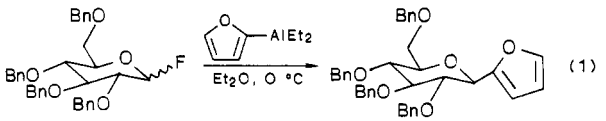
The first coupling was carried out by addition of the mainly β-fluoride (1) to 5 equiv of (diethylaluminio)furan (3) at 0 °C (eq 1). The reaction was monitored by TLC



β:α = 2.5:1

crude yield 78%
purified yield 45%

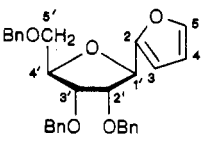
and was over within 5 min. After quenching with a mixture of water, brine and a saturated solution of sodium hydrogen carbonate (1:1:1 v:v:v), and workup,[8] the crude product (78% yield of reasonably pure material) was purified by chromatography and recrystallization to give 2-(2,3,4,6-tetra-*O*-benzyl-β-D-glycopyranosyl)furan as white crystals in 45% yield.

The retention of configuration of this coupling reaction is demonstrated by the results given in Table I.[9] The stereochemistry of the products was determined by decoupling and 2-D COSY NMR experiments, in which the diastereotopic nature of the methylenes of the benzyl protecting groups caused considerable difficulties in the assignment of the anomeric protons.

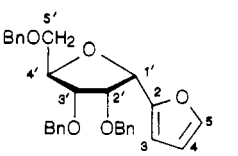
The mechanistic reasons for high retention of configuration in the coupling reaction is not yet known. For these examples though it appears that oxonium ions are not likely to be intermediates. Posner had demonstrated stereospecificity in the case of a bridged 1,6-anhydro sugar where one fluorine isomer reacted with retention of configuration at C-6 (cf. ref 3c).

In contrast to the retention of configuration observed with couplings of pyranosyl fluorides, coupling with ribofuranosyl fluorides gave predominantly the β-coupled products (Table I).[9] In one experiment however, starting with an anomeric mixture of ribofuranosyl fluorides **6** and **9** and using an acidic workup, a separable 1:1 mixture of anomeric (ribofuranosyl)furans **7** and **10** (56% total yield) was obtained. Having both anomers facilitated the assignment of the stereochemistry of the coupled products, principally through NOE experiments.

Thus for **7** ($J_{1'2'}$ = 6.1 Hz) irradiation of H-1′ gave NOE enhancements at H-3 (4.4%), H-4′ (3.9%), and H-2′ (3.8%). Irradiation of the two H-5′ signals gave enhancements at H-3′ (4.5%) and H-4′ (11.6%) but none at H-1′, H-3, H-4, or H-5.



7



10

For **10** ($J_{1'2'}$ = 9.8 Hz) irradiation of H-1′ gave NOE enhancements at H-3 (4.7%), 2H-5′ (4.9%), and H-2′ (2.3%). Irradiation of the two H-5′ signals gave enhancement at H-1′ (12.5%) (no enhancements at H-3′ or H-4′ were observed due to the proximity in chemical shifts of H-3′, H-4′, and H-5′).

The coupling reaction has been attempted with other aluminated heterocycles (1-methylimidazole, thiophene, and thiazole) and benzene derivatives without much success.[10] It is not yet clearly understood why these couplings fail, while those with aluminated 1-methylpyrrole and furan succeed. The use of benzyl protecting groups on the sugar is also important, as the use of ester protecting groups (acetate or benzoate) results in either a substantial drop in yield or no reaction at all.

The synthetic and mechanistic aspects of these reactions are being actively pursued in these laboratories. The complete spectroscopic analysis and experimental details of these and other examples will be described elsewhere in due course.

Acknowledgment is made to the National Institutes of Health (CA 36868-03) for financial support and to Dr. K. Belmore (University of Alabama) and Dr. R. Jones (Emory University) for NMR experiments.

(7) Chadwick, D. J.; Willbe, C. *J. Chem. Soc., Perkin Trans. I* **1977**, 887.

(8) Although this workup produces insoluble aluminum salts, it avoids the possibility of epimerization that is associated with an acidic workup.

(9) All new compounds gave satisfactory spectral and analytical data. A representative experimental procedure is as follows. To a stirred solution of 1-methylpyrrole (0.82 mL, 9.2 mmol) in dry diethyl ether (30 mL) under a nitrogen atmosphere was added freshly distilled tetramethylethylenediamine (1.39 mL, 9.2 mmol) and *n*-butyllithium (2.5 M solution in hexanes) (3.7 mL, 9.2 mmol). The mixture was stirred at room temperature for $^1/_2$ h and then cooled to −78 °C. After purging the solution with dry nitrogen, diethylaluminum chloride (1.8 M solution in toluene) (5.1 mL, 9.2 mmol) was added and the mixture allowed to warm to room temperature and then stirred overnight. A white precipitate was formed. To this mixture cooled to 0 °C was added a nitrogen-purged solution of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl fluoride (a 2.5:1 mixture of β:α anomers) in toluene (dried over 4A molecular sieves) (10 mL of solution, 1.00 g, 1.84 mmol), and the coupling was followed by TLC (80:20 hexanes/ethyl acetate). After 1 h the reaction was quenched with a mixture of water, brine, and a saturated sodium hydrogen carbonate solution (1:1:1, v:v:v, 60 mL) and stirred for $^1/_2$ h. The product was extracted with diethyl ether (3 × 50 mL) and the combined extracts were washed with 1 M hydrochloric acid (4 × 25 mL) and water (1 × 25 mL) and then dried ($MgSO_4$). Solvent removal and chromatography on Davisil eluting with hexanes/ethyl acetate (90:10), followed by recrystallization (hexanes/ethyl acetate) gave 2-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-1-methylpyrrole (0.77 g, 70%) as a white solid, mp 107–108 °C.

(10) The exception to this statement is the coupling between aluminated thiophene and the β-ribofuranosyl fluoride which proceeds in moderate yield.

(11) Maeba, I.; Iwata, K.; Usami, F.; Furukawa, H. *J. Org. Chem.* **1983**, *48*, 2998.

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Accelerated Inverse Electron Demand Diels–Alder Reactions of 1-Oxa-1,3-butadienes: [4 + 2] Cycloaddition Reactions of β,γ-Unsaturated α-Keto Esters

Summary: The demonstration and full investigation of the scope of the accelerated 4π participation of methyl *trans*-4-methoxy-2-oxo-3-butenoate (**1**) and methyl *trans*-4-phenyl-2-oxo-3-butenoate (**2**), electron-deficient 1-oxa-1,3-butadienes bearing a C-2 electron-withdrawing substituent, in productive endo selective inverse electron demand Diels–Alder reactions suitable for the preparation of 2-alkoxy-3,4-dihydro-2*H*-pyran-6-carboxylates are detailed.

Sir: The 4π participation of simple α,β-unsaturated aldehydes and ketones, electron-deficient heterodienes bearing a terminal oxygen atom, in $LUMO_{diene}$-controlled Diels–Alder reactions typically suffers from low conversions, competitive polymerization, and harsh reaction conditions.[1,2] Consequently, a limited number of 1-oxa-

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Table I. Diels–Alder Reactions of Methyl *trans*-4-Methoxy-2-oxo-3-butenoate (1) and Methyl *trans*-4-Phenyl-2-oxo-3-butenoate (2)

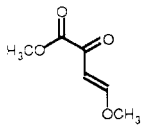
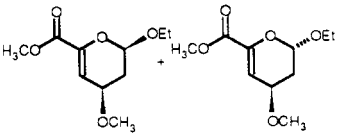
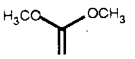
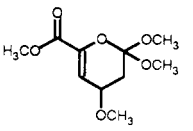
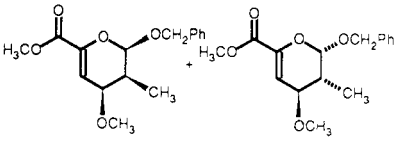
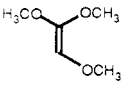
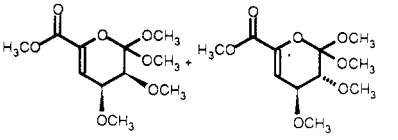
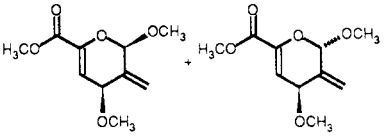
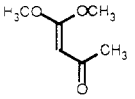
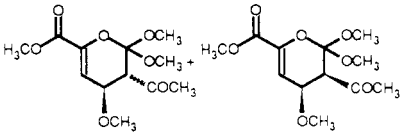
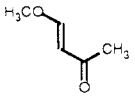
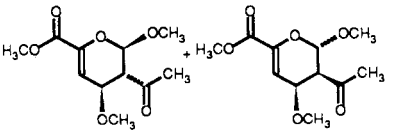
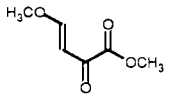
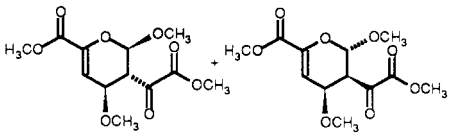
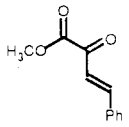
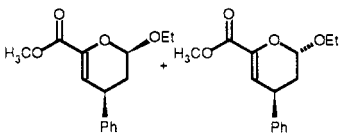
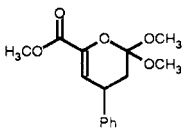
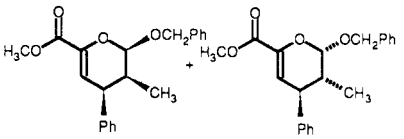
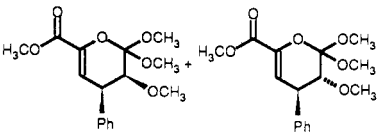
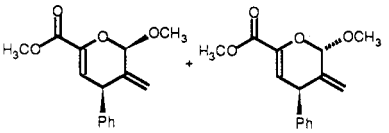
entry	diene	dienophile[a]	reaction conditions: equiv of 3, solvent, temp, °C (time, h)	product[b] (endo:exo)[c]	yield[d]
					
	1	3a		5 6	
1			5.0, toluene, 110 (29)	1.8:1.0	(≥95) 48
2			2.5, neat, 13 kbar, 24 (65)	5.7:1.0	(≥95) 82
3			2.5, CH_2Cl_2, 6.2 kbar, 24 (108)	5.7:1.0	(≥95) 75[e]
4			2.5, CH_2Cl_2, −78, 5 min, $EtAlCl_2$ (0.1 equiv)	0.8:1.0	(≥95) 75[f]
5			2.5, CH_2Cl_2, −78, 5 min, $TiCl_4$ (0.1 equiv)	1.0:3.0	(≥95) 61[g]
					
	1	3b		7	
6			2.5, CH_2Cl_2, 40 (6)		(90) 63
7			2.5, CH_2Cl_2, 13 kbar, 24 (48)		(85) 41
					
	1	3c		8 9	
8			1.5, CH_2Cl_2, 9.5 kbar, 24 (48)	19:1	(≥95) 50[h]
9			1.7, benzene, 80 (20)	3:1	(20) 11[h]
10			1.2, CH_2Cl_2, −78, 5 min, $EtAlCl_2$ (0.1 equiv)	6:1	(≥95) 46[h]
					
	1	3d		10 11	
11			2.0, CH_2Cl_2, 9.5 kbar, 24 (108)	1:2	(≥95) 41[i]
					
	1	3e		12 13	
12			1.8, CH_2Cl_2, 9.5 kbar, 24 (108)	1:1	(≥95) 51[i]
					
	1	3f		14 15	
13			1.8, CH_2Cl_2, 12 kbar, 24 (96)	2.3:1	(85) 31[j]
					
	1	3g		16 17	
14			1.4, CH_2Cl_2, 13 kbar, 24 (98)	2:1	(85) 39

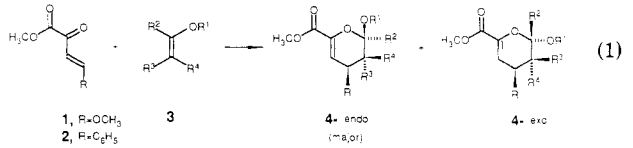
Table I (Continued)

entry	diene	dienophile[a]	reaction conditions: equiv of **3**, solvent, temp, °C (time, h)	product[b] (endo:exo)[c]	yield[d]
					
	1	1		18 19	
15			1.0, CH_2Cl_2, 13 kbar, 24 (84)	35:1	(85) 15[k]
					
	2	**3a**		20 21	
16			10, benzene 80 (16)	4:1	(80) 73
17			20, neat, 6.2 kbar, 24 (124)	9:1	(≥95) 86
18			2.5, CH_2Cl_2, −78, 5 min, $EtAlCl_2$ (0.15 equiv)	1:2.5	(≥95) 94[l]
					
	2	**3b**		22	
19			2.5, CH_2Cl_2, 40 (1.5)		(80) 65
20			4.0, CH_2Cl_2, 6.2 kbar, 24 (124)		
					
	2	**3c**		23 24	
21			2.0, CH_2Cl_2, 6.2 kbar, 24 (124)	25:1	(≥95) 78[m]
					
	2	**3d**		25 26	
22			3.6, CH_2Cl_2, 10 kbar, 24 (96)	1:1	(≥95) 72[i]
					
	2	**3e**		27 28	
23			6.0, CH_2Cl_2, 10 kbar, 24 (96)	3:1	(≥95) 49

[a] Dienophiles **3a** (ethyl vinyl ether), **3b** (1,1-dimethoxyethylene), and **3g** (4-methoxy-3-buten-2-one) were obtained from commercial sources. Dienophiles **3c**, **3d**, **3e**, and **3f** were prepared as previously described: ref 12, 13, 14, and 15 respectively. [b] All products exhibited the expected or previously reported ^1H NMR, IR, and MS characteristics consistent with the assigned structure. All new compounds gave satisfactory HRMS exact mass information. [c] The endo:exo ratio was obtained from ^1H NMR analysis (200 or 300 MHz) of the crude reaction mixture. [d] Isolated yield of purified product isolated by chromatography (SiO_2). The yield in parentheses is the % yield estimated by ^1H NMR analysis of the crude mixture prior to purification on SiO_2. The [4 + 2] cycloadducts are not completely stable to contact with SiO_2, alumina, or Florisil; see ref 18. [e] The minimum reaction time was determined to be 50 h. [f] The endo:exo ratio was found to vary from 0.8:1 to 1:6, and longer reaction times (30 min) resulted in exclusive formation of **6** (by epimerization). [g] Under identical reaction conditions (0.1 equiv, −78 °C, 5 min), $Cu(BF_4)_2$, BF_3·OEt_2, and $Ti(O\text{-}i\text{-}Pr)_3Cl$ provided cycloadducts **5**/**6** in the following yields [(80) 45, (60) 29, (25) 0] and endo:exo ratios (1:2, 2:1, –). $ZnCl_2$ promoted the cycloaddition [2.5 equiv, CH_2Cl_2, 24 °C, 10 min, 5:6 = 2:1, (40) 24], but longer reaction times led to complex mixtures. [h] Only **8** could be isolated (SiO_2). Epimerization [$EtAlCl_2$ (0.1 equiv), CH_2Cl_2, −78 °C, 30 min] of **8** provided a 1:9 mixture of **8** and its C-2 epimer **8a**. [i] The diastereomers could be separated by flash chromatography. [j] A 2.3:1 ratio of **14**/**15** was observed in the ^1H NMR spectrum of the crude reaction mixture. Chromatography (SiO_2) led to the isolation of **14** only. [k] Compound **18** was not stable to contact with SiO_2, alumina, or Florisil. [l] Longer reaction times (10 min) resulted in a 1:4 mixture of **20**/**21** (by epimerization). [m] Only **23** could be isolated.

1,3-butadiene structural variations and modified reaction conditions have been successfully introduced that have permitted the productive or accelerated 4π participation of α,β-unsaturated carbonyl compounds in [4 + 2] cycloaddition reactions. These include the use of intramolecular cycloadditions,[3] 1-oxa-1,3-butadienes bearing a C-3 electron-withdrawing substituent,[4] as well as the use of Lewis acid catalyzed[5] and pressure-promoted[6] cycloaddition reaction conditions. In the conduct of synthetic efforts applicable to the preparation of the carbohydrate components of naturally occurring antitumor antibiotics including bleomycin, we have examined alternative approaches to predictably accelerate the 4π participation of 1-oxa-1,3-butadienes in $LUMO_{diene}$-controlled Diels–Alder reactions.[7]

Herein, we detail studies that demonstrate the accelerated, productive participation of β,γ-unsaturated α-keto esters in endo selective inverse electron demand Diels–Alder reactions suitable for the diastereoselective preparation of 2-alkoxy-3,4-dihydro-2*H*-pyran-6-carboxylates. The expected enhanced reactivity of β,γ-unsaturated α-keto esters was based on the predictable stabilization of the 1-oxa-1,3-butadiene LUMO achieved through the noncomplementary[8] addition of a C-2 electron-withdrawing substituent.[9] The results of the initial investigation of the [4 + 2] cycloaddition reactions of methyl *trans*-4-methoxy-2-oxo-3-butenoate (**1**)[10] and methyl *trans*-4-phenyl-2-oxo-3-butenoate (**2**),[11] representative β,γ-unsaturated α-keto esters, with a full range of electron-rich dienophiles **3a–h**[12–15] are summarized in Table I, eq 1.



(1)

Inspection of the examples provided in Table I illustrate that **1** and **2** are more reactive than simple α,β-unsaturated ketones and aldehydes[2,16] in [4 + 2] cycloaddition reactions with electron-rich dienophiles. Both **1** and **2** exhibited excellent thermal reactivity with ethyl vinyl ether (80–110 °C) and 1,1-dimethoxyethylene (40 °C, 1.5–6 h) cleanly providing the [4 + 2] cycloadducts. The thermal, pressure-promoted, and Lewis acid catalyzed [4 + 2] cycloaddition reaction of **1** and **2** proved to proceed predominantly through an endo transition state, the endo selectivity predictably increased as the temperature of the reaction was decreased and the pressure increased (25 °C, 6–13 kbar > 40–110 °C, 1 atm), and the diene **2** possessing a C-4 phenyl substituent proved slightly more endo selective than diene **1**. The observed endo selectivity and the exclusive preservation of dienophile olefin geometry (entries 8–10, 21) observed in the reactions of **1** and **2** are characteristic of a concerted [4 + 2] cycloaddition reaction. The presence of the α-dicarbonyl in **1** and **2** facilitated the Lewis acid catalyzed [4 + 2] cycloadditions of the dienes, and of the catalysts surveyed (Table I, entries 4 and 5), ethylaluminum dichloride proved to be the most effective and manageable (0.1 equiv of $EtAlCl_2$, −78 °C, <5 min). In the Lewis acid catalyzed cycloadditions of **1** and **2**, the endo:exo product ratio proved dependent on the reaction conditions. Under the conditions of Lewis acid catalysis, the predominant, kinetic endo [4 + 2] cycloadducts suffer C-2 epimerization to provide the more stable isomer.[17] The extent of epimerization proved dependent on the reaction conditions, and as the reaction time, reaction temperature, and amount of catalyst were increased, the extent of observable C-2 epimerization increased. These empirical observations were confirmed by the subjection of **5** and **8** to the reaction conditions (0.1 equiv of $EtAlCl_2$, −78 °C, 5 and 30 min, respectively) cleanly affording the more stable C-2 epimers.[17]

The thermal, pressure-promoted, and Lewis acid catalyzed [4 + 2] cycloaddition reactions of β,γ-unsaturated α-keto esters, e.g., **1** and **2**, provide a productive, endo selective $LUMO_{diene}$-controlled [4 + 2] cycloaddition reaction of 1-oxa-1,3-butadienes. The endo selectivity observed under thermal reaction conditions may be enhanced through use of pressure-promoted reaction conditions. Conventional Lewis acids effectively catalyze the [4 + 2] cycloaddition to afford predominant, kinetic endo [4 + 2] cycloadducts which subsequently suffer epimerization (C-2) to yield the thermodynamically stable products. The

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(9) In a refined comparison with full structure optimization (MOPAC, AM1 Hamiltonian, Version 1.00) including a final, single geometry SCF calculation with CI (CI = 2), the *E* (LUMO) for methyl *trans*-4-methoxy-2-oxo-3-butenoate (**1**) proved substantially lower (0.706 eV) than that of *trans*-3-methoxypropenal. A full summary is provided as supplementary material.
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continued exploration of the [4 + 2] cycloaddition reactions of β,γ-unsaturated α-keto esters and their applications are in progress and will be reported in due course.

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Supplementary Material Available: Representative experimental procedures, full spectral and physical characterizations of **1**, **2**, **5-8**, **10-14**, **16-18**, **20-23**, **25-28**, and a summary of the semiempirical computational (MOPAC, AM1 Hamiltonian) comparison of **1** and *trans*-3-methoxypropenal including HOMO and LUMO three-dimensional molecular orbital plots (21 pages). Ordering information is given on any current masthead page.

(19) National Institutes of Health research career development award recipient, 1983-1988 (CA 01134). Alfred P. Sloan research fellow, 1985-1989.

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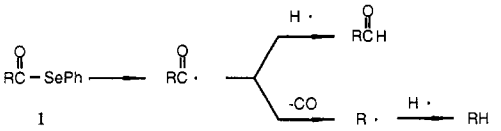
Acyl Radicals: Functionalized Free Radicals for Intramolecular Cyclization Reactions

Summary: A study describing the use of phenyl selenoesters as direct precursors to acyl radicals suitable for the initiation of intramolecular free-radical cyclization reactions is detailed.

Sir: The rapid emergence of intramolecular free-radical cyclization reactions as a means of constructing carbocyclic systems can be attributed largely to the compatibility of most functional groups to the reaction conditions relative to the corresponding ionic reactions.[1,2] The required reaction conditions permit useful functionality to be employed at the reaction centers (initiator, terminator groups) without the need for protection or masking of proximal or distal functionality. Consequently, a wide variety of functionalized precursors suitable for initiation of intramolecular free-radical cyclization reactions have been introduced and include α-acylamino sulfides and selenides,[3] β-bromo acetals,[4] vinyl bromides/iodides,[5] and α-bromo or α-seleno ketones and esters.[6] Surprisingly, only selected and isolated reports of the intramolecular free-radical cyclization reactions of acyl derivatives have been described[7] despite their synthetic potential as fundamental functionalized free radicals. Herein we report that phenyl selenoesters serve as excellent precursors to acyl radicals suitable for use in intramolecular free-radical cyclization reactions.

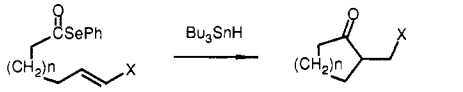
Phenyl selenoesters **1**, readily available from the corresponding carboxylic acids,[8] have been reported to undergo reduction to the corresponding aldehydes and alkanes (decarbonylation and reduction) in the presence of trialkyltin hydrides and a free-radical initiator through generation of acyl radicals, eq 1.[9] This observation and



(1)

1

the report that the free-radical generated from phenyl selenocarbonates effectively participate in intramolecular free-radical cyclization reactions[7c,d] suggested that in the presence of a proximal, unsaturated functionality (C=C, C≡C) the acyl radicals generated under such conditions possess the capability to cyclize directly to ketones **2**, eq 2, competitive with intermolecular reduction and intramolecular decarbonylation.[10] The results summarized in Table I illustrate that the intramolecular free-radical cyclization reactions of acyl radicals generated from phenyl selenoesters proceed efficiently and in most cases with little or no competing reduction or decarbonylation.[11] This contrasts the comparable attempts to productively generate and trap acyl radicals in intramolecular free-radical cyclization reactions employing the corresponding acid chlorides[7a] and phenyl thioesters as precursors; Table I, entries 2 and 3.



(2)

2

The productive participation of acyl radicals generated from phenyl selenoesters in intramolecular free-radical cyclization reactions has proven independent of the free-radical acceptor group and both activated (C=CCO$_2$R) and unactivated (C=C) π-systems serve as suitable intramolecular acceptors. In the absence of directing functionality (e.g., C=CCO$_2$R) the intramolecular acyl radical–alkene cyclization reactions follow the anticipated mode of cyclization:[2] 5-*Exo-Trig* > 6-*Exo-Trig*, 5-*Exo-Trig*

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(11) At present only one instance (Table I, entry 15) of competitive decarbonylation has been observed and presumably is the direct result of generation (and cyclization) of a stabilized benzylic radical.

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