pentane solution of **17** with dilute HCl, followed by neutralization of the aqueous layer and reextraction into pentane.

***in,out*-Bicyclo[4.4.4]tetradecane (11).** *in*-Bicyclo[4.4.4]-1-tetradecene (**5**, 10 mg, 0.1 mmol), platinum(IV) oxide (10 mg, 0.044 mmol), and 1 mL of MeOH were shaken in a Parr apparatus under 50 psi of H_2 pressure for 24 h. The mixture was diluted with 1:1 ether-pentane (5 mL) and filtered through a small amount of silica gel. The bulk of the solvent was removed by rotary evaporation (caution: product is highly volatile), followed by high vacuum for 15 s. The crude product was purified by preparative GC (10% SP 1000 on 80/100 Supelcoport at 170 °C) to yield 6 mg (60%) of a white solid: mp 159-161 °C (sealed tube). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.50 (m, 1 H), 1.73 (m, 6 H), 1.53 (m, 1 H), 1.13 (m, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 36.45 (t), 32.88 (d, J = 122.4 Hz), 31.48 (d, J = 111.2 Hz), 31.32 (t), 28.94 (t), 25.31 (t). GC-MS (Cl) m/e 194 (M^+). High-resolution MS, calcd for $C_{14}H_{26}$, 194.2034; found, 194.2038.

***in*-Bicyclo[4.4.4]-1-tetradecenylium Triflate (3-Triflate).** Alkene **5** (2.0 mg, 0.01 mmol) was dissolved in dry CD_2Cl_2 (0.5 mL) in a dry NMR tube under an argon atmosphere. Trifluoromethanesulfonic acid (5.0 mg, 0.033 mmol) was added to the solution via syringe at 0 °C, and the tube was capped and shaken to yield a light yellow solution that proved stable indefinitely at room temperature. ^{1}H NMR (300 MHz) δ 2.5 (br s, 12 H), 1.9 (br s, 12 H), -3.46 (br s, 1 H). ^{13}C NMR (22.49 MHz) 19.3 (t), 41.6 (t), 139.3 (d, J_{C-H} = 47 Hz). Solutions of the corresponding chloride and trifluoroacetate salts were prepared similarly, and all showed identical NMR spectra. An infrared spectrum was taken of the trifluoromethanesulfonate salt: FTIR (CH_2Cl_2) 2113 cm^{-1}. The chloride salt showed an identical absorption.

***in*-Bicyclo[4.4.4]-1-tetradecenylium Acetate (3-Acetate).** Alkene **5** (5.0 mg, 0.025 mmol) was dissolved in 0.5 mL of neat CD_3COOD. NMR analysis revealed a 1:1 mixture of cation **3** and starting alkene **5**.

***in*-Deuteriobicyclo[4.4.4]-1-tetradecenylium Triflate (19-Triflate).** Deuterated cation **19** was prepared identically to **3** substituting **18** for **5**. ^{2}D NMR (100 MHz) δ -3.36. FTIR (chloride salt, CH_2Cl_2) 1558 cm^{-1}.

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Atom Transfer Addition and Annulation Reactions of Iodomalonates

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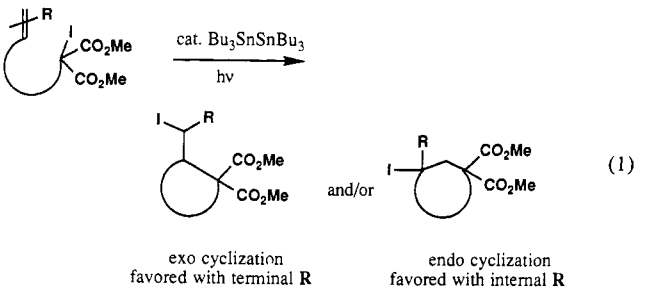
Abstract: Atom transfer addition and annulation reactions of iodomalonates with alkyl- and phenyl-substituted alkenes are described. For example, sunlamp irradiation of dimethyl methyliodomalonate and 1-hexene in the presence of 10% hexabutylditin provides dimethyl 2-methyl-2-(2-iodohexyl)malonate in 69% yield. Treatment of this reaction mixture with tributyltin hydride prior to workup provides dimethyl 2-methyl-2-hexylmalonate in comparable yield. Good yields of adducts are observed with terminal alkenes, and in addition to γ-iodomalonates and reduced products, lactones (resulting from intramolecular substitution) and alkenes (resulting from elimination of HI) can also be formed in many cases. When allyl- or progargyliodomalonates are used, annulated products are formed in a single step. For example, sunlamp irradiation of propargyliodomalonate and 1-hexene in the presence of 10% hexabutylditin provides 3,3-dicarbomethoxy-1-(iodomethylene)cyclopentane in 52% yield. Mechanistic considerations that will allow the design of successful annulation reactions with electrophilic radicals like iodomalonates are presented.

Malonates and related 1,3-dicarbonyl compounds are central functional groups in organic synthesis because they are rapidly assembled by classical alkylation reactions (the malonic ester synthesis[2]) and modern organometallic reactions [Pd(0)-promoted allylic alkylations[3]], and because they are readily transformed into other functional groups. We have recently shown[4] that iodomalonates, a hitherto little-known class of molecules,[5] are readily prepared and are excellent substrates for radical cyclizations conducted by the atom transfer method (see eq 1).[4,6] We now



(1)

report that atom transfer addition and annulation[7] reactions of

(1) Sloan Foundation Fellow, 1985-1987; Dreyfus Teacher-Scholar, 1985-1989; Eli Lilly Grantee, 1985-1987; Merck Faculty Development Awardee, 1986-1987; Recipient of a National Institutes of Health Career Development Award, 1987-1992.

(2) Cope, A. C.; Holmes, H. L.; House, H. O. *Org. React.* **1957**, *9*, 107. Freeman, F. *Chem. Rev.* **1969**, *69*, 591.

(3) Trost, B. M.; Verhoeven, T. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Eds.; Pergamon: Oxford, U.K., 1982; Vol. 8, pp 799-938.

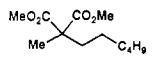
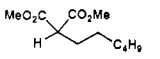
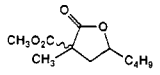
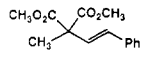
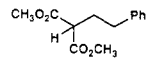
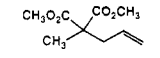
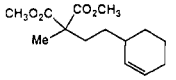
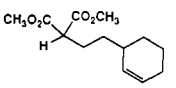
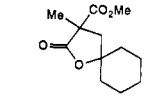
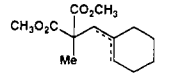
(4) (a) Curran, D. P.; Bosch, E.; Kaplan, J.; Newcomb, M. *J. Org. Chem.* **1989**, *54*, 1826-1831. (b) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140-3157.

(5) For a recent electrochemical preparation of an iodomalonate, see: Shono, T.; Matsumura, Y.; Katoh, S.; Ohshita, J. *Chem. Lett.* **1988**, 1065.

(6) For leading references to related atom transfer reactions such as the metal-promoted addition of perhalocarbonyls to alkenes, see: Reference 4b. (a) Curran, D. P. *Synthesis* **1988**, Part 2, 496-508. (c) Curran, D. P.; Chen, M.-H.; Kim, D. *J. Am. Chem. Soc.* **1989**, *111*, 6265-6276.

0002-7863/89/1511-8872$01.50/0

Table I. Addition Reactions of Iodomalonates **1**-Me and **1**-H

entry	iodomalonate	alkene	workup	% yield	product	structure
1	**1**-Me	1-hexene	tin hydride	66	**4a**-Me	
2	**1**-H	1-hexene	tin hydride	60	**4a**-H	
3	**1**-Me	1-hexene	heat	69	**5a**-Me	
4	**1**-Me	styrene	DBU	70	**6b**-Me	
5	**1**-H	styrene	tin hydride	40	**4b**-H	
6	**1**-Me	**2d**	none	66	**7d**-Me	
7	**1**-Me	**2g**	tin hydride	68	**4g**-Me	
8	**1**-H	**2g**	tin hydride	60	**4g**-H	
9	**1**-Me	**2j**	none	47	**5j**-Me	
				25[a]	**6j**/**7j**-Me	

[a] 8/1 ratio of endo alkene (**7j**) to exo alkene (**6j**).

iodomalonates with terminal alkenes are of preparative value and provide powerful new options for the construction of funtionalized malonates.[8]

Atom Transfer Additions. Most radical addition reactions pair nucleophilic alkyl radicals with electron-deficient alkene acceptors.[9] Because malonyl radicals are generally regarded as electrophilic, they should pair with electron-rich alkene acceptors in additions, thus complementing existing radical addition reactions. Literature precedent supports this simple[10] analysis: Boldt systematically studied the atom transfer addition reactions of bromomalononitrile to alkyl-substituted alkenes[11] and Giese reported the tin hydride mediated additions (of diethyl chloromalonate) and the atom-transfer additions (of diethyl bromomalonate) to enol ethers and enamines.[12] After the completion of our work, Gleicher reported a study of rate effects on the atom transfer addition reactions of bromomalonates and related compounds that will be useful for synthetic planning.[13] Our observations are in qualitative agreement with the results of this study.

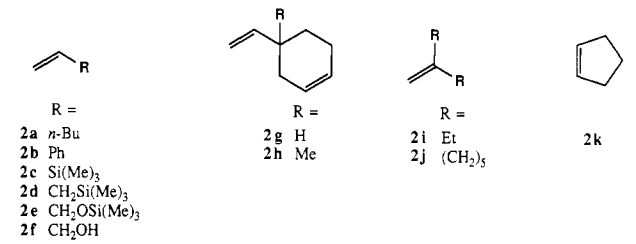
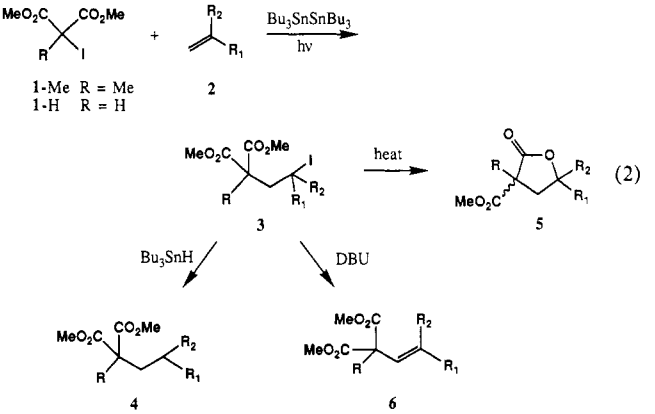


Figure 1. Alkene acceptors for addition and annulation reactions.

We initially investigated the addition reactions of dimethyl methyliodomalonate (**1**-Me) and dimethyl iodomalonate (**1**-H) as illustrated in eq 2. The tertiary iodomalonate **1**-Me was easily



(2)

prepared by the quenching of dimethyl methylsodiomalonate with *N*-iodosuccinimide.[4a] Although this technique is very general for the preparation of substituted iodomalonates, it failed to produce the unsubstituted parent **1**-H.[14] Other methods to iodinate di-

(7) Although it is used very commonly by organic chemists, the word "annulation" has yet to find a standard spelling or meaning. An authoritative review (Jung, M. E. *Tetrahedron* **1976**, *32*, 3) recommends the spelling "annulation", not "annelation". The latter spelling is not listed in any of the dictionaries that we consulted. We subscribe to the definition of Danheiser (Danheiser, R. L.; Gee, S. K.; Sard, H. *J. Am. Chem. Soc.* **1982**, *104*, 7670) that an annulation is a "ring-forming process in which two molecular fragments are united with the formation of two new bonds". A ring need not be appended to a preexisting ring to qualify as an annulation.

(8) Several of these reactions have been presented in preliminary form in ref 6a.

(9) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*; Pergamon Press: Oxford, U.K., 1986.

(10) Recent results suggest that all carbonyl-substituted radicals may not be electrophilic: (a) Giese, B.; He, J.; Mehl, W. *Chem. Ber.* **1988**, *121*, 2063. (b) Beraneki, I.; Fisher, H. In *Free Radicals in Synthesis and Biology*; Minisci, F., Ed.; Kluwer: Dordrecht, The Netherlands; 1989, p 303. (c) Curran, D. P.; Kim, D., manuscript in preparation.

(11) Riemenschneider, K.; Bartels, H. M.; Dornow, R.; Dreschel-Grau, E.; Eichel, W.; Luthe, H.; Matter, Y. M.; Michaelis, W.; Boldt, P. *J. Org. Chem.* **1987**, *52*, 205. Bartels, H. M.; Boldt, P. *Liebigs Ann. Chem.* **1981**, 40.

(12) Giese, B.; Horler, H.; Leising, M. *Chem. Ber.* **1986**, *119*, 444.

(13) Gleicher, G. J.; Mahiou, B.; Aretakis, A. J. *J. Org. Chem.* **1989**, *54*, 308.

(14) Diethyl iodomalonate has been prepared in solution by iodination of diethyl malonate with iodine: Bell, R. P.; Engel, P. *J. Chem. Soc.* **1957**, 247. This technique is not preparatively useful because, under these equilibrating conditions, the noniodinated malonate is heavily favored.

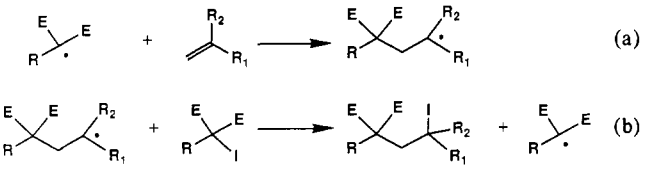
methyl sodiomalonate were equally unsuccessful. We were finally able to prepare **1**-H by oxidation of dimethyl malonate with pyridinium chlorochromate in the presence of iodine (CH_2Cl_2, molecular sieves).[15] After standard workup, a crude product containing ~80% **1**-H was isolated in 60–70% yield.[16] Attempts to further purify the crude product resulted in decomposition. In contrast to substituted iodomalonates (such as **1**-Me), which are stable to storage in the dark, iodomalonate **1**-H decomposed during storage in the dark over several days. Although the structure of **1**-H was assigned only by obtaining ^{1}H NMR and mass spectra of the crude product, the successful addition reactions of this product strongly support this assignment.

Seven of the alkenes illustrated in Figure 1, along with anisole, were selected as representative acceptors to survey the addition reactions of **1**-Me and **1**-H. The protocol for the reaction varied from substrate to substrate as summarized in eq 2. Under the standard procedure, the iodomalonate (1 equiv, 0.3–1.0 M in benzene), the alkene (2 equiv), and hexabutylditin (10 mol %) were irradiated with a 275-W sunlamp for 10–120 min. In many cases, the crude addition product **3** could be observed by NMR; however, it was not generally isolated. Depending on the substrate, we either added tributyltin hydride to form the reduced product **4**, added DBU to form eliminated product **6**, or heated the mixture to form lactone **5**.[17] These products were then purified to obtain the isolated yields reported in Table I.

The substituted malonate **1**-Me added reasonably well to mono- and 1,1-disubstituted alkenes under the standard conditions. Addition to 1-hexene (entries 1 and 3) gave the reduced product **4a**-Me in 66% yield and the lactone **5a**-Me in 69% yield. With styrene, the intermediate benzylic iodide **3b**-Me was observed by NMR but was not stable. Treatment of the crude reaction mixture with DBU (entry 4) gave the *E*-substituted styrene **6b**-Me in 70% yield. In the addition to allyltrimethylsilane (entry 6), no intermediate was observed and **7d**-Me was the direct product of the reaction. However, we believe **7d** results from a standard atom transfer addition to form **3d**-Me followed by ionic loss of iodotrimethylsilane.[18] Addition to diene **2g** was completely selective for the monosubstituted alkene and gave **4g**-Me in 68% yield after tin hydride reduction. The primary adduct **3j**-Me was again not observed in the reaction of **1**-Me with the methylene cyclohexane (entry 9). A mixture of eliminated alkenes **6j**/**7j**-Me and lactone **5j**-Me was obtained directly after photolysis. We suspect that these products result from ionic reactions of the intermediate tertiary iodide.

As implied by the selective addition to **2g**, the steric deceleration provided by alkene substituents at the attacking carbon outweighed any possible electronic activation. The addition of **1**-Me to cyclopentene (**2k**, a relatively reactive disubstituted alkene) gave only traces of the addition product (<15%). More remote steric factors were also important; **1**-Me added successfully to **2g** but failed to add to **2h** (Figure 1). Also, no addition product was detected with anisole.[19] The other products of these reactions were not investigated, but a major product in the unsuccessful cases (and a minor product in the successful ones) was dimethyl methylmalonate. The source of the hydrogen atom in this reduction product is not certain.

Scheme I



Additions of the unsubstituted malonate **1**-H were conducted with the crude iodination product within 1 or 2 days after its preparation. Addition of **1**-H to 1-hexene, followed by tin hydride reduction, gave **4a**-H in 60% yield (entry 2). However, under the standard conditions, the addition product of **1**-H and styrene was not detected during a 20-min irradiation period (even though **1**-H was consumed). By using an increased amount of ditin (40 mol %) and a high concentration of iodide (1.0 M), we were able to form the adduct **3b**-H. Following tin hydride reduction, **4b**-H was isolated in 40% yield (entry 5). Under these modified conditions, **1**-H also added to **2g** to give **4g**-H in 60% yield (entry 8). For comparison, addition of the more stable dimethyl bromomalonate[12] to **2g** gave **4g**-H in 40% yield after reduction. Like **1**-Me, iodomalonate **1**-H also failed to give useful quantities of addition products with **2h** and **2k**.

We believe that these reactions occur by a standard atom transfer chain as summarized in Scheme I. The possible roles of the ditin as an initiator and as an iodine scavenger have recently been discussed.[6b] The propagation steps are addition of the malonyl radical to the alkene (step a) and iodine atom transfer (step b). Although absolute rate constants for addition or cyclization reactions of malonyl radicals are not known, we assume that the electrophilic nature of these radicals facilitates the addition step. We do know that malonyl iodides are excellent iodine donors to primary alkyl radicals,[4a] and we assume that reactions with secondary and tertiary alkyl radicals, while less exothermic, should still be quite rapid. Somewhat surprisingly, our results indicate that even primary benzyl radicals abstract iodine from **1**-Me.[20]

While the addition reactions of the unsubstituted iodomalonate **1**-H will be less useful because of difficulties associated with its instability, we believe that the atom transfer addition of substituted iodomalonates such as **1**-Me across terminal alkenes will be a general reaction that has reversed electronic requirements from the Giese reaction (the tin hydride promoted addition of a nucleophilic radical to an electron-deficient alkene). It will not supplant standard alkylation for the preparation of simple malonates; however, we do believe that it will provide a powerful complement to malonate alkylation in fine synthesis for several reasons: (1) Products containing different functional groups (**3**, **4**, **5**, **6**) can be directly obtained from the addition reactions depending on reaction conditions and substrate. (2) Terminal alkenes are commonly used as precursors to extend carbon chains, but typical procedures take three or more steps (for example, a conventional conversion of **2g** to **4g** would probably entail selective hydroboration with 9-BBN, oxidation, activation of the alcohol, and malonate alkylation). (3) Functional groups can be incorporated in the alkene that will not tolerate a malonate alkylation (or will require protection).

Atom Transfer Annulations. With careful planning, radical addition and cyclization reactions can often be sequenced to form several carbon–carbon bonds at once.[6a] The formation of a ring from an acyclic precursor by the sequencing of an addition and a cyclization reaction, called radical annulation,[7] is particularly valuable. Like their simple counterparts that form one C–C bond, existing annulations begin with the addition of a nucleophilic

(15) D'Auria, M.; D'Onofrio, F.; Piancatelli, G.; Scettri, A. *Synth. Commun.* **1982**, *12*, 1127.

(16) The major impurity was dimethyl malonate, but other unidentified products were present in small quantities.

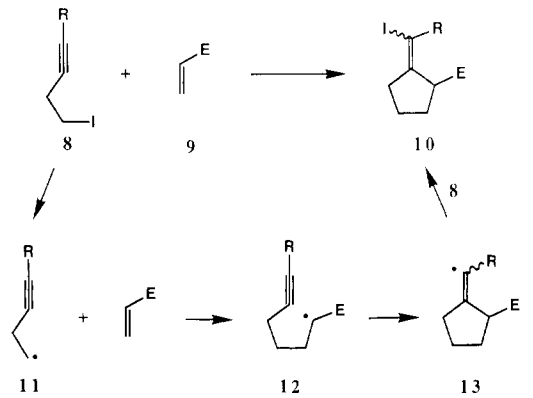
(17) Lactones and other related products can be formed by the manganese acetate oxidation of malonates and acetoacetates in the presence of alkenes. Leading references: Heiba, E. I.; Dessau, R. M.; Rodewald, P. G. *J. Am. Chem. Soc.* **1974**, *96*, 7977. Fristad, W. E.; Peterson, J. R.; Ernst, A. B.; Urbi, G. B. *Tetrahedron* **1986**, *42*, 3429. Corey, E. J.; Kang, M. *J. Am. Chem. Soc.* **1984**, *106*, 5384. Corey, E. J.; Ghosh, A. K. *Tetrahedron Lett.* **1987**, *28*, 175; *Chem. Lett.* **1987**, 223. Snider, B. B.; Mohan, R.; Kates, S. A. *J. Org. Chem.* **1985**, *50*, 3659. Snider, B. B.; Patricia, J. J.; Kates, S. A. *J. Org. Chem.* **1988**, *53*, 2137. Oumar-Mahamat, H.; Moustrou, C.; Surzur, J.-M.; Bertrand, M. P. *Tetrahedron Lett.* **1989**, *30*, 331.

(18) It is known that β-silyl radicals are not susceptible to rapid fragmentation. See: Light, J. P., II; Ridenour, M.; Beard, L.; Hershberger, J. *J. Organomet. Chem.* **1987**, *326*, 17.

(19) For metal-promoted additions of malonyl radicals to aromatics, see: Baciocchi, E.; Dell'Aira, D.; Ruzziconi, R. *Tetrahedron Lett.* **1986**, *27*, 2763. Citterio, A.; Santi, R.; Fancelli, D.; Pagani, A.; Bonsignore, S. *Gazz. Chim. Ital.* **1988**, *118*, 1855.

(20) The benzylic iodide might be formed by direct atom transfer from an iodomalonate (effectively an inner-sphere electron transfer) or by outer-sphere electron transfer from a benzyl radical to an iodomalonate to give a malonyl radical, a benzyl cation, and iodide anion. The former mechanism is perhaps more probable, because if a secondary benzylic cation were formed under the reaction conditions, it might be inclined to lose a proton (to give **6b** directly) rather than to combine with I^- to give a secondary benzylic iodide (**3b**).

Scheme II



radical to an electron-deficient alkene.[6a,21] We have developed such a sequence mediated by atom transfer chemistry.[22] Sunlamp irradiation of homopropargylic iodides **8** in the presence of electron-deficient alkenes **9** (10% $Bu_3SnSnBu_3$) gives annulated products **10** in 40–65% yields by the sequence of steps outlined in Scheme II. Of relevance to the present work is that adduct radical **12** is more stable than the starting radical **11**. Thus, it is not likely to be intercepted by iodine atom abstraction from **8** (an endothermic bimolecular reaction) prior to cyclization to **13** (an exothermic unimolecular reaction). With annulations that start by addition of an electrophilic radical to an alkyl-substituted alkene, this favorable condition will not be met. Nonetheless, atom transfer annulations of iodomalonates can be conducted with ease.

The reaction of readily prepared propargyliodomalonate **14** with 1-hexene served as a starting point for the annulation reactions because we knew that, even if adduct alkyl radicals were indeed derailed by atom transfer prior to cyclization, we could still isomerize the resulting acyclic alkyl iodides to cyclic vinyl iodides[6b] (see Scheme III). Sunlamp irradiation of **14** (1 equiv, 0.3 M in benzene) and 1-hexene (2 equiv) in the presence of 10 mol % hexabutylditin required 20 min for completion (as evidenced by consumption of **14**). At that point, a complex mixture of products was present. In the crude gas chromatogram, there were five peaks with retention times in the region where the product was expected. After addition of tributyltin hydride (1.2 equiv) and brief heating, all five products were apparently converted to a single deiodinated product **18a**, which was isolated in 65% yield. To demonstrate the importance of the atom transfer method, solutions of **14** and 1-hexene were directly reduced with tin hydride at several concentrations between 0.03 and 1.0 M. In no case was **18a** detected by GC. Instead, **14** was simply deiodinated to give dimethyl propargylmalonate in good yield.

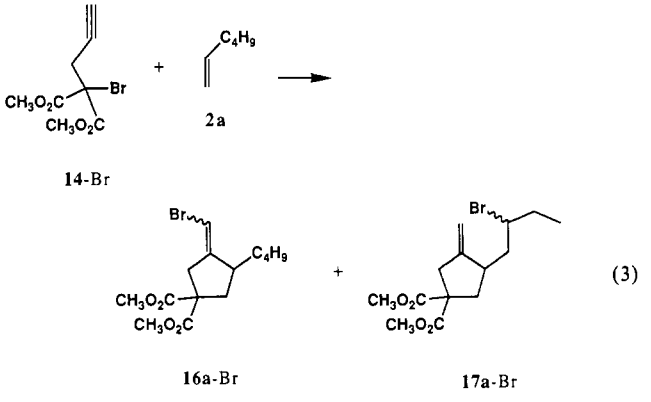
To identify the intermediates that were present prior to the addition of the tin hydride, we repeated the addition experiment and carefully separated the crude mixture by medium-pressure liquid chromatography. Three fractions were obtained: The major fraction was pure vinyl iodide (*E*)-**16a**, the intermediate fraction was its stereoisomer (*Z*)-**16a** (52% combined yield of **16a**, 2.7/1 ratio of *E*/*Z*), and the minor fraction was a mixture of equal parts of two diastereomers assigned as **17a** (9% yield). A separate reduction of each of the fractions with tin hydride gave **18a** as the only product in each case. The fifth product was present in trace amounts in this experiment and it was not isolated; but it was tentatively identified by GC–MS as **15a**.

From these results, we formulate the mechanism shown in Scheme III. Addition of malonyl radical **19** to 1-hexene gives **20**. Adduct **20** partitions between iodine transfer from the starting malonate **14** (to form **15**) and cyclization (to form **21**). In turn, the cyclic vinyl radical **21** partitions between iodine transfer from **14** or **15** (to form (*E*/*Z*)-**16**) and intramolecular 1,5 hydrogen atom transfer followed by iodine atom transfer from **14** or **15** (to form **17**). In the early stages of the reaction, iodomalonate **14** is the iodine donor because it is much more reactive than **15**. Later, as the concentration of **14** decreases, **15** becomes the best atom donor for radical **21**. Thus, any of **15** that has accumulated is isomerized to (*E*/*Z*)-**16** and **17**. Our past studies on the isomerization of alkyl iodides to vinyl iodides indicate that this last reaction is highly probable under the reaction conditions.[6b,23]

A variety of experiments supported this mechanism. Several reactions were followed by GC with the following results: First, the ratio of (*E*)-**16** to (*Z*)-**16** was 2.7/1 throughout the course of the reaction. (This demonstrates that iodine transfer to **21** is kinetically controlled.) Second, the ratio of acyclic iodide **15** to vinyl iodides (*E*)-**16** plus (*Z*)-**16** was higher at early reaction times[24] or when higher starting concentrations of **14** were used. (This demonstrates that higher concentrations of **14** favor the partitioning of **20** to form **15**.) Third, the ratio of H transfer product **17** to (*E*/*Z*)-**16** was higher at longer reaction times or when lower starting concentrations of **14** were used. (This demonstrates that lower concentrations of **14** favor H atom transfer of **21** relative to I atom transfer.)

In a different series of experiments, **14** and 1-hexene were heated with AIBN in place of ditin. Poor conversions resulted (only ~15% in 60 min) but a high ratio of **15**/(*E*)-**16** + (*Z*)-**16** was observed (1.4/1).[25] We believe that this is because the isobutyronitrile radical can initiate chains by abstracting iodine from **14** but not from **15**, and thus **15** accumulates in the reaction. This result implies that, even under the ditin conditions, some of **20** cyclizes directly to **21**. However, a significant portion is temporarily sequestered at the stage of **15** before being converted back to **20** and on to **21**. After these experiments were complete, we measured the rate constant for the reaction of a primary radical ($C_8H_{17}^{\bullet}$) with iodomalonate **1**-Me and found that it was not far below the diffusion-controlled limit ($k_I \approx 2 \times 10^9$ M^{-1} s^{-1} at 50 °C).[4a] In retrospect, it is not surprising that bimolecular atom transfer from **14** can compete with cyclization of **20**.

The results of an annulation experiment with bromomalonate **14**-Br under the standard conditions were also consistent with the mechanistic picture (eq 3). Products **16a**-Br (4.5/1, *E*/*Z*) and



(3)

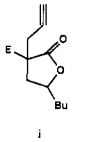
(21) For references to other radical annulations, see: Curran, D. P.; van Elburg, P. A. *Tetrahedron Lett.* **1989**, *30*, 2501. For related annulations of carbonyl-substituted radicals that are based on the chemistry of vinyl cyclopropanes, see: Feldman, K. S.; Romanelli, A. L.; Ruckle, R. E., Jr.; Miller, R. F. *J. Am. Chem. Soc.* **1988**, *110*, 3300. Miura, K.; Fugami, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 5135. A manganese-based oxidative radical annulation has recently been developed: Snider, B. B.; Buckman, B. O., submitted for publication.

(22) Curran, D. P.; Chen, M.-H. *J. Am. Chem. Soc.* **1987**, *109*, 6558.

(23) Curran, D. P.; Chen, M.-H.; Kim, D. *J. Am. Chem. Soc.* **1986**, *108*, 2489.

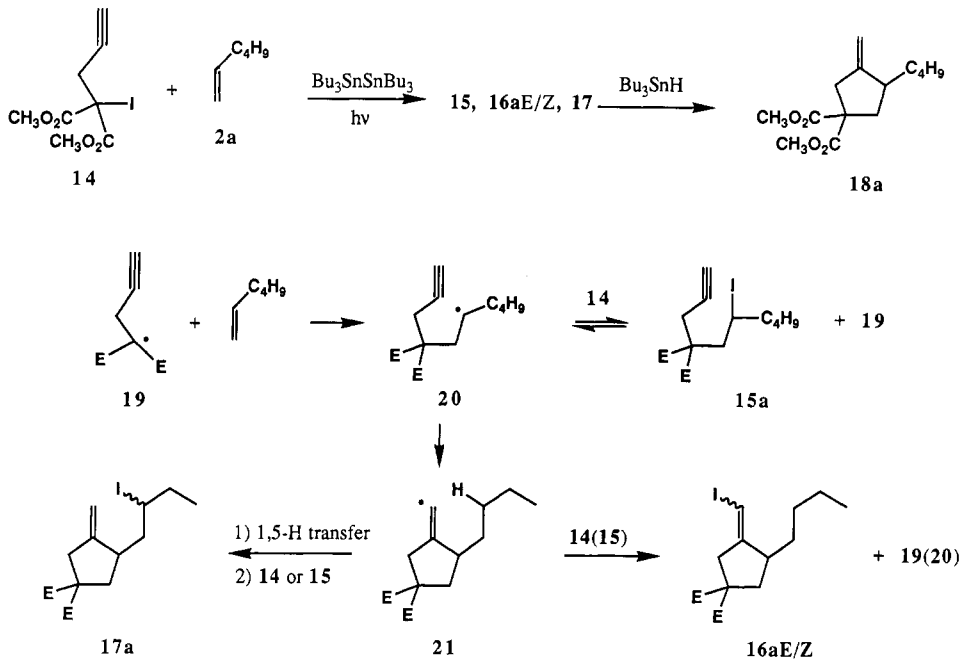
(24) For example, the following ratios of **15**/(*E*)-**16** + (*Z*)-**16** were observed under the standard conditions: 5 min, 0.51; 10 min, 0.23; 15 min, 0.11, 20 min, 0.04.

(25) These experiments were somewhat complicated by the conversion of **15** to lactone i (two diastereomers) over the course of several hours. Lactone



i could be isolated from the ditin annulations in yields of 2–4%.

Scheme III



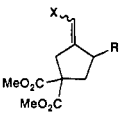
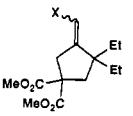
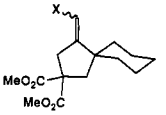
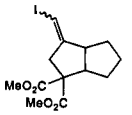
17a-Br (1/1 mixture of diastereomers) were isolated in 36 and 17% yields, respectively. No acyclic alkyl bromide corresponding to **15** was detected. Bromomalonates are poorer atom donors than iodomalonates by ~3 orders of magnitude.[4a] This decreased rate of atom transfer results in less of **15** and more of **17** relative to **16**.

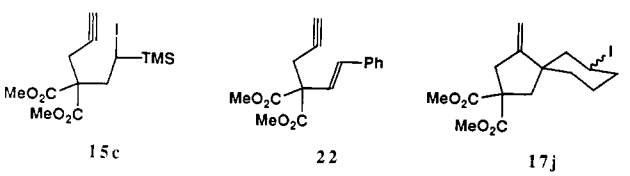
The mechanism provides a framework for planning reactions conditions. For example, if **16** is the desired product, the reaction should be run a high iodomalonate concentration to suppress 1,5 hydrogen transfer. Depending on the reactivity of the adduct radical, **15** may be an intermediate under such conditions, and sufficient time must be allowed for complete isomerization to **16**. If the reduced product is desired, the concentration and time make little difference because all of the intermediate products (including **15**) are reduced by tributyltin hydride to **18**.

In practice, reasonable yields of either the vinyl iodides or the reduced products can be obtained as illustrated in Table II. Iodomalonate **14** was reacted with a variety of alkenes under the standard reaction conditions. In all cases, the crude product was purified to give the cyclic vinyl iodides **16** (*E*/*Z* mixture). In most cases, a second experiment was conducted and the crude product was reduced by direct addition of tin hydride to the reaction mixture. This gave the reduced product **18**.

Several comments are in order: (1) We did not carefully investigate each reaction for the presence of acyclic iodide **15**, but in two cases there was evidence of such intermediates; with vinyltrimethylsilane (entry 2), iodide **15c** (see Figure 2) was detected at short reaction times, and with styrene (entry 1), traces (<5%) of alkene **22** (see Figure 2) were observed. (2) Accessible hydrogens for possible 1,5 hydrogen shift are present in the products from entries 2, 4, and 5. In the first two cases the appropriately located hydrogens are on methyl groups, and no 1,5 H transfer products were detected. In the third case, methylene hydrogens are available, and the product **17j** (see Figure 2) was observed (ratio **16j**/**17j**, 85/15). (3) Only 5-exo products were observed due to the Thorpe–Ingold effect of the geminal diester.[26] (4) Addition to allyltrimethylsilane gives the cyclic product (entry 3) rather that the eliminated product observed during addition (Table 1, entry 3). This provides additional circumstantial evidence that this eliminated product is formed by a subsequent ionic reaction of an intermediate β-iodo silane. (5) As with the additions, terminal alkenes gave good yields of annulated products

Table II. Atom Transfer Annulation Reactions of Propargyliodomalonate **14**

entry	alkene	products	% vinyl iodide **16** X = I (*E*/*Z*)	% reduced **18** X = H
				
1	styrene	R = Ph **16b, 18b**	59 (3.0/1)	65
2	**2c**	R = TMS **16c, 18c**	49 (2.7/1)	58
3	**2d**	R = CH_2TMS **16d**	74 (3.0/1)	not conducted
				
4	**2i**	**16i, 18i**	77 (4.4/1)	67
				
5	**2j**	**16j, 18j**	80 (3.0/1)	65
				
6	**2k**	**16k**	19 (2.3/1)	not conducted

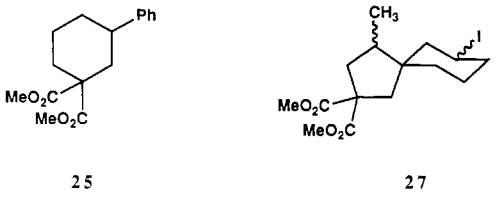


15c 22 17j

Figure 2.

but cyclopentene gave a poor yield (19%, entry 6). Attempted annulations with butyl vinyl ether and dihydropyran failed. (6) The major stereoisomer of **16** was assigned (by ^1H NMR trends and by analogy to related cyclizations[6b,22,23]) as *E* in all cases. An X-ray crystal structure of (*E*)-**16j** provided a rigorous assignment

(26) Beckwith, A. L. J.; Easton, C. J.; Lawrence, T.; Serelis, A. K. *Aust. J. Chem.* **1983**, *36*, 545.

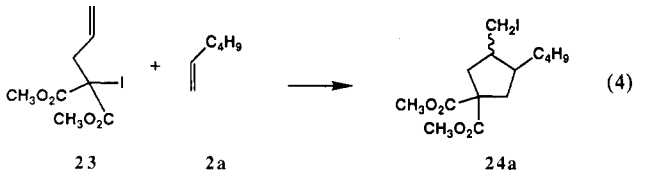


25 27

Figure 3.

for this example (full details are contained in the supplementary material).

Because iodomalonates are such good iodine atom donors, it should not be necessary to terminate the annulation sequence with a vinyl radical. To demonstrate this, we investigated the annulation reactions of allyliodomalonate **23** (eq 4). Reaction of **23** with



(4)

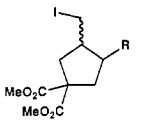
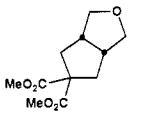
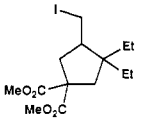
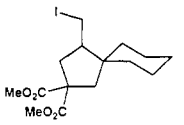
23 2a 24a

1-hexene under the standard conditions provided **24a** in 53% isolated yield as an inseparable mixture of stereoisomers (ratio 4/1). On the basis of precedent only,[27] we assign the cis stereochemistry to the major product.

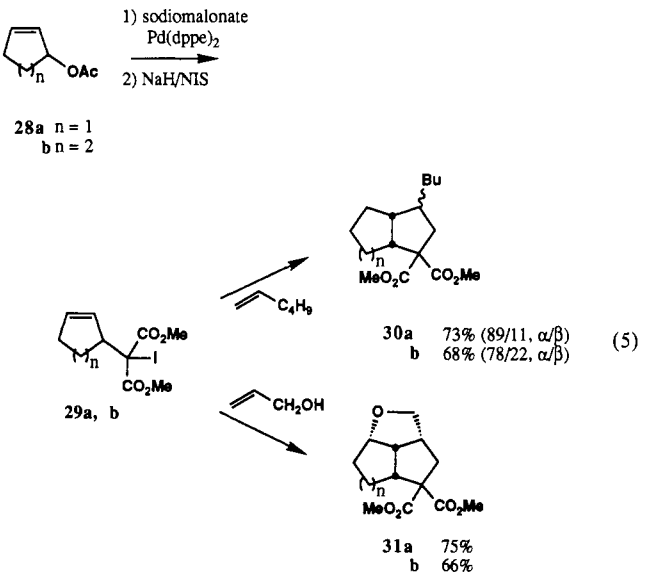
Table III summarizes the results of the reactions of **23** with a series of alkenes. The following comments are relevant: (1) With monosubstituted alkenes, cis/trans mixtures resulted. The cis stereochemistry was assigned to the major isomers of **24c** (entry 2) and **24d** (entry 3) by analogy only. The major isomer of **24e** (entry 4) can be securely assigned as cis because treatment of this compound with tetrabutylammonium fluoride gave tetrahydrofuran **26** (the product of entry 5). The trans stereochemistry was assigned to the major product of **24b** (entry 1) by ^{1}H NMR.[28,29] (2) In the addition to styrene (entry 1), a small amount of a 6-endo product **25** (**24b**/**25**, 96/4) was isolated (see Figure 3).[29] In all other cases, only 5-exo products were formed. (3) Tetrahydrofuran **26** was the direct product of the reaction of allyl alcohol with **23** (entry 5). Presumably, the intermediate iodo alcohol undergoes intramolecular substitution.[30] This transformation is illustrative of the way in which radical annulations can be combined with subsequent transformations to make polycyclic systems. (4) With methylene cyclohexane, the 1,5 hydrogen shift product **27** (see Figure 3) was present with **24h** (ratio **24h**/**27**, 82/18). (5) Although we conducted only one in situ tin hydride reduction in this series,[28] there is no reason to believe that others would not succeed.

Simple acyclic allyl malonates such as **23** are available by classical alkylations. More complex allyl malonates are now

Table III. Atom Transfer Annulation Reactions of Allyliodomalonate **23**

entry	alkene	products	% yield (cis/trans)
			
1	styrene	R = Ph **24b**	70 (1/1.4)
2	**2c**	R = TMS **24c**	46 (2/1)
3	**2d**	R = CH_2TMS **24d**	71 (5/1)
4	**2e**	R = CH_2OTMS **24e**	29 (4.6/1)
			
5	**2f**	**26**	40
			
6	**2i**	**23i**	72
			
7	**2j**	**24j**	68

available with a high degree of stereo- and regiocontrol by Pd(0)-promoted allylic alkylations of allyl acetates and related compounds.[3] Thus, the annulation reactions of iodomalonates will be a valuable adjunct to allylic alkylation reactions by allowing the rapid construction of a new ring.[31] Several examples of the three-step process—allylic alkylation, iodination, annulation—are outlined in eq 5.



28a n = 1 **29a, b** **30a** 73% (89/11, α/β) (5)
b n = 2 **b** 68% (78/22, α/β)
31a 75%
b 66%

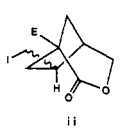
Alkylation of cyclopentenyl acetate (**28a**) or cyclohexenyl acetate (**28b**) was accomplished by the usual procedure of Trost.[3]

(27) The formation of cis isomers in related cyclizations is common. For a leading reference and a discussion of stereochemistry, see: RajanBabu, T. V.; Fukunaga, T. *J. Am. Chem. Soc.* **1989**, *111*, 296.

(28) Reduction of the mixture **24b** cis/trans with tributyltin hydride gave a 1/1.4 mixture of reduced methyl cyclopentanes. The major isomer exhibited a methyl doublet at 0.90 ppm in the ^{1}H NMR spectrum, while the minor isomer exhibited a shielded doublet at 0.59 ppm. This indicates that the methyl group is cis to the phenyl ring in the minor product.

(29) The cyclizations of related benzyl radicals are known to be reversible: Pines, H.; Sih, N. C.; Rosenfeld, D. B.; *J. Org. Chem.* **1966**, *31*, 2255. Walling, C.; Cioffari, A. *J. Am. Chem. Soc.* **1972**, *94*, 6064. We suspect that we have obtained the kinetic ratio of 5-exo cis/5-exo trans/6-endo because the iodine-transfer step is rapid. However, there is no experimental evidence in support of this suspicion.

(30) A cis/trans mixture of lactone ii was also isolated from this reaction in 3% yield. When this mixture was treated with DBU in methanol for 3 h,



ii

the trans isomer (of hydroxymethyl relative to iodomethyl) did not react but the cis isomer was converted to **26**.

(31) This radical annulation chemistry complements a growing class of metal-catalyzed isomerizations and "ene" reactions of substrates that are often prepared by allylic alkylations. For leading references, see: (a) Trost, B. M.; Luengo, J. L. *J. Am. Chem. Soc.* **1988**, *110*, 8239. (b) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 38. (c) Negishi, E.; Iyer, S.; Rousset, C. J. *Tetrahedron Lett.* **1989**, *30*, 291.

Standard iodination of the malonates provided **29a** and **29b** in 79 and 71% overall yield, respectively. The reaction of **29a** with 1-hexene was conducted under the usual conditions, and the crude product[32] was treated with tributyltin hydride in situ. Purification gave **30a** as mixture of α and β isomers[33] (89/11) in 73% yield. A similar annulation with **29b** gave **30b** (α/β, 78/22)[33] in 68% yield. Reaction of iodomalonate **29a** with allyl alcohol gave tricyclic tetrahydrofuran **31a** as the direct product of the reaction (tin hydride was not added) in 75% isolated yield. Homologue **31b** was formed from **29b** in 66% isolated yield. In these two reactions, tetrahydrofuran products can only be formed if the cyclization gives an α-oriented hydroxymethyl group. It is likely that small amounts of the β-oriented products were formed, as in the case of 1-hexene, but we did not isolate these products.

The work described herein illustrates the basic principles that one must consider when planning an annulation reaction of an electrophilic radical with an alkyl-substituted alkene. Compared to annulation reactions of nucleophilic radicals with electron-deficient alkenes, additional complications are present. However, given appropriate consideration, these complications do not limit the method. We believe that the relatively simple reactions that we have studied so far represent only a beginning. It is likely that other types of iodide and alkene partners could be used to generate different types of carbo- and heterocyclic rings.

Experimental Section

Dimethyl Iodomalonate (1-H). A mixture of 4-Å molecular sieves (1.06 g), molecular iodine (506 mg, 2.0 mmol), pyridinium chlorochromate (863 mg, 4.0 mmol), and methylene chloride (20 mL) was stirred under nitrogen for 30 min at 25 °C.[15] To this was added dimethyl malonate (0.23 mL, 2.0 mmol) in methylene chloride (5 mL). After being stirred for 13 h at 25 °C, the mixture was filtered through silica gel, eluting with ether. After concentration, the residue was dissolved in ether (50 mL) and washed with saturated sodium bisulfite (2 × 25 mL). Concentration gave the crude product as a yellow oil that darkened and decomposed over a period of 2 or 3 days at 25 °C in the dark. This crude product, containing ~80% **1-H**, was used for the addition reactions: ^{1}H NMR (C_6D_6) δ 4.72 (1 H, s), 3.17 (6 H, s); MS m/z 258 (M^+).

Dimethyl Methyliodomalonate (1-Me). A detailed procedure for the preparation of **14**[4a] and other substituted iodomalonates[4b] has recently appeared.

Dimethyl Propargyliodomalonate (14).[4] To a solution of propargylsodiomalonate [prepared from propargyl malonate (250 mg, 1.46 mmol) and sodium hydride (77 mg, 3.2 mmol)] in THF (15 mL) was added *N*-iodosuccinimide (335 mg, 1.0 mmol) in THF (2 mL) in the dark at room temperature. The mixture was stirred for 10 min and then filtered through silica gel, eluting with ether. Concentration gave **14** as a pale yellow oil in 73% yield (317 mg): ^{1}H NMR ($CDCl_3$) δ 3.83 (6 H, s), 3.25 (2 H, d, J = 3 Hz), 2.21 (1 H, t, J = 3 Hz); MS m/z 296, 237, 169, 137, 69, 59; HRMS calcd for $C_8H_9O_4I$, 295.9546, found, 295.9545.

Dimethyl Allyliodomalonate (23). This was prepared following the above procedure[4] with dimethyl allylmalonate (346 mg, 2.0 mmol), sodium hydride (156 mg, 6.5 mmol), and *N*-iodosuccinimide (472 mg, 2.1 mmol) in THF (20 mL). A pale yellow oil of **23** was obtained in 91% yield (540 mg) after filtration through silica gel: ^{1}H NMR ($CDCl_3$) δ 5.76 (1 H, m), 5.17 (2 H, m), 3.80 (6 H, s), 2.99 (2 H, d, J = 7 Hz); MS m/z 298, 171, 139, 71, 59; HRMS calcd for $C_8H_{11}O_4I$, 297.9702, found, 297.9702.

Standard Procedure for Addition and Annulation Reactions. A solution of iodomalonate (1 equiv), alkene (2 equiv), and hexabutylditin (0.1 equiv) in benzene (0.3 M in iodide, under argon atmosphere) was irradiated with a GE 275-W sunlamp for 10–120 min. A standard NMR tube (5 or 10 mm) was typically used as the reaction vessel and the sunlamp was kept at a distance of ~8 cm from the tube. At this distance, the reaction was warmed by the light (estimated temperature 65–85 °C) but did not reflux. After cooling, the reaction was either directly chromatographed, or treated with tin hydride (1.1 equiv, 12 h, 85 °C) or DBU, or heated. These standard procedures are described in the supplementary material.

Acknowledgment. We thank the National Institutes of Health (GM 33372) for funding of this work and we also thank Hoffman-La Roche for support.

Supplementary Material Available: Contains a detailed general experimental section, procedures for preparation of all the annulation products reported in Tables II and III and eq 5 with accompanying spectral and physical characterizations and 300-MHz ^{1}H NMR spectra for representative products, and a summary of the X-ray crystal structure determination of **16j** (23 pages). Ordering information is given on any current masthead page.

(32) Although four stereoisomeric iodides are possible, only two were detected at this stage in a ratio of 89/11. These are probably the two isomers epimeric at the butyl-bearing carbon that have abstracted iodine from the less hindered exo face.

(33) We assign the stereochemistry of these products by analogy to the major products resulting from the reactions with allyl alcohol.

Carbanion-Accelerated Claisen Rearrangements. 6. Preparative and Stereochemical Studies with Sulfonyl-Stabilized Anions†

Scott E. Denmark,* Michael A. Harmata,[1a,b] and Kathleen S. White[1c]

Contribution from the Roger Adams Laboratory, Department of Chemistry, University of Illinois, Urbana, Illinois 61801. *Received April 20, 1989*

Abstract: The aliphatic Claisen rearrangement is markedly accelerated by an arylsulfonylmethide substituent at position 2. The generality of this anion variant has been extensively examined (31 allyl vinyl ethers) with regard to substitution, stereochemistry, and anion-stabilizing groups. The reactions generally proceed in good yield and with high regio- and stereoselectivities. The regiochemical course of the reaction is independent of the structure of the anionic precursor (α,β- or β,γ-unsaturated). The anionic rearrangement is highly diastereoselective producing either syn or anti products with 90–96% de. Vicinal quaternary centers are constructed easily. Other sulfur-based, anion-stabilizing groups were found to be inferior (sulfide, sulfoxide, and sulfilimine).

The Claisen rearrangement in its manifold variations (Scheme I) is without doubt the most synthetically useful [3,3]-sigmatropic rearrangement.[2] The widespread application in organic synthesis can be ascribed to several characteristics: (1) the γ,δ-unsaturated carbonyl compounds produced are versatile, differentially functionalized intermediates, (2) the wide range of carbonyl derivatives,

† Dedicated to the late Roger Adams on the occasion of the 100th anniversary of his birth, January 1889.

(1) (a) Taken in part from Harmata, M. A. Ph.D. Thesis, University of Illinois, Urbana, 1985. (b) Present address: Department of Chemistry, University of Missouri-Columbia, Columbia, MO 65211. (c) Taken in part from White, K. S. M.S. Thesis, University of Illinois, Urbana, IL, 1986.

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