Competition between Alkenes in Intramolecular Ketene−Alkene [2 + 2] Cycloaddition: What Does It Take to Win?

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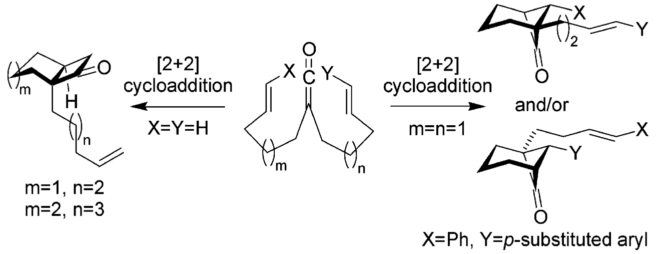

In the course of developing a new synthetic methodology using ketenes in sequential cycloaddition steps, we were faced with a competition problem with molecules containing a ketene tethered to more than one reacting partner. To pinpoint the electronic and tethering requirements for a chemoselective reaction, we undertook a series of ketene−alkene [2 + 2] cycloaddition competition experiments. Those experiments were conducted on molecules containing either two identical alkenes having different tether lengths or two alkenes having the same tether length but being electronically different. We demonstrated that the reaction is much faster for forming five-membered rings than six-membered rings and calculated the Hammett constant ρ for intramolecular ketene−alkene [2 + 2] cycloadditions to be −1.39.

Introduction

Since their first preparation in 1905,[1] ketenes have been widely studied due to their unique reactivity. Many different ketene−alkene [2 + 2] cycloaddition mechanisms have been proposed,[2] and nowadays, two of them are commonly accepted: a stepwise mechanism involving sequential nucleophilic additions via a zwitterionic intermediate[3] and a concerted cycloaddition. The latter is an antarafacial process, thermally allowed according to the frontier molecular orbital (FMO) theory,[4] and could be highly asynchronous.[2,5] It is also suggested that these two mechanisms may compete, depending on the nature of the alkene reacting with the ketene.[2]

As we were developing a new synthetic strategy using ketenes in sequential cycloaddition steps, we were faced with a competition issue with molecules containing a ketene tethered to more than one reacting partner. In fact, our strategy is to build tricyclic skeletons of natural products in one step from linear precursors (Scheme 1). Because the first [2 + 2] cycloaddition would need to be chemoselective, we turned our attention to competition studies to determine the electronic and tethering requirements for such a chemoselectivity.

Intramolecular ketene−alkene [2 + 2] cycloadditions[6] were shown to form five-membered rings more easily than six-membered rings.[7] However, the only evidence supporting this affirmation is based on shorter reaction time and higher yields for the formation of five-membered rings. No competition experiments were run to quanti-

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(1) Staudinger, H. *Chem. Ber.* **1905**, *38*, 1735−1739.

(2) For a review on proposed [2 + 2] cycloaddition mechanisms of ketenes with alkenes, see: Tidwell, T. T. *Ketenes*; Wiley: New York, 1995; pp 486−502, and references therein.

(3) (a) Corey, E. J.; Arnold, Z.; Hutton, J. *Tetrahedron Lett.* **1970**, 307−310. (b) Wagner, H. U.; Gompper, R. *Tetrahedron Lett.* **1970**, 2819−2822. (c) Gompper, R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 312−327. (d) Becker, D.; Brodsky, N. C. *J. Chem. Soc., Chem. Commun.* **1978**, 237−238.

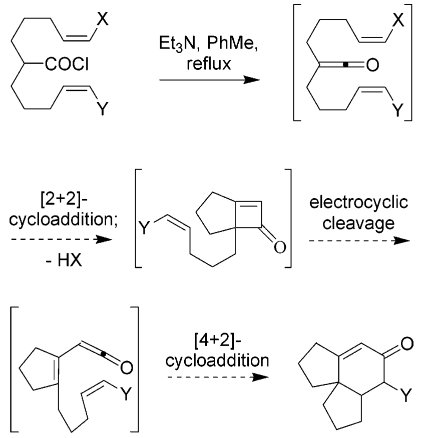
(4) (a) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: New York, 1976; pp 110−148. (b) Woodward, R. B.; Hoffmann, R. *Angew. Chem., Int. Ed, Engl.* **1969**, *8*, 781−853. (c) Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Verlag Chimie/Academic: New York, 1970.

(5) For calculations of transition states for ketene−alkene [2 + 2] cycloadditions, see: (a) Bernardi, F.; Bottoni, A.; Robb, M. A.; Venturini, A. *J. Am. Chem. Soc.* **1990**, *112*, 2106−2114. (b) Wang, X.; Houk, K. N. *J. Am. Chem. Soc.* **1990**, *112*, 1754−1756.

(6) For a review on intramolecular ketene−alkene [2 + 2] cycloadditions, see: Snider. B. B. *Chem. Rev.* **1988**, *88*, 793−811.

10.1021/jo0483466 CCC: $30.25

SCHEME 1

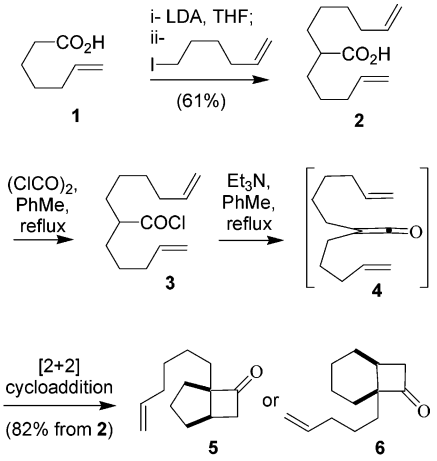


tatively assess the ring size effect on the relative cycloaddition rates. Second, it is known that ketenes are electron deficient and react preferentially with electron-rich alkenes, as was nicely demonstrated in ketene [2 + 2] cycloadditions with various para-substituted styrenes.[8] However, this is the only study of the influence of the electronic character of alkenes in [2 + 2] cycloadditions involving ketenes, and the interpretation of the results was neither conclusive nor quantitative.[9] Because this information is crucial to us in order to develop our synthetic methodology, we decided to run a series of ketene−alkene [2 + 2] cycloaddition competition experiments. The results presented herein are divided into two main parts: the study of the influence of the tether length and the study of the influence of the electronic character of alkenes in intramolecular [2 + 2] cycloadditions with ketenes.

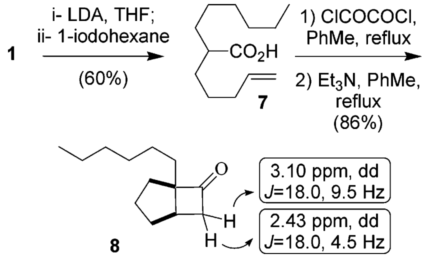
Results and Discussion

Study of the Influence of the Tether Length between a Ketene and an Alkene in Intramolecular [2 + 2] Cycloadditions. We chose substrates containing identical alkenes attached to the ketene with different tether lengths. The synthesis of the first model compound is described in Scheme 2. An alkylation of the dianion of hept-6-enoic acid (**1**) with 6-iodohex-1-ene gave the branched acid **2** (61% yield).[10] The latter was then treated with oxalyl chloride in refluxing toluene, and the resulting acyl chloride **3** was clean and was used without purification for the generation of ketene **4** by deprotonation with triethylamine in refluxing toluene. This was followed by an in situ [2 + 2] cycloaddition. We were pleased to obtain only one product (>95:5 by ^{1}H NMR analysis of the crude material) in excellent yield (82%). At that point, spectral analysis could not tell us which of the two possible adducts (**5** or **6**) was preferentially formed.

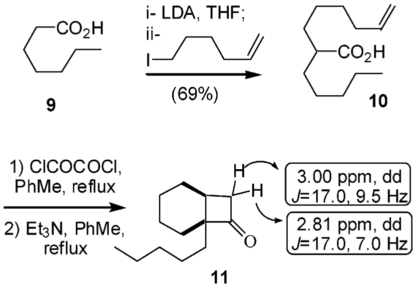
SCHEME 2



SCHEME 3



SCHEME 4



To determine the identity of the cycloadduct, we independently prepared both the [3.2.0] and the [4.2.0] bicyclic adducts. On one hand, the synthesis of **8** was accomplished in three steps, starting with the alkylation of **1** with 1-iodohexane (60% yield, Scheme 3). The ketene was prepared from the corresponding acyl chloride and gave the bicyclo[3.2.0]heptanone **8** in 86% yield.

On the other hand, the bicyclo[4.2.0]octanone **11** was prepared from ethyl heptanoic acid (**9**; Scheme 4) using exactly the same reactions as described in Scheme 2. We were delighted to observe that the methylene next to the carbonyl of **11** had measurably different chemical shifts and coupling constants for its protons compared to those of compound **8** (Scheme 3).

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(7) (a) Markó, I.; Ronsmans, B.; Hesbian-Frisque, A.-M.; Dumas, S.; Ghosez, L. *J. Am. Chem. Soc.* **1985**, *107*, 2192−2194. (b) Snider, B. B.; Hui, R. A. H. F.; Kulkarni, Y. S. *J. Am. Chem. Soc.* **1985**, *107*, 2194−2196. (c) Brady, W. T.; Giang, Y. F. *J. Org. Chem.* **1985**, *50*, 5177−5179. (d) Intramolecular [2 + 2] cycloadditions using ketene iminiums have been for different ring sizes: Brady, W. T.; Giang, Y. F.; Weng, L.; Dad, M. M. *J. Org. Chem.* **1987**, *52*, 2216−2220.

(8) (a) Baldwin, J. E.; Kapecki, J. A. *J. Am. Chem. Soc.* **1970**, *92*, 4868−4873. (b) For the ketenes' preference for electron-rich alkenes, see also: Brady, W. T.; O'Neal, H. R. *J. Org. Chem.* **1967**, *32*, 2704−2707.

(9) The Hammett constant ρ for [2 + 2] cycloadditions of diphenylketene with para-substituted styrenes reported by Baldwin is −0.73.[8a] This value is solely based on *p*-(trifluoromethyl)styrene and *p*-methylstyrene. With only two points in the Hammett plot, the linearity of the Hammett equation could not be verified,[23] thus casting doubt on the validity of the reported ρ value.

(10) Snider, B. B.; Vo, N. H.; Foxman, B. M. *J. Org. Chem.* **1993**, *58*, 7228−7237.

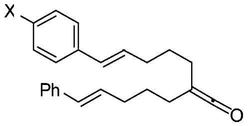
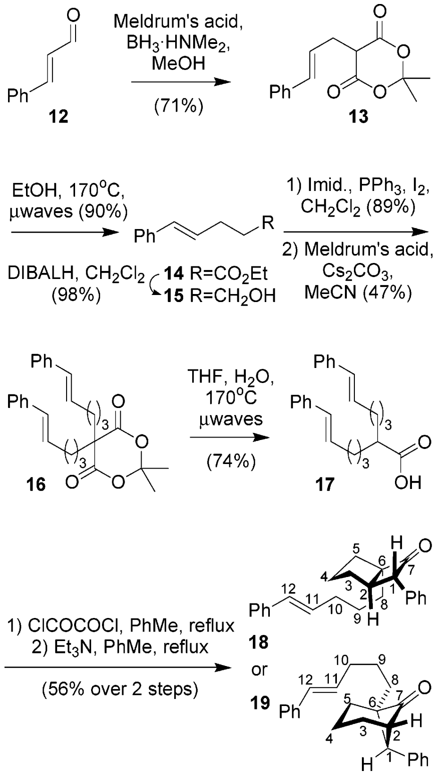


FIGURE 1. Model for electronic study.

SCHEME 5



We then reduced the alkene of the crude material (**5** or **6**) obtained from the competition experiment (Scheme 2), and the product obtained gave an NMR spectrum that matched perfectly that of compound **8**. This result confirmed that the adduct **5** was the only product obtained from the competition experiment, thus showing a strong dependence of the intramolecular ketene−alkene [2 + 2] cycloaddition on the size of the ring that is formed.

Study of the Influence of Alkene Electronic Character in Intramolecular [2+2] Cycloadditions with Ketenes. This study was designed to pit a tethered alkene substituted with either an electron-withdrawing or an electron-donating substituent against a tethered, unsubstituted alkene. Because we wanted to study only the influence of the electronic character of the substituted alkene in the cycloaddition, we had to make sure that the steric hindrance of the substituent would not interfere with the reaction rate. For this reason, we elected to put the substituent on a remote position, separated from the alkene by an aromatic ring (Figure 1).

Because no intramolecular ketene−styrene cycloaddition has been reported in the literature,[11] we first decided to prepare the bicyclo[3.1.1]heptane **19** (Scheme 5). The alkene on the cycloaddition precursor needed to be stereochemically pure (trans preferably);[12] therefore, we started from *trans*-cinnamaldehyde (**12**) and did a one-pot Knoevenagel condensation−hydroboration reaction. This procedure constitutes an efficient way to synthesize monoalkylated dicarbonyls.[13] The resulting diester **13** was then transesterified and decarboxylated in ethanol using microwaves at 170 °C. The stereochemical integrity of the alkene was preserved.[14] After a DIBALH reduction of the ester **14** in 98% yield, the resulting alcohol **15** was iodinated (89% yield) and then doubly alkylated on Meldrum's acid in 47% yield using cesium carbonate. A microwave-assisted hydrolysis−decarboxylation of **16** cleanly generated the corresponding monoacid **17**, which was transformed into the desired cycloadduct **19** (or **18**) via the acyl chloride and ketene intermediates.

TABLE 1. NMR Data of Possible Adducts 19

	^{1}H			^{13}C
position	δ (ppm)	multiplicity	*J* (Hz)	δ (ppm)
1	3.04	s		48
2	3.16	t	3.5	61
3	2.45 (eq) 2.45 (ax)	m m		36
4	1.70 (eq) 1.90 (ax)	dqn[a] m	14.5, 8.5	19
5	2.25 (eq) 2.45 (ax)	ddd m	13.0, 8.5, 4.0	40
6				72
7				219
8	1.12 1.28	td td	13.0, 3.5 13.0, 4.5	29
9	1.22 1.45	m m		23
10	1.85 1.95	m sept[b]	 7.0	35
11	5.90	dt	16.0, 7.0	130
12	6.20	d	16.0	130

[a] Doublet of quintets. [b] Septuplet.

Finding suitable proton signals in the ^{1}H NMR spectrum to use in the determination of product ratios was not easy, since the vinylic proton signals were overlapping with unreacted starting material and/or with an anhydride side product.[15] The assignations of proton and carbon signals in adduct **19** (or **18**) were accomplished using ^{1}H, COSY, NOESY, TOCSY,[16a] HSQC,[16b] and HMBC[16c] and are gathered in Table 1. From a portion of

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[11] Only the intermolecular version has been reported.[8]

[12] Trans-1,2-disubstituted alkenes react more quickly than cis-1,2-disubstituted alkenes with ketenes in intramolecular [2 + 2] cycloadditions, due to steric reasons. See: (a) Huisgen, R.; Mayr, H. *Tetrahedron Lett.* **1975**, *16*, 2965−2968. (b) Snider, B. B. Walner, M. B. *Tetrahedron* **1989**, *45*, 3171−3182. (c) Snider, B. B., Allentoff, A. J., Walner, M. B. *Tetrahedron* **1990**, *46*, 8031−8042. Also, we wanted to diminish the chance of side reactions, such as alkene isomerization, in the cycloaddition step, which occurs at elevated temperature (refluxing toluene).

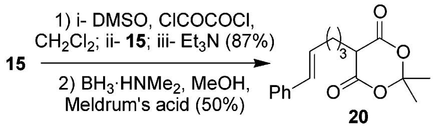
[13] Hrubowchak, D. M.; Smith, F. X. *Tetrahedron Lett.* **1983**, *24*, 4951−4954.

[14] For cis alkenes, used in other sequences of reactions that are not mentioned in this paper, this step gave partial isomerization.

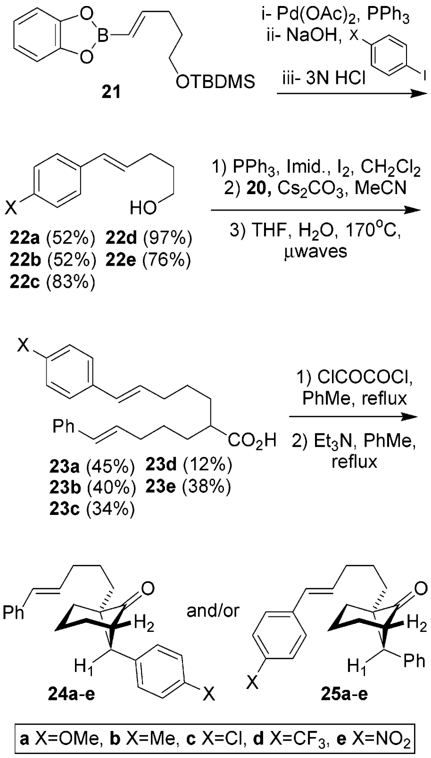
[15] Even with careful manipulations, traces of water could generate an anhydride from two molecules of acyl chloride. The formation of anhydride occurs during the ketene formation step, when the acyl chloride is heated in the presence of triethylamine. The acyl chloride formation itself is clean and usually quantitative. The amount of anhydride observed is greater when the alkenes are deactivated toward the [2 + 2] cycloaddition with the ketene.

[16] (a) TOCSY stands for total correlation spectroscopy and gives long-range ^{1}H−^{1}H coupling, typically over three to four bonds. (b) HSQC stands for heteronuclear single quantum correlation and gives ^{1}H−^{13}C coupling over one bond. (c) HMBC stands for heteronuclear multiple bond correlation and gives long-range ^{1}H−^{13}C coupling, typically over two to three bonds.

SCHEME 6



SCHEME 7



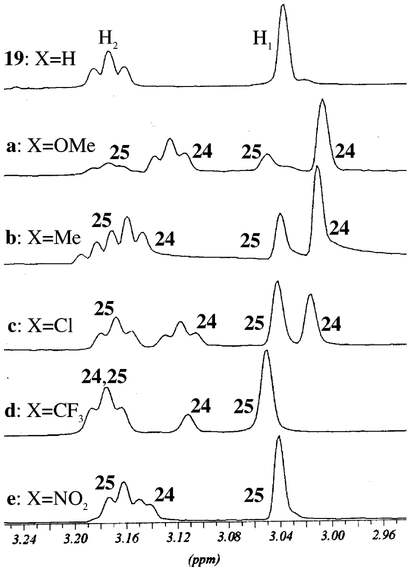


FIGURE 2. Crude cycloadduct ^{1}H NMR spectra.

TABLE 2. Ratios of Cycloadducts 24a−e and 25a−e

X	**24**:**25**[a]	σ_p value[19]
OMe (**a**)	3.2:1.0	−0.27
Me (**b**)	2.4:1.0	−0.17
Cl (**c**)	1.0:1.3	0.23
CF_3 (**d**)	1.0:4.1[b]	0.54
NO_2 (**e**)	1.0:9.0[c]	0.78

[a] Ratios determined from the average of the integration of H_1 singlets and integration of H_2 triplets. [b] The H_1 singlets of **24d** and **25d** are overlapping.[20] [c] The H_1 and H_2 signals of **24e**, as well as the H_2 triplet of **25e**, are all in the same multiplet (3.19−3.13 ppm).[21]

the HMBC spectrum, three pieces of evidence allowed us to unambiguously assign the structure as being **19**.[17]

Moreover, from the ^{1}H NMR spectrum of **19**, we identified two characteristic signals of the cycloadduct: the 3.16 ppm triplet and the 3.04 ppm singlet, corresponding to H_2 and H_1, respectively. These peaks are clearly identifiable in the crude mixture of the reaction. This information proved crucial for ratio determination in the following competition experiments.

With the structure of the cycloaddition product **19** secured, we then undertook the construction of a series of substrates, depicted in Figure 1. We selected five aryl substituents (X = methoxy, methyl, chloro, trifluoromethyl, and nitro) that would enable us to generate a standard Hammett plot and determine the ρ constant of the reaction. The syntheses of the substrates are depicted in Schemes 6 and 7. The alcohol **15** was oxidized using Swern's conditions, and then the monobranched Meldrum's acid **20** was prepared using the usual Knoevenagel−hydroboration procedure (Scheme 6).

The para-substituted aryls were introduced by a Suzuki coupling between the vinylic boronate **21**[18] and the appropriate aryl iodide followed by a hydrochloric acid cleavage of the silyl ether in the workup (Scheme 7). The resulting para-substituted styrenes **22a**−**e** were iodinated in good yields and alkylated on **20**. The Meldrum's acid moiety was then hydrolyzed and decarboxylated to the corresponding carboxylic acids **23a**−**e**. The latter were transformed into the acyl chlorides followed by a triethylamine treatment to generate the ketenes in situ, which underwent the [2 + 2] cycloaddition. Mixtures of **24a**−**e** and **25a**−**e** were obtained, depending on the nature of the X substituent on the aryl.

It is reasonable to think that the ^{1}H NMR chemical shifts for the H_1 singlet and H_2 triplet of **25** should be nearly the same on going from X = OMe (**25a**) to X = NO_2 (**25e**), as these groups are far from the bicyclic core. This is exactly what we observed (Figure 2).

The product ratios (**24**:**25**) were derived from these crude ^{1}H NMR spectra (Figure 2). The integration of the H_1 singlets on both **24** and **25** gave a ratio that matched perfectly that obtained from the integration of the H_2 triplets of **24** and **25**. The average ratio from the integrated singlets and triplets as well as the reported σ_p values[19] for every X substituent are given in Table 2.

Extracting kinetic data for competition experiments usually involves determining ratios at different times during the advancement of the reaction, since the concentration of the more reactive partner goes down as the reaction proceeds. This is true for *inter*molecular reac-

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[17] The spectral evidence that allowed us to assign the structure as being **19** is discussed in detail in the Supporting Information, section V.

[18] Muir, J. C.; Pattenden, G.; Ye, T. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2243−2250.

[19] Hansch, C.; Leo, A.; Taft, W. *Chem. Rev.* **1991**, *91*, 165−195 and references therein.

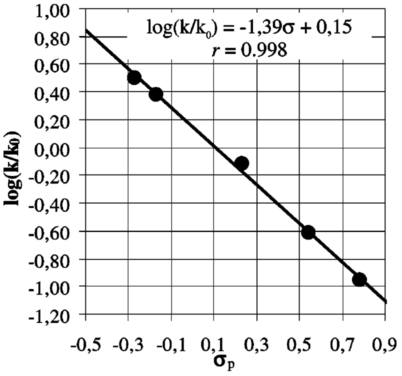

FIGURE 3. Hammett plot for [2 + 2] cycloaddition.

tions. In our case, for the *intra*molecular cycloaddition, we ran the reaction at 0.055 M until complete consumption of the starting material and determined the ratio of the cycloadducts directly from the crude material by ^{1}H NMR. We think this is rigorous for three reasons: (1) the ketene, being attached to the two alkenes in competition, is always in the presence of exactly 1 equiv of each alkene throughout all of the reaction, (2) the cycloaddition is irreversible, and (3) any intermolecular cycloaddition is essentially negligible.[22]

From these ratios, we constructed a graph of the reported σ_p values[19] for each X group we used against the log (k/k_0) value, which is the ratio of **24** to **25** (Figure 3).[23] The correlation coefficient r is 0.998, a value that exceeds the required 0.95 for significant linear Hammett correlation.[24] This suggests that these [2 + 2] cycloadditions are following the same reaction path and mechanism for every X substituent.[25] The slope of −1.39 is the Hammett ρ value for this reaction.

Conclusion

We demonstrated that the rate of intramolecular ketene−alkene [2 + 2] cycloadditions is strongly dependent on the size of the ring that is being formed during the reaction: a five-membered ring is the only one observed when competing with a six-membered ring. We also determined that the ρ value for this reaction is −1.39 in toluene, from competition experiments between phenyl-substituted alkenes and alkenes bearing a para-substituted aryl. Having a negative sign of the ρ value means that the reaction is accelerated by electron-donating groups, which is in accordance with reported data.[8] The absolute ρ value of 1.39 is the first clear and quantified indication of a modest charge development at the transition state, stabilized by electron-donating groups on the styrene, for [2 + 2] cycloadditions with a tethered ketene. The Hammett plot also serves as an extremely useful prediction tool that will be crucial for the development of our synthetic strategy using cascades of ketene cycloadditions, as well as for any reacting partner of known σ value.

Experimental Section

(5′*E*)-1-(Hex-5′-enyl)bicyclo[3.2.0]heptan-7-one (5). A solution of carboxylic acid **2** (400 mg, 1.9 mmol) in toluene (2.0 mL) was placed in a tube under argon. Oxalyl chloride (830 μL, 9.5 mmol) was added at room temperature, and the tube was sealed, heated to 120 °C for 2 h in an oil bath, and then cooled to room temperature and opened. The solution was concentrated under mechanical pump vacuum. The crude acyl chloride **3** was dissolved in toluene (33 mL), and Et_3N (1.6 mL, 11.4 mmol) was added at room temperature. The tube was sealed, heated to 120 °C overnight, cooled to room temperature, and opened. Saturated aqueous NH_4Cl was added, and the biphasic mixture was extracted with EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude material was purified by flash chromatography (19:1 hexanes−EtOAc) to give 300 mg (82%) of pure **5** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.69 (ddt, J = 17.0, 10.0, 6.5 Hz, 1H), 4.90 (dd, J = 17.5, 1.5 Hz, 1H), 4.84 (d, J = 11.5 Hz, 1H), 3.01 (dd, J = 18.0, 9.5 Hz, 1H), 2.49−2.44 (m, 1H), 2.33 (dd, J = 18.0, 4.5 Hz, 1H), 1.99−1.87 (m, 4H), 1.78−1.15 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.8, 138.6, 114.3, 75.8, 49.1, 35.3, 33.8, 33.5, 32.9, 32.6, 29.3, 25.0, 24.9; IR (film) ν 3077, 2935, 2865, 1774, 1068, 964 cm^{-1}; MS (EI) m/z 192 (15) [M$^+$], 150 (100), 135 (70), 121 (91), 108 (71); HRMS (EI) m/z calcd for $C_{13}H_{20}O$ 192.1514, found 192.1519.

(*E*)-2,2-Dimethyl-5-(3′-phenylallyl)-1,3-dioxane-4,6-dione (13). Meldrum's acid (9.51 g, 66.0 mmol) was added to a solution of $BH_3\cdot HNMe_2$ complex (3.88 g, 65.9 mmol) in MeOH (60 mL) at room temperature in a water bath. *trans*-Cinnamaldehyde (**12**; 8.32 mL, 66.0 mmol) was then added dropwise (exothermic). After 3 h at room temperature, H_2O (160 mL) was added (a white precipitate was formed) followed by 3 N HCl (240 mL). The suspension was stirred overnight and then was filtered and dried under vacuum over P_2O_5 to afford 12.1 g (71%) of pure **13** as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.19 (m, 5H), 6.61 (d, J = 15.5 Hz, 1H), 6.26 (dt, J = 15.5, 7.5 Hz, 1H), 3.66 (t, J = 5.0 Hz, 1H), 3.06−3.01 (m, 2H), 1.79 (s, 3H), 1.75 (s, 3H); HRMS (CI) calcd for $C_{15}H_{20}NO_4$ (MNH_4^+) 278.1392, found 278.1386.[26]

(4*E*)-Ethyl 5-Phenylpent-4-enoate (14). A solution of **13** (2.70 g, 10.4 mmol) in EtOH (22 mL) was placed in a sealed tube and heated to 170 °C for 1.5 h in a microwave oven. The tube was then cooled to room temperature and opened, and the solution was transferred to a round-bottom flask. Silica gel was added, and the slush was concentrated under reduced pressure. The resulting crude material adsorbed on silica gel was loaded directly on a column and was purified by flash chromatography (19:1 hexanes−EtOAc) to give 1.9 g (90%) of pure **14** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.17 (m, 5H), 6.43 (d, J = 16.0 Hz, 1H), 6.21 (dt, J = 16.0, 6.5

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[20] The ^{1}H NMR spectrum of **24d** with Ph = $CF_3C_6H_4$ (i.e. with two p-CF_3-styrene branches) prepared independently showed an H_1 singlet at 3.11 ppm and an H_2 triplet at 3.18 ppm.

[21] See the ^{1}H NMR spectra of isolated and purified **24e** and **25e** in the Supporting Information.

[22] As an indication of the difference in reaction rates between an intramolecular and an intermolecular reaction, 4-bromobutyl-1-amine cyclizes in a five-membered ring 10^4 times faster than the dimerization rate in a 1 M solution (Streitwieser, A., Jr *Solvotic Displacement Reactions*; McGraw-Hill: New York, 1962; p 105), or 200 000 times faster in a 0.055 M solution. Although the folding of the molecule for this 5-exo-tet cyclization is not the same as for the [2 + 2] cycloaddition, it is nonetheless an indication that the intermolecular reaction should be negligible.

[23] See the Supporting Information for the details of the log (k/k_0) calculation. See also: Logan, S. *Introduction à la cinétique chimique*; Dunod: Paris, 1998; pp 47−50. Schaal, R. *Chemical Kinetics of Homogeneous Systems*, D. Riedel: Dordrecht, The Netherlands, 1974; pp 30−32.

[24] As a criterion of linearity, the correlation coefficient r is required to be at least 0.95 and preferably above 0.98. See: Connors, K. A. *Chemical Kinetics*; VCH: New York, 1990; pp 315−320.

[25] For reactions that do not follow the same mechanism depending on the nature (electron withdrawing or electron donating) of the substrate (alkene in this case), a change of slope is usually observed in the σ vs log (k/k_0) graph.

[26] The characterization is identical with that reported for the same compound, but prepared through another route. See: Prat, M.; Moreno-Mañas, M.; Ribas, J. *Tetrahedron* **1988**, *44*, 7205−7212.

Hz, 1H), 4.15 (q, $J = 7.0$ Hz, 2H), 2.60−2.34 (m, 4H), 1.24 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 172.3, 137.1, 130.7, 128.1, 126.8, 125.8, 59.9, 33.6, 28.0, 13.9; MS (EI) *m/z* 204 (29) [M$^+$], 130 (100), 117 (63), 91 (26); HRMS (EI) *m/z* calcd for $C_{13}H_{16}O_2$ 204.1150, found 204.1142.[27]

(4′*E*)-2,2-Dimethyl-5,5-bis(5′-phenylpent-4′-enyl)[1,3]-dioxane-4,6-dione (16). I$_2$ (1.95 g, 7.7 mmol) was added to a solution of **15** (1.25 g, 7.7 mmol), PPh$_3$ (1.99 g, 7.6 mmol), and imidazole (630 mg, 9.2 mmol) in CH$_2$Cl$_2$ (20 mL) at 0 °C. The solution was stirred overnight at room temperature and then silica gel was added and the slush was concentrated under reduced pressure. The resulting crude material adsorbed on silica gel was loaded directly on a column and was purified by flash chromatography (19:1 hexanes−Et$_2$O) to give 1.86 g (89%) of pure iodide as a colorless oil: ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.41−7.23 (m, 5H), 6.49 (d, $J = 15.5$ Hz, 1H), 6.18 (dt, $J = 15.5$, 7.0 Hz, 1H), 3.26 (t, $J = 7.0$ Hz, 2H), 2.36 (q, $J = 7.0$ Hz, 2H), 2.05 (qn, $J = 7.0$ Hz, 2H); HRMS (EI) *m/z* calcd for $C_{11}H_{13}I$ 272.0062, found 272.0069.[28] Cs$_2$CO$_3$ (3.40 g, 10.5 mmol) was added to a solution of Meldrum's acid (430 mg, 2.99 mmol) and the previously prepared iodide (1.86 g, 6.8 mmol) in acetonitrile (10 mL) at room temperature. The reaction mixture was stirred for 3 days at room temperature and then silica gel was added and the slush was concentrated under reduced pressure. The resulting crude material adsorbed on silica gel was loaded directly on a column and was purified by flash chromatography (9:1 hexanes−EtOAc) to give 0.60 g (47%) of pure **16** as a colorless oil: ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.34−7.17 (m, 10H), 6.37 (d, $J = 16.0$ Hz, 2H), 6.31 (dt, $J = 16.0$, 7.0 Hz, 2H), 2.11 (q, $J = 7.0$ Hz, 4H), 2.09−2.03 (m, 4H), 1.73 (s, 6H), 1.53−1.42 (m, 4H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 169.4, 137.4, 130.9, 129.0, 128.4, 127.0, 126.0, 105.5, 54.6, 53.8, 38.8, 32.7, 29.8, 25.3; IR (film) ν 3001, 2933, 2859, 2366, 1743, 1280, 1206 cm^{-1}; MS (CI) *m/z* 450 (100) [MNH$_4^+$], 348 (48), 130 (89); HRMS (CI) *m/z* calcd for $C_{28}H_{30}NO_4$ (MNH$_4^+$) 450.2644, found 450.2651.

(4′*E*,6*E*)-7-Phenyl-2-(5′-phenylpent-4′-enyl)hept-6-enoic Acid (17). A solution of **16** (500 mg, 1.16 mmol) in THF (3.8 mL) and H$_2$O (1.8 mL) was placed in a sealed tube and heated to 165 °C for 4 h in a microwave oven. The tube was then cooled to room temperature and opened, and the solution was extracted with EtOAc, dried over anhydrous MgSO$_4$, filtered, and concentrated. The crude material was purified by flash chromatography (9:1 hexanes−EtOAc) to give 300 mg (74%) of pure **17** as a white solid: mp 88−92 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.35−7.16 (m, 10H), 6.38 (d, $J = 16.0$ Hz, 1H), 6.18 (dt, $J = 16.0$, 7.0 Hz, 1H), 2.48−2.39 (m, 1H), 2.22 (q, $J = 7.0$ Hz, 4H), 1.75−1.46 (m, 8H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 182.6, 137.7, 130.2, 128.5, 126.9, 125.9, 45.2, 32.8, 31.6, 27.0; IR (film) ν 3434 (br), 3024, 2931, 2856, 1699, 1452, 1238, 964 cm^{-1}; MS (EI) *m/z* 348 (65) [M$^+$], 143 (100), 117 (97), 91 (95); HRMS (EI) *m/z* calcd for $C_{24}H_{28}O_2$ 348.2089, found 348.2083.

(4′*E*)-7-Phenyl-1-(5′-phenylpent-4′-enyl)bicyclo[3.1.1]-heptan-6-one (19). Following the procedure used to form **5**, **17** (100 mg, 0.29 mmol) was treated with oxalyl chloride (125 μL, 1.4 mmol) in toluene (2.0 mL) and then with Et$_3$N (240 μL, 1.7 mmol) in toluene (5.0 mL) to give, after purification by flash chromatography (9:1 hexanes−EtOAc), 53 mg (56%) of pure **19** as a colorless oil: ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.28−7.13 (m, 10H), 6.20 (d, $J = 16.0$ Hz, 1H), 5.90 (dt, $J = 16.0$, 7.0 Hz, 1H), 3.16 (s, 1H), 3.04 (t, $J = 3.5$ Hz, 1H), 2.52−2.43 (m, 3H), 2.25 (ddd, $J = 13.0$, 8.5, 4.0 Hz, 1H), 1.97−1.84 (m, 2H), 1.95 (sept, $J = 7.0$ Hz, 1H), 1.70 (dqn, $J = 14.5$, 8.5 Hz, 1H), 1.45−1.41 (m, 1H), 1.28 (td, $J = 13.0$, 4.5 Hz, 1H), 1.28−1.20 (m, 1H), 1.12 (td, $J = 13.0$, 3.5 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 216.0, 140.1, 137.7, 130.2, 130.0, 128.5, 128.3, 127.5, 126.7, 126.0, 70.7, 60.4, 48.0, 40.1, 34.6, 33.1, 28.9, 22.8, 18.3; IR (film) ν 3028, 2940, 2865, 1765, 1491, 1447 cm^{-1}; MS (EI) *m/z* 330 (14) [M$^+$], 200 (36), 185 (22), 169 (52), 141 (21), 130 (100), 118 (80), 91 (78); HRMS (EI) *m/z* calcd for $C_{24}H_{26}O$ 330.1984, found 330.1990.

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Supporting Information Available: Text giving experimental procedures for compounds **2**, **7**, **8**, **10**, **11**, **15**, **20**, and **22**−**25**, figures giving ^{1}H and ^{13}C NMR spectra for compounds **2**, **5**, **7**, **8**, **10**, **11**, **13**−**17**, **19**, **20**, and **22**−**25**, and figures giving COSY, NOESY, TOCSY, HSQC, and HMBC spectra for **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[27] The characterization is identical with that reported for the same compound, but prepared through another route. See: Arnold, R. T.; Kulenovic, S. T. *J. Org. Chem.* **1980**, *45*, 891−894.

[28] See: Ren, X. F.; Turos, E.; Lake, C. H.; Churchill, M. R. *J. Org. Chem.* **1995**, *60*, 6468−6483.