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

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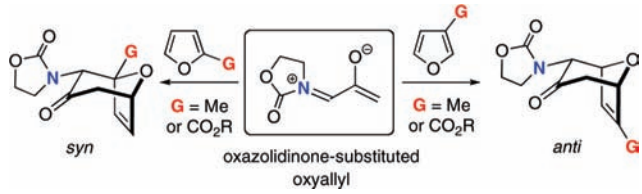
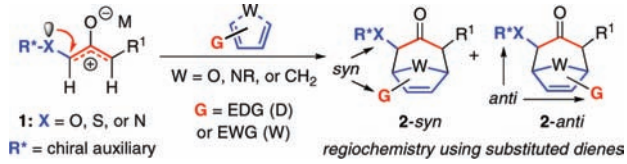
ABSTRACT



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.

Scheme 1. Regioselectivities in (4 + 3) Cycloadditions of Oxyallyls with Substituted Dienes



We have previously reported a method for (4 + 3) cycloadditions that commences with the oxazolidinone-

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(1) Reviews: (a) Harmata, M. *Acc. Chem. Res.* **2001**, *34*, 595–605. (b) Harmata, M.; Rashatasakhon, P. *Tetrahedron* **2003**, *59*, 2371–2395. (c) Hartung, I. V.; Hoffmann, H. M. R. *Angew. Chem., Int. Ed.* **2004**, *43*, 1934–1949. (c) The designation (*m* + *n*) is used here in accordance with Woodward−Hoffmann/IUPAC conventions for describing cycloadditions based on the number of atoms, as opposed to the bracketed [*m* + *n*] description that indicates numbers of electrons.

(2) (a) Walters, M. A.; Arcand, H. R. *J. Org. Chem.* **1996**, *61*, 1478–1486. (b) Cramer, C. J.; Barrows, S. E. *J. Org. Chem.* **1998**, *63*, 5523–5532. (c) Cramer, C. J.; Barrows, S. E. *J. Phys. Org. Chem.* **2000**, *13*, 176–186. (d) Cramer, C. J.; Harmata, M.; Rashatasakhon, P. *J. Org. Chem.* **2001**, *66*, 5641–5644. (e) Harmata, M.; Schreiner, P. R. *Org. Lett.* **2001**, *3*, 3663–3665. (f) Sáez, J. A.; Arnó, M.; Domingo, L. R. *Org. Lett.* **2003**, *5*, 4117–4120. (g) Arnó, M.; Picher, M. T.; Domingo, L. R.; Andrés, J. *Chem.—Eur. J.* **2004**, *10*, 4742–4749. (h) Sáez, J. A.; Arnó, M.; Domingo, L. R. *Tetrahedron* **2005**, *61*, 7538–7545. (i) Krenske, E. H.; Houk, K. N.; Harmata, M. *Org. Lett.* **2010**, *12*, 444–447.

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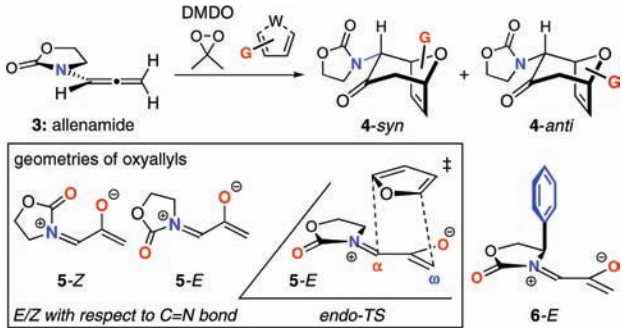
Scheme 2. (4 + 3) Cycloadditions of Allenamide-Derived Oxyallyls



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 ($ZnCl_2$). 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 diradical[7]), and there is substantial electron delocalization from the nitrogen onto the 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 $ZnCl_2$.

(3) For (4 + 3) cycloadditions of donor-substituted oxyallyls, including regioselective examples, see: (a) Föhlisch, B.; Krimmer, D.; Gehrlach, E.; Kaeshammer, D. *Chem. Ber.* **1988**, *121*, 1585–1594. (b) Murray, D. H.; Albizati, K. F. *Tetrahedron Lett.* **1990**, *31*, 4109–4112. (c) Walters, M. A.; Arcand, H. R.; Lawrie, D. J. *Tetrahedron Lett.* **1995**, *36*, 23–26. (d) Lee, J. C.; Jin, S.; Cha, J. K. *J. Org. Chem.* **1998**, *63*, 2804–2805. (e) Harmata, M.; Rashatasakhon, P. *Synlett* **2000**, 1419–1422. (f) Beck, H.; Stark, C. B. W.; Hoffmann, H. M. R. *Org. Lett.* **2000**, *2*, 883–886. (g) Myers, A. G.; Barbay, J. K. *Org. Lett.* **2001**, *3*, 425–428. (h) Harmata, M.; Ghosh, S. K.; Hong, X.; Wacharasindhu, S.; Kirchhoefer, P. *J. Am. Chem. Soc.* **2003**, *125*, 2058–2059. (i) Harmata, M. *Adv. Synth. Catal.* **2006**, *348*, 2297–2306. (j) MaGee, D. I.; Godineau, E.; Thornton, P. D.; Walters, M. A.; Sponholtz, D. J. *Eur. J. Org. Chem.* **2006**, 3667–3680. (k) Chung, W. K.; Lam, S. K.; Lo, B.; Liu, L. L.; Wong, W. T.; Chiu, P. *J. Am. Chem. Soc.* **2009**, *131*, 4556–4557.

(4) For a review on allenamide chemistry, see: (a) Wei, L.-L.; Xiong, H.; Hsung, R. P. *Acc. Chem. Res.* **2003**, *36*, 773–782. For chemistry of nitrogen-stabilized oxyallyls, see: (b) Xiong, H.; Hsung, R. P.; Berry, C. R.; Rameshkumar, C. *J. Am. Chem. Soc.* **2001**, *123*, 7174–7175. (c) Xiong, H.; Huang, J.; Ghosh, S. K.; Hsung, R. P. *J. Am. Chem. Soc.* **2003**, *125*, 12694–12695. (d) Rameshkumar, C.; Hsung, R. P. *Angew. Chem., Int. Ed.* **2004**, *43*, 615–618. (e) Huang, J.; Hsung, R. P. *J. Am. Chem. Soc.* **2005**, *127*, 50–51. (f) Antoline, J. E.; Hsung, R. P.; Huang, J.; Song, Z.; Li, G. *Org. Lett.* **2007**, *9*, 1275–1278.

(5) We use the term "*endo*" to denote the relationship between the diene unit and the oxyallyl oxygen in **4**-*syn*/*anti* and the TSs leading to them. Hoffmann has used the term "compact" to describe this geometry, see: Hoffmann, H. M. R. *Angew. Chem., Int. Ed.* **1973**, *12*, 819−835.

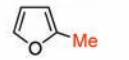
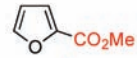
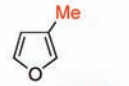
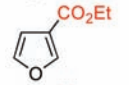
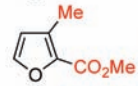
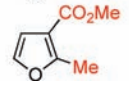
(6) Krenske, E. H.; Houk, K. N.; Lohse, A. G.; Antoline, J. E.; Hsung, R. P. *Chem. Sci.* **2010**, *1*, 387–392.

(7) (a) Coolidge, M. B.; Yamashita, K.; Morokuma, K.; Borden, W. T. *J. Am. Chem. Soc.* **1990**, *112*, 1751–1754. (b) Ichino, T.; Villano, S. M.; Gianola, A. J.; Goebbert, D. J.; Velarde, L.; Sanov, A.; Blanksby, S. J.; Zhou, X.; Hrovat, D. A.; Borden, W. T.; Lineberger, W. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 8509–8511.

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** toward 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.

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
	**12**	$ZnCl_2$	**4f** [**≥95**:5]	56

[a] 4.0 equiv of DMDO in acetone/CH_2Cl_2 was added over 18 h via syringe pump to a solution of the allenamide (concn 0.05 M) and furan in CH_2Cl_2 at −78 °C. Where applicable, 2.0 equiv of Lewis acid was used. [b] 3.0 equiv of the furan was used, except for **7** and **9**, where 6.0 equiv was used. [c] Isomer ratios were determined by ^1H and/or ^{13}C NMR. [d] Isolated yield. [e] $NaClO_4$ gave higher yields than $ZnCl_2$.

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 ≥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) level[9] in Gaussian 03.[10] Activation energies in

(8) Antoline, J. E.; Hsung, R. P. *Synlett* **2008**, 739–744.

(9) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652. (b) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623–11627. (c) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789.

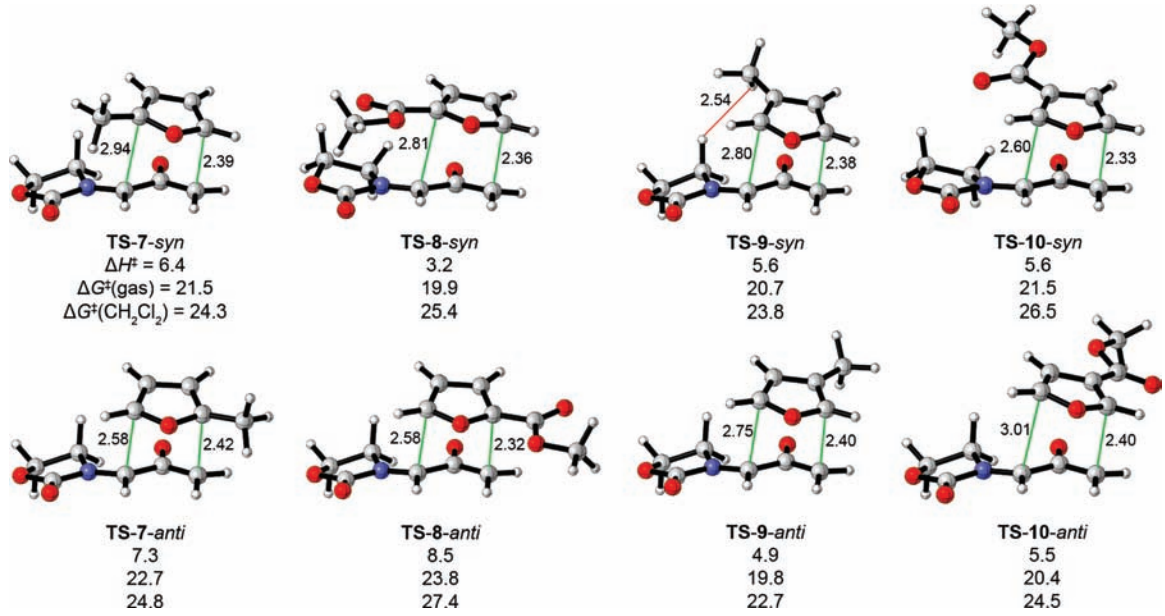
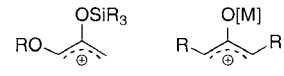


Figure 1. Transition states for the (4 + 3) cycloadditions of **5**-*E* with substituted furans. Distances in Å, $\Delta H^{\ddagger}$ in kcal/mol at 0 K, $\Delta G^{\ddagger}$ in kcal/mol at 298.15 K and 1 mol/L.

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 energies[12] 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 toward 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_ω). 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.

Scheme 3. Electrophilic Oxyallyl Cations



13 **14:** M = metal

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 located[15] 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**

(10) Frisch, M. J.; et al. *Gaussian 03*, Revision C.02, Gaussian, Inc., Wallingford, CT, 2004. A complete citation is available in the Supporting Information.

(11) (a) Barone, V.; Cossi, M. *J. Phys. Chem. A* **1998**, *102*, 1995–2001. (b) Barone, V.; Cossi, M.; Tomasi, J. *J. Comput. Chem.* **1998**, *19*, 404–417.

(12) Activation energies were calculated with respect to the oxazolidinone-substituted cyclopropanone isomer of **5**-*E*, which is 5.2 kcal/mol more stable than **5**-*E*.

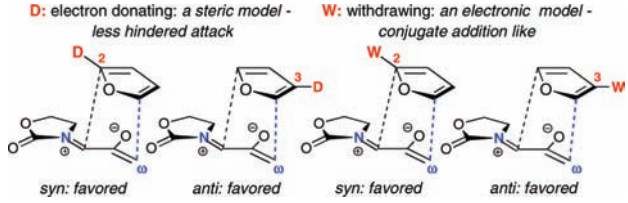
(13) Orbitals were calculated at the HF/6-31G//B3LYP/6-31G(d) level.

(14) Mulliken charges at the B3LYP/6-31G(d) level.

(15) Singlet diradicals were modeled with the guess=mix keyword in Gaussian.

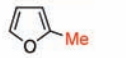
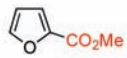
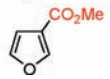
yielded predominantly the *syn* cycloadducts, with selectivities of ≥95:5. The *syn*-directing influence of the 2-substituent, arising from steric and (for COOMe) electronic components, is stronger than the *anti*-directing effect of the 3-substituent. The selectivities are summarized in Scheme 4.

Scheme 4. Summary of Preferred Regioisomers



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 ($\Delta E^{\ddagger}_{dist}$) and the energies of interaction between the distorted reactants at the TS ($\Delta E^{\ddagger}_{int}$); these two quantities add up to the activation energy $\Delta E^{\ddagger}$.[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).

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

furan	regioisomer	$\Delta E^{\ddagger}$	$\Delta E_{dist}^{\ddagger}$	$\Delta E_{int}^{\ddagger}$
	*syn*	5.4	11.3	–5.9
	anti	6.3	14.6	–8.3
	*syn*	1.9	13.3	–11.3
	anti	7.8	15.6	–7.9
	*syn*	4.6	12.1	–7.4
	anti	3.9	12.3	–8.4
	*syn*	4.4[b]	15.7	–11.3
	anti	4.7	10.4	–5.7

[a] Electronic energies in kcal/mol. [b] $\Delta E^{\ddagger}$ predicts *syn*, but $\Delta H^{\ddagger}$ and $\Delta G^{\ddagger}$ favor *anti*.

(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.

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

OL1023745

(16) (a) Ess, D. H.; Houk, K. N. *J. Am. Chem. Soc.* **2008**, *130*, 10187–10198. (b) Hayden, A. E.; Houk, K. N. *J. Am. Chem. Soc.* **2009**, *131*, 4084–4089. (c) Schoenebeck, F.; Houk, K. N. *J. Am. Chem. Soc.* **2010**, *132*, 2496–2497.