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REGIOSELECTIVITY IN THE DIELS-ALDER REACTIONS OF α-PYRONES WITH ALKYNES

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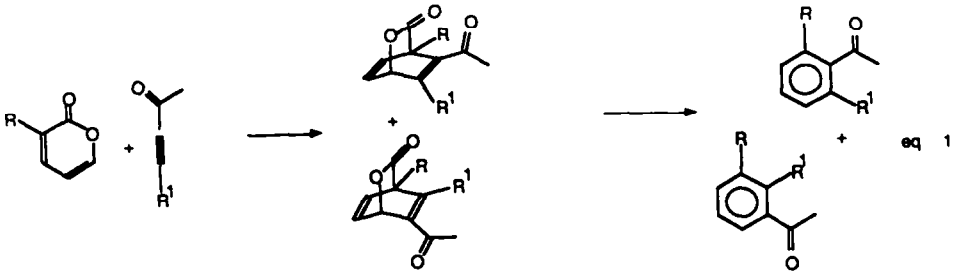
Abstract: 4-Ethyl-5-methyl-6-methylthio-2(H)-pyranone (**4**) undergoes Diels-Alder reactions with ethyl hexynoate (**5**), 3-heptyn-2-one (**6**), ethyl propiolate (**7**), and 3-butyn-2-one (**8**) to afford substituted benzenes with high regioselectivity upon extrusion of CO_2. 4-Ethyl-5,6-dimethyl-(**1**), 4-ethyl-3,6-dimethyl-(**2**) and 4-ethyl-5-methyl-(2H)-pyranone (**3**) gave excellent to good regioselectivity with internal alkynes **5** and **6** and poor regioselectivity with terminal alkynes **7** and **8**. MNDO calculations have been carried out on the pyrones and alkynes and qualitative FMO analysis correctly predicts the major products.

Introduction

α-Pyrones undergo Diels-Alder reactions with alkynes to afford substituted benzene derivatives after extrusion of carbon dioxide under the reaction conditions (eq. 1). Although these Diels-Alder reactions are well known[1] many of the studies have employed α-pyrones with strongly directing substituents or symmetrical alkynes where the problem of regiochemistry does not arise. Several studies[2] have explored the regiochemistry in the reactions with unsymmetrical



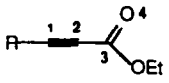
eq 1

reactants. Although many of the results could be rationalized by net atomic charge densities or by secondary orbital interactions, results were obtained that did not conform with either model and the possibility of steric effects was suggested.[2b] More recently the relative importance of secondary orbital interactions and steric effects in the Diels-Alder reaction has been examined.[3] The earlier studies exploring Diels-Alder regiochemistry employed α-pyrones containing phenyl or carboalkoxy substituents which could enhance the importance of secondary orbital interactions or net atomic charge distribution within the diene unit in controlling the regiochemistry of these reactions. The ready availability of simple alkyl[4a] or alkylthio[4b] substituted α-pyrones prompted us to examine the question of regiochemical control in the Diels-Alder reactions of pyrones with unsymmetrical alkynes more closely.

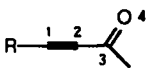
Qualitative Frontier Molecular Orbital (FMO) theory has proven valuable in rationalizing and predicting regiochemistry in Diels-Alder reactions.[5,6] Nevertheless, difficulties arise in the application of the theory to 1-substituted dienes containing an electron withdrawing substituent (Z). These difficulties involve predicting the relative directing ability of substituents in poly-substituted dienes and in accounting for the relative directing effects of substituents at various positions on the diene unit. These weaknesses of the FMO approach have been delineated and an alternative model for predicting regiochemistry based upon atomic reactivity surfaces has been developed by Hehre.[6] MNDO calculations have been carried out on both the pyrones and acetylenes in an effort to compare the experimentally determined regioisomeric ratios with the qualitative FMO predictions. Although the experimental results are generally consistent with qualitative FMO predictions, these Diels-Alder reactions involving complex poly-substituted (Z)-dienes provide some insight into the complexity and problems involved in predicting regiochemistry when both pairs of frontier molecular orbitals play a significant role.

Results

α-Pyrones **1-4** were reacted with seven or more equivalents of ethyl hexynoate (**5**), 3-heptyn-2-one (**6**), ethyl propiolate (**7**), or 3-butyn-2-one (**8**) in a sealed NMR tube immersed in a hot oil bath. The regioisomeric aromatic compounds, with one exception, were not separated and structural

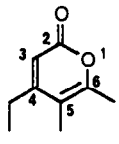
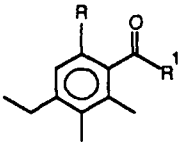
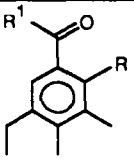
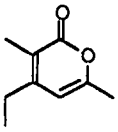
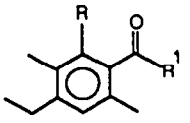
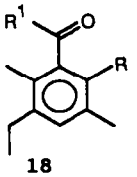
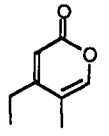
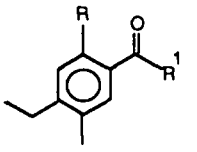
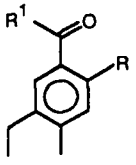
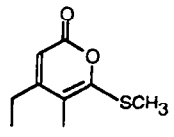
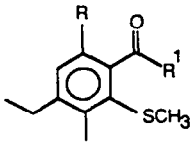
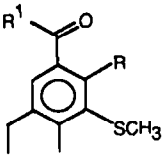


5 R = C_3H_7
7 R = H

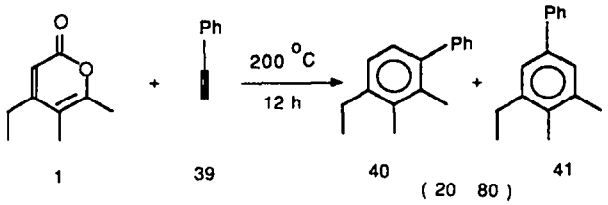


6 R = C_3H_7
8 R = H

Table 1. Diels-Alder Reactions of 2(H)-Pyrones with Electron Deficient Alkynes.

Entry	Pyrone	Dienophile RC≡CCOR^1 R	R^1	Rxn Cond[a] °C (hr)	Products Major	Minor	% Yield (ratio)
							
1	**1**	n-Pr	OEt	175 (36)	**9**	**10**	85 (90:10)
2			Me	150 (52)	**11**	**12**	92 (86:14)
3		H	OEt	125 (24)	**13**	**14**	86 (61:39)
4			Me	100 (36)	**15**	**16**	95 (52:48)
							
5	**2**	n-Pr	OEt	210 (72)	**17**	**18**	86 (75:25)
6			Me	210 (42)	**19**	**20**	54 (63:37)
7		H	OEt	125 (36)	**21**	**22**	84 (59:41)
8			Me	100 (62)	**23**	**24**	98 (55:45)
							
9	**3**	n-Pr	OEt	170 (22)	**25**	**26**	99 (77:23)
10		H	OEt	125 (15)	**27**	**28**	72 (52:48)
11			Me	95 (24)	**29**	**30**	61 (80:20)
							
12	**4**	n-Pr	OEt	235 (38)	**31**	**32**	83 (94: 6)
13			Me	190 (72)	**33**	**34**	88 (87:13)
14		H	OEt	125 (24)	**35**	**36**	75 (90:10)
15			Me	95 (21)	**37**	**38**	95 (>95:5)

[a] 0.1 mmol pyrone, 1.0 mmol dienophile.



1 39 40 41
(20 80)

eq 2

assignments were made on the basis of high field (200 MHz) NMR analysis which generally provided sufficient signal dispersion for determination of product ratios and structures.

α-Pyrone **1** (Table 1) afforded excellent regioselectivity with the internal acetylenes **5** and **6** (entries 1-2) and little selectivity with the terminal acetylenes **7-8** (entries 3-4). The regioisomeric products from the internal alkynes could be assigned from the chemical shifts of the single aromatic proton. The major regioisomers **9** and **11** exhibit aromatic proton absorptions upfield (δ 6.81, 6.79 respectively) from those of the minor isomers **10** and **12** (δ 7.73, 7.07 respectively). Although chemical shift additivity rules do not work well for highly substituted benzene derivatives containing ortho substituents[7a], the downfield absorptions for the minor isomers are consistent with structures **10** and **12** in which the aromatic proton is ortho to a carbonyl functionality.[7b] The regioisomers from the terminal alkynes contain two aromatic protons which are either ortho or meta to each other. The major isomers display two doublets expected for **13** [δ 7.45, 6.56 (J = 8.0 Hz)] and **15** [δ 7.35, 7.05 (J = 7.8 Hz)] while the minor isomers display broad singlets consistent with structures **14** (δ 7.75, 7.71) and **16** (δ 7.60). Acetophenones **15** and **16** were separated and the NMR spectra of the isolated compounds provide additional support for structural assignments **9-14** which are based upon NMR data of the mixtures.

The 3,4,6-trialkyl substituted α-pyrone **2** afforded good but diminished regioselectivity with the internal alkynes **5-6** (entries 5-6) and almost no selectivity with the terminal alkynes **7-8** (entries 7-8). This series of compounds contain an aromatic proton which is either para or meta to the carbonyl functionality. The major isomers resulting from the internal alkynes display aromatic proton absorptions upfield (δ 6.74 and 6.70 for **17** and **19**) from the minor isomers (δ 7.16 and 6.85 for **18** and **20**) permitting the assignments indicated in Table 1 by analogy with the general trend observed in the model compounds. The regioisomers obtained from the terminal alkynes will have one proton that is always ortho to the carbonyl functionality (and can be assigned to the low field absorption)[7a] and one which will be either meta or para to the carbonyl functionality. In these compounds the major isomers display aromatic proton absorptions (δ 7.00 and 7.03 for **21** and **23**) upfield relative to the minor isomers (δ 7.10 for **22** and **24**) leading to the indicated structural assignments. The only significant relative change in these compounds is the position of the carbonyl functionality and the qualitative patterns observed in the model compounds should be expected to hold.

Pyrone **3**, with no substituents in the 3 and 6-positions, afforded good regioselectivity with the internal acetylenic ester **5** (entry 9) and very poor selectivity with the terminal acetylenic ester **7** (entry 10). Reaction of **3** with the terminal acetylenic ketone **8** (entry 11) gave good regioselectivity and the result appears to be anomalous within the series. The regioisomers obtained with 2-hexynoate (**5**) will each have one aromatic proton ortho and one meta to the ester functionality, although the ortho proton will be ortho to a methyl group in one isomer and to an ethyl group in the other. Similarly, the meta proton will be ortho to an ethyl and a propyl group in one isomer and ortho to a methyl and a propyl group in the other. Since the ortho protons in toluene (δ -0.17 relative to benzene) are shifted upfield relative to those of ethyl benzene (δ -0.15 relative to benzene)[7a] the two isomers **25** and **26** should display an inside and outside pair of signals. The major isomer displays absorptions at δ 7.89 and 6.93 while the minor isomer exhibits resonances at δ 7.95 and 6.90 consistent with structures **25** and **26** respectively. Structures **27-30** are difficult to assign based upon NMR data and assignment of major and minor products is made by analogy with the regiochemistry observed for **25** and **26**.

The 6-alkylthio pyrone **4** afforded excellent regioselectivity with both the internal (**5-6**) and terminal acetylenes (**7-8**) (entries 12-15). Structure assignments can be made by analogy with the arguments employed for compounds **9-16**. The major regioisomers obtained from the reaction of **4** with ethyl 2-hexynoate (**5**) and 3-heptyn-2-one (**6**) display aromatic proton absorptions (δ 6.85 and 6.84 for **31** and **32**) upfield from the minor isomers [δ 7.75, (7.53 $CDCl_3$, 90 MHz) and 7.12 ($CDCl_3$, 90 MHz) for **32** and **34**] supporting the indicated structural assignments. The major products obtained with the terminal alkynes display aromatic doublets consistent with structures **35** [δ 7.35, 6.79 (J = 7.8 Hz)] and **37** [δ 7.18, 7.03 (J = 8.03 Hz)] containing ortho aromatic protons.

Reaction of **1** with phenylacetylene (**39**) afforded an 80:20 mixture of two regioisomeric biphenyls (eq. 2). The chemical shifts for 2-, 3-, and 4-methylbiphenyl[8] (δ 2.18, 2.28, and 2.30 respectively) reveal that the phenyl group shields an ortho substituent in contrast to the carboalkoxy group which deshields ortho and para substituents. The 200 MHz NMR spectrum of a mixture of **40** and **41** in benzene displays four singlets with the outside pair (δ 2.14, 2.01) corresponding to the major isomer and the inside pair (δ 2.10, 2.04) to the minor isomer. Since both phenyl and methyl groups shield an adjacent methyl substituent, structure **41** is tentatively assigned to the major isomer which has the lowest field methyl absorption. The major isomer

Table 2. HOMO or HO π-MO Coefficients for Pyrones and Acetylenes.[a]

Cpd	C3 (C1)	C4 (C2)	C5 (C3)	C6[b] • (O4)[c]	difference[d]	energy (e.v.)
pyrones						
1	+ 0.485	+ 0.215	- 0.530	- 0.455	0.030	- 9.28
2	+ 0.515	+ 0.274	- 0.495	- 0.437	0.078	- 9.27
3	+ 0.495	+ 0.227	- 0.522	- 0.455	0.040	- 9.36
4	+ 0.449	+ 0.169	- 0.544	- 0.409	0.040	- 9.11
42	+ 0.523	+ 0.204	- 0.532	- 0.437	0.086	- 9.82
43	+ 0.533	+ 0.270	- 0.522	- 0.399	0.134	- 9.85
acetylenes						
5[e]	+ 0.566	+ 0.627	- 0.083	- 0.373	0.066	- 11.21
6[f]	+ 0.585	+ 0.640	- 0.087	- 0.330	0.055	- 11.07
7[e]	+ 0.530	+ 0.536	- 0.129	- 0.524	0.006	- 11.53
	(0.23)[g]	(0.16)[g]				(- 11.15)[h]
8[f]	+ 0.646	+ 0.654	- 0.120	- 0.374	0.008	- 11.41
39	+ 0.385	+ 0.243			- 0.142	- 9.05
	(0.45)[g]	(0.28)[g]				(- 8.82)[h]

[a] MNDO calculations unless otherwise noted. [b] Numbering system for pyrones. [c] Numbering system for acetylenes. [d] Carbon 3 - carbon 6 for the pyrones and carbon 2 - carbon 1 for the acetylenes. [e] Calculations were performed on the methyl ester analogues. [f] Coefficients for the highest occupied π molecular orbital. [g] Absolute values from CNDO/2 calculations. See ref. 10, p. 500. [h] See ref. 10, p. 500.

Table 3. LUMO Coefficients for Pyrones and Acetylenes.[a]

Cpd	C3 (C1)	C4 (C2)	C5 (C3)	C6[b] (O4)[c]	difference[d]	energy (e.v.)
pyrones						
1	+ 0.513	- 0.505	- 0.252	+ 0.536	0.023	- 0.67
2	+ 0.527	- 0.531	- 0.229	+ 0.504	- 0.023	- 0.68
3	+ 0.523	- 0.536	- 0.213	+ 0.516	- 0.007	- 0.64
4	+ 0.508	- 0.518	- 0.235	+ 0.527	0.019	- 0.71
42	+ 0.505	- 0.567	- 0.198	+ 0.535	0.030	- 1.09
43	+ 0.423	- 0.366	- 0.321	+ 0.675	0.252	- 1.00
acetylenes						
5[e]	+ 0.548	- 0.396	- 0.540	+ 0.425	0.152	+ 0.17
6	+ 0.501	- 0.339	- 0.585	+ 0.495	0.162	+ 0.09
7[e]	+ 0.548	- 0.375	- 0.567	+ 0.441	0.173	+ 0.24
	(0.50)[f]	(0.29)[f]				(+ 0.30)[g]
	(+ 0.326)[h]	(- 0.195)[h]	(- 0.341)[h]			
8	+ 0.495	- 0.315	- 0.609	+ 0.509	0.180	+ 0.16
39	+ 0.329	- 0.179			0.150	- 0.05
	(0.37)[f]	(0.19)[f]				(+ 1.30)[g]

[a] MNDO calculations unless otherwise noted. [b] Numbering system for pyrones. [c] Numbering system for acetylenes. [d] Carbon 6 - carbon 3 for pyrones and carbon 1 - carbon 2 for acetylenes. [e] Calculations were performed on the methyl ester analogues. [f] Absolute values from CNDO/2 calculations. See ref. 10, p. 500. [g] See ref 10, p. 500. [h] Huckel calculations. See ref. 11.

Table 4. HOMO-LUMO Energy Gaps.

Pyrone	$\Delta\varepsilon_1$[a]				$\Delta\varepsilon_2$[b]			
alkyne	5	6	7	8	5	6	7	8
1	9.44	9.37	9.51	9.44	10.54	10.40	10.86	10.74
2	9.44	9.37	9.51	9.43	10.54	10.39	10.85	10.73
3	9.53	9.46	9.60	9.52	10.57	10.42	10.89	10.77
4	9.28	9.20	9.35	9.27	10.50	10.35	10.82	10.70
42			10.06				10.44	
43			10.09				10.53	

[a] $\Delta\varepsilon_1 = LUMO_{alkyne} - HOMO_{pyrone}$. [b] $\Delta\varepsilon_2 = LUMO_{pyrone} - HOMO_{alkyne}$.

displays the lowest field methyl absorption at 90 MHz in $CDCl_3$ (δ 2.36) but the minor isomer displays the highest field methyl absorption (δ 2.18) indicating that the observed pattern is solvent dependent. In both benzene-d_6 and $CDCl_3$, however, the major isomer displays the lowest field methyl absorption consistent with structure 41.

Eigenvectors, eigenvalues, and charge densities were obtained from MNDO[9] calculations (Tables 2-3, 5) for the pyrones and acetylenes. The HOMO of the acetylenic ketones (Table 2) corresponds to a non-bonding molecular orbital largely localized on the carbonyl oxygen which would not be involved in [4 + 2] cycloadditions.

Discussion

Although concerted and multi-stage mechanisms proposed for the Diels-Alder reaction are a matter of continuing debate on theoretical grounds,[5b,14] experimental regioselectivities can be explained by assuming an unsymmetrical transition state and several models[5,6,15] have been proposed. Regioselectivities in cycloaddition reactions are poorly explained in terms of electronic or steric effects[3,5b,d] and FMO theory[5,6] has been remarkably successful in providing a qualitative picture that can rely on generalized FMO's.[16] Regioselectivity, in FMO theory, is governed by the relative size of the atomic coefficients of the FMO's which reflect the contribution of the overlap integral to the stablizing interaction energy arising from interaction of the HOMO of one reactant with the LUMO of the other reactant. This interaction energy is greater when the HOMO-LUMO frontier orbital pair is close in energy and the pair with the smaller energy gap is generally considered. The present reactions involve electron poor dienes and dienophiles and the full interaction energy given by $E = \sum_{m}^{occ}\sum_{n}^{unocc}(c_{im}c_{jn}H_{ij})^2/E_n-E_m + \sum_{m}^{unocc}\sum_{n}^{occ}(c_{im}c_{jn}H_{ij})^2/E_m-E_n$ must be considered[5b,d,6] since both pairs of frontier orbitals are close in energy and will jointly influence the regiochemistry of the reaction.

Qualitatively, the pyrones may be viewed as 1,4-disubstituted dienes containing carboalkoxy and acetoxy type substituents. These substituents enhance the terminal coefficient (C_4) in generalized FMO's[16] (Scheme I) and therefore oppose each other in determining the regiochemistry. On this simple basis, poor regiochemistry in pyrone [4 + 2] cycloadditions might be expected. There are several problems with this analysis. First, the FMO theory poorly orders substituents in terms of their relative directing abilities and fails to account for the greater effect of a 1-methyl substituent over a 2-alkoxy substituent,[6,15a] although the 2-alkoxy group dominates with asymmetrically (Z)-substituted dienophiles.[15b] Second, several reports have noted that when calculated atomic coefficients are employed[5h,16-17] the FMO theory fails to account for ortho regiochemistry experimentally observed for 1-(Z)-substituted dienes. Although this has been cited as evidence against the theory[17b], the failure may reside in the variation of atomic orbital coefficient magnitudes with calculational level[6,16,18] or in the complex influence of both pairs of frontier molecular orbitals.[5d] FMO theory correctly predicts the regiochemistry in the reaction of trans-2,4-pentadienoic acid with methyl acrylate when generalized FMO coefficients[16], secondary orbital interactions[19], or both pairs of FMO interactions are considered.[5d] The use of transition state FMO coefficients has been proposed as a solution to the general failure of the FMO's of unperturbed ground state reactants to account for the observed regiochemistry of 1-Z-substituted dienes.[20] In both the unperturbed and transition state models the largest coefficient is located on the terminal substituted carbon atom in the diene HOMO (incorrectly predicting meta regiochemistry) and on the unsubstituted carbon in the diene LUMO. Thus, the $LUMO_{diene}$ - $HOMO_{dienophile}$ interaction appears to control the regiochemistry and is better accounted for by the transition state model.

The orbital energy gaps for the pyrone/alkyne reactants (Table 4) parallel those reported for 1-Z-substituted dienes and electron deficient dienophiles and the orbital coefficients of the pyrones generally parallel those of trans-2,4-pentadienoic acid.[20] The largest coefficients are located on C_3 in the pyrone HOMO's (Table 2) correctly predicting the meta isomer with respect to the carbonyl. Examination of the pyrone LUMO coefficients (Table 3) reveals the largest coefficient to be on C_6 for 1 and 4 (paralleling trans-2,4-pentadienoic acid) and on C_3 for 2-3. Consequently, the two pairs of FMO's promote the same regiochemistry for 1 and 4 and the opposite regiochemistry for 2-3. This should lead to greater regioselectivity in the reactions of 1 and 4 relative to 2-3 which is indeed the case (Table 1). The differences in the HOMO terminal coefficients of the pyrones are significant[6] (> 0.01).

Examination of both pairs of FMO's and utilization of the equation for the full interaction energy qualitatively gives the correct regiochemical preferences. However, the difference in the stabilizing interaction energy for the two possible orientations is greater for the terminal alkynes than for the internal alkynes in contrast to the experimental results. In general, the

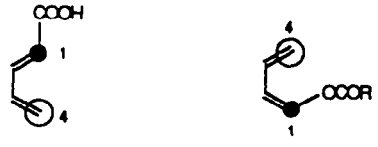
$LUMO_{pyrone}$ - $HOMO_{alkyne}$ interaction, which has the larger energy separation, provides the largest numerical contribution to the stabilization energy.

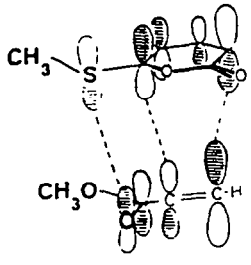
The alkynes **5-8** have the largest coefficient on the α-carbon (C_2) in the HOMO (although this is dependent upon the type of calculation)[16,18] and on the β-carbon (C_1) in the LUMO (Tables 2-3). The coefficient differences for the alkyne LUMO's are inversely proportional to the experimentally observed isomer ratios which is the opposite of what is expected for a controlling interaction. The differences in the alkyne HOMO's parallel the isomer ratios. The internal alkynes **5** and **6** show large HOMO coefficient differences (0.066-0.055) and good to excellent regioselectivities while the terminal alkynes show insignificant differences (0.006-0.008) and very poor regioselectivities. The difference in the HOMO atomic coefficients becomes larger as the energy of the HOMO orbital increases in the substituted alkynes. Consequently, the increase in HOMO atomic coefficient differences parallels the decrease in the $LUMO_{pyrone}$-$HOMO_{acetylene}$ energy gap and both trends are consistent with the greater selectivity observed for the internal alkynes in the reactions with pyrones **1-3**.

Although the above correlation holds for the interaction of pyrones **1-3** with alkynes **5-8** it does not hold for pyrone **4** which shows excellent regioselectivity with both internal and terminal alkynes in contrast to pyrones **1-3**. Pyrone **4** differs from the other substrates in containing an alkylthio substituent at C_6. Examination of the pyrone HOMO, alkyne LUMO's, and Dreiding molecular models indicate that a secondary orbital interaction can occur between the pyrone sulfur and acetylenic carbonyl oxygen heteroatoms which reinforces the regiochemistry observed in the other pyrones (I).

Reaction of pyrone **1** with phenylacetylene (**39**) affords an 80:20 mixture of regioisomers in which the tentatively assigned major isomer is correctly predicted by FMO theory. The relative magnitudes of the coefficients of the acetylenic carbons in **39** is opposite to that found in the acetylenic ketones and esters which is consistent (Table 2) with the experimental results. This reaction is clearly $LUMO_{pyrone}$-$HOMO_{alkyne}$ (8.38 e.v.) controlled since this involves the pair of FMO's closest in energy (vs 9.23 e.v.).

Scheme I





I

Table 5. Net Atomic Charges.[a]

Cpd	O1	C2 (C1)	C3 (C2)	C4 (C3)	C5 (O4)	C6 (O5) [c]	O7 [b]
pyrone							
1	- 0.247	+ 0.375	- 0.164	+ 0.039	- 0.205	+ 0.130	- 0.309
2	- 0.235	+ 0.367	- 0.170	+ 0.038	- 0.186	+ 0.112	- 0.311
3	- 0.237	+ 0.368	- 0.165	+ 0.043	- 0.226	+ 0.158	- 0.306
4	- 0.253	+ 0.379	- 0.171	+ 0.049	- 0.199	+ 0.111	- 0.307
42	- 0.239	+ 0.391	- 0.203	+ 0.111	- 0.221	+ 0.178	- 0.290
43	- 0.246	+ 0.376	- 0.188	+ 0.085	- 0.254	+ 0.246	- 0.285
acetylenes							
5		- 0.043	- 0.159	+ 0.492	- 0.350	- 0.338	
6		- 0.068	- 0.197	+ 0.331	- 0.283		
7		- 0.020	- 0.182	+ 0.492	- 0.350	- 0.338	
EHT[d]		+ 0.008	+ 0.033				
Huckel[e]		- 0.026	+ 0.176				
CNDO/2[f]		- 0.031	- 0.054				
CNDO/2 (π)[g]		+ 0.057	- 0.027				
8		- 0.044	- 0.222	+ 0.331	- 0.283		
39		- 0.120	- 0.125				
EHT[d]		- 0.079	- 0.052				
CNDO/2[f]		+ 0.126	+ 0.008				
CNDO/2 (π)[g]		- 0.0024	- 0.0019				

[a] MNDO calculations unless otherwise noted. [b] Pyrone numbering system. [c] Acetylene numbering system. [d] Extended Huckel Theory. See ref. 4b. [e] Huckel calculations. See ref. 13. [f] See ref. 12. [g] π-charges. See ref. 12.

The reaction of 2-carbomethoxy pyrone (**42**) with methyl propiolate (7-methyl ester) is reported to afford the meta isomer as the major product (80:20)[2e] contrary to predictions based on secondary orbital interactions or Huckel net atomic charges. Both FMO interactions (Tables 2-3) and MNDO net atomic charges predict preference for the meta isomer in accord with experiment. Reaction of **42** with **7** affords greater regioselectivity than the corresponding reaction of **1** with **7**. Although the differences in coefficient magnitudes is greater for **42** than for **1**, the opposite regiochemistry is predicted by secondary orbital interactions for reaction of **42** with **7**. This is consistent with the general view that secondary orbital interactions can alter selectivity ratios but do not dominate regiochemical preferences.[6,19b] Reaction of 4-carbomethoxypyrone (**43**) with methyl propiolate afforded a 60:40 mixture of para and meta bis-carbomethoxy benzenes.[2e] Both pairs of FMO interactions (Tables 2-3) and the full interaction energy incorrectly predict the meta isomer by MNDO. The C1-C2 HOMO atomic coefficient magnitude differences for **7** (methyl ester) are insignificant (0.006) by MNDO and reversed by CNDO/2 (providing the correct prediction). Consequently, if the $LUMO_{pyrone}$ - $HOMO_{alkyne}$ interaction is controlling (coefficient differences are almost twice as large in the pyrone LUMO than in the HOMO) as it appears to be in the other reactions, poor regioselectivity should be expected. The para isomer is not accounted for by MNDO net atomic charges (Table 5), although it is predicted by Huckel net atomic charges.[2e,21]

Calculated charge densities indicate pyrone resonance contributors that are polarized in the expected orientation; negative charge density adjacent to the carbonyl functionality and positive character at the β or δ-carbon atoms. This polarization correctly predicts the observed regioselectivities in a qualitative manner. Huckel and CNDO/2 π-electron densities correctly predict the experimental regiochemical preference for the reaction of phenylacetylene with **1** while net atomic charge densities obtained for all valence electrons by MNDO or CNDO/2 fail (Table 5).[21]

Although qualitative FMO theory successfully predicts regiochemistry in the reactions of unsymmetrical pyrones and alkynes, several interesting questions and observations are raised.

1. The pyrone HOMO coefficients correctly predict the observed regiochemistry qualitatively in contrast, generally, to 1-(Z)-substituted dienes. Is this merely fortuitious in view of error magnitudes in calculated stabilization energies and variation of coefficient magnitudes with type of calculation?
2. The energy and coefficients of the alkyne HOMO's correlate with the observed selectivities indicating an influence of the $HOMO_{alkyne}$-$LUMO_{pyrone}$ interaction in controlling regiochemistry. This interaction predicts regiochemistry correctly for **1** & **4** and fails for **2-3** indicating the importance of both interactions. Alston's transition state FMO approach[20] also provides the correct regiochemical prediction for trans-2,4-pentadienoic acid by favoring the higher energy $HOMO_{dienophile}$-$LUMO_{diene}$ interaction in the transition state. The transition state approach for pyrones should also favor the higher energy $HOMO_{alkyne}$-$LUMO_{pyrone}$ interaction in the transition state.[22] While Hehre[6] found a correlation between the dienophile LUMO energy and selectivity in the case of electron rich dienes reacting with electron poor dienophiles, the present reaction of electron poor dienes and dienophiles shows a correlation with dienophile HOMO energy.
3. Although the apparent failures of simple FMO theory have been frequently and controversially[6] accounted for by secondary orbital interactions, the results obtained with pyrone **4** indicate that these interactions can make a significant contribution to the overall selectivity.
4. Although qualitative FMO theory correctly predicts observed regiochemistry, the same predictions could be made by simple resonance theory consistent with the calculated net atomic charge densities.
5. The calculated HOMO and LUMO atomic coefficients for pyrones **1-4** indicate that simple changes in the substitution patterns of poly-substituted dienes can significantly change the magnitude of the coefficients. These changes are consistent (in these examples) with the experimentally observed changes in the general pattern of regioselectivity.

In conclusion, simple qualitative FMO theory provides a powerful empirical approach to predicting regiochemistry in the Diels-Alder reaction. It is not clear whether the reported failures result from the inherent weakness of the theory, failure to examine the complete set of interactions, or dependence of the FMO coefficient magnitudes upon the substitution patterns as well as the type and level of the calculations. The present study reveals several interesting correlations between selectivity and orbital energies and coefficients. Finally, the 6-alkylthio substituents serve as effective regiocontrol elements through secondary orbital interactions making 6-alkylthio α-pyrones potentially useful Diels-Alder dienes for synthetic purposes.

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Experimental

Proton NMR spectra were recorded on either an IBM-NR-200 AF (unless specified) or JEOL FX-90Q instrument as C_6D_6 solutions unless otherwise noted. Chemical shifts are reported as δ-values in parts per million relative to tetramethylsilane as internal standard. The ^{13}C NMR chemical shifts are reported as δ-values in parts per million downfield from tetramethylsilane and are referenced with respect to internal $CDCl_3$. Infrared spectra were recorded on a Perkin-Elmer 1310B spectrophotometer as $CHCl_3$ solutions unless otherwise noted. High resolution mass spectra were run on a Dupont CEC-110 mass spectrometer at the Massachusetts Institute of Technology Mass Spectrometry Laboratory. Calculations were performed with the 1980 version of MNDO[9] [available from the Quantum Chemistry Program Exchange at Indiana University, Bloomington, IN 47405, (812) 337-4784 (QCPE Program No. 353)]. The initial parameters for bond lengths, bond angles and dihedral angles were obtained from the CRC Handbook of Chemistry and Physics[23] for the acetylenes and from microwave data[24] and the CRC handbook[23] for the pyrones. All of the molecules were placed in nearly planar conformations oriented along the x-y plane and dummy atoms[25] were used to define the geometry about the triple bond. The eigenvector corresponding to the P_z atomic orbital was the predominant contributor for the atoms in the system of the root no. corresponding to the HOMO and LUMO molecular orbitals in the eigenvector matrix.

General Procedure:

The dienophile (1.0 mmol, 10 equiv) was added to an NMR tube which contained 0.10 mmol of the appropriate 2(H)-pyran-2-one. The solution was subjected to three freeze-vaccum evacuation-thaw cycles under nitrogen and the tube was then sealed. The tube was placed in an oil bath and the reaction was periodically monitored by NMR until the starting pyrone was consumed. After complete disappearance of pyrone the tube was opened and the contents poured into a diethyl ether / water mixture. The organic phase was separated, the aqueous phase extracted with 2 X 25 mL of ether and the combined ether extracts were dried over $MgSO_4$, concentrated in vacuo, and purified by medium pressure liquid chromatography (MPLC) on silica gel (petroleum ether / 3% ethyl acetate, v/v).

Ethyl 2,3-Dimethyl-4-ethyl-6-propylbenzoate (9) and Ethyl 3,4-Dimethyl-5-ethyl-2-propylbenzoate (10).

Reaction of pyrone 1 (18 mg, 0.12 mmol) with ethyl 2-hexynoate at 175°C for 36 h afforded, after MPLC purification (R_f 0.46), a 90:10 mixture of regioisomeric benzoates in 85% yield: IR 3020 (m), 2980 (s), 2940 (m), 2880 (m), 1715 (s), 1270 (s) cm^{-1}; ^1H NMR (Major isomer) δ 6.81 (s, 1 H), 4.20 (q, J = 7.14 Hz, 2 H), 2.50-2.62 (AA'XX' multiplet, 2 H), 2.16 (s, 3 H), 1.89 (s, 3 H), 1.70 (sept, J = 7.43 Hz, 2 H), 1.08 (t, J = 7.11 Hz, 3 H), 1.07 (t, J = 7.57 Hz, 3 H), 0.93 (t, J = 7.30 Hz, 3 H), (Minor isomer) δ 7.73 (s, 1 H), 4.19 (q, J = 7.11 Hz, 2 H), 3.08-3.19 (AA'XX' multiplet, 2 H), 2.44 (q, J = 7.55 Hz, 2 H), 2.04 (s, 3 H), 1.95 (s, 3 H); ^{13}C NMR (Major isomer) δ 171.0, 143.4, 136.1, 132.7, 132.5, 132.2, 127.0, 60.8, 35.8, 27.3, 24.7, 17.4, 14.9, 14.8, 14.3, 14.1, (Minor isomer) δ 33.9 (8.8%), 24.0 (9.5%).

2,3-Dimethyl-4-ethyl-6-propylacetophenone (11) and 3,4-Dimethyl-5-ethyl-2-propylacetophenone (12)

Reaction of pyrone 1 (23 mg, 0.13 mmol) with 3-heptyn-2-one (230 mg, 2.09 mmol, 16 equiv) at 160°C for 52 h afforded, after MPLC purification (R_f 0.34), an 86:14 mixture of regioisomeric acetophenones in 92% yield: IR 3020(s), 2980(s), 2940(s), 2880(s), 1695(vs) cm^{-1}; ^1H NMR (Major isomer) δ 6.79 (s, 1 H), 2.35-2.53 (m, 4 H), 2.15 (s, 3 H), 1.92 (s, 3 H), 1.89 (s, 3 H), 1.61 (sept, J=7.61 Hz, 2 H), 1.08 (t, J=7.51Hz, 3 H), 0.87 (t, J=7.30 Hz, 3 H), (Minor isomer) δ 7.07 (s, 1 H), 2.86-2.93 (m, complex AA^1XX^1 pattern, 2 H), 2.25 (s, 3 H), 2.02 (s, 3 H), 1.96 (s, 3 H), 1.04 (t, J=7.62 Hz, 3H); ^{13}C NMR (Major isomer) δ 209.2, 142.4, 140.4, 134.0, 132.3, 130.4, 126.9, 35.0, 33.1, 27.1, 24.8, 17.0, 14.7, 14.4, 14.0; mass spectrum m/e 203.1441 $(M - CH_3)^+$ (Calcd for $C_{14}H_{19}O$, 203.1436).

Ethyl 2,3-Dimethyl-4-ethylbenzoate (13) and Ethyl 3,4-Dimethyl-5-ethylbenzoate (14).

Reaction of pyrone 1 (18 mg, 0.12 mmol) with 120 mg (1.20 mmol, 10 equiv) of ethyl propiolate afforded, after MPLC purification (R_f 0.36), a 61:39 mixture of regioisomeric benzoates in 86% yield: IR 3040(m), 3020(m), 2980(s), 2940(s), 2880(m), 1715(vs), 1600(m), 1450(s) cm^{-1}; ^1H NMR (Major isomer) δ 7.45 (d, J=8.0 Hz, 1 H), 6.56 (d,J=8.0 Hz, 1 H), 3.87 (q, J=7.1 Hz, 2 H), 2.24 (s, 3 H), 2.10 (q, J=7.53 Hz, 2 H), 1.61 (s, 3 H), 0.77 (t,J=7.13 Hz, 3 H), 0.71 (t,J=7.55 Hz, 3 H), (Minor isomer) δ 7.75 (br s, 1 H), 7.71 (br s, 1 H), 3.92 (q,J=7.1 Hz, 2 H), 2.12 (q,J=7.51 Hz, 2 H), 1.71 (s, 3 H), 1.56 (s, 3 H), 0.78 (t,J=7.12 Hz, 3 H), 0.72 (t,J=7.54 Hz, 3 H); ^{13}C (Major isomer) 169.0, 142.4, 136.9*, 135.6, 129.3, 125.5, 60.6, 27.5, 17.1, 15.1, 14.6, 14.3, (Minor isomer) δ 167.1, 146.0, 140.0, 137.4*, 128.4, 127.4, 127.1, 26.9, 20.6 (* =may be reversed).

2,3-Dimethyl-4-ethylacetophenone (15) and 3,4-Dimethyl-5-ethyl-acetophenone (16).

Reaction of pyrone 1 (19.0 mg 0.125 mmol) with 150 mg (2.21 mmol, 17.6 equiv) of freshly distilled 3-butyn-2-one at 100°C for 36 h afforded **15**, after purification by MPLC (R_f 0.28) in 49 % yield: IR 3030(vs), 2980(m), 2940(m), 2880(w), 1680(s), 1530(m) cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 1.20 (t, J=7.4 Hz, 3 H), 2.24 (s, 3 H), 2.37 (s, 3 H), 2.54 (s, 3 H), 2.68 (q, J=7.4 Hz, 2 H), 7.05 (d, J=7.8 Hz, 1 H), 7.35 (d,J=7.8 Hz, 1 H); ^{13}C NMR δ 203.6, 145.6, 137.8, 136.1, 135.6, 125.6, 125.4, 30.3, 27.4, 17.1, 15.1, 14.5; mass spectrum m/e 176.1201 (M^+) (Calcd for $C_{12}H_{16}O$, 176.1201). **16** (R_f 0.23) was obtained in 45 % yield: IR 3020(vs), 2980(m), 2860(w), 1680(s) cm^{-1}; NMR ($CDCl_3$, 90MHz) δ 1.22 (t, J=7.5 Hz, 3 H), 2.26 (s, 3 H), 2.34 (s, 3 H), 2.57 (s, 3 H), 2.71 (q,J=7.5 Hz 2 H), 7.60 (s, 2 H).

Ethyl 3,6-Dimethyl-4-ethyl-2-propylbenzoate (17) and Ethyl 3,6-Dimethyl-5-ethyl-2-propylbenzoate (18).

Reaction of pyrone **2** (30 mg, 0.2 mmol) with 200 mg (1.43 mmol, 7.2 equiv) of ethyl 3-hexynoate at 210°C for 72 h afforded, after MPLC purification (R_f 0.48), a 75:25 mixture of regioisomeric benzoates in 86% yield: IR 3020(s), 2980(s), 2940(s), 2880(s), 1720(vs), 1605(w) cm^{-1}; ^1H NMR (Major isomer) δ 6.74 (s, 1 H), 4.19 (q, J = 7.11 Hz, 2 H), 2.72-2.65 (m, complex AA'XX' pattern, 2 H), 2.43 (q, J = 7.54 Hz, 2 H), 2.27 (s, 3 H), 2.02 (s, 3 H), 1.81-1.65 (m, 2 H), 1.08 (t, J = 7.11 Hz, 3 H), 1.07 (t, J = 7.52 Hz, 3 H), 0.95 (t, J = 7.30 Hz, 3 H), (Minor isomer) δ 7.16 (s, 1 H), 4.21 (q, J = 7.12 Hz, 2 H), 2.72-2.65 (m, complex AA'XX' pattern, 2 H), 2.37 (q, J = 7.52 Hz, 2 H), 2.17 (s, 3 H), 2.12 (s, 3 H), 1.81-1.65 (m, 2 H), 1.09 (t, J = 7.03 Hz, 3 H), 1.02 (t, J = 7.24 Hz, 3 H), 0.94 (t, = 7.31 Hz, 3 H); ^{13}C NMR (Major isomer) 170.8, 143.7, 137.4, 132.5, 131.3, 131.2, 127.8, 60.7, 33.9, 27.0, 23.7, 19.1, 14.5-14.2 (4 C), (Minor isomer) 171.6, 140.0, 135.3, 134.4, 133.7, 131.1, 129.0, 33.2, 26.0.

3,6-Dimethyl-4-ethyl-2-propylacetophenone (19) and 3,6-Dimethyl-5-ethyl-2-propylacetophenone (20).
Reaction of pyrone 2 (30 mg, 0.2 mmol) with 170 mg of 3-heptyn-2-one (1.55 mmol, 7.85 equiv) at 210°C for 42 h afforded, after MPLC purification (R_f 0.52), a 63:37 mixture of regioisomeric acetophenones in 54% yield: IR 3020(m), 2980(s), 2940(s), 2885(m), 1700(vs) cm^{-1}; ^1H NMR (Major isomer) δ 6.70 (s, 1 H), 2.52-2.27 (m, 4 H), 2.15 (s, 3 H), 2.04 (s, 3 H), 2.01 (s, 3 H), 1.55 (sept, J = 7.34 Hz, 2 H), (Minor isomer) δ 6. 85 (s, 1 H), 2.52-2.27 (m, 4 H), 2.15 (s, 3 H), 2.11 (s, 3 H), 1.94 (s, 3 H), 1.66-1.44 (m, 2 H), 1.03 (t, J = 7.62 Hz, 3 H); mass spectrum m/e 218.1675 (Calcd for $C_{15}H_{22}O$, 218.1671).

Ethyl 2,5-Dimethyl-4-ethylbenzoate(21) and Ethyl 2,5-Dimethyl-3-ethylbenzoate (22).
Reaction of pyrone 2 (30.4 mg, 0.2 mmol) with 200 mg of ethyl propiolate (2.04 mmol, 10.2 equiv) at 125°C for 36 h afforded after MPLC purification (R_f 0.40), a 59:41 mixture of regioisomeric benzoates in 84% yield: IR 3020(s), 2980(s), 2940(s), 2880(m), 1710(vs), 1615(m) cm^{-1}; ^1H NMR (Major isomer, $CDCl_3$) δ 7.70 (s, 1 H), 7.00 (s, 1 H), 4.34 (q, J = 7.13 Hz, 2 H), 2.61 (q, J = 7.42 Hz, 2 H), 2.55 (s, 3 H), 2.29 (s, 3 H), 1.38 (t, J = 7.13 Hz, 3 H), 1.20 (t, J = 7.52 Hz, 2 H), (Minor isomer) δ 7.40 (d, J = 1.5 Hz, 1 H), 7.10 (d, J = 1.5 Hz, 1 H), 4.35 (q, J = 7.14 Hz, 2 H), 2.65 (q, J = 7.40 Hz, 2 H), 2.43 (s, 3 H), 2.32 (s, 3 H), 1.38 (t, J = 7.13 Hz, 3 H), 1.18 (t, J = 7.57 Hz, 2 H); ^{13}C NMR (Major isomer) δ 167.7, 146.6, 137.6, 133.1*, 132.0, 131.3, 127.8, 60.3, 26.7, 21.3, 18.4, 14.3, 14.1, (Minor isomer 168.9, 143.4, 134.7*, 133.0, 132.3, 131.6, 127.0, 60.6, 26.1, 20.7, 15.5, 14.5, 14.3 (* = may be reversed).

2,5-Dimethyl-4-ethylacetophenone (23) and 2,5-Dimethyl-3-ethylacetophenone (24).
Reaction of pyrone 2 (30.0 mg, 0.2 mmol) with 205 mg (3.01 mmol, 15.3 equiv)of 3-butyn-2-one at 100°C for 62 h afforded, after MPLC purification (R_f 0.30), a 55:45 mixture of regioisomeric acetophenones in 98% yield: IR 3020(s), 2980(s), 2940(s), 2880(m), 1685(vs) cm^{-1}; ^1H NMR (Major, $CDCl_3$): δ 7.51 (s, 1 H), 7.03 (s, 1 H), 2.62 (q,J=7.57 Hz, 2 H), 2.57 (s, 3 H), 2.55 (s, 3 H), 2.33 (s, 3 H), 1.21 (t, J=7.60 Hz, 3 H), (Minor isomer) 7.19 (d, J=1.8 Hz, 1 H), 7.10 (d, J=1.8 Hz, 1 H), 2.64 (q, J= 7.55 Hz, 2 H), 2.57 (s, 3 H), 2.50 (s, 3 H), 2.32 (s, 3 H), 1.19 (t, J=7.58 Hz, 3 H); ^{13}C NMR (Major isomer) δ 201.5, 146.6, 140.2*, 134.8*, 131.8, 131.6, 126.1, 29.3, 26.1, 21.3, 18.6, 14.1, (Minor) 204.5, 143.8, 136.4, 132.9, 131.8, 131.1, 126.1, 30.5, 26.6, 20.9, 15.4, 14.6 (*=assignments may be reversed); mass spectrum m/e 176.1202 (M^+) (Calcd for $C_{12}H_{16}O$, 176.1202).

Ethyl 4-Ethyl-5-methyl-2-propylbenzoate (25) and Ethyl 5-Ethyl-4-methyl-2-propylbenzoate (26).
Reaction of pyrone 3 (16.0 mg, 0.116 mmol) with 200 mg of ethyl 2-hexynoate (1.43 mmol, 12 equiv) at 170°C for 22 h afforded, after MPLC purification, a 77:23 mixture of benzoates in 99% yield: IR 3020(s), 2980(s), 2940(s), 2880(s), 1715(vs), 1615(w) cm^{-1}; ^1H NMR (Major isomer) 7.89 (s, 1 H), 6.93 (s, 1 H), 4.17 (q, J=7.13 Hz, 2 H), 3.15-3.02 (m, 2 H), 2.36 (q, J=7.55 Hz, 2 H), 2.02 (s, 3 H), 1.87-1.65 (m, 2 H), 1.07 (t, J=7.12 Hz, 3 H), 1.02 (t, J=7.46 Hz, 6 H), (Minor isomer) δ 7.95 (s, 1 H), 6.90 (s, 3 H), 2.36 (q,J=7 Hz, 2 H); ^{13}C NMR (Major isomer) δ 167.9, 146.4, 142.0, 133.1, 132.1, 130.7, 127.0,* 60.4, 36.3, 26.2, 25.0, 18.5, 14.2-14.0(3 C), (Minor isomer) δ 139.7, 130.1*, 34.1, 25.6, 19.1 (* = may be reversed).

Ethyl 4-Ethyl-3-methylbenzoate (27) and Ethyl 3-Ethyl-4-methylbenzoate (28).
Reaction of pyrone 3 (23.0 mg, 0.17 mmol) with 220 mg (2.20 mmol, 13.2 equiv) of ethyl propiolate at 125°C for 15 h afforded, after MPLC purification (R_f 0.36), a 52:48 mixture of regioisomeric benzoates in 72% yield: IR 3020(m), 2980(s), 2940(m), 1710(vs), 1610(m) cm^{-1} ; ^1H NMR (Major isomer) δ 8.16-8.02 (m, 2 H), 7.01-6.88 (m, 1 H), 4.18 (q, J=7.13 Hz, 2 H), 2.32 (q, J=7.37 Hz, 2 H),* 1.95 (s, 3 H), 1.05 (t, J=7.11 Hz, 3 H), 0.97 (t, J=7.85 Hz 2 H)$^+$, (Minor isomer) 2.28 (q, J=7.37 Hz, 2 H),* 1.98 (s, 3 H), 0.94 (t, J=7.63 Hz, 3 H)$^+$ (+,* = may be reversed); ^{13}C NMR (Major isomer) 166.8, 147.7, 142.4, 135.8, 131.0, 127.3, 126.9, 60.6, 26.0, 19.1, 14.3, (2C), (Minor isomer) 141.3, 130.0, 129.0, 127.8, 26.3, 19.3.

4-Ethyl-3-methylacetophenone (29) and 3-Ethyl-4-methylacetophenone (30).
Reaction of pyrone 3 (28 mg, 0.20 mmol) with 200 mg (2.94 mmol, 15 equiv) of 3-butyn-2-one at 95°C for 24 h afforded, after MPLC purification (R_f 0.26), a 80:20 [^{13}C and capillary GC (30 m x 0.53 mm, supelcowax 10, 140°C for 10 min, 10°C/min to 200°C, 22 min)] mixture of regioisomeric acetophenones in 61% yield: IR 3030(s), 2980(s), 2940(s), 2880(w), 1680(s), 1530(w) cm^{-1}; ^1H NMR δ 1.24 (t, J = 7.57 Hz, 3 H), 2.36 (s, 3 H), 2.57 (s, 3 H), 2.68 (q, J = 7.57 Hz, 2 H), 7.22 (d, J = 10.0 Hz, 1 H), 7.60-7.80 (m, 2 H); ^{13}C NMR (Major isomer) 198.1, 142.7, 141.8, 135.3, 130.2, 127.7, 126.0, 26.5, 26.1, 19.2, 14.2, (Minor isomer) 129.9, 128.0, 126.3, 26.3, 19.3, 14.0; mass spectrum m/e 162.1016 (M^+) (calcd. for $C_{11}H_{14}O$, 162.1045).

Ethyl 4-Ethyl-3-methyl-2-methylthio-6-propylbenzoate (31) and Ethyl 5-Ethyl-4-methyl-3-methylthio-2-propylbenzoate (32).
Reaction of 4 (17.5 mg, 0.1 mmol) with 200 mg (1.43 mmol, 15.0 equiv) of ethyl 2-hexynoate at 235°C for 38 h afforded, after MPLC purification (R_f 0.67), a 94:6 mixture of benzoates in 83% yield: IR 3030(s), 2980(s), 2940(s), 2880(m), 1720(s), 1530(w) cm^{-1}; ^1H NMR (Major isomer) δ 6.85 (s, 1 H), 4.33 (q, J = 7.15 Hz, 2 H), 2.57-2.67 (m, 2 H), 2.38 (s, 3 H and q, J = 7.45 Hz, 2 H), 2.07 (s, 3 H), 1.67 (sept, J = 7.35 Hz, 2 H), 1.14 (t, J = 7.14 Hz, 3 H), 1.02 (t, J = 7.61 Hz, 3 H), 0.90 (t, J = 7.34 Hz, 3 H), (Minor isomer) δ 7.75 (s, 1 H), 4.18 (q, J = 7 Hz, 2 H), 3.63-3.51 (m, 2 H), 1.81 (s, 3 H); ^{13}C NMR (Major isomer) 169.3, 144.1, 138.9, 137.9, 136.5, 131.4, 129.8, 60.9, 35.5, 27.4, 24.3, 20.0, 15.8, 14.3, 14.1, 13.9.

4-Ethyl-3-methyl-4-methylthio-6-propylacetophenone (33) and 5-Ethyl-4-methyl-3-methylthio-2-propylacetophenone (34).
Reaction of pyrone 4 (21.0 mg, 0.114 mmol) with 200 mg (1.82 mmol, 16.0 equiv) of 3-heptyn-2-one at 195°C for 72 h afforded, after MPLC purification (R_f 0.34), an 87:13 mixture of acetophenones in 89% yield: IR 3020(m), 2980(s), 2940(m), 2880(m), 1700(s), 1600(w) cm^{-1}; ^1H NMR (Major isomer) δ 6.84 (s, 1 H), 2.34-2.48 (m, 4 H), 2.42 (s, 3 H), 2.38 (s, 3 H), 1.96 (s, 3 H), 1.58 (sept, J = 7.56 Hz, 2 H), 1.04 (t, J = 7.32 Hz, 3 H), 0.85 (t, J = 7.32 Hz, 3 H); ^{13}C NMR (Major isomer) δ 205.6, 146.2, 143.4, 137.9, 135.1, 130.0, 129.3, 34.9, 33.1, 27.3, 24.6, 20.3, 15.6, 14.4, 14.1; mass spectrum m/e 250.1413 (M^+) (calcd for $C_{15}H_{22}OS$, 250.1391).

Ethyl 4-Ethyl-3-methyl-2-methylthiobenzoate (35) and Ethyl 3-Ethyl-4-methyl-5-methylthiobenzoate (36).
Reaction of pyrone 4 (17.5 mg, 0.1 mmol) with 150 mg (1.53 mmol, 16.1 equiv) of ethyl propiolate at 125°C for 24 h afforded, after MPLC purification (R_f 0.50), a 90:10 mixture of regioisomeric benzoates in 75% yield: IR 3030(s), 2980(s), 2940(s), 2880(m), 1720(vs), 1595(w) cm^{-1}; ^1H NMR δ 7.35 (d, J = 7.8 Hz, 1 H), 6.79 (d, J=7.8 Hz, 1 H), 4.25 (q, J=7.17 Hz, 1 H), 4.24 (q, J=7.11 Hz 1

H), 2.17 (q, J=7.63 Hz, 2 H), 2.14 (s, 3 H), 1.08 (t, J=7.13 Hz, 3 H), 0.87 (t, J=7.49 Hz, 3 H), (90 MHz, $CDCl_3$) δ 1.21 (t, J=7.33 Hz, 3 H), 1.39 (t, J=7.08 Hz, 3 H), 2.31 (s, 3 H), 2.56 (s, 3 H), 2.68 (q, J=7.33 Hz, 3 H), 4.38 (q, J=7.08 Hz, 2 H), 7.15 (d, J=7.8 Hz, 1 H), 7.28 (d, J=7.8 Hz, 1 H), ^{13}C NMR δ 169.2, 145.5, 140.9, 137.5, 128.3, 128.2, 125.3, 60.4, 27.5, 22.3, 14.3 (2C), 14.1. Minor isomer: ^1H NMR (90 MHz, $CDCl_3$) δ 1.22 (t, J=7.81 Hz, 3 H), 1.39 (t, J=7.08 Hz, 3 H), 2.28 (s,3 H), 2.45 (s, 3 H), 2.65 (q, J=7.0 Hz, 2 H), 4.37 (q, J=7.08 Hz, 2 H), 7.03 (br s, 1 H), 7.77 (br s, 1 H); ^{13}C NMR δ 166.3, 147.2, 139.7, 132.5, 131.0, 124.5, 124.0, 60.5, 26.4, 18.1, 15.5, 14.1, 14.0.

4-Ethyl -3-methyl-2-methylthioacetophenone (37).

Reaction of pyrone **4** (16 mg, 0.87 mmol) with 150 mg (20.6 mmol, 24 equiv) of 3-butyn-2-one at 95°C for 21 h afforded, after MPLC purification (R_f 0.26), one regioisomeric acetophenone in 99% yield: IR 3040(m), 3020(s), 2980(s), 2940(s), 2880(m), 1695(vs), 1590(w) cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 1.21 (t, J=7.5 Hz, 3 H), 2.26 (s, 3 H), 2.57 (s, 3 H), 2.59 (s, 3 H), 2.67 (q, J=7.5 Hz, 2 H), 7.03 (d, J=8.05 Hz, 1 H), 7.18 (d, J=8.05 Hz, 1 H); ^{13}C NMR δ 204.7, 146.1, 144.9, 140.8, 131.3, 128.5, 123.4, 31.6, 27.4, 20.2, 16.1, 14.3,; mass spectrum m/e 208.0916 (M^+) (Calcd for $C_{12}H_{16}OS$, 208.0922).

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