Felkin−Anh Stereoselectivity in Cycloadditions of Acetylketene: Evidence for a Concerted, Pseudopericyclic Pathway

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The cycloadditions of acetylketene with α-chiral aldehydes and ketones are shown to be diastereoselective, forming a tertiary or quaternary chiral center at an acetal or ketal carbon with good stereocontrol. X-ray crystallography of a minor product (**5b**) shows that the major products (e.g., **4b**) are those predicted by the Felkin−Anh model. Transition states are reported at the MP2/6-31G* level for the addition of ethanal to formylketene and at the B3LYP/6-31G* level for the addition of 2-phenylpropanal. The ground-state conformations of the reactants and products are used to rationalize the relative energies and geometries of the transition states without the need to invoke the Cieplak hypothesis. However, chiral substituents on the α-oxoketene show no diastereoselectivity. These experimental and computational results are only consistent with the nearly planar, pseudopericyclic transition state previously proposed.

Introduction

α-Oxoketenes (**1**) have been the focus of numerous experimental and theoretical investigations[1−5] and have been utilized in synthesis as well.[6−8] Of particular interest is their tendency to undergo [4 + 2] cycloadditions, in contrast to the [2 + 2] cycloadditions characteristic of ketenes and of vinylketenes.[2,9,10] Numerous ab initio calculations by our group[4,11] and others[12] predict that these [4 + 2] cycloadditions are concerted and that the transition state is approximately planar with a pseudopericyclic orbital topology (Figure 1), rather than the familiar and thoroughly studied π-face-to-π-face geometry of the Diels−Alder reaction.[13,14] This theoretical prediction of an unusual mechanism now requires experimental studies to either support or correct it.

Some efforts have been made toward this end. Comparison of ab initio calculations for the additions of water and formaldehyde to formylketene (**1a**) predicted that water would be significantly more reactive. [4] We recently reported that indeed, despite its high reactivity, acetylketene (**1b**) shows remarkable chemoselectivity, discriminating among amines, alcohols, and carbonyl compounds.[15] This experimental verification of the prior theoretical prediction is reassuringly consistent with the calculations, but does not provide direct evidence regarding the transition-state geometry.

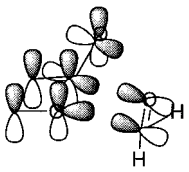
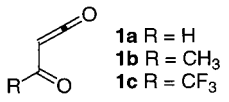


Figure 1. Qualitative orbital interactions in the pseudopericyclic cycloaddition of formylketene and formaldehyde.



Stereochemical studies are often used to provide insight into the subtle questions of transition-state geometries. Acetylketene lacks any stereochemical markers; cycloadditions as in eq 1 produce neither stereocenters nor geometrical isomers on the acetylketene moiety. There is, however, one new stereocenter formed in the reaction with an aldehyde or unsymmetrical ketone. The factors that control this stereochemistry can potentially shed light on the transition-state geometry. In this paper, we report that such cycloadditions with α-chiral aldehydes and ketones can proceed with significant Felkin−Anh diastereoselectivity while chirality on the ketene gives essentially no diastereoselectivity. We discuss these results as they relate to the questions of

† Author for correspondence regarding X-ray structures.

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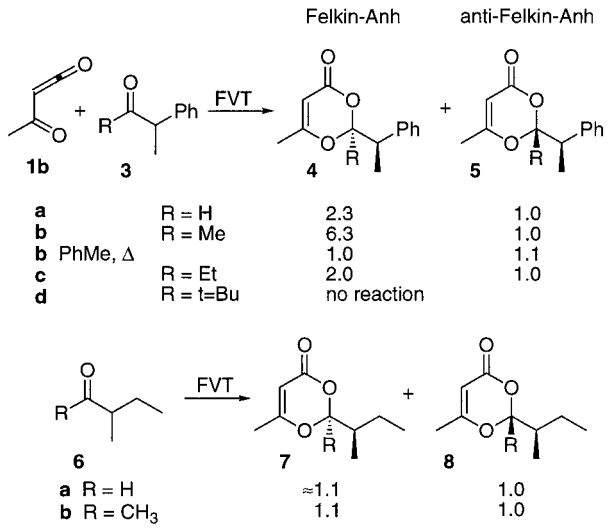
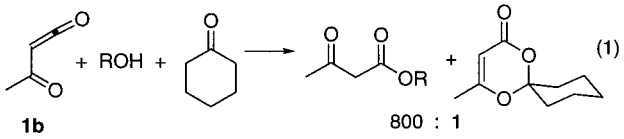
Scheme 1

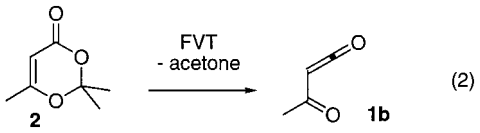


concerted vs stepwise mechanisms and pseudopericyclic vs pericyclic transition states.



Results

Reactions of acetylketene (1b). The thermolysis of 2,2,2-trimethyl-4*H*-1,3-dioxin-4-one (**2**) has been widely used as a convenient source of acetylketene (**1b**, eq 2).



As in our previous study of competitive reactions, [15] we used flash vacuum thermolysis (FVT) and in situ trapping to probe the stereoselectivity of reactions of acetylketene with chiral, racemic aldehydes and ketones. Compounds **3a**, **3b**, **6a**, and **6b** have been used in the pioneering studies of Felkin[16,17] and extensively since then.[18,19] Their use in this work allows for direct comparisons of selectivity. The ratios of products obtained are based on NMR integrations of the crude reaction mixtures and are presented in Scheme 1. Note that in the case of **3b** we also generated **1b** by refluxing **2** in toluene; in this case, the trapping reaction was reversible and an equilibrated product mixture was obtained.

Several aspects of the data are noteworthy. First and foremost, there is indeed significant stereoselectivity in the FVT reactions. For example, the stereoselectivity in the reaction of **3b** is 6.3:1; this reaction forms a quaternary chiral center at a ketal carbon. Such a level of diastereoselectivity can be synthetically useful and is comparable to, or better than, that observed in other reactions of **3b**. For example, the $LiAlH_4$ reduction of **3b** has a selectivity of only 2.8:1. [17] The selectivity reported here is comparable to the selectivities observed in many reactions of **3a** and **3b**. (See Table 4 in ref 19.) Other recent results suggest that higher selectivities are possible at lower temperatures for reactions of **3**.[20] As found in other reactions of **3**, [17,19] the selectivity increases as the size of the achiral group is increased from **3a** to **3b**. The diastereoselectivity for **3c** does not follow this trend, being only 2:1. As has been found in other cases,[16] the similar steric bulk of the methyl and ethyl groups in **6a** and **6b** leads to the poor selectivity observed in the formation of **7a**,**b** and **8a**,**b**.

Table 1. Results of Flash Vacuum Pyrolysis Reactions of 10a−f [R−C(O)-R′] with 3

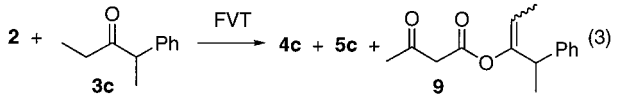
reactant	R	R′	product	% yield	enol ester?
10a	Me	Et	**11a**	58	no
10b	Et	Et	**11b**	29	no
10c	Et	*i*-Pr	**11c**	25	no
10d	*i*-Pr	*i*-Pr	**11d**	4	no
10e	Et	*t*-Bu	**11e**	0	no
10f	Et	Bn	**11f**	*a*	no

[a] Not determined.

Increasing the steric congestion around the carbonyl disfavors the reaction. The combined yield of cycloadducts decrease in the series **3a**−**3d** (40%, 11%, 5.4% for **4a** + **5a**, **4b** + **5b**, **4c** + **5c**, respectively). Although the reaction with *tert*-butyl ketone (**3d**) was attempted, no cycloadduct was obtained.

We were unable to determine the relative stereochemistry of the adjacent chiral centers in any of the adducts **4** or **5** based on the NMR spectra. Fortunately, we were able to obtain crystals of one minor diastereomer, **5b**. X-ray crystallography proved the relative stereochemistry is anti-Felkin−Anh; thus, the major diastereomer **4b** is the Felkin−Anh product. (The structure is shown in Figure S1, Supporting Information. Full X-ray data are in the Supporting Information. Selected distances and angles are given in Figure 4, below.) The stereochemical assignments of the other cycloadducts (**4** and **5**) are by analogy.

Interestingly, in the reaction of dioxinone **2** with the ethyl ketone **3c**, we found that although **4c** was formed in preference to **5c** as expected (combined yield of only 5.4%), the selectivity was low (2.0:1.0) and the major product was the vinyl ester **9** (24%, eq 3). We were



curious as to the factors that led to the formation of this unusual product, and so looked for similar products in the reactions of several related ketones (**10a**−**f**, Table 1). These compounds all contain either ethyl or isopropyl groups with an α hydrogen that could give similar products. The other groups have varying steric demands, yet none of these gave detectable quantities of enol esters; they all gave dioxinones (**11**) from [4 + 2] cycloadditions. The yields decreased with increasing steric bulk, as found

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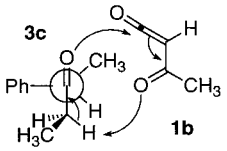
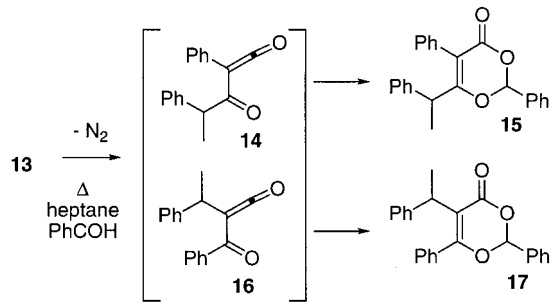


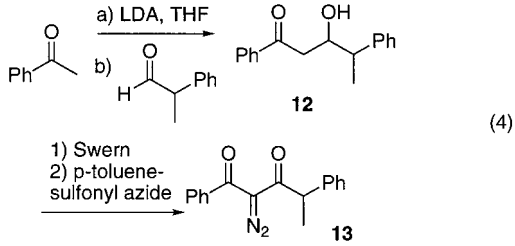
Figure 2. Possible pseudopericyclic eight-centered reaction of **1b** and **3c** to give **9**.

Scheme 2



in the reactions of **3**. We can rationalize the formation of **9** as an eight-centered (and therefore pseudopericyclic) elimination, as shown in Figure 2. However, we have no explanation for why only **3c** gives this unusual product.

Reactions of Chiral α-Oxoketenes 14 and 16. In the pseudopericyclic transition state in Figure 1, any chiral substituent on an α-oxoketene would be far removed from the reacting partner and thus not expected to lead to any diastereoselectivity. However, the *π*-face to *π*-face Diels−Alder mechanism puts the endo substituent on the dienophile relatively close to the chiral substituent. The α-oxoketenes **14** and **16** have chiral groups that are similar to the chiral groups in **6a**−**6c**. The diazodiketone **13** was synthesized by diazo transfer from *p*-toluenesulfonyl azide, as shown in eq 4. Thermolysis of **13** at 82 °C in heptane or in refluxing heptane, benzene, and toluene in the presence of benzaldehyde gave the regioisomers **15** and **17** as mixtures of diastereomers. These presumably were formed as in Scheme 2. Loss of nitrogen from **13** followed by the two possible Wolff rearrangements would generate both α-oxoketenes **14** and **16** (Scheme 2). Then [4 + 2] cycloaddition with benzaldehyde would give **15** and **17**. These were separated with flash chromatography, but the stereochemistries of the individual diastereomers were not determined. The observed diastereomer ratios are reported in Table 2. In refluxing heptane the two diastereomers of **15** are formed in a 1:1.22 ratio, while at 82 °C in heptane the ratio for **17** is 1:1.28. There is almost no diastereoselectivity in either of these cycloadditions.



(4)

To verify that these ratios reflect the kinetic trapping and not reversibility of the cycloaddition, the products were resubmitted to the reaction conditions. Chromatographic separation of **15** and **17** provided diastereomeric ratios that were different from those obtained above. Heating **15** (1:1.35 mixture of diastereomers) in refluxing heptane for 1.5 h did not change the diastereomeric ratio (1:1.39). Similarly, although the diastereomers of **17** equilibrated more readily than did **15**, heating **17** (1:4.85 mixture of diastereomers) at 82 °C for 2.0 h again did not change the ratio of diastereomers (1:4.94). Heating **17** at higher temperatures led to essentially a single diastereomer. Thus, chirality at either position on an α-oxoketene (e.g., **14** or **16**) leads to essentially no diastereoselectivity in the kinetic products from the [4 + 2] cycloaddition with benzaldehyde.

Table 2. Ratio of Diastereomers Formed by Static Thermolysis of Diazodiketone 13 in the Presence of Benzaldehyde

conditions	**15**	**17**
heptane (82 °C)	na[a]	1:1.28
heptane (98 °C)	1:1.22	1:1.72
benzene (80 °C)	1:1.22	na
toluene (111 °C)	1:1.32	na
control experiments: thermolysis of **15** and **17**	**15**	**17**
initial	1:1.35[b]	1:4.85[c]
final	1:1.39[b]	1:4.94[c]

[a] na: not applicable, due to low levels of **15** or significant equilibration of **17**. [b] Refluxing heptane (98 °C), 1.5 h. [c] Heptane 82 °C, 2.0 h.

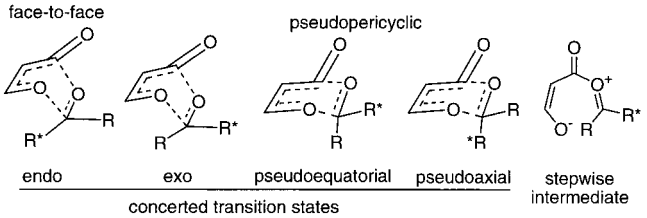


Figure 3. Five conceivable mechanisms for the reaction of a carbonyl compound and an α-oxoketene. Exo and endo, pseudoequatorial and pseudoaxial refer to the location of the chiral group (R*).

In the Wolff rearrangement, the phenyl migrated more readily than the sp^3 benzylic carbon. The ratio of **15** to **17** was 1:10 (combined yields of diastereomers). This parallels the reported migration preferences for planar di-substituted-2-diazo-1,3-propanediones, in which alkyl group migration is favored as compared to an aryl group.[1]

Discussion

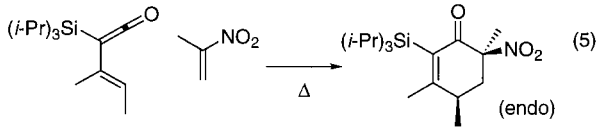
Figure 3 summarizes five conceivable mechanisms for [4 + 2] cycloadditions of acetylketene with an α-chiral aldehyde or ketone. On the basis of analogy with hydrocarbon reactions, there are two concerted, pericyclic, *π*-face-to-*π*-face Diels−Alder transition states, with the chiral group either exo or endo. However, ab initio calculations predict instead two nearly planar, pseudopericyclic transition states. The calculated transition state for the concerted cycloaddition of formylketene and formaldehyde is not completely planar, but has the CH_2 slightly out of plane. [4] This geometry is similar to the "sofa" conformation [21] of the product dioxinone. Thus, the α-chiral group can be either pseudoaxial or pseudoequatorial. Finally, a stepwise pathway would proceed with

(21) Sato, M.; Murakami, M.; Sunami, S.; Kaneko, C.; Furuya, T.; Kurihara, H. *J. Am. Chem. Soc.* **1995**, *117*, 4279−4287.

nucleophilic addition on the in-plane π-system of the ketene, forming a zwitterionic intermediate (Figure 3); such pathways are believed to be important in [2 + 2] cycloadditions of imines and ketenes, in which the nitrogen provides additional stabilization for the zwitterion.[2,22]

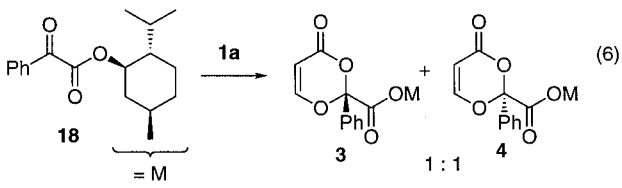
The observed Felkin−Anh selectivity in reactions of **3a**−**3c** requires nucleophilic attack of the acetyl oxygen from **1b** on the α-chiral carbonyl in the product-determining step. If the addition were stepwise, via a zwitterion (Figure 3) and assuming that there was no bias in the initial conformation of the intermediate, the observed stereoselectivity would require that ring closure of the zwitterion be slower than rotation around the partial double bonds of the C=O$^+$−C moiety. The fact that aldehydes and ketones react competitively with acetylketene also argues for a concerted, rather than stepwise mechanism.[15,23]

In all of the concerted transition states in Figure 3, there is bonding between the acetyl oxygen of **1b** and the α-chiral carbonyl. Viewed in isolation, the observed Felkin−Anh selectivity appears to be consistent with both the conventional Diels−Alder and the pseudopericyclic transition states. When viewed in the context of related reactions, however, it becomes clear that only the pseudopericyclic reaction is a permissible mechanism. Trialkylsilylvinylketenes, which cannot react in a pseudopericyclic manner, show endo selectivity (eq 5).[24,25] α,β-



(5)

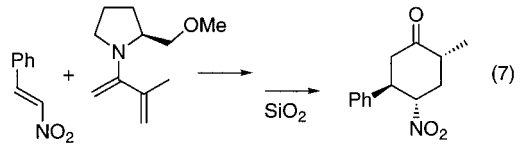
Unsaturated menthyl esters also show modest diastereoselectivity in uncatalyzed, pericyclic Diels−Alder reactions, presumably via an endo transition state.[29,30] Dimenthyl fumarate shows somewhat higher diastereoselectivity, presumably due to cooperative effects between the endo and the exo chiral esters.[30,31] However, when Sato et al. reacted menthyl ester **18** with formylketene (**1a**), no stereoselectivity was observed (eq 6).[32] This negative result argues against both the endo and the exo Diels−Alder transition states in reactions of α-oxoketenes with ketones.



(6)

α-Chiral dienophiles do show diastereoselectivity in Diels−Alder reactions, whether the chiral group is endo or exo. For leading references, see Casas et al.[33] However, such reactions often give anti-Felkin−Anh selectivity. Thus, the Felkin−Anh selectivity observed here in the reactions of **3a**−**3c** is consistent with neither the endo nor the exo Diels−Alder transition states.

Chiral dienes have not been studied as extensively as chiral dienophiles, although there are examples that show high diastereoselectivity in Diels−Alder reactions.[34] For example, the reaction in eq 7 proceeds with >96% ee. Although it is not known for certain whether this reaction (eq 7) is concerted or stepwise, it would be reasonable to expect the [4 + 2] cycloadditions of **14** and **16** (Scheme 2) to show diastereoselectivity as well, if they were also Diels−Alder reactions. The lack of diastereoselectivity in Table 2 is consistent with the pseudopericyclic transition state that puts the benzaldehyde far away from the chiral groups in **14** and **16**.



(7)

However, the pseudopericyclic transition state with a pseudoequatorial α-chiral group is consistent with the Felkin-Anh selectivities of **3a**−**c**. In particular, the increased selectivity of **3b** (R = Me) is consistent with the pseudoaxial methyl group forcing the nucleophilic trajectory closer to the chiral center. This effect can be seen in the ab initio transition states **19eqTS** and **19axTS** reported below (Figure 4). Interestingly, the transition state also offers a least-motion pathway to the more stable, pseudoequatorial sofa conformation of the dioxinone **5b**, as determined by X-ray crystallography.[21] Thus, as strange as it may seem, of the five mechanisms in Figure 3, the only one that is consistent with the accumulated experimental evidence is the concerted, pseudopericyclic mechanism with the α-chiral group in the pseudoequatorial position.

Ab Initio Calculations

Because the experimental results were consistent with calculations for the model system of formylketene and formaldehyde,[4] it seemed appropriate to carry out more extensive calculations on the observed Felkin−Anh stereoselectivity. We calculated pseudoaxial and pseudoequatorial transition states for the addition of ethanal to formylketene (**1a**) up to the MP2/6-31G* level. It was more practical to use the B3LYP/6-31G* level for calcula-

(22) Georg, G. I.; Ravikumar, V. T. *Stereocontrolled Ketene−Imine Cycloaddition Reactions*; Georg, G. I., Ed.; VCH: New York, 1993; pp 295−368.

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(34) For a review, see: Krohn, K. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1582−1584.

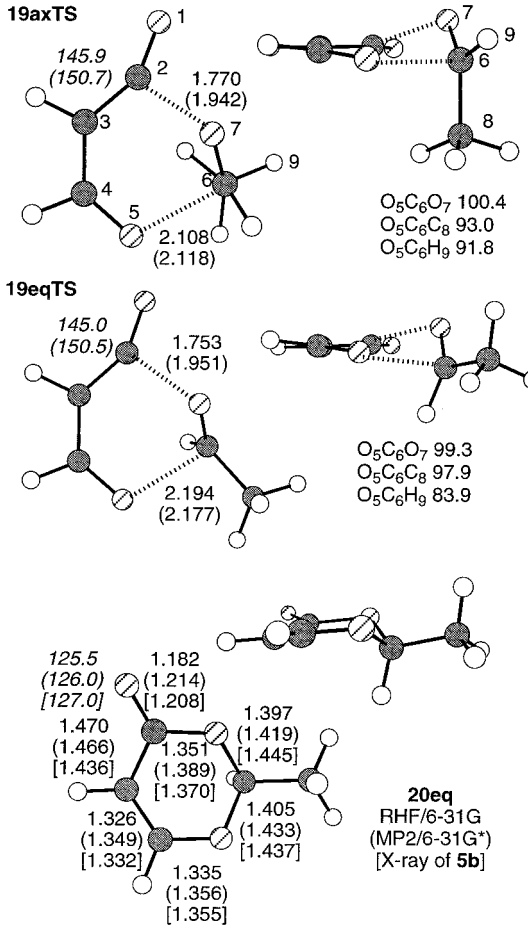

Figure 4. Geometries of pseudoaxial and pseudoequatorial transition states (**19axTS** and **19eqTS**) for the addition of ethanal to formylketene (**1a**) and the product **20eq** optimized at the RHF/6-31G* and (MP2/6-31G*) levels. Data from the X-ray structure of **5b** are shown in brackets for comparison with the calculated geometry of **20eq**. Distances are in angstroms, angles in degrees. Hydrogens are open; carbons are shaded; oxygens are striped.

tions on the addition of 2-phenylpropanal (**3a**) to **1a**. Both correlated levels are expected to give reasonable results for concerted reactions.

Computational Methods. Ab initio and density functional theory calculations were carried out using Gaussian 94.[35] For the addition of ethanal, geometries were optimized at the RHF/3-21G, RHF/6-31G* and MP2/6-31G* levels. For the addition of 2-phenylpropanal, the geometries were optimized at the same RHF levels, and then at the B3LYP/6-31G* level.[36] There were no qualitative differences between the geometries at the RHF or correlated levels. Frequency calculations served to provide free energy corrections and to confirm the nature of the transition states. Structures are shown in Figures 4 and 5, relative energies in Tables 3 and 4, and some additional geometrical parameters in Table 5. Absolute energies are available in the Supporting Information. For the following discussion, energies are at the correlated levels with ZPE corrections, as reported in Tables 3 and 4.

For the addition of ethanal, the transition state with the methyl group pseudoequatorial (**19eqTS**, Figure 4) is 1.8 kcal/mol more stable (MP2/6-31G* + ZPE, 2.6 kcal/mol at the RHF/6-31G* level) than with the methyl pseudoaxial (**19axTS**), as might be expected. In the products, **20eq** is more stable than **20ax** by 2.8 kcal/mol. This preference is in accord with the X-ray structures of **5b** and of related dioxinones [21] that have the larger group pseudoequatorial.

For the addition of 2-phenylpropanal to formylketene, there are 12 possible pseudopericyclic transition states. There are three conformations of 2-phenylpropanal (**3a1**, **2**, or **3**), each of which can be attacked in Felkin-Anh (**FA**) or anti-Felkin-Anh (**AFA**) sense. In addition, each transition state could have the chiral group either pseudoaxial or pseudoequatorial. In our initial studies, a pseudoaxial Felkin−Anh and a pseudoaxial anti-Felkin−Anh transition state were located at the AM1 level. The former optimized to a pseudoequatorial one at the RHF/3-21G level. In view of this instability of the axial transition states, but more importantly because the equatorial one was significantly more stable in the model addition of ethanal (Figure 4), we focused the rest of our studies on the six pseudoequatorial transition states shown in Figure 5. The significant stereoselectivity observed (6.3:1 for **3b**) requires that only one of these transition states be favored. Indeed, the pseudoequatorial Felkin−Anh transition state (**21TS1FA**) is calculated to be 1.1 kcal/mol below the next lowest energy transition state (**21TS1AFA**). Thus the calculations are consistent with the observed Felkin−Anh diastereoselectivity.

The simplest explanation of the calculated diastereoselectivity is that the conformational preferences of 2-phenylpropanal (**3a**) are preserved in the transition state.[37] Thus, since **3a1** is the most stable conformation, **21TS1FA** and **21TS1AFA** are the lowest energy transition states. Similarly, **3a2** is lower in energy than **3a3** and thus **21TS2AFA** is lower in energy than **21TS3AFA**. Although **21TS2FA** was located at the RHF/3-21G level, attempts to optimize it at the B3/LYP/6-31G* level led to **21TS1FA**; apparently in the former, steric crowding between the phenyl ring and the nucleophilic carbonyl overcomes the rotational barrier. For each conformation of the 2-phenylpropanal moiety, the Felkin−Anh attack is favored by steric interactions with the incoming nucleophile. Although such trends have been suggested before, [37] this is a particularly clear example of the ground state conformation dictating the relative energetics of conformationally related transition states.

Cieplak has proposed an alternative explanation of facial selectivity in additions to carbonyl compounds.[38] He suggested that anti-periplanar electron donation from a σ-bond into the σ^* of the forming bond stabilizes the transition state and the so-called "large" group in the Felkin−Anh model has the most electron-donating σ-bond. Much of the controversy generated by this idea has been focused on cyclic systems, in which sterics and constrained torsions have been argued to play a role as well.[37−41] The current study examines an acyclic system in which the torsions obviously change dramatically.

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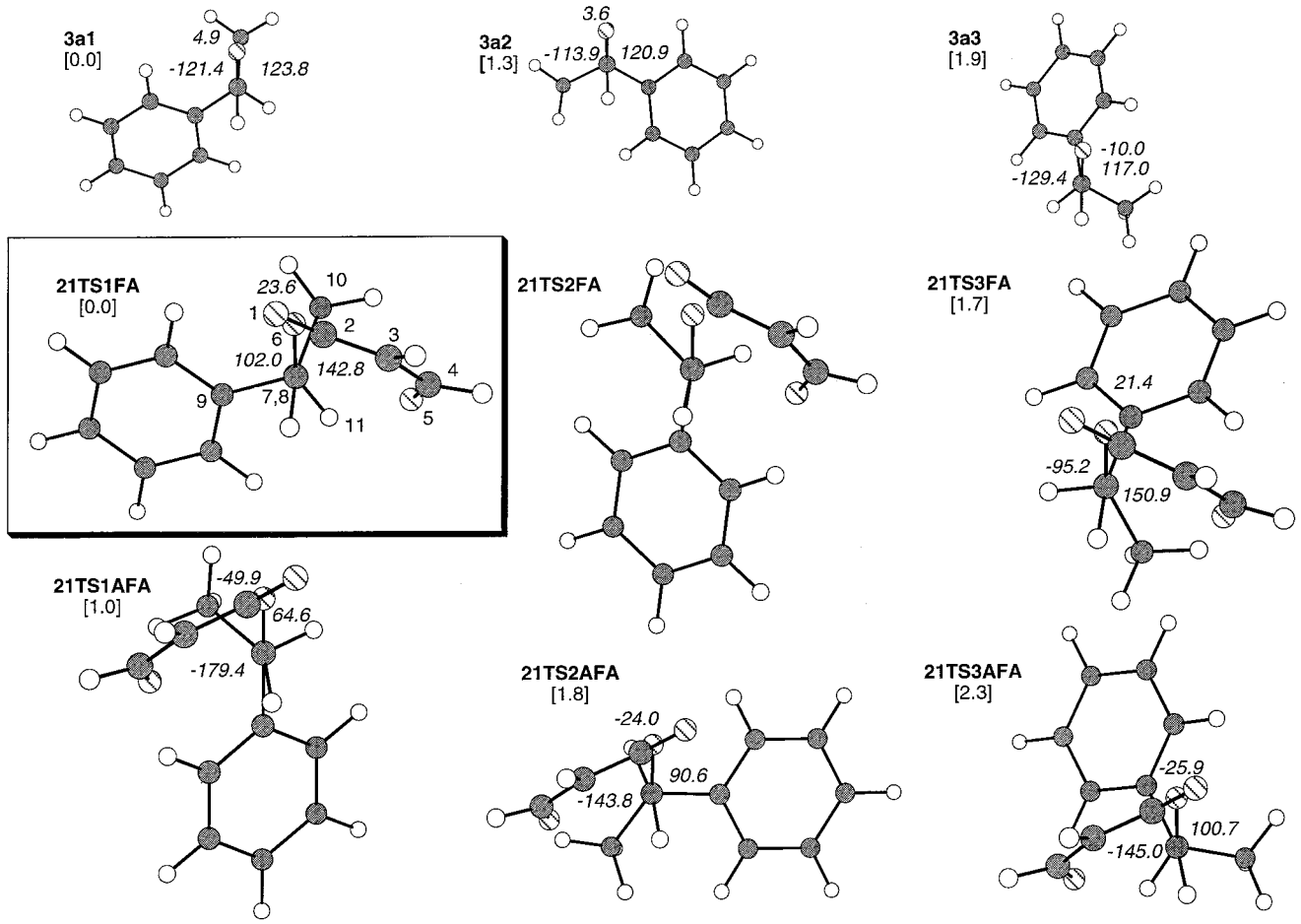

Figure 5. Newman projections (aldehyde to stereogenic center) of pseudoequatorial transition states for the addition of formylketene (**1a**) to 2-phenylpropanal (**3a**). Geometries are optimized at the B3LYP/6-31G* level, except for **21TS2FA**, which is at the RHF/3-21G level; see text. Atom numbering is as in **21TS1FA**, dihedral angles O6−C7−C8−(C9, C10, or H11) in degrees, [relative energies] in kcal/mol. See Table 5 for additional distances.

Table 3. Relative Energies (kcal/mol) of the Calculated Transition States for the Addition of Ethanal to Formylketene (1a) To Give 2-Methyl-4*H*-1,3-dioxin-4-one (20)

structure	RHF/3-21G	RHF/6-31G*	MP2/6-31G*	low freq	+ ZPE
1a, ethanal	0.0	0.0	0.0	144.9, 146.6	0.0
19eqTS	3.0	14.9	3.0	−247.9	5.4
19axTS	3.9	17.5	4.6	−311.4	7.2
20eq	−40.7	−27.9	−31.8	144.2	−25.6
20ax	−39.7	−25.3	−28.9	117.7	−22.8

Table 4. Relative Energies (kcal/mol) of 2-Phenylpropanal (3a) Conformations and the Calculated Transition States for the Addition of Formylketene (1a)

structure	RHF/3-21G	RHF/6-31G*	MP2/6-31G*//RHF/6-31G*	B3LYP/6-31G*	low freq (cm^{-1})	B3LPY + ZPE
3a1	0.0	0.0	0.0	0.0	45.8	0.0
3a2	2.6	1.5	1.7	1.3	23.8	1.2
3a3	2.1	2.2	1.9	1.7	47.1	1.7
1a + **3a1**	0.0	0.0	0.0	0.0	143.8, 45.8	0.0
21TS1FA	1.3	14.4	1.5	0.4	−103.4	2.0
21TA2FA[a]	4.0					
21TS3FA	4.5	16.8	3.4	2.1	−117.6	3.7
21TS1AFA	2.3	15.7	3.1	1.4	−125.8	3.1
21TS2AFA	4.2	16.6	4.1	2.2	−109.9	4.0
21TS3AFA	4.7	17.4	3.9	2.7	−129.6	4.3
Axial AFA[b]	4.9					

[a] Regardless of starting geometry, **21TS2FA** optimized to **21TS1FA** at all levels except RHF/3-21G. [b] An axial,anti Felkin−Anh transition structure was only optimized at the RHF/3-21G level. An axial Felkin−Anh transition structure could only be located at the AM1 level. At the RHF/3-21G level, it optimized to one of the equatorial structures.

The Cieplak hypothesis requires that the bond anti to the incoming nucleophile be lengthened as it donates electron density. Indeed, the Ph(C_9)−C_8 bond in **21TS1FA** is slightly longer than the same bond in **3a1** (1.529 vs 1.525 Å, Table 5). However, before this is taken as support for the Cieplak hypothesis, it should be noted

Table 5. Geometrical Parameters of Transition States Optimized at the B3LYP/6-31G* Level[a]

	21TS1FA	21TS3FA	21TS1AFA	21TS2AFA	21TS3AFA
C_2-O_6	2.100	2.045	2.031	2.039	2.084
O_5-C_7	2.318	2.374	2.359	2.356	2.280
C_8-C_9	1.529	1.518	1.519	1.535	1.517
C_8-C_{10}	1.535	1.543	1.544	1.534	1.550
C_8-H_{11}	1.097	1.104	1.102	1.096	1.097
O_5-C_7-O_6	96.5	94.0	94.2	94.0	98.0
$O_5-C_7-O_6-C_8$	−105.0	−109.9	−109.3	−110.0	−106.5

	3a1	3a2	3a3
C_8-C_9	1.525	1.523	1.515
C_8-C_{10}	1.534	1.543	1.550
C_8-H_{11}	1.100	1.095	1.100

[a] Atom numbering as in Figure 2. Distances in angstroms, angles in degrees. Bond lengths in bold are bonds that are either eclipsed or anti to the C═O.

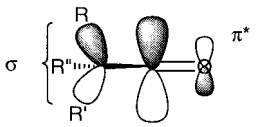

Figure 6. Orbital overlap between the carbonyl π^* orbitals and the π-like combination of the σ-bonds.

that there are similar changes in this bond length simply in the different conformations of **3a**. In fact, in the three conformations of **3a** and in the six transition states (Table 5), the bond lengths for the Ph(C_9)−C_8, Me(C_{10})−C_8 and $H_{11}-C_8$ bonds are shortest when their dihedral angle with the carbonyl is closest to 0° or 180° and is longest when it is closest to 90°, independent of the presence of a nucleophile and irrespective of the bond's orientation to the incoming nucleophile.

The ground-state conformations of ketones have been explained as the overlap of the occupied π-like antisymmetric combination of the sigma orbitals with the π^* orbital of the carbonyl, as in Figure 6. In **3a1** the HOMO-3 clearly shows this orbital interaction. This orbital interaction would be expected to give rise to the calculated lengthening of the out-of-plane bonds. Furthermore, the modest differences in the bond lengths in various transition states can be rationalized simply by assuming that steric effects rotate the stereogenic center relative to the carbonyl, changing the degree of overlap and thus the bond lengths. This rotation can easily be seen in the transition states in Figure 5.

Superimposed on the ground state conformational preference is the product preference for the pseudoequatorial conformation. **20eq** is calculated to be approximately 2.8 kcal/mol more stable than **20ax** (Table 3). Thus, the energies of the transition state conformations reflect a combination of factors that stabilize both the reactants and the products as well as steric interactions of the substrate with the incoming nucleophile.

As the size of the pseudoaxial group is increased, Anh's analysis of the transition state suggests that the angle of nucleophilic attack should move toward the chiral group, thus enhancing the stereoselectivity.[19,42] This trend in geometries is most easily seen by comparing the pseudoequatorial and pseudoaxial transition states **19eqTS** and **19axTS**. In **19eqTS**, the aldehyde hydrogen is tucked well under the forming ring, while in the **19axTS**, the substituent is more or less orthogonal to the forming ring. Quantitatively, this corresponds to the Nu-C═O- - -C(eq) dihedral angle of 105.2° in **19eqTS** and Nu-C═O- - -H(eq) of 97.4° in **19axTS**. Clearly, a larger axial group moves the angle of nucleophilic attack closer to the equatorial group. The result is consistent with the observed increase in selectivity from **3a** to **3b**. In the case of **3c**, the low yield of cycloadducts and the concomitant formation of **9** means that any discussion of selectivity in this case is speculative at best.

Conclusions

The [4 + 2] cycloadditions of chiral α-oxoketenes **14** and **16** with benzaldehyde have been studies and do not exhibit any significant diastereoselectivity. However, in the cycloadditions of acetylketene with a series of α-chiral aldehydes and ketones (**3a**−**3c**), significant diastereoselectivity is experimentally observed in the Felkin-Anh sense. This selectivity is comparable to that obtained in other nucleophilic additions to the same carbonyl compounds. This selectivity is reproduced by B3LYP/6-31G* calculations that predict nearly planar, pseudopericyclic transition states. The lowest energy transition state (**21TS1FA**) reflects the low energy conformations of the reactants and the products, as suggested by Anh. The Cieplak hypothesis is not required to explain these results. The observed Felkin−Anh selectivity, in conjunction with previous experimental results, is consistent only with a concerted, pseudopericyclic transition state that we had previously proposed based on ab initio calculations. The observed trends in stereoselectivity with increasing size of the R group are consistent with such a transition state in which the larger, α-chiral group adopts a pseudoequatorial position. The Felkin−Anh model and the ground state conformations, as applied to the pseudopericyclic transition state geometry offers the only full explanation of the experimental and computational results.

Experimental Section

THF was freshly distilled from either sodium or NaK, dichloromethane was freshly distilled from calcium hydride and ethyl ether was freshly distilled from sodium. 2,2,6-Trimethyl-4*H*-1,3-dioxin-4-one was purified by passing it through a pad of silica gel and eluting with ether. Other reagents were used as received. Flash chromatography was performed using 230−400 mesh 60 Å silica gel. NMR spectra

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were obtained in $CDCl_3$ at 300 MHz ^1H and 75 MHz (^{13}C) unless otherwise indicated. Chemical shifts are reported in ppm, couplings in Hz. HPLC separations were performed using an absorbance detector at 260 nm, and a 19 mm × 30 cm 60 Å, 60 μm silica gel column.

3-Phenyl-2-butanol. In a 100 mL round-bottom flask, THF (20 mL) and 2-phenylpropanal (1.8 mL, 14.9 mmol) were cooled to −78 °C. To this reaction mixture methyllithium solution (10.0 mL, 16.4 mmol, 1.4 M) was slowly added. After complete addition the reaction was warmed to room temperature. The reaction was worked up in ether then washed successively with sodium bicarbonate and brine solutions: 99% yield.[43]

3-Phenyl-2-butanone (3b). In a 100 mL round-bottom flask with dichloromethane (20 mL) and DMSO (2.50 mL, 25.6 mmol) were cooled to −78 °C. Oxalyl chloride (1.70 mL, 19.2 mmol) was added and allowed to stir for 30 min. To this solution a mixture of 3-phenyl-2-butanol (1.90 mL, 12.8 mmol) and dichlormethane (5 mL) was added and allowed to stir for 30 min. To this reaction mixture Et_3N (8.9 mL, 64 mmol) was added, allowed to stir 10 min and then warmed to room temperature. This Swern oxidation was worked up in ether and washed with sodium bicarbonate and brine solutions. Evaporation of solvent followed by silica gel chromatography (Hexane/EtOAc, 95/5, 200 mL) gave **3b** in 58% yield.[44]

2-Phenyl-3-pentanol. In a 100 mL round-bottom flask fitted with a reflux condenser magnesium turnings (0.38 g, 12.2 mmol), THF (20 mL), and bromoethane (1.14 mL, 15.3 mmol) were added and stirred. After 2 h the consumption of magnesium stopped and the reaction cooled indication completion of reaction. The resultant Grignard was transferred slowly via cannula to a 250 mL three neck flask fitted with a reflux condenser and containing THF (20 mL) and 2-phenylpropanal (1.61 mL, 12.2 mmol). The reaction was monitored by TLC and worked up after 2 h by extraction with ether and washed with sodium bicarbonate and brine solutions. Evaporation of solvent followed by silica gel chromatography (hexane/EtOAc, 95/5, 500 mL) gave a 36% yield.[45]

2-Phenyl-3-pentanone (3c). The procedure for the preparation of **3b** was followed, using 0.69 mL of DMSO (7.6 mmol), 0.50 mL of oxalyl chloride (5.7 mmol), 0.63 g of 2- phenyl-3-pentanol (3.8 mmol), and 2.65 mL of Et_3N (19.0 mmol). Purification by silica gel chromatography (hexane/EtOAc, 9/1, 100 mL, then hexane/EtOAc, 8/2, 100 mL) gave **3c** in 80% yield.[46]

2,2-Dimethyl-4-phenyl-3-pentanol. In a 100 mL round-bottom flask, hexane (25 mL), diethyl ether (15 mL) and 2-phenylpropanal (1.4 mL, 10.4 mmol) were cooled to −5 °C and *tert*-butyllithium (12.3 mL, 20.9 mmol, 1.7 M) was added slowly. The reaction was allowed to stir 30 min and monitored by TLC. The reaction was worked up in ether and washed with sodium bicarbonate and brine solutions. Evaporation of the solvent followed by silica gel chromatography (hexane/EtOAc, 9/1, 200 mL, hexane/EtOac, 8/2, 200 mL) produced a mixture of the two diastereomers in 50% yield.[47]

2,2-Dimethyl-4-phenyl-3-pentanone (3d). The procedure for the preparation of **3b** was followed, using 0.37 mL of DMSO (4.0 mmol), 0.32 mL of oxalyl chloride (3.6 mmol), 0.39 g of 2,2-dimethyl-4-phenyl-3-pentanol (2.0 mmol), and 1.42 mL of Et_3N (10.0 mmol). Purification by silica gel chromatography (hexane/EtOAc, 95/5, 100 mL) gave a 57% yield.[47]

Flash Vacuum Thermolysis (FVT). All FVT experiments were carried out in the following manner unless otherwise noted. A quartz tube approximately 50 cm in length was placed vertically and heated by a tube furnace to approximately 400 °C as measured with a thermocouple. A trap placed at the receiving end of the quartz tube used with liquid nitrogen as the trapping agent. An addition funnel was placed on the top of the quartz tube and used for sample delivery into the heated tube. The apparatus was evacuated by a rough pump that provided approximately 0.25 Torr vacuum. In each experiment the vacuum and tube furnace were allowed at least 2 h to equilibrate before samples were introduced. After each experiment the apparatus was filled with helium, the tube furnace cooled, and the trap warmed to room temperature. Reported selectivities were reproduced in at least two experiments.

6-Methyl-2-(1-phenylethyl)-4*H*-1,3-dioxin-4-one (4a, 5a). A mixture of 2-phenyl-3-propanal (**3a**) (2.03 mL, 15.4 mmol), **2** (1.0 mL, 7.7 mmol), and dichloromethane (2 mL) was subjected to FVT conditions. The resultant liquid was rotovapped and the ratio of diastereomers determined by NMR to be 2.3:1. The products were purified by silica gel chromatography (hexane/EtOAc, 24/1, 250 mL, hexane/EtOAc, 95/5, 400 mL), giving a 40% combined yield. Separation of the diastereomers was accomplished by successive HPLC (hexane/EtOAc, 95/5).

4a: ^1H NMR (200 MHz) 1.46 (d, 3H, J = 7.2 Hz), 1.97 (s, 3H), 3.30 (dq, 1H), 5.26 (s, 1H), 5.50 (d, 1H, J = 5.0), 7.32 (m, 5H); ^{13}C NMR (50 MHz) 14.90, 19.34, 42.78, 95.94, 102.92, 127.26, 128.42, 128.47, 139.55, 162.54, 172.02. Anal. Calcd $C_{13}H_{14}O_3$; C, 71.54; H, 6.47. Found; C, 71.24; H, 6.38.

5a: ^1H NMR (200 MHz) 1.46 (d, 3H, J = 7.2 Hz), 1.97 (s, 3H), 3.30 (dq, 1H), 5.26 (s, 1H), 5.50 (d, 1H, J = 5.0), 7.32 (m, 5H); ^{13}C NMR (50 MHz) 14.42, 19.34, 42.63, 95.94, 102.80, 127.26, 128.42, 128.47, 139.55, 162.54, 172.02.

2,6-Dimethyl-2-(1-phenylethyl)-4*H*-1,3-dioxin-4-one (4b, 5b). A mixture of 3-phenyl-2-butanone (**3b**, 1.08 g, 7.4 mmol), **2** (0.97 mL, 7.4 mmol) and dichloromethane (2 mL) were subjected to FVT conditions. The resultant liquid was rotovaped and the ratio of diastereomers determined by NMR to be 6.4:1. The products were purified by silica gel chromatography (hexane/EtOAc, 98/2, 200 mL, hexane/EtOAc, 95/5, 400 mL) giving an 11% combined yield/Separation of diasteriomers was accomplished by HPLC (hexane/EtOAc, 95/5). A crystal structure of **5b** was obtained by X-ray diffraction.

4b: ^1H NMR (200 MHz) 1.44 (d, 3H, J = 7.23 Hz), 1.48 (s, 3H), 1.96 (s, 3H), 3.30 (q, 1H, J = 7.13 Hz), 5.20 (s, 1H), 7.27 (m, 5H); ^{13}C NMR (50 MHz) 15.4, 19.9, 20.6, 47.5, 93.7, 109.3, 116.4, 122.2, 128.2, 129.1, 140.7, 160.9, 168.6. Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.42; H, 7.05.

5b: ^1H NMR (200 MHz) 1.44 (d, 3H, J = 7.13 Hz), 1.49 (s, 3H), 1.96 (s, 3H), 3.25 (q, 1H, j = 7.12 Hz), 5.18 (s, 1H), 7.27 (m, 5H); ^{13}C NMR (50 MHz) 15.4, 19.9, 20.9, 47.9, 93.8, 109.1, 127.2, 128.2, 129.1, 140.2, 161.0, 168.5.

2-Ethyl-6-methyl-2-(1-phenylethyl)-4*H*-1,3-dioxin-4-one (4c, 5c). A mixture of 2-phenyl-3-pentanone (**3c**, 1.02 g, 5.8 mmol), **2** (0.82 mL, 5.8 mmol), and dichloromethane (3.0 mL) was subjected to FVT conditions. The resultant liquid was rotovapped and the ratio of diastereomers determined by NMR to be 2:1. The products were purified by silica gel chromatography (hexane/EtOAc, 24/1, 250 mL, hexane/EtOAc, 95/5, 200 mL) giving a combined yield of 5.4% for **4c** and **5c**. Further separation of diasteriomers was accomplished by HPLC (hexane/EtOAc, 95/5).

4c: ^1H NMR 0.89 (t, 3H, J = 7.5 Hz), 1.40 (d, 3H, J = 7.2 Hz), 1.66 (m, 1H), 1.97 (s, 3H), 2.06 (m, 1H), 3.42 (q, 1H, J = 7.1 Hz), 5.14 (s, 1H), 7.26 (m, 5H); ^{13}C NMR 7.3, 15.6, 19.9, 26.4, 44.9, 93.4, 111.5, 127.1, 128.3, 129.0, 140.3, 163 (tentative assignment), 168.5.

5c: ^1H NMR 0.92 (t, 3H, J = 7.2 Hz), 1.40 (d, 3H, J = 7.2 Hz), 1.67 (m, 1H), 1.94 (s, 3H), 2.0 (m, 1H), 3.37 (q, 1H, J = 7.1 Hz), 5.07 (s, 1H), 7.26 (m, 5H); ^{13}C NMR 7.3 15.5, 19.9, 26.9, 45.2, 93.4, 111.3, 127.1, 128.2, 129.2, 140.2, 161 (tentative assignment), 168.4.

1-(1-Phenylethyl)-1-propenyl 3-oxobutanoic Ester (9). This was formed in 24% yield in the reaction that formed **4c** and **5c**. Final purification was done by HPLC (hexane/Et_2O, 3/1); this failed to separate the cis and trans isomers. The NMR spectrum shows keto−enol tautomers of both isomers: ^1H NMR (d, 3H, J = 6.2), 1.19 (d, 0.7H, J = 6.2), 1.28 (d, 3.7H, J = 6.3), 2.0 (s, 0.6H), 2.22 (s, 3H), 2.85 (m, 1.4H), 3.26 (s 0.4H),

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3.43 (s, 2H) 5.07 (1.4H), 7.25 (m, 6.1H); ^{13}C NMR 16.94, 17.42, 17.53, 17.77, 18.14, 18.28, 21.23, 21.95, 29.72, 30.16, 44.53, 45.01, 45.30, 50.37, 50.45, 75.69, 76.17, 90.02, 126.15, 126.6, 126.64, 127.82, 127.87, 128.05, 128.13, 128.18, 128.31, 128.43, 128.49, 128.56, 142.83, 142.93, 166.49, 166.72, 175.49, 200.61. Anal. Calcd $C_{15}H_{18}O_3$: C, 73.10; H, 7.37. Found: C, 71.80; H, 7.55.

Attempted Synthesis of 2-(2,2-Dimethylethyl)-6-methyl-2-(1-phenylethyl)-4*H*-1,3-dioxin-4-one. A mixture of *tert*-butyl ketone **3d** (0.14 g, 1.2 mmol), dioxinone **2** (0.13 g, 1.0 mmol), and 2 mL dichloromethane were subjected to FVT conditions. The pyrolysate was rotovaped and purified by silica gel chromatography (hexane/EtOAc 9:1). Starting material was recovered, but there was no evidence for product in either the crude NMR or after purification.

2-(1-Methylpropyl)-6-methyl-4*H*-1,3-dioxin-4-one (7a, 8a). A mixture of **2** (1.0 mL, 7.7 mmol) and *sec*-butyl aldehyde (**6a**, 1.52 mL, 15.3 mmol) was transferred to the FVT apparatus and washed with dichlormethane (2 mL). The solution was subjected to FVT conditions. The products were allowed to warm slowly by allowing liquid nitrogen to evaporate from the trap while leaving the sample in the trap. The resultant liquid was rotovaped and products separated by silica gel chromatography (hexane/EtOAc, 24/1, 1000 mL, hexane/EtOAc, 9/1, 200 mL). Further purification was accomplished by HPLC (hexane/EtOAc, 95/5); this failed to separate the diastereomers. Crude combined yield based on NMR was 10%. The ratio of diasteriomers as determined by NMR was found to be 85:100: ^{1}H NMR (mixture of diastereomers) 0.94 (t, 3H, J = 7.5 Hz), 1.02 (d, 3H, J = 6.9 Hz), 1.32 (m, 1H), 1.60 (m, 1H), 1.88 (m, 1H), 2.01 (s, 3H), 5.26 (s, 1H), 5.29 (dd, 1H); ^{13}C NMR 11.44, 11.48, 12.88, 12.91, 19.52, 23.49, 37.85, 37.89, 95.94, 103.46, 103.50, 163.19, 172.23.

2-(1-Methylpropyl)-2,6-dimethyl-4*H*-1,3-dioxin-4-one (7b, 8b). A mixture of **2** (1.0 mL, 7.7 mmol) and 3-methyl-2-pentanone **6b** (1.88 mL, 15.3 mmol) was transferred to the FVT apparatus and washed with dichlormethane (2 mL). The solution was subjected to FVT conditions. The products were allowed to warm slowly by allowing liquid nitrogen to evaporate from the trap while leaving the sample in the trap. The resultant liquid was rotovaped and products separated by silica gel chromatography (hexane/EtOAc, 24/1, 500 mL, hexane/EtOAc, 8/2, 200 mL). Further purification was accomplished by HPLC (hexane/EtOAc, 95/5); this failed to separate the diastereomers. Crude combined yield based on NMR was 22%. The ratio of diasteriomers as determined by NMR was found to be 90:100: ^{1}H NMR 0.91 (t, 6H, J = 7.4 Hz), 0.98 (d, 3H, J = 5.7 Hz), 1.07 (d, 3H, J = 5.7), 1.14 (m, 2H), 1.54 (m, 2H), 1.69 (s, 6H), 1.93 (m, 2H), 1.94 (s, 6H), 5.18 (s, 2H); ^{13}C NMR 12.08, 12.91, 13.14, 19.15, 19.96, 23.15, 23.42, 42.33, 42.88, 93.68, 93.69, 110.36, 110.38, 161.28, 161.32, 168.49, 168.51. Anal. Calcd $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.39; H, 8.91.

1,4-Diphenyl-3-hydroxy-1-pentanone (12). This compound was synthesized following the method outlined by Davis et al. [48] We now provide the experimental details. In a 100 mL round-bottomed flask, THF (25 mL) and acetophenone (1.0 mL, 8.5 mmol) were cooled to −78 °C. To this mixture was added LDA (8.7 mL, 9.4 mmol, 2.0 M in THF). The resultant solution was stirred for 20 min and then allowed to warm to room temperature and recooled to −78 °C. This solution was then transferred to a 250 mL round-bottomed flask containing THF (25 mL) and 2-phenylpropanal (1.2 mL, 8.5 mmol) that was also at −78 °C. The resultant solution was stirred for 20 min, then warmed to room temperature. The reaction was quenched with saturated ammonium chloride solution (5 mL). This was worked up by extracting with ether and washed successively with sodium bicarbonate and brine solutions. Drying with $MgSO_4$, filtration and evaporation of the solvent followed by silica gel chromatography (hexane/EtOAc 95/5) gave the product as a mixture of diastereomers in 63% yield.

(48) Davis, A. P.; Plunkett, S. J. *J. Chem. Soc., Chem. Commun.* **1995**, *21*, 2173-2174.

1,4-Diphenyl-1,3-pentanedione. This compound has previously been synthesized via a different route. [49] For this work, it was synthesized in a fashion similar to **6b** using 0.55 mL of DMSO (7.70 mmol), 0.50 mL of oxalylchoride (5.7 mmol), 0.93 mL of 1,4-diphenyl-3-hydroxy-1-pentanone (**12**, 3.9 mmol) and 2.68 mL of Et_3N (19.2 mmol): 53% yield.

***p*-Toluenesulfonyl Azide.** Following the *Organic Syntheses* preparation, a quantitative yield was obtained. [50]

2-Diazo-1,4-diphenyl-1,3-pentanedione (13). In a 100 mL round-bottomed flask, 1,4-diphenyl-1,3-pentanedione (1.04 mL, 4.1 mmol) was dissolved in 15 mL acetonitrile and cooled to −4 °C. Triethylamine (0.58 mL, 4.2 mmol) was added, followed by *p*-toluenesulfonyl azide (0.69 g, 4.51 mmol). The reaction was stirred at −4 °C for 2 h. The reaction was worked up in dichloromethane and successfully washed with saturated sodium bicarbonate and then brine. Drying with $MgSO_4$, evaporation of the solvent and silica gel chromatography (hexane/EtOAc 12/238, 250 mL, then 12/188, 200 mL) gave the product in 51% yield: ^{1}H NMR (500 MHz) δ 1.43 (d, 3H, J = 7.0 Hz), 4.84 (q, 1H, J = 7.0 Hz), 7.33 (m, 10 H); ^{13}C NMR (125 MHz) δ 18.94, 48.72, 83.21, 127.14, 127.34, 128.21, 128.24, 128.50, 128.63, 128.73, 132.54, 137.37, 140.12, 184.85, 193.64.

Generation of Ketenes 14 and 16 from Diazo Precursor (13) and Trapping To Form 15 and 17. In a 50 mL round-bottomed flask were mixed heptane (15 mL), diazo precursor (**13**, 0.10 g, 0.36 mmol), and benzaldehyde (0.10 mL, 0.98 mmol), and the mixture was heated to reflux for 2 h. Solvent was then evaporated with a vacuum pump at room temperature. Crude ^{1}H NMR gave the product ratios, based on integration of the peaks in the vicinity of δ 6.5. Separation of major and minor regiochemical products (**15** and **17**) was accomplished by silica gel chromatography (hexane/EtOAc 95/5). Purification of single diastereomers was accomplished by HPLC (hexane/EtOAc 95/5). Compounds **15** and **17** were distinguished on the basis of gradient HMQC NMR experiments (Supporting Information).

6-(1-Phenylethyl)-2,5-diphenyl-4*H*-1,3-dioxin-4-one (16). Thermodynamic diastereomer: ^{1}H NMR (500 MHz) δ 1.50 (d, 3H, J = 7.0 Hz), 4.09 (q, 1H, J = 7.0 Hz), 6.55 (s, 1H), 7.35 (m, 15 H); ^{13}C NMR (125 MHz) δ 18.63, 40.91, 99.84, 110.16, 126.76, 127.52, 127.70, 128.12, 128.51, 128.84, 130.06, 130.51, 130.96, 132.04, 134.14, 140.49, 162.89, 172.58.

Other diastereomer, δ 6.37 (s, 1H) diagnostic peak, used for diastereomer ratio determination.

5-(1-Phenylethyl)-2,6-diphenyl-4*H*-1,3-dioxin-4-one (17). Thermodynamic diastereomer: ^{1}H NMR (500 MHz) δ 1.87 (d, 3H, J = 7.0 Hz), 4.05 (q, 1H, J = 7.0 Hz), 6.40 (s, 1H), 7.41 (m, 15H); ^{13}C NMR (125 MHz) δ 17.94, 37.08, 99.28, 113.34, 126.26, 126.69, 127.56, 128.17, 128.57, 128.72, 129.12, 130.29, 131.25, 131.74, 133.80, 148.83, 162.37, 164.87.

Other diastereomer, δ 6.58 (s, 1H) diagnostic peak, used for diastereomer ratio determination.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra of **4c**, **5c**, **7a**, **8a**, **9**, **15**, and **17**, an X-ray crystallographic report for **5b**, experimental details for **10e** and **11a**−**f**, and absolute energies and optimized geometries for all calculated structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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