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Effect of Double-Bond Substituents on the Rate of Cyclization of α-Carbomethoxyhex-5-enyl Radicals

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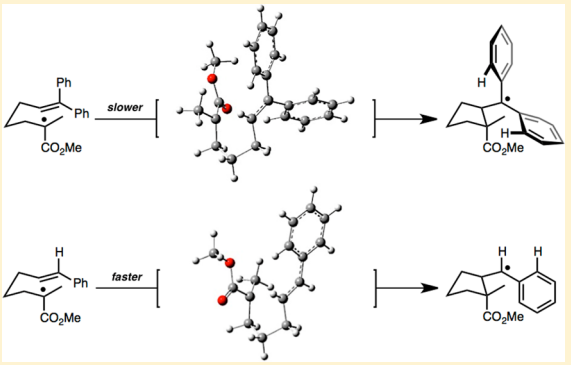
Supporting Information

ABSTRACT: Rate constants have been calculated, and compared with experimental results, for the cyclizations of 1-carbomethoxy-1-methyl-5-hexenyl radicals (**2**) with various substituents on C6. The calculations have been done by DFT at the B3LYP/6-311++G** level of theory. They show considerable interaction between C5 and the radical centers even in the ground state of all of the radicals **2**. Experimentally, the radicals have been generated by H• transfer to the corresponding acrylate esters **1** and the yields of cyclized products compared to the calculated rate constants. (The "cyclized products" include those from cyclohydrogenation, **4**, and those from cycloisomerization, **9**.) Two phenyl substituents on C6 (**2i**), or a phenyl and a methyl substituent (**2g**, **2h**), increase the rate of cyclization, but a *single* phenyl substituent on C6 produces a *greater* increase. The calculations show that the two phenyl substituents are twisted in the transition state for cyclization, while a single phenyl substituent remains flat in that transition state. A methyl substituent on C6 along with a single phenyl causes the phenyl to twist in the transition state and decreases the rate constant for cyclization below that of the H/Ph-substituted **2e**, **2f**.

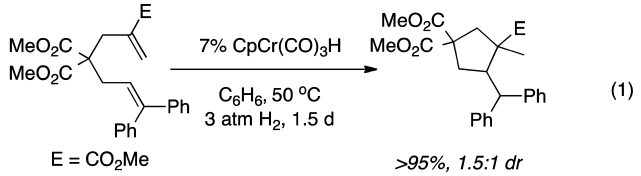


INTRODUCTION

Radical cyclizations have been used extensively in synthesis.[1−3] They are tolerant of functional groups and can be carried out under mild conditions. However, they have generally involved the stoichiometric use of Bu_3SnH and of a heavy element X (often Br or I, sometimes Cl, PhSe, or PhS) that is easily abstracted by $Bu_3Sn^•$ radicals. Such methods are obviously not "atom-economical" and frequently leave toxic levels of tin compounds in the products.

We have explored H• transfer to olefins from transition metals as an alternative method of generating carbon-centered radicals. We have found that $CpCr(CO)_3H$ carries out such transfers and can be regenerated from $CpCr(CO)_3^•$ under modest H_2 pressures (eq 1)[4] and that $Co(dmgBF_2)_2(H_2O)_2$ gives transferable H• from H_2 under similar conditions (eq 2).[5] Both reactions are *catalytic* and far more atom-economical than traditional methods. Effective use of our reaction, however, requires not only a respectable rate of H• transfer from M−H to the substrate **1** (k_{tr}) but also a rate of cyclization k_{cyc} that competes with hydrogenation (k_H[M−H]) and isomerization (k_{iso}[M•]). As Scheme 1 makes apparent, the yield will be a function of k_{cyc} vs (k_H[M − H] + k_{iso}[M•]).

Newcomb and co-workers reported experimental rate constants for the cyclization of the related (ethyl esters) diphenyl-substituted radicals **7a**,**b** to the corresponding radicals **8** (easily monitored by their strong absorbance at 335 nm).[6] (They also reported an experimental rate constant for the cyclization of the ethyl ester of **2a**.[7]) Later Guan, Phillips, and



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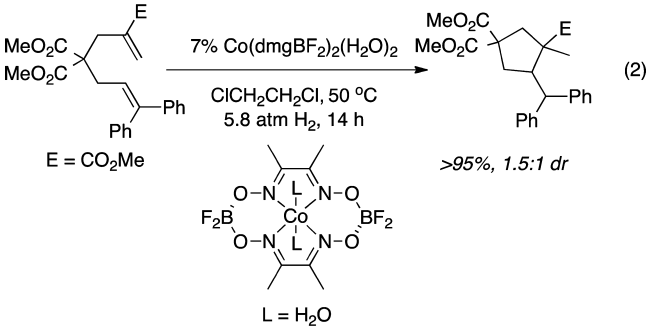

(2)

Yang reported DFT calculations on such radicals (**7**) with a variety of substituents E and R.[8] We therefore began with two phenyl substituents on the **b** double bond of the substrate **1**, giving us two radical-stabilizing phenyl substituents (R^1 = R^2 =

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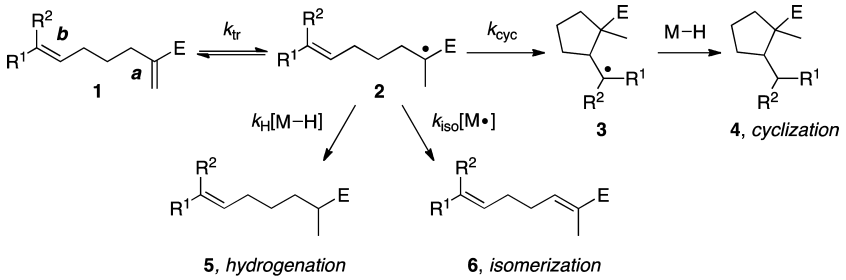
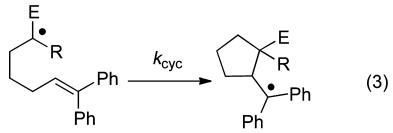
Scheme 1. Pathways Available for an α-Carbomethoxy Radical 2

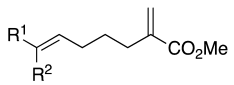


Ph, **2i**) on C6 of the radical **2**. We expected **2i** to cyclize quickly, and it did.[4a] However, mindful of Curran's remark[2d] that "most substituents accelerate 5-exo cyclizations", we have now sought to quantify, both theoretically and experimentally, k_{cyc} for substrates that bear *different* radical-stabilizing substituents on the **b** double bond. We have thus been able to generate radicals **2** that cyclize more rapidly than **2i**.



a, E = CO_2Et, R = H
b, E = CO_2Et, R = CH_3

Houk[9] and others[8a,10] have shown that DFT, in particular with the B3LYP functional, is useful in predicting the rate constants of various radical reactions, including cyclizations and retrocyclizations. We have therefore calculated k_{cyc} for the acrylates below, with different substituents R^1 and R^2 on the **b** double bonds. These calculations, and the corresponding experiments in which these radicals are generated by H• transfer from $CpCr(CO)_3H$, should enable synthetic chemists to design substrates with confidence.



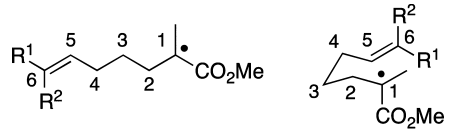
1a R^1 = H, R^2 = H
1b R^1 = Me, R^2 = H
1c R^1 = H, R^2 = Me
1d R^1 =Me, R^2 = Me
1e R^1 = Ph, R^2 = H
1f R^1 = H, R^2 = Ph
1g R^1 = Ph, R^2 = Me
1h R^1 = Me, R^2 = Ph
1i R^1 = Ph, R^2 = Ph

COMPUTATIONAL DETAILS

The calculations were performed with the Gaussian03[11] and 09[12] suites of programs. There is precedent for the use of the 6-31G*, 6-31+G*, and 6-31+G** basis sets in DFT calculations on radical cyclizations[8a,10c,e] and retrocyclizations.[9b] Coote and co-workers have questioned the ability of DFT methods to provide accurate energetics for radical reactions,[13] while Fleurat−Lessard and co-workers have shown that B3LYP gives qualitatively inaccurate results for two *nonradical* organic reactions.[14] However, Fu, Liu, and co-workers, despite admitting that "the UB3LYP method cannot accurately predict the absolute free energy barriers", have argued that "it can reliably predict the relative free energy barriers".[10e] We have tested two functionals (BP86 and B3LYP) with two basis sets (6-31G* and 6-311++G**) in the calculation of the rate constants for our cyclizations. A combination of B3LYP and 6-311++G** gave the most reasonable results (relative rate constants like those implied by our yields of cyclized products), presumably because α-carbomethoxy radicals only contain light atoms and their HOMO−LUMO energy gap is large. For substrates containing conjugated double bonds, CASSCF (MCSCF) calculations with various numbers of occupied and unoccupied orbitals taken into their "active space" were carried out to check for CI interactions and for charge transfer from occupied to empty orbitals; these calculations did not show any significant charge transfer.

RESULTS AND DISCUSSION

Substituted hexenyl radicals **2a−i** can adopt an "open" or a "chair" conformation.[15]



B3LYP/6-311++G** DFT calculations imply that these radicals are unstrained when open, with C−C−C angles (around the saturated carbons C2, C3, and C4) equal or very close to tetrahedral (109.5°). Such calculations do suggest considerable strain in their chair forms, with the C−C−C angles increased to around 115°. However, at room temperature the calculated energies of the open forms of these radicals are approximately equal to those of their chair forms. Similar calculations on the hydrogenation product **5** show its chair form to be 7 kcal/mol higher in energy than its open form, implying that the chair forms of the radicals **2** have strain energies around 7 kcal/mol. To understand how the electronic stabilization of these chair forms of **2** offsets their strain energies we must consider their molecular orbitals (Figure 1).

Figure 1 shows the surfaces of the HOMO, the highest fully occupied orbital, for the chair forms of the radical **2a** (with no substituents on C6) and the radical **2d** (with two methyl substituents on C6). The surfaces of HOMO for **2b,c** and **2e−i** have similar features. It is apparent in Figure 1 that there is a strong bonding interaction between C1 and C5 (the carbons to be bonded by cyclization), although there is no formal σ bond between them and the distance between them is large. This interaction stabilizes the chair structures but introduces strain (and the 115° C−C−C angles).

The calculated distance in the chair between C1 and C5 is equal to 3.23 Å for radical **2a** and 3.20 Å for radical **2d**, twice the length of a normal carbon−carbon single bond. A similar interaction, with an even shorter distance (3.11 Å), is implied by DFT calculations on the related primary radical **7**.[8a] The result is some pyramidalization. For example, in the initial chair of **2i** the C5−C1−CH_3 angle increases to 95.65°, while the C5−C1−CO_2Me angle increases to 101.22°; more pyramidalization is observed at C5, where the C1−C5−C6 angle becomes essentially tetrahedral (110.79°).

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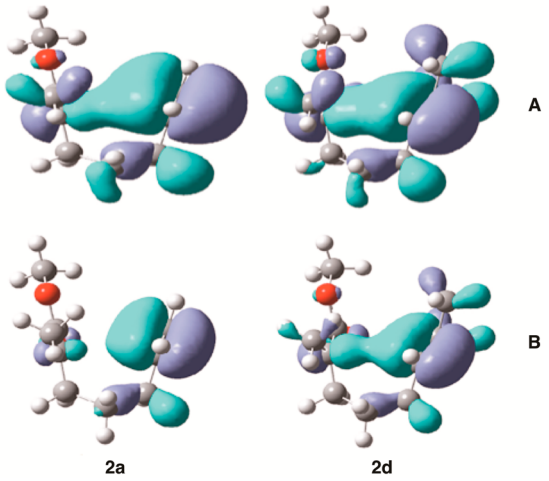


Figure 1. HOMO surfaces calculated for **2a** (the *Z*, *β* rotamer) and **2d** (the *Z*, *β* rotamer). The lower drawings (B) have an electron density isovalue limit of 0.02 au (normal); the upper drawings (A) have an electron density isovalue limit of 0.04 au.

Resonance leads to restricted rotation about the C1−CO_2Me bond in the radicals **2**, so they exist as *Z*-**2** (with resonance structure *Z*-**2**′) and *E*-**2** (with resonance structure *E*-**2**′). The rates at which such conformers interconvert were studied some time ago by Fischer and co-workers.[16] More recently, Newcomb and co-workers considered the relationship between such conformational interconversions and the rates at which carboalkoxy-substituted radicals cyclize[6a] and concluded that interconversion is faster than cyclization for tertiary radicals like **2**. Our DFT calculations show a barrier to *E*/*Z* interconversion <5 kcal/mol for **2i** (see Figure 2 below) and imply a similar barrier for other radicals **2**.

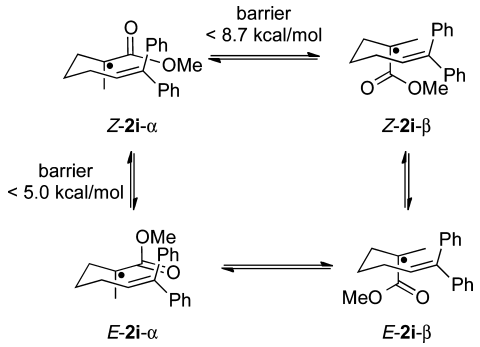


Figure 2. Rotamers of radical **2i** and barriers to their interconversion (calculated with Gaussian 09, B3LYP, and 6-311++G**). The C1−C5 distance must increase temporarily during rotation about either the C1−CO_2Me bond or the C1−C2 bond.

The barrier to cyclization for **2i** is much larger, 10.1 kcal/mol (see Table 2), suggesting that *E*/*Z* interconversion will be facile during cyclization of all the radicals **2a**−**i**. For simplicity, given that our interest is in *relative* cyclization rates, we have calculated k_{cyc} values for the *Z* conformer of each radical **2**.

There is, however, an additional conformational issue. A radical like **2** can exist as either of two rotamers, **2***α* and **2***β*, about the bond between C1 and C2. (These rotamers lead to alternate diastereomers **3***α* and **3***β* upon cyclization.) For **2i**, we have calculated (see Figure 2) the barriers to rotation about the

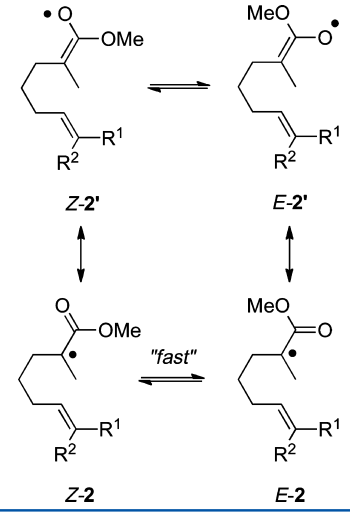
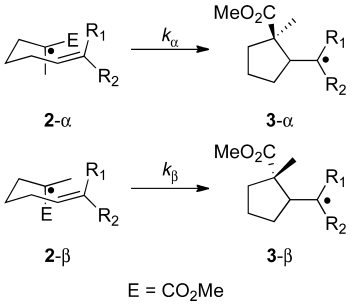


Table 2. Calculated Rate Constants (Gaussian 03, B3LYP, and 6-311++G) for Cyclization of Each Conformation (*α* and *β*) of *α*-Carbomethoxy Radicals (*Z*)-2 at 298 K**

compd	k_α, s^{-1} ($\Delta G^\ddagger$, kcal/mol)	k_β, s^{-1} ($\Delta G^\ddagger$, kcal/mol)	$K = [\alpha]/[\beta]$
Z-**2a**	9.35×10^2 (13.40)	2.24×10^2 (14.25)	0.30
Z-**2b**	4.39×10^3 (12.48)	5.42×10^2 (13.72)	0.14
Z-**2c**	1.61×10^3 (13.08)	1.90×10^2 (14.35)	0.088
Z-**2d**	2.33×10^3 (12.86)	9.80×10^2 (13.37)	0.18
Z-**2e**	1.18×10^6 (9.07)	2.60×10^4 (11.43)	0.18
Z-**2f**	8.84×10^4 (10.71)	3.52×10^4 (11.25)	0.95
Z-**2g**	6.56×10^4 (10.88)	3.39×10^3 (12.64)	0.25
Z-**2h**	4.05×10^3 (12.53)	2.80×10^2 (14.12)	0.47
Z-**2i**	7.81×10^3 (12.14)	2.71×10^{4a} (11.41)	0.26[a]

[a]See ref 15.

C−CO_2Me and C1−C2 bonds. The barrier to rotation about C1−C2 is larger.



For **2a**−**i** we took the *Z* conformers and calculated the energies of their *α* and *β* orientations about the C1−C2 bond, which gave us the relative populations in Table 1. The *β* orientation is favored in all cases.

From our calculated barriers for **2i** we believe that the interconversion of the *α* and *β* orientations is always fast relative to cyclization (for which the barrier is over 10 kcal/mol). This situation, with the free energy surface illustrated in Figure 3, thus qualifies for Curtin−Hammett kinetics.[18] Separate transition states, and separate k_{cyc}, have been calculated (Gaussian 03, B3LYP functional, 6-311++G** basis set) for the *α* and *β* orientations of each compound **2**. The results are shown in Table 2, along with the equilibrium constants $K = \alpha/\beta$ implied by the conformer populations in Table 1.

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Table 1. Calculated Populations (Gaussian 03, B3LYP, and 6-311++G) of the α and β Conformers for Z-2 at 298 K**

	R^1	R^2	α	β
2a	H	H	23.0	77.0
2b	Me	H	11.9	88.1
2c	H	Me	8.1	91.9
2d	Me	Me	15.5	84.5
2e	Ph	H	15.5	84.5
2f	H	Ph	48.6	51.4
2g	Ph	Me	19.8	80.2
2h	Me	Ph	32.1	67.9
2i[a]	Ph	Ph	20.9	79.1

[a]See ref 17.

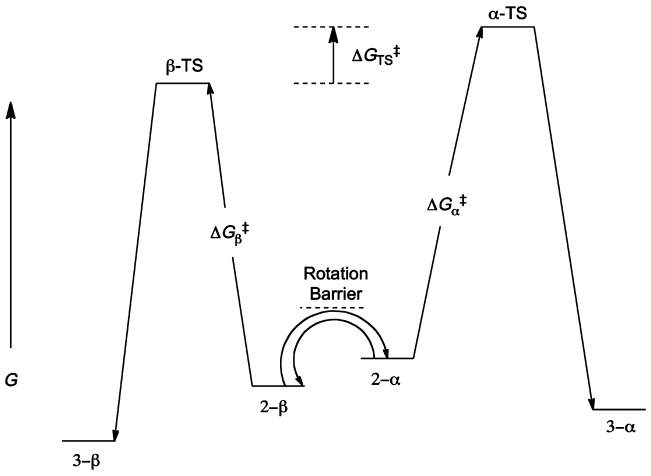

Figure 3. Free energy surface for a typical radical **2** with rapid interconversion of its α and β rotamers.

The values of k_{cyc} for **2a–i** in Table 2 reflect the ability of the substituents R^1 and R^2 to stabilize the cyclized radicals **3a–i**. Replacing the hydrogens on C6 in **2a** by carbon substituents increases the interaction between C1 and C5 in the HOMO, as can be seen in Figure 1 (above). The HOMO surfaces for **2a** and **2c** are shown with the standard 0.02 au electron density isovalue limit in the lower section, **B**, and then with an isovalue limit of 0.04 au in the upper section, **A**. For **2a** there is no interaction between C1 and C5 at isovalue limits equal to or greater than 0.04 (section **A**), while for **2b–i** there is interaction between C1 and C5 in both sections.

Figure 4 shows the π energy levels of radicals **2** with symmetric substituents on the **b** double bond (**2a**, $R^1 = R^2 = H$; **2d**, $R^1 = R^2 = CH_3$; and **2i**, $R^1 = R^2 = Ph$). The radical center in **2** is sufficiently electrophilic that the most important interaction of its SOMO during its cyclization is with its HOMO. As radical-stabilizing substituents are added to C6, the HOMO rises, the HOMO–LUMO and HOMO–SOMO energy differences decrease, the barrier to cyclization decreases, and k_{cyc} increases. If we compare **2a** with **2d** in Figure 4, we can see that methyl substituents ought to produce a slight increase in the calculated k_{cyc}, and we see a slight increase in Table 2. If we compare **2a** with **2i** in Figure 4, we can see that aromatic substituents ought to produce a much larger increase in the calculated k_{cyc}, and we see a large increase in Table 2.

The effect of C6 substituents on the cyclization of primary hex-5-enyl radicals has been extensively investigated. Most substituents have little effect on k_{cyc}: two methyl substituents increase it by a factor of only 2.4,[19] while two fluorine substituents decrease it slightly.[20] On the other hand, two phenyl substituents increase it by a factor of over 200.[21]

We expected similar substituent effects on the cyclization of our tertiary α-carbomethoxy radicals **2**; we expected mono-

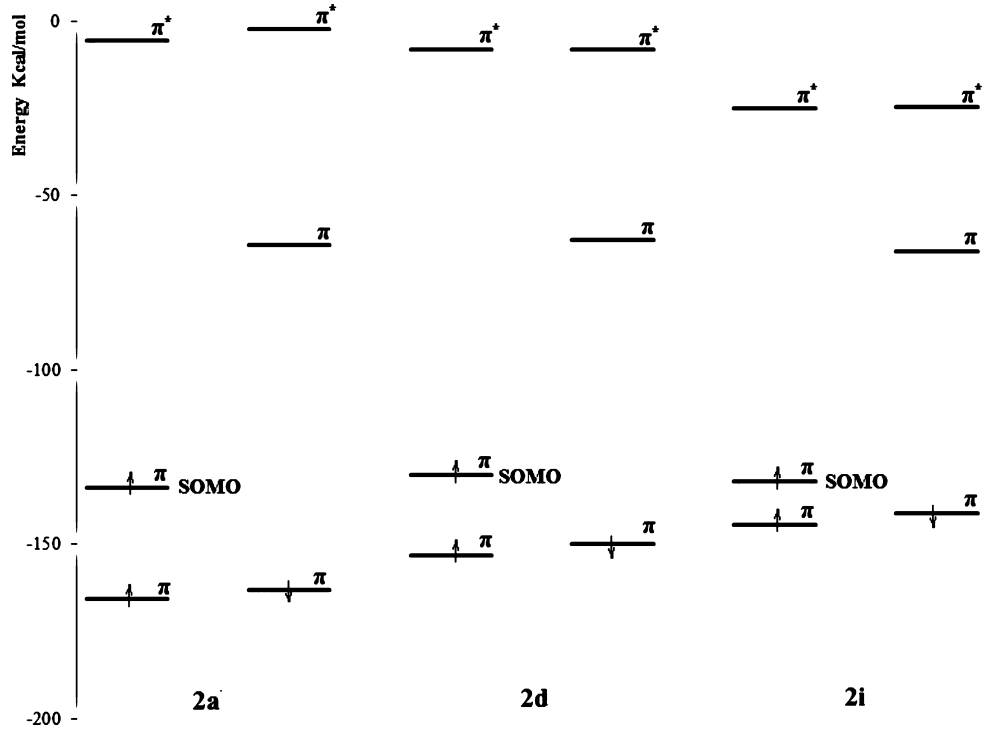

Figure 4. Calculated HOMO–LUMO π energy levels for the chair forms of variously substituted radicals **2**. The first two columns are those of **2** with no substituents on the b double bond (**2a**), the middle two columns are those of **2** with two methyl substituents (**2d**), and the last two columns on the right are those of **2** with two phenyl substituents (**2i**).

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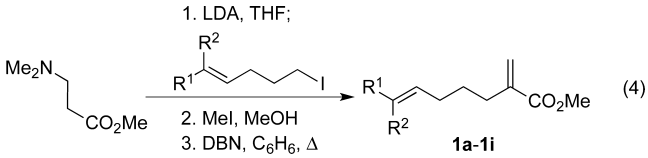
substitution on C6 to produce an effect similar to (but smaller than) the effect of disubstitution. The calculations in Table 2 corroborate the first prediction but not the second. A *single* phenyl substituent on C6 increases the calculated k_{cyc} by over 10^3 (compare k_{cyc} for **2e** with that for **2a**), but the addition of a methyl substituent *decreases* the calculated k_{cyc} somewhat (compare **2g** with **2e**, **2h** with **2f**), and the addition of a *second* phenyl substituent decreases the calculated k_{cyc} by a factor of around 40 (compare k_{cyc} for **2i** with those for **2e**, **2f**).

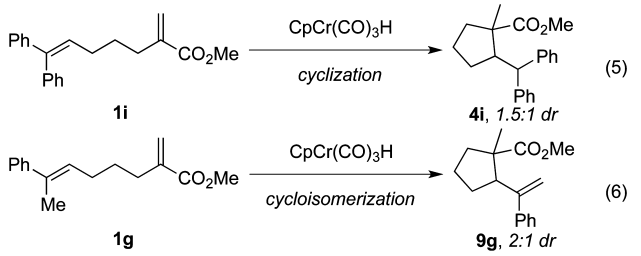
In order to test these predictions experimentally we have examined the product distributions from the catalytic cyclizations of **1a,e−g,i**.

Cyclization of α-Carbomethoxy Radicals 2 with $Cp(CO)_3CrH$. We prepared the diene substrates **1a−i** by the method we had previously used for other substrates (eq 4).[4a]



(4)

We treated these dienes with a stoichiometric amount of $CpCr(CO)_3H$ under standard conditions (benzene-d_6, 323 K) and quantified the products by ^1H NMR. From substrates without methyl substituents on C6 (**1a,e,f,i**) we obtained cyclization products like **4i** (eq 5), presumably arising from



transfer of a second H$^\bullet$ to the cyclized radical **3i**. However, from substrates bearing methyl groups at C6 (**1b−d** or **1g,h**) we obtained unsaturated products like **9g** (eq 6), presumably the result of H$^\bullet$ abstraction from the methyl of the cyclized radical **3g** (and of the congestion around the radical center in **3g**). The conversion of **1g** to **9g** involves neither the gain nor the loss of hydrogen atoms and is thus a *cycloisomerization*.[22]

A cycloisomerization, for example, that of **1g** to **9g** (41%), does not consume $CpCr(CO)_3H$. Only the hydrogenation of **1g** (to **5**, 49%) affects the $[CpCr(CO)_3H]/[CpCr(CO)_3^\bullet]$ ratio; approximately 1 equiv of $CpCr(CO)_3H$ remains at the end of the reaction if we begin with 2 equiv.

Table 3 gives the yields for cyclization (to **4** or **9**), hydrogenation (to **5**), and isomerization (to **6**).

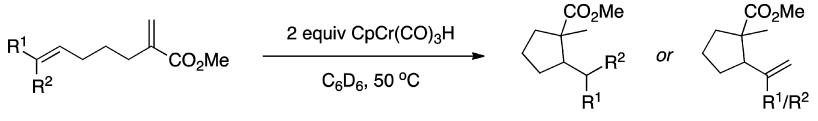
The rate constants for the hydrogenation (k_H) of **2a−i** should be little affected by substituents on C6. For a particular substrate, with a given $[CpCr(CO)_3H]$, the relative rates of cyclization and hydrogenation will be determined by k_{cyc}, as Scheme 1 implies (eq 7). Indeed, the cyclization yields for the various substrates in Table 3 are approximately what we expect from the calculated k_{cyc} in Table 2. For example, the yield of **4** or **9** increases (and the yield of the hydrogenation product **5** decreases) as the calculated k_{cyc} increases, in the order **1a** < **1b** < **1d**. Of course, $[CpCr(CO)_3H]$ decreases in the course of a stoichiometric cyclization.

$$\frac{k_{cyc}}{k_{hyd}[CpCr(CO)_3H]} = \frac{\text{rate of formation of the cyclization product (4 or 9)}}{\text{rate of formation of the hydrogenation product 5}} \quad (7)$$

In the course of a *catalytic* reaction $[CpCr(CO)_3H]$ will remain approximately constant and lower than during the stoichiometric reactions in Table 3. (Although the hydrogen in a catalytic reaction keeps most of the Cr in the form of $CpCr(CO)_3H$, only 7 mol % of Cr is present.) We thus expect higher yields of the cyclization products **4**/**9** under catalytic conditions, and these are apparent in Table 4. The relative yields in Table 4 from the various substrates show a pattern like that in Table 3, approximately what we would expect from the calculated rate constants in Table 2.

Why Do the Monophenyl Radicals (2e,f) Cyclize More Quickly Than the Ph_2 (2i) and the Ph(Me) (2g, 2h) Radicals? In general, the addition of radicals to RCH═CPh_2 is faster than the addition of the same radicals to RCH═CHPh, although the effect is smaller than would be expected if the substituent effects were additive. For the cyclization of **10a**, k_{cyc} at 20 °C is 1.9×10^5 s^{-1}, whereas for **10b** it is 3.2×10^5 s^{-1}.[23] For the cyclization of **11a**, k_{cyc} at 20 °C is 5.4×10^6 s^{-1}, whereas for **11b** it is 1.7×10^7 s^{-1}.[24] For the addition of ambiphilic/electrophilic radicals like $(CH_3)_2(NC)C^\bullet$ (which resembles **2**

Table 3. NMR Yields of the Products from Treatment of 1a,b,1d−g,i with Stoichiometric $CpCr(CO)_3H$



1 4 9

	R^1	R^2	cyclization of **4**[a] (%)	cycloisomerization **9**[a] (%)	hydrogenation **5** (%)	isomerization **6** (%)
1a	H	H	5	0	76	19
1b	Me	H	0	16	56	28
1d	Me	Me	0	18	51	31
1e	Ph	H	52	0	37	11
1f	H	Ph	53	0	38	9
1g	Ph	Me	0	41	49	10
1i	Ph	Ph	27	0	55	18

[a]Combined yields of both diastereomers.

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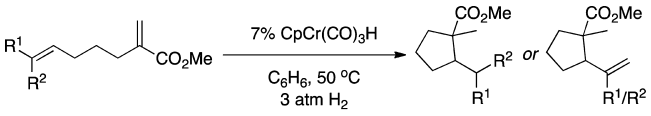
Table 4. Isolated Yields of Cyclization Products from the Treatment of 1a,b,d−g,i with Catalytic Amounts of $CpCr(CO)_3H$ under H_2

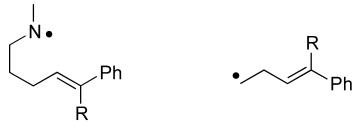


1 **4** **9**

	R^1	R^2	cyclization **4**[a] (%)	cycloisomerization **9**[a] (%)
1a	H	H	10	0
1b	Me	H	0	42
1d	Me	Me	0	45
1e	Ph	H	97	0
1f	H	Ph	92	0
1g	Ph	Me	0	74
1i	Ph	Ph	71	0

[a]Combined yields of both diastereomers.

electronically) to CH_2=CHPh the rate constant is 2410 M^{-1} s^{-1} at 315 K, whereas for the same addition to CH_2=CPh_2 the rate constant is 7010 M^{-1} s^{-1}.[10a]

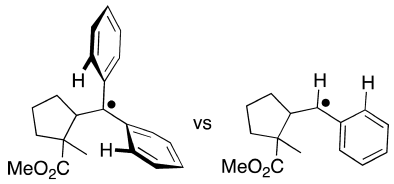


10a: R = H
10b: R = Ph

11a: R = H
11b: R = Ph

However, the yield of the cyclized product **4** in Tables 3 and 4 is *higher* with one Ph (substrates **1e,f**) than with two (substrate **1i**), in agreement with the calculated k values in Table 2 for **2e** and **2f** vs **2i**. The higher yields suggest faster k_{cyc}, consistent with the implications of our DFT calculations.

The lack of substituent additivity in all these reactions presumably arises from the gearing of two phenyls on the same carbon. For example, neither phenyl is coplanar with the radical center in the cyclized radical **3i**, whereas planarity and stabilization are easily achieved by the single phenyl substituent in **3e** and **3f**.



3i **3e** or **3f**

The interaction of two phenyl rings attached to the same sp^2 carbon is illustrated by the X-ray structures of Ph_2CO and Ph_2C=CH_2 and their derivatives. Benzophenone (which exists in two different crystalline forms) shows an average twist angle of 33°.[25] (We define the "twist angle" as the angle between the normal to the purple phenyl ring plane and the normal to the pink "carbonyl plane" in Figure 5.) Various para-substituted derivatives of 1,1-diphenylethylene show twist angles averaging 39°.[26] The diphenylethylene derivatives have larger twist angles because of repulsion between the ethylenic hydrogens and the ortho hydrogens on the phenyl rings. These precedents suggest a considerable twist of the two phenyl substituents in our substrate **1i**, which our DFT calculations confirm.

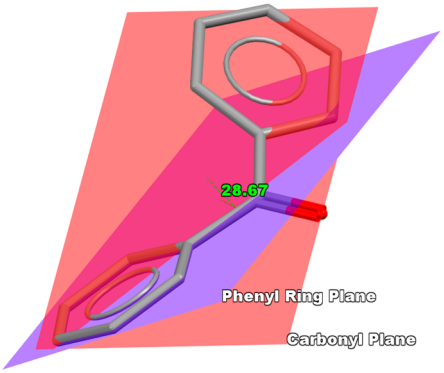
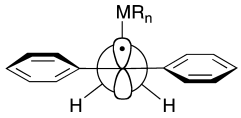


Figure 5. Definition of "twist angle" for one of the phenyl rings in benzophenone.

Such twisting has also been found by EPR for two phenyl substituents on a *radical center*, i.e., for 1,1-diphenylethyl radicals like the one shown (M = a variety of group 4 elements).[27] (At low temperature, the H's pictured are inequivalent.) A twist angle of 22° was obtained for benzophenone ketyl by early ab initio calculations.[28]



The twisting of two phenyl substituents on a radical center is responsible for the decrease between the effect of the first phenyl substituent and the effect of the second on the C−H bond strengths below.[29] (Halgren, Roberts, Newcomb and co-workers have also noted the differential effect of Ph substitution on C−H bond strengths.[24])

$$CH_3{-}H \rightleftharpoons CH_3^{\bullet} + H \quad (105.0\ \text{kcal/mol})$$

$$PhCH_2{-}H \rightleftharpoons PhCH_2^{\bullet} + H \quad (88.5\ \text{kcal/mol})$$

$$Ph_2CH{-}H \rightleftharpoons Ph_2CH^{\bullet} + H \quad (84.5\ \text{kcal/mol})$$

With our radicals **2** we expect twisting to decrease as cyclization begins and the C5−C6 bond lengthens; it should, however, remain substantial. Our calculations predict a large twist angle in **2i** itself (an average of 51.9° for the two phenyls), which decreases as cyclization begins (and C5−C6 lengthens) but remains substantial in the transition state in Figure 6 (an average of 41.3°) and in the cyclized radical **3i** (an average of 36.1°).

Similar but smaller twists are found in the transition state for the cyclization of the 6,6-diphenyl carbethoxy-substituted hexenyl radical **7a**, the subject of DFT calculations by Phillips et al.[8a] From their results, we compute an average twist angle for the two phenyls of 46.7° in the initial radical, an average angle of 40.4° in the transition state, and an average angle of 31.9° in the cyclized radical **8a**. (They considered only cases with two phenyl substituents on C6.)

Why is the Ph_2/Ph(H) effect so large in our cyclizations that Ph(H) (**2e,f**) is now *faster* than Ph_2 (**2i**) in the radicals **2**? The Newcomb aminyl radicals **10** resemble secondary carbon radicals, the Newcomb radicals **11** are primary, and the radicals in the Fischer−Radom table are secondary and primary. The radicals **2** are *tertiary* and thus more sensitive (when forming the C1−C5 bond) to repulsion by twisted phenyl substituents on C6. The C1−C5 distance in the transition state for the

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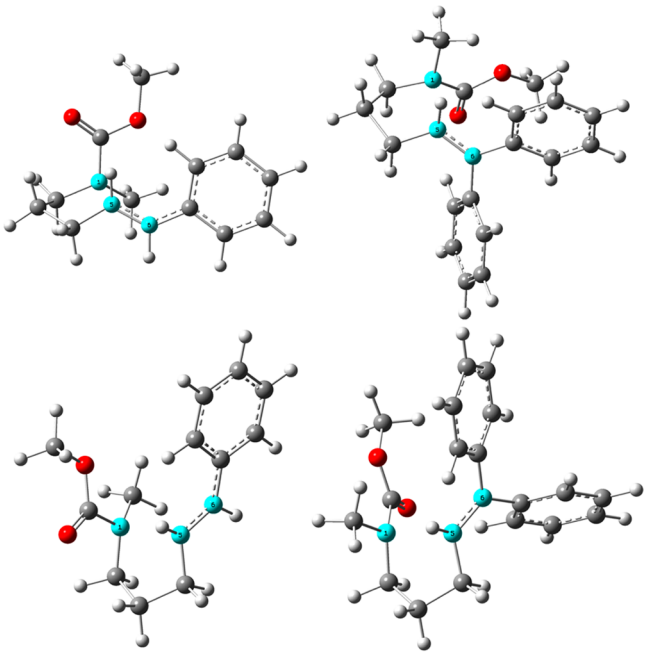

Figure 6. Two views of the transition state for cyclization by radicals **2e** and **2i**; oxygen atoms are red, C1, C5, and C6 are blue. In the transition state for **2e** the C1−C5 distance is 2.22 Å and the C5−C6 distance is 1.39 Å; in that for **2i** C1−C5 is 2.22 Å and C5−C6 is 1.40 Å.

cyclization of **2** is *0.10 Å longer* for the Ph_2 case (**2i**) than for the H_2 (**2a**) and Me_2 (**2d**) cases. Note that the Ph twist is smaller (previous paragraph) in the transition state for the cyclization of the Newcomb/Phillips/Yang secondary hexenyl radical **7a** than for the cyclization of the tertiary radical **2i**.

Twists are also found when C6 bears a methyl along with a phenyl substituent. In the transition state for the cyclization of *Z*-**2g** the phenyl is twisted by an average (over the α and β rotamers) of 34°. In the transition state for the cyclization of *Z*-**2h** the phenyl is twisted considerably more, with the angle averaging 61° between the α and β rotamers — presumably because the carbon chain cis to the phenyl can contribute to its twist.

A *single* phenyl substituent, however, is flat in the substrates **1e** (*E*) and **1f** (*Z*) and remains so as **2e** and **2f** cyclize. It makes cyclization more exothermic (the cyclization of the Ph_1-substituted *Z*-**2e**-α to *Z*-**3e**-α is 8.3 kcal/mol downhill, whereas the cyclization of the Ph_2-substituted *Z*-**2i**-α to *Z*-**3i**-α is only 5.1 kcal/mol downhill (both calculated with Gaussian 09, B3LYP, and 6-311++G**). It stabilizes the transition state substantially, and increases the rate constant for cyclization. A similar acceleration is to be expected for any single aryl substituent.

EXPERIMENTAL SECTION

All reactions were carried out under an atmosphere of argon in glassware that had been flame-dried under vacuum and backfilled with argon. High-pressure reactions were carried out in a Fisher−Porter bottle equipped with a pressure gauge, gas inlet, and pressure release valve. Hexamethylphosphoramide (HMPA) was distilled from CaH_2. Deuterated benzene (C_6D_6) was purified by vacuum transfer from CaH_2. THF and benzene (C_6H_6) were distilled from sodium−benzophenone ketyl. Et_2O and CH_2Cl_2 were dried by filtration through alumina. $CpCr(CO)_3H$ was stored and manipulated in an inert argon atmosphere glovebox (O_2 <1 ppm). Reaction mixtures involving $CpCr(CO)_3H$ were all prepared in the glovebox. ^1H NMR and ^{13}C NMR spectra were recorded at ambient temperature (298 K) at 500, 400, or 300 MHz and 125, 100, or 75 MHz, respectively. High-resolution mass spectra were acquired (after ionization by EI) by peak matching on a double-focusing magnetic sector instrument.

General Method for the Synthesis of Diene Substrates 1a,b,d−g,i. The synthesis of substrates followed a known procedure (eq 5).[4a] To a solution of LDA in THF was added methyl-3-(dimethylamino)propionate (1.1 mmol) dropwise at −78 °C. The mixture was stirred for 0.5 h before the addition of a solution of alkyl halide (1 mmol) in THF and freshly distilled HMPA (1 mmol). The mixture was then warmed to room temperature, stirred for 48 h, quenched with saturated NH_4Cl, and extracted with Et_2O. The extract was dried over $MgSO_4$, filtered, concentrated, and taken up in 5 mL MeOH, and excess MeI (13 mmol) was added; the flask was wrapped in foil and the mixture stirred overnight (16−18 h). After concentration in vacuo, the residue was washed with Et_2O three times; removal of the remaining solvent afforded the ammonium iodide salt as a bright yellow solid. Benzene (20 mL) was then added, along with excess DBN (2 mL), and the bright yellow mixture was stirred at reflux for 4 h. After being cooled to room temperature, the solution was washed with 1 N HCl, and Et_2O was added. The collected organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (10% EtOAc/hexanes) on silica gel afforded the desired 1,6-diene.

*Methyl 2-Methylenehept-6-enoate (**1a**).* Compound **1a** was prepared in 28% yield (43 mg) over three steps from 1 mmol of 5-iodopent-1-ene as a bright yellow oil. Spectroscopic data matched the literature.[30]

*Methyl 2-Methyleneoct-6-enoate (**1b**).* Compound **1b** was prepared in 55% yield (91 mg) over three steps from 1 mmol of (*E*)-6-iodohex-2-ene[31] as a golden yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 6.13 (s, 1 H), 5.52 (s, 1 H), 5.43 (d, J = 3.9 Hz, 2 H), 3.75 (s, 3 H), 2.30 (t, J = 7.6 Hz, 2H), 2.06−1.93 (m, 2 H), 1.65 (s, 3 H), 1.52 (qn, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 140.7, 130.9, 125.3, 124.6, 51.8, 32.1, 31.4, 28.3, 17.9; IR (neat) 2932, 2859, 1725, 1632 cm^{-1}; HRMS (FAB^+) calcd for $C_{10}H_{16}O_2$ $[M]^+$ 168.1150, found 168.1149.

*Methyl 7-Methyl-2-methyleneoct-6-enoate (**1d**).* Compound **1d** was prepared in 65% yield (59 mg) over three steps from 0.5 mmol of 6-iodo-2-methylhex-2-ene[32] as a golden yellow oil: ^1H NMR (500 MHz, $CDCl_3$) δ 6.15 (s, 1H), 5.55 (s, 1H), 5.14 (t, J = 7.0 Hz, 1H), 3.77 (s, 3H), 2.32 (t, 2H), 2.03 (q, J = 7.2 Hz, 2H), 1.71 (s, 3H), 1.62 (s, 3H), 1.57−1.48 (qn, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 140.8, 131.8, 124.5, 124.2, 64.5, 51.7, 31.5, 28.6, 27.6, 25.7; IR (neat) 2927, 2858, 1725, 1630 cm^{-1}; HRMS (FAB^+) calcd for $C_{11}H_{18}O_2$ $[M]^+$ 182.1307, found 182.1315.

*(E)-Methyl 2-Methylene-7-phenylhept-6-enoate (**1e**).* Compound **1e** was prepared in 39% yield (90 mg) over three steps from 1 mmol of (*E*)-(5-iodopent-1-en-1-yl)benzene[33] as a cloudy pale yellow oil: ^1H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, J = 7.2 Hz, 2H), 7.28 (t, J = 7.3 Hz, 2H), 7.18 (t, J = 6.8 Hz, 1H), 6.39 (d, J = 15.8 Hz, 1H), 6.27−6.17 (m, 1H), 6.16 (s, 1H), 5.55 (s, 1H), 3.74 (s, 3H), 2.36 (t, J = 7.3 Hz, 2H), 2.24 (q, J = 13.6, 6.6 Hz, 2H), 1.66 (qn, J = 14.6, 7.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.7, 140.4, 137.8, 130.34, 130.31, 128.5, 126.9, 126.0, 124.9, 51.8, 32.5, 31.5, 28.1; IR (neat) 3082, 3060, 3026, 2962, 2853, 1723, 1631, 1495 cm^{-1}; HRMS (FAB^+) calcd for $C_{15}H_{18}O_2$ $[M]^+$ 230.1307, found 230.1314.

*(Z)-Methyl 2-Methylene-7-phenylhept-6-enoate (**1f**).* Compound **1f** was prepared in 35% yield (122 mg) over three steps from 1.5 mmol of (*Z*)-(5-iodopent-1-en-1-yl)benzene[34] as a golden yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.29 (m, 2H), 7.26 (dd, J = 7.7, 1.4 Hz, 2H), 7.24−7.19 (m, 1H), 6.43 (dt, J = 11.8, 1.9 Hz, 1H), 6.11 (d, J = 1.5 Hz, 1H), 5.66 (dt, J = 11.7, 7.3 Hz, 1H), 5.48 (q, J = 1.4 Hz, 1H), 3.74 (s, 3H), 2.41−2.29 (m, 4H), 1.69−1.57 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.7, 140.3, 137.6, 132.3, 129.3, 128.7, 128.1, 126.5, 124.9, 51.8, 31.5, 28.6, 28.0; IR (neat) 3082, 3060, 3026, 2962, 2853, 1723, 1631, 1495 cm^{-1}. HRMS (FAB^+) calcd for $C_{15}H_{18}O_2$ $[M]^+$ 230.1307, found 230.1314.

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*(E)-Methyl 2-Methylene-7-phenyloct-6-enoate (**1g**).* Compound **1g** was prepared in 36% yield (89 mg) over three steps from 1 mmol of (*E*)-(6-iodohex-2-en-2-yl)benzene as a bright yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41−7.27 (m, 4H), 7.25−7.17 (m, 1H), 6.16−6.15 (m, 1H), 5.77 (td, J = 7.2, 1.4 Hz, 1H), 5.55 (q, J = 1.4 Hz, 1H), 3.76 (s, 3H), 2.38 (t, J = 7.5 Hz, 2H), 2.23 (q, J = 7.3 Hz, 2H), 2.03 (dd, J = 2.1, 0.8 Hz, 3H), 1.65 (qn, J = 7.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 143.9, 140.5, 135.1, 128.2, 127.9, 126.5, 125.6, 124.8, 51.8, 31.6, 28.3, 28.3, 15.9; IR (neat) 2919, 2853, 1722, 1630, 1494 cm^{-1}; HRMS (FAB$^+$) calcd for $C_{16}H_{20}O_2$ [M]$^+$ 244.1463, found 244.1470.

General Method for Stoichiometric Cyclizations. To a J. Young tube were added $CpCr(CO)_3H$ (50 mg, 0.13 mmol) and a C_6D_6 (0.6 mL) solution of the substrate (0.06 mmol). The bright green reaction mixture was then kept overnight (16−18 h) at 50 °C before product yields were determined by ^{1}H NMR.

General Method for Catalytic Cyclizations. To a Fisher−Porter pressure apparatus were added $CpCr(CO)_3H$ and a C_6H_6 solution of the substrate (0.1 M) before the apparatus was thoroughly purged with H_2 and pressurized to 3 atm. The bright green reaction mixture was kept for 16 h at 50 °C and the reaction examined by ^{1}H NMR before being cooled to room temperature and quenched with O_2. The resulting dark green reaction mixture was filtered, concentrated, and purified by flash chromatography on silica gel (0−10% EtOAc/hexanes), affording the cyclized product (always a clear oil) as a mixture of two inseparable diastereomers.

The structures of the isolated major and minor diastereomers of **4g** were confirmed by 2D NMR as previously reported by Pulling, Smith, and Norton.[4a] The stereochemical assignments of cyclization products **4b−f** are based on predictions from the Beckwith[15b]−Houk[15c] model.

*Methyl 1,2-Dimethylcyclopentanecarboxylate (**4a**).* Compound **4a** was isolated as a mixture of diastereomers (61:39) in 10% yield (5 mg) from 0.3 mmol **1a**. The spectroscopic data matched those in the literature.[35]

*Methyl 1-Methyl-2-vinylcyclopentanecarboxylate (**9b** or **9c**).* The compound was isolated as a mixture of diastereomers (57:43) in 42% yield (21 mg) from 0.3 mmol of **1b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ major: 5.77 (p, J = 10 Hz, 1H), 5.44 (m, 1H), 5.02 (dd, 1H), 3.68 (s, 3 H), 2.88 (q, J = 10 Hz, 1H), 2.2−2.10 (m, 2H), 1.89−1.49 (m, 4H), 1.07 (s, 3 H); minor: 5.69 (p, J = 10 Hz, 1H), 5.44 (m, 1H), 4.99 (dd, 1H), 3.62 (s, 3 H), 2.51 (q, J = 10 Hz, 1H), 2.2−2.10 (m, 2H), 1.89−1.49 (m, 4H), 1.25 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ *major*: 177.9, 137.5, 117.6, 52.5, 46.4, 44.3, 36.2, 31.1, 23.0, 20.3; HRMS (FAB$^+$) calcd for $C_{10}H_{16}O_2$ [M]$^+$ 168.1150, found 168.1155.

*Methyl 1-Methyl-2-(prop-1-en-2-yl)cyclopentanecarboxylate (**9d**).* Compound **9d** was isolated as a mixture of diastereomers (59:41) in 45% yield (33 mg) from 0.4 mmol of **1d**: ^{1}H NMR (500 MHz, $CDCl_3$) δ major: 4.86 (s, 1 H), 4.70 (s, 1 H), 4.11, (t, J = 6.5 Hz, 1 H), 3.72 (s, 3 H), 2.35 (q, J = 10 Hz, 1H) 1.65 (d, J = 5 Hz, 3H); minor: 4.80 (s, 1 H), 4.73 (s, 1 H), 4.00 (t, J = 6.5 Hz, 1 H), 3.62 (s, 3 H), 2.50 (q, J = 10 Hz, 1H), 1.73 (d, J = 5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ *major*: 177.9, 147.7, 110.6, 53.1, 52.5, 43.9, 36.5, 30.1, 23.3, 24.3, 20.6; HRMS (FAB$^+$) calcd for $C_{11}H_{18}O_2$ [M]$^+$ 182.1307, found 182.1310.

*Methyl 2-Benzyl-1-methylcyclopentanecarboxylate (**4e** or **4f**).* The compound was isolated as a mixture of diastereomers (52:48) in 97% yield (44 mg) from 0.2 mmol of **1e**: ^{1}H NMR (400 MHz, $CDCl_3$) δ major: 7.19−7.13 (m, 5H), 3.70 (s, 3H), 2.83−2.77 (m, 2H), 2.61−2.07 (m, 3H), 1.94−1.47 (m, 4H), 1.30 (s, 3H); minor: 7.19−7.13 (m, 5H), 3.58 (s, 3H), 2.61−2.07 (m, 5H), 1.94−1.47 (m, 4H), 1.17 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ major: 177.5, 141.6, 128.8, 128.2, 125.8, 53.6, 52.4, 51.3, 38.8, 37.4, 30.8, 22.5, 17.5; minor: 178.5, 141.5, 128.8, 128.2, 125.7, 51.7, 51.2, 49.1, 37.3, 36.8, 30.0, 24.3, 21.9; IR (neat) 3026, 2926, 2871, 2855, 1725, 1603, 1496 cm^{-1}; HRMS (FAB+) calcd for $C_{15}H_{21}O_2$ [M + H]$^+$ 233.1542, found 233.1555.

*Methyl 1-Methyl-2-(1-phenylvinyl)cyclopentanecarboxylate (**9g** or **9h**).* The compound was isolated as a mixture of diastereomers (67:33) in 74% yield (36 mg) from 0.2 mmol of **1g**: ^{1}H NMR (400 MHz, $CDCl_3$) δ major: 7.29 (d, J = 8.2 Hz, 2 H), 7.25 (d, J = 3.6 Hz, 2 H), 7.21 (m, 1 H), 5.19 (s, 1 H), 5.08 (s, 1 H), 3.61 (m, 1 H), 3.15 (s, 3 H), 2.27 (m, 1 H), 2.00−1.79 (m, 3 H), 1.58 (m, 2 H), 0.94 (s, 3 H); minor: 7.29 (d, J = 8.2 Hz, 2 H), 7.25 (d, J = 3.6 Hz, 2 H), 7.21 (m, 1 H), 5.14 (s, 1 H), 5.04 (s, 1 H), 3.48 (s, 3 H), 2.96 (m, 1 H), 2.38 (m, 1 H), 2.00−1.79 (m, 5 H), 1.06 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ major: 178.5, 149.0, 142.7, 128.0, 127.9, 127.2, 127.1, 127.0, 114.3, 55.4, 52.4, 51.3, 40.1, 29.3, 22.6, 18.9; minor: 176.7, 150.1, 143.9, 128.0, 127.9, 127.2, 127.1, 127.0, 113.4, 53.9, 51.0, 50.2, 37.8, 31.8, 25.6, 22.9; IR (neat) 3082, 3057, 3024, 2951, 2874, 1733, 1627, 1600, 1575, 1495 cm^{-1}; HRMS (FAB$^+$) calcd for $C_{16}H_{20}O_2$ [M]$^+$ 244.1442, found 244.1466.

■ ASSOCIATED CONTENT

Supporting Information

All NMR (^{1}H, ^{13}C) spectra and calculated Cartesian coordinates. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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