxyallyl (**5-E**, **6-E**) is involved, because the $Z_{C=N}$ isomer (**5-Z**) is destabilized by electrostatic repulsion between the oxygen atoms, even when coordinated to $ZnCl_2$.

The methodology in Scheme 2 has previously been applied to a variety of asymmetric cycloadditions.^{4,8} Here we present an experimental and theoretical study of the regioselectivity of the achiral oxyallyl **5** towards unsymmetrical furans.

The cycloadditions of **5** with monosubstituted furans were examined first. Methyl was chosen as a representative electron-donating group, and COOMe or COOEt for the electron-withdrawing group. Cycloadditions involving the more electron-rich 2-methoxyfuran failed, due to competing oxidation and decomposition.⁸ The measured regioselectivities for cycloadditions of **5** with **7–12** are shown in Table 1.

The cycloadditions were conducted either under thermal conditions or in the presence of a Lewis acid ($ZnCl_2$ or $NaClO_4$). Inclusion of the Lewis acid generally increased the yield, but did not alter the regioselectivity. Surprisingly, the regioselectivities for both the 2- and the 3-substituted furans were found to be independent of the electronic character of the substituent. Both 2-methylfuran (**7**) and methyl 2-furoate (**8**) gave predominantly the *syn* cycloadducts, with *syn:anti* ratios of 86:14 and $\geq 95:5$, respectively. The 3-methylfuran (**9**) and ethyl 3-furoate (**10**) both gave predominantly the *anti* cycloadducts, with *syn:anti* ratios of 22:78 and 9:91, respectively.

The origins of these regioselectivities were investigated with density functional theory calculations at the B3LYP/6-31G(d) level⁹ in Gaussian 03.¹⁰ Activation energies in CH_2Cl_2 were simulated by computing free energies of solvation with the Conductorlike Polarizable Continuum Model (CPCM).¹¹ Transition states for the *syn* and *anti* cycloadditions of **5-E** with furans **7–10** were located (using COOMe as a model for COOEt in **10**). The TS geometries and activation energies¹² are shown in Figure 1. The cycloadditions are concerted but asynchronous processes. Stepwise transition states were also located, but were at least 2.6 kcal/mol higher in energy.

Three of the substituted furans are predicted to react more easily than furan itself, which has an activation energy of $\Delta H^\ddagger = 6.4$ kcal/mol ($\Delta G^\ddagger 20.8$ kcal/mol) (Supporting Information). The oxyallyl is therefore ambiphilic towards furans, although the Me substituent effect is quite small and the ester substituent effect is relatively large. The energies of the HOMO and LUMO of **5-E** are calculated to lie between those of furan.¹³ The presence of both an electron-rich O^- atom and electron-withdrawing iminium group on the central carbon confers both nucleophilic and electrophilic character to the unsubstituted terminus (C_o). There is, however, only a small degree of charge transfer in any of the transition states. The oxyallyl is calculated to have a charge of $-0.14e$ in the transition state for reaction with furan; this value increases to $-0.17e$ for the methylfurans, and drops to $-0.05e$ in the furoate ester TSs.¹⁴ The ambiphilicity of **5** distinguishes it from other synthetically-useful oxyallyl derivatives such as **13** and **14**^{1–3} (Scheme 3), which are cationic, electrophilic species.

The calculated regioselectivities ($\Delta\Delta H^\ddagger$ and $\Delta\Delta G^\ddagger$) in Figure 1 predict the correct major product for each furan. In spite of the ambiphilic character displayed in the reactivity patterns, the transition states do all show more bonding at the enolate terminus than the iminium terminus. The ester group has a regiochemical preference consistent with electronic effects, while the regioselectivities observed for methylfurans likely result from steric effects: for 2-methylfuran, the oxyallyl attacks the less substituted (5-) terminus, while for 3-methylfuran, the favored *anti* TS avoids steric hindrance involving the oxazolidinone (see **TS-9-syn** in Figure 1). The regioselectivities are also the same as would be expected for a

diradical mechanism; however, all diradical TSs that we have located¹⁵ lie at least 2.0 kcal/mol higher than the closed-shell TSs.

From our investigation of cycloadditions of **5** with the 2,3-disubstituted furans **11** and **12** (Table 1), both **11** and **12** yielded predominantly the *syn* cycloadducts, with selectivities of $\geq 95:5$. The *syn*-directing influence of the 2-substituent, arising from steric and (for COOMe) electronic components, is stronger than the *anti*-directing effect of the 3-substituent. The selectivities are summarized in Scheme 4.

We have also analyzed the regioselectivities, by computing the distortion of the reactants and interactions that occur in the transition states. In Table 2 are listed the distortion energies ($\Delta E_{\text{dist}}^\ddagger$) and the energies of interaction between the distorted reactants at the TS ($\Delta E_{\text{int}}^\ddagger$); these two quantities add up to the activation energy ΔE^\ddagger .¹⁶ Both of the 2-substituted furans incur a smaller distortion penalty in their *syn* TS. This is supplemented, in the 2-COOMe case, by a stronger interaction energy in the *syn* TS. The analysis for the 3-substituted furans is less clear-cut. For 3-methylfuran, both regioisomers have similar distortion energies, and the balance is tipped in favor of the *anti* isomer by the interaction energy. For 3-COOMe, the distortion energies strongly favor the *anti* isomer, but the overall selectivity is small, because the early *anti* TS has only a weak interaction between the reactants. The *anti* preference becomes more pronounced when entropic effects and solvation are taken into consideration ($\Delta\Delta G^\ddagger = 2.0$ kcal/mol in CH_2Cl_2).

(4+3) cycloadditions of donor-substituted oxyallyl *cations* have often been calculated to occur by stepwise pathways, with the oxyallyl cation exhibiting clearly electrophilic behavior.² Amino-substituted oxyallyls such as **5** are a distinct class of oxyallyl with ambiphilic properties. Even for the achiral **5**, an instantaneous facial selectivity is present at the TS, which leads to the high *anti* selectivity observed with 3-methylfuran. This steric feature, and their relatively electron-rich character, provide oxazolidinone-substituted oxyallyls with well-defined and unique regiochemical properties, leading to a coherent and predictive model.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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 13. Orbitals were calculated at the HF/6–31G//B3LYP/6–31G(d) level.
 14. Mulliken charges at the B3LYP/6–31G(d) level.
 15. Singlet diradicals were modeled with the guess=mix keyword in Gaussian.
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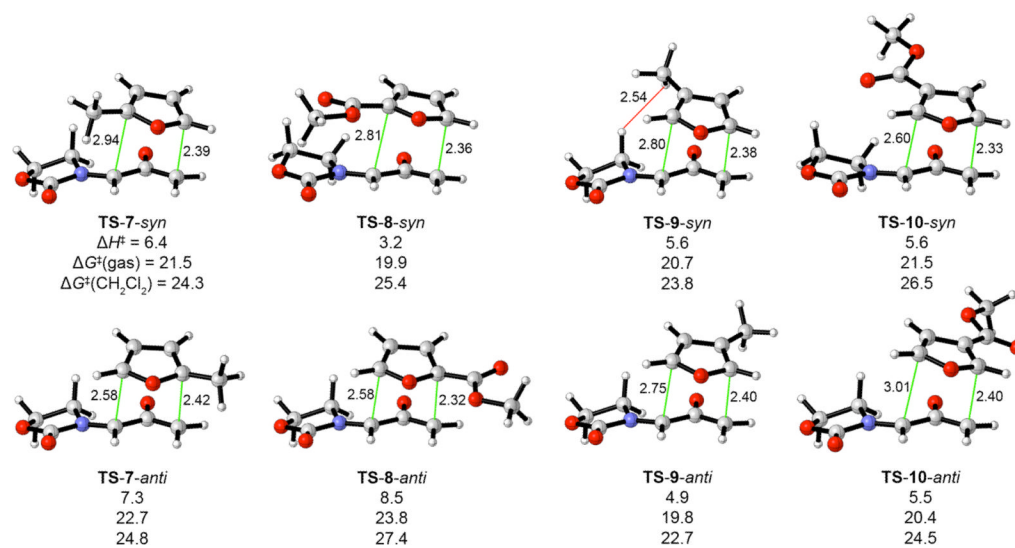
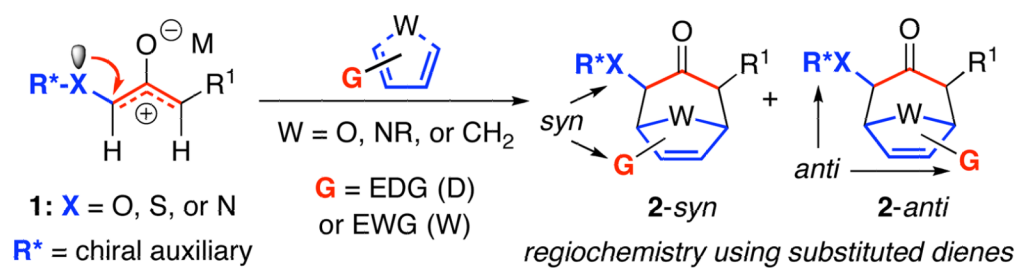
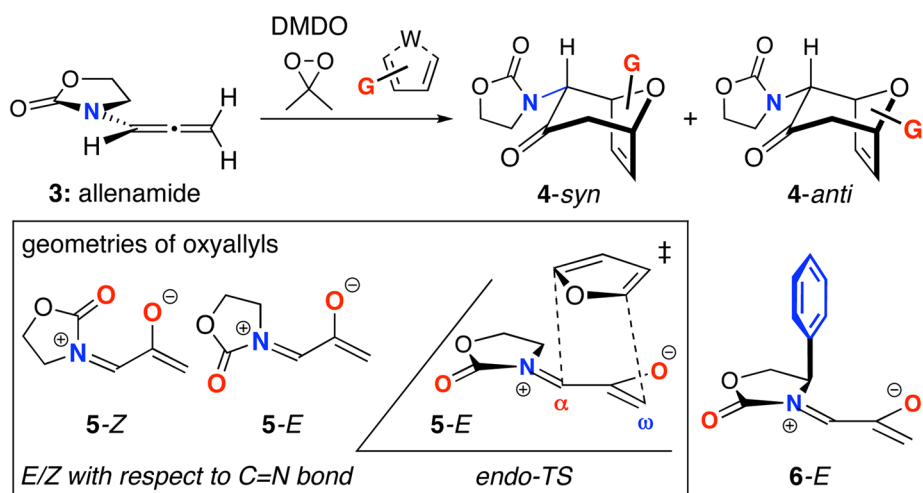


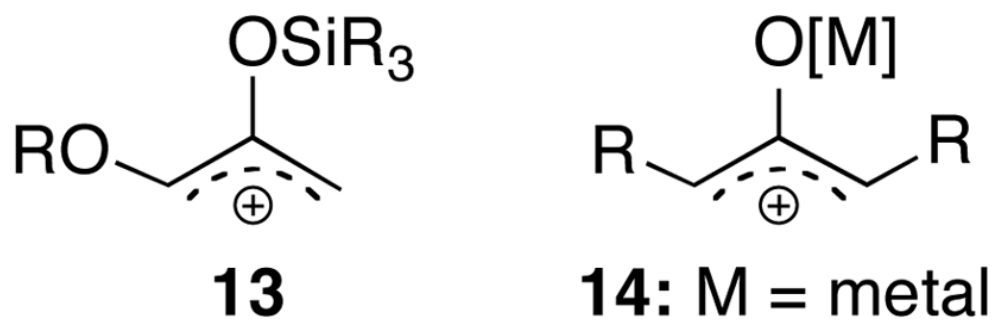
Figure 1. Transition states for the (4+3) cycloadditions of **5-E** with substituted furans. Distances in Å, ΔH^\ddagger in kcal/mol at 0 K, ΔG^\ddagger in kcal/mol at 298.15 K and 1 mol/L.

**Scheme 1.**

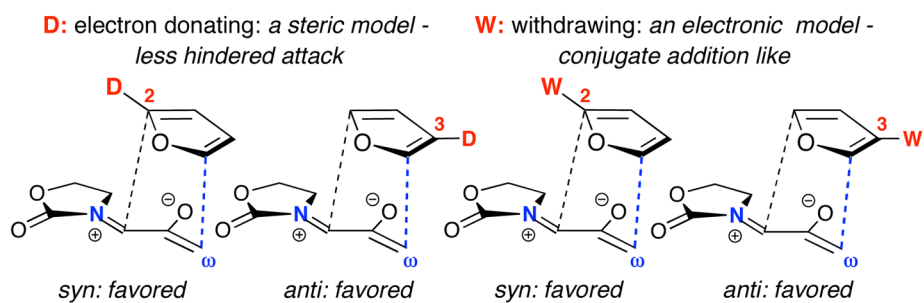
Regioselectivities in (4+3) Cycloadditions of Oxyallyls with Substituted Dienes.



Scheme 2.
(4+3) Cycloadditions of Allenamide-Derived Oxyallyls.




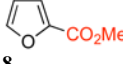


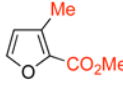
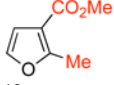
Scheme 3.
Electrophilic Oxyallyl Cations.



Scheme 4.
Summary of Preferred Regioisomers.

Table 1

Cycloadditions of Oxyallyl 5 with Furans 7–12.^a

furan ^b	additive	4 [syn:anti ratio ^c]	yield (%) ^d
 7	–	4a [83:17]	90
	ZnCl ₂	4a [86:14]	97
 8	–	4b [≥95:5]	41
	NaClO ₄ ^e	4b [≥95:5]	67
 9	–	4c [13:87]	95
	ZnCl ₂	4c [22:78]	96
 10	–	4d [9:91]	36
	ZnCl ₂	4d [9:91]	53
 11	ZnCl ₂	4e [≥95:5]	65
	ZnCl ₂	4f [≥95:5]	56
 12			

^a 4.0 equiv DMDO in acetone/CH₂Cl₂ was added over 18 h via syringe pump to a solution of the allenamide (conc. 0.05 M) and furan in CH₂Cl₂ at –78 °C. Where applicable, 2.0 equiv of Lewis acid were used.


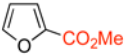

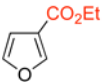
^b 3.0 equiv of the furan were used, except for 7 and 9, where 6.0 equiv was used.

^c Isomer ratios were determined by ¹H and/or ¹³C NMR.

^d Isolated yield.

^e NaClO₄ gave higher yields than ZnCl₂.

Table 2Distortion and Interaction Energies of Transition States for Cycloadditions of 5-*E* with Furans.^a

furan	regioisomer	ΔE^\ddagger	$\Delta E_{\text{dist}}^\ddagger$	$\Delta E_{\text{int}}^\ddagger$
	<i>syn</i>	5.4	11.3	-5.9
	<i>anti</i>	6.3	14.6	-8.3
	<i>syn</i>	1.9	13.3	-11.3
	<i>anti</i>	7.8	15.6	-7.9
	<i>syn</i>	4.6	12.1	-7.4
	<i>anti</i>	3.9	12.3	-8.4
	<i>syn</i>	4.4 ^b	15.7	-11.3
	<i>anti</i>	4.7	10.4	-5.7

^aElectronic energies in kcal/mol.^b ΔE^\ddagger predicts *syn*, but ΔH^\ddagger and ΔG^\ddagger favor *anti*.