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On the Mechanism of the Intramolecular Samarium Barbier Reaction. Probes for Formation of Radical and Organosamarium Intermediates

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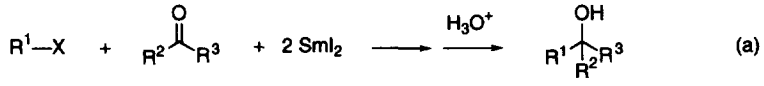
Summary: *A new type of mechanistic probe for the intramolecular samarium Barbier reaction has been designed, and two different probe substrates have been investigated in detail. Remarkably, no unambiguous evidence could be obtained in favor of any of the obvious intermediates (free alkyl or alkoxy radicals, ketyls, organosamarium species) that are postulated for this reaction. Several possibilities for modified mechanisms are suggested.* © 1997 Elsevier Science Ltd.

Introduction: Since its discovery by Kagan and coworkers in 1980,[1] the samarium Barbier reaction has grown to become an important and popular method to couple alkyl halides and dialkyl ketones.[2] In the "Barbier" procedure (eq 1a), all three components—the halide, the ketone, and samarium diiodide (SmI_2)—are mixed together and allowed to react. In 1990, we expanded the scope of this chemistry by introducing the samarium Grignard reaction.[3] In the Grignard procedure (eq 1b), the halide and SmI_2 are prereacted to generate an alkylsamarium reagent in situ, and then the ketone is added. This procedure is valuable because many other electrophiles besides dialkyl ketones (aryl alkyl ketones, aldehydes, disulfides, etc.) can be used. These electrophiles often fail in the Barbier procedures, presumably because the intended electrophile is itself reduced by SmI_2. However, the in situ generated samarium reagents are unstable, so for certain types of halides the Barbier procedure remains superior to the Grignard procedure.

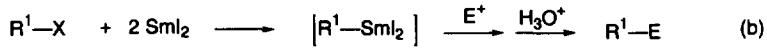
eq 1

The Samarium Barbier Reaction



(a)

The Samarium Grignard Reaction



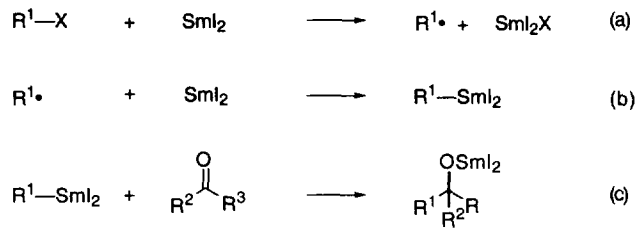
(b)

In part because all three components are mixed together simultaneously, the mechanisms of all types of Barbier reactions are difficult to pin down with certainty. The samarium Barbier reaction has been no exception, and no fewer than four basic mechanisms (each with its own nuances) have been considered over the years. All the mechanisms (and most of the nuances) were proposed at

†We dedicate this paper to Prof. Paul Dowd, who died on November 21, 1996.

one time or another by Kagan.[4] Over the last few years, a consensus has begun to emerge that an "ionic addition" mechanism is common in the samarium Barbier reaction.[5] The essence of this mechanism is shown in eqs 2a-c. Alkyl halides are reduced to (free) radicals with the first equivalent of SmI_2 (step a), and these radicals are subsequently reduced to organosamarium intermediates with the second equivalent (step b). These intermediates then add to the ketone to produce samarium alkoxides (step c). The involvement of both free radicals and organosamarium intermediates has been the basis for a number of sequential "radical/ionic" reactions that can be conducted under Barbier and Grignard procedures.[6]

eq 2

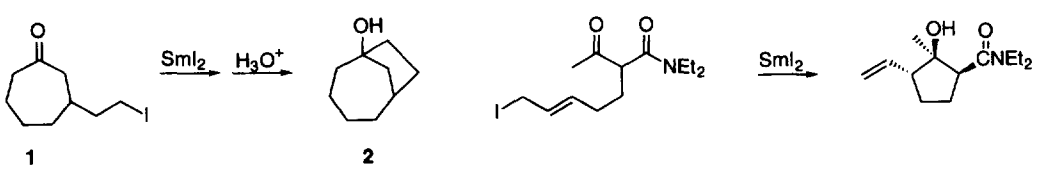


Much of the best evidence for the ionic addition mechanism has come from complementary studies in Molander's group and ours. Early evidence for the ionic addition mechanism came from in situ trapping experiments.[7] These experiments first suggested that organosamarium intermediates could form, but their value has been compromised because it is now known that the presence of in situ traps such as D_2O can alter the reducing power of SmI_2.[8] By conducting samarium Grignard reactions, we unambiguously showed that many types of organosamarium intermediates can form. However, trapping experiments conducted in the absence of the ketone cannot alone identify the mechanism of a samarium Barbier reaction since they only probe how a reduction evolves in the absence of a ketone. The best evidence that organosamarium intermediates are involved in the samarium Barbier reaction is a stereochemical parallel: Grignard and Barbier reactions typically give the same ratio of stereoisomers in additions to ketones.[3,5] Thus, trapping experiments in the absence of ketone show that samarium reagents can form, and the Barbier/Grignard stereochemical parallel suggests that they do form in the presence of ketones.

The intramolecular Barbier reaction has been developed into a powerful synthetic tool by Molander[9] and others.[10] The reaction has remarkable scope, and often occurs with high stereoselectivity, as illustrated by the examples in eq 3a. It is tempting to assume by analogy that the intramolecular samarium Barbier reaction proceeds by an ionic addition mechanism (eq 3b) analogous to that for the intermolecular Barbier reaction (eq 2). However, this assumption is not easily supported by experimental evidence. By definition, one cannot conduct an "intramolecular samarium Grignard reaction,"[11] and therefore it is not possible to establish that organosamarium intermediates can be formed from haloketones in the same way that it can be established that they are formed from halides.

eq 3a

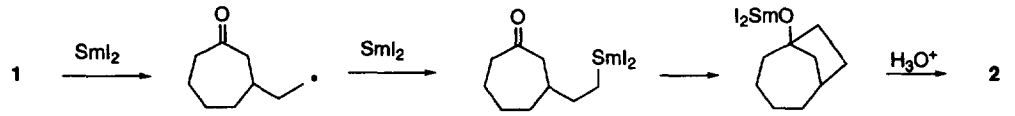
Examples of Intramolecular Samarium Barbier Reactions



1 2

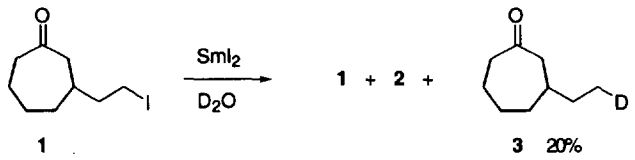
eq 3b

Ionic addition mechanism

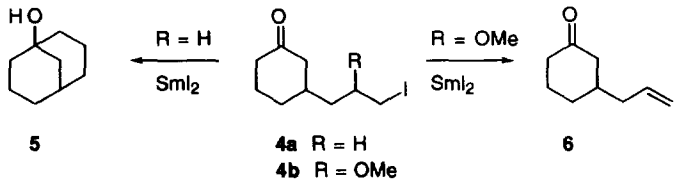


Molander and McKie have provided the best evidence to date that organosamarium intermediates are involved in the intramolecular Barbier reaction.[9a] Two of their key experiments are summarized in eq 4. In the first, reduction of **1** at low temperature followed by rapid addition of D_2O leads to the trapping of 20% deuterated product **3** along with recovered **1** and product **2** in unspecified amounts. This is in contrast to the result in eq 3a; when the trap is not present, **2** is formed in high yield. In the second experiment, reduction of **4a** results in cyclization to **5** while similar treatment of **4b** result in β-elimination to **6**. Molander and McKie concluded that these experiments provided the first irrefutable evidence that organosamarium intermediates can be involved in the samarium Barbier reaction.[9a] These experiments do indeed provide strong evidence for the organosamarium intermediates; however, the evidence may not be irrefutable. For example, it is known that water increases the reducing ability of SmI_2,[8] so it is conceivable that the formation of the organosamarium precursor of **3** was induced by adding the water. Similarly, the methoxy group of **4b** will significantly lower the reduction potential of a radical β to it, thereby compromising the mechanistic analogy between **4a** and **4b**. In raising these concerns, we do not seek to refute the reasonable conclusions of Molander and McKie, but simply to highlight the difficulties in obtaining unambiguous mechanistic evidence for Barbier reactions in general.

eq 4a



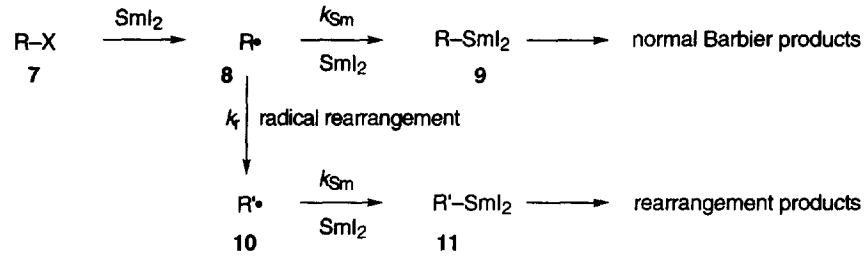
eq 4b



The preparative importance of the intramolecular samarium Barbier reaction coupled with the difficulties in designing unambiguous experiments to probe the mechanisms of intramolecular Barbier reactions in general prompted us to design a new type of mechanistic experiment to address this question. In this paper, we employ a class of mechanistic probe possessing a "radical clock"[12] that is designed to record the lifetime of a radical intermediate with respect to its conversion to an organosamarium intermediate by reduction with SmI_2. Surprisingly, the results suggest that the substrates under study do not cyclize by the simple "ionic addition" mechanism outlined in eqs 2 and 3b.

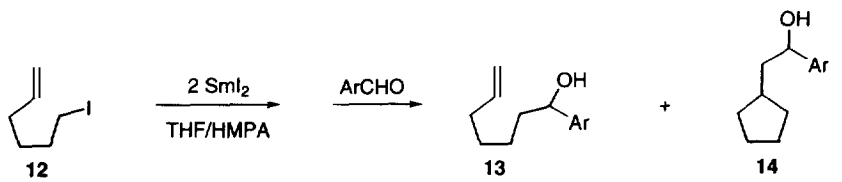
Results and Discussion: Equation 5 illustrates the design of the mechanistic probe experiments in the context of the ionic addition mechanism. Reduction of a precursor **7** by SmI_2 will generate a radical **8** that can partition between direct reduction to an organosamarium intermediate **9** and rearrangement to **10** prior to reduction. By measuring the rate constants k_{Sm} and k_r, it becomes possible to predict the ratio of normal Barbier products to rearranged products at a given concentration. The experimental verification of the predictions over a range of concentrations would provide strong support for the ionic addition mechanism.

eq 5



We recently estimated the rate constants k_{Sm} for reduction of a 1°-alkyl radical by SmI_2 as a function of HMPA concentration.[13] Rate constants in this study were measured by reducing hexenyl iodide **12** with 0.1M SmI_2, quenching the reaction with *p*-methoxybenzaldehyde (Grignard procedure), and then measuring the ratio of unrearranged to rearranged products (**13/14**, eq 6a). The rate constant k_{Sm} increased as a function of HMPA concentration from about 5×10^5 M^{-1} s^{-1} (with 2 equiv HMPA per SmI_2) to a plateau of 6×10^6 M^{-1} s^{-1} (with ≥ 4 equiv HMPA per SmI_2). Since it is known that ketones are rapidly (but probably also reversibly) reduced by SmI_2 to ketyls[3,4] we felt that a rate constant k_{Sm} for this study should be determined in the presence of a ketone. Therefore, we conducted a series of experiments analogous to the earlier work, but this time the reactions of hexenyl iodide with SmI_2 and HMPA were conducted in the presence of 2-octanone (eq 6b). The data for both the prior and new series of experiments are shown side by side in Table 1. Surprisingly, when the ketone is present in the medium (Barbier procedure), the ratio of **16** to **17** no longer depends on the HMPA concentration, and the rate constant k_{Sm} is already at the "plateau" level even when no HMPA is present.

eq 6a



eq 6b

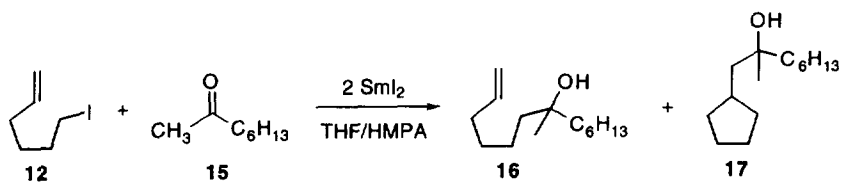


Table 1. Ratios 13/14 and 16/17 as a Function of HMPA Quantity

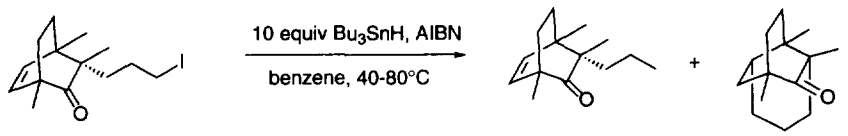
Entry	HMPA equiv vs SmI_2	**16/17** (%) Barbier method[a]	**13/14** (%) Grignard method[b]
1	0	61 : 39	**
2	2.3	**	8 : 92
3	2.8	**	10 : 90
4	3.2	57 : 43	34 : 66
5	3.7	**	50 : 50
6	4.4	**	54 : 46
7	5.0	60 : 40	56 : 44
8	6.0	**	54 : 46
9	7.0	57 : 43	52 : 48

a) this work; b) reference 13; ** not conducted

Thus, reductions of 1°-alkyl radicals by SmI_2 in THF are accelerated by ketones by at least a factor of 10 (the actual acceleration cannot be estimated because the rate constant for reduction an alkyl radical in THF with no HMPA is not known).[13] One possible explanation for this acceleration is that ketyls behave as intermediaries in the reduction of radicals by SmI_2. Alternatively, either the ketone or the samarium alkoxide product of the Grignard reaction (or both) may behave as ligands for the SmI_2 and accelerate the reduction in the same way that HMPA does. In any event, this observation simplifies the kinetic analysis by suggesting the single value 6 x 10^6 M^{-1} s^{-1} should be used for k_{Sm} under all Barbier conditions.

The first mechanistic probe, bicyclic ketoalkene **18**, has already been used to provide insight into the origins of reaction products in lithium/halogen exchange reactions.[14] The Arhenius equation for cyclization of a radical (derived from **18**) was determined by reduction under pseudo-first order conditions with tributyltin hydride over a range of temperatures in benzene. The ratios of reduced (**19**) to cyclized (**20**) products shown in Table 2 were processed as usual[12] to provide the indicated equation. From this, we calculate that k_c at 25°C = 3 x 10^6 s^{-1}.

Table 2. Measurements of Rate Constant for Reduction of 18



18 **19** **20**

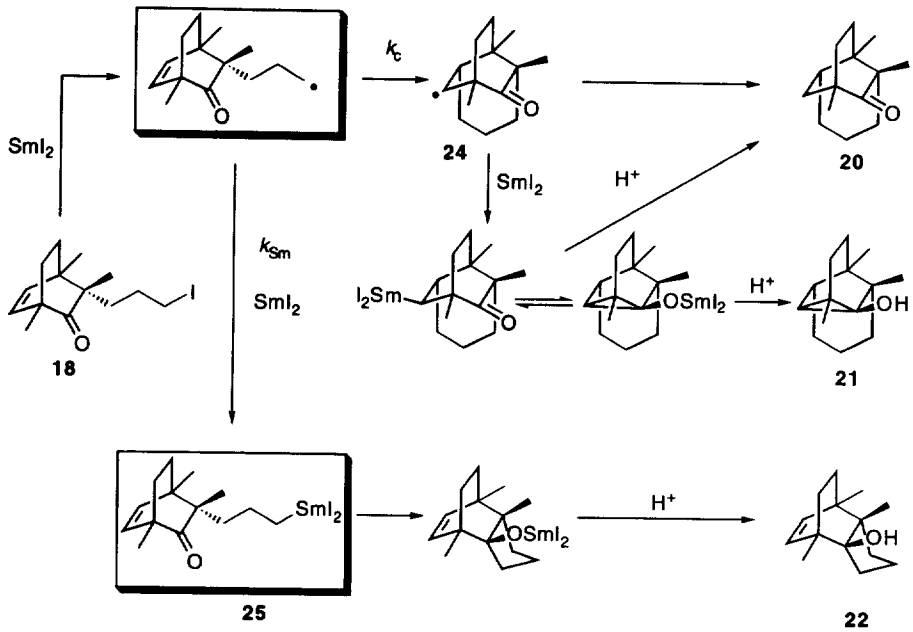
$\log k_c = 9.07 - 3.69/2.3\ RT$

temp (°C)	$[Bu_3SnH]$ (M)	product ratios **20**	**19**	k_c/k_H (M)	k_H (x 10^6) ($M^{-1}s^{-1}$)	k_c (x 10^7) s^{-1}
40	0.43	82.4	17.6	2.02	3.09	0.62
50	0.43	83.8	16.2	2.22	3.72	0.83
60	0.43	84.5	15.5	2.34	4.42	1.04
70	0.43	85.3	14.7	2.52	5.20	1.29
80	0.43	86.4	13.6	2.72	6.06	1.65

Earlier cyclizations of **18** under various conditions provided differing amounts of ketone **20** and alcohols **21** and **22**. The previously proposed mechanism[14] modified for the reduction of **18** under samarium Barbier conditions is shown in Scheme 1. Product **22** is thought to arise via radical

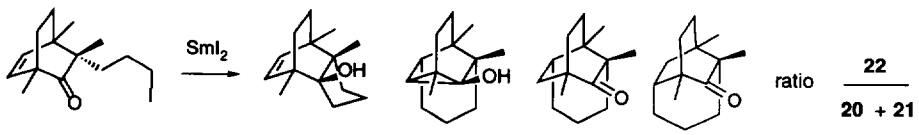
reduction and cyclization of an organosamarium reagent, while products **20** and **21** are thought to arise by radical cyclization. Thus, by applying the measured rate constants k_{Sm} and k_c, one can calculate the ratio of **22**/[**20** + **21**] at a given SmI_2 concentration.

Scheme 1



The reduction of **18** was conducted in THF with 2 equiv of SmI_2 and 20 equiv of HMPA. Table 3 shows the observed product ratios as well as the calculated and observed ratios of **22**/[**20** + **21**]. In addition to these three expected products, a fourth product tentatively assigned structure **23** was produced in small amounts. The observed ratios are inconsistent with the predictions. Worse yet, the observed trends are opposite to those predicted: the ratio **22**/[**20** + **21**] should increase with increasing SmI_2 concentration as the reduction of radical **24** to organosamarium reagent **25** becomes more efficient, but instead this ratio decreases significantly as the concentration of SmI_2 is raised.

Table 3. Reduction of 18 with SmI_2



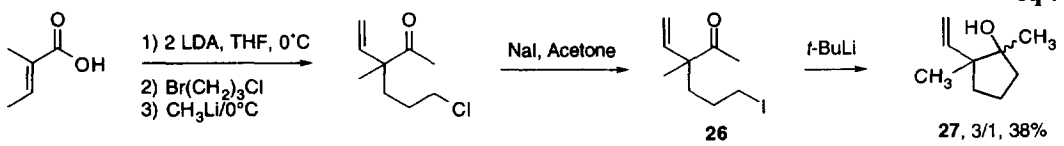
ratio $\frac{22}{20 + 21}$

18 SmI_2 (M)	**22**	**21**	**20**	**23**	obs	calc
0.01	64%	21%	11%	4%	2.0	0.01
0.03	42%	42%	11%	5%	0.8	0.03
0.05	27%	55%	13%	5%	0.4	0.05
0.07	20%	59%	15%	6%	0.23	0.07

The data in Table 3 currently defy straightforward interpretation. For example, the origin of the minor product **23** is not known. Further, it is not clear why the amounts of **20** and **23** remain almost invariant while those of **22** and **21** decrease and increase, respectively, with increasing SmI_2 concentration. At 0.01M [SmI_2], the analysis predicts that the yield of **22** will be <1%, yet the observed yield is 64%! Regardless of speculative interpretations, one thing is clear: the data in Table 3 are grossly inconsistent with the mechanism in eq 2 as expressed in Scheme 1.

The bicyclic ring in **18** holds the ketone and the alkene in a favorable orientation for interaction. In these mechanistic experiments, this interaction may be undesirable, since these two functional groups are designed as the ultimate traps by which rearranged and unrearranged ratios are measured. Therefore, we have studied in more depth the acyclic ketoalkene **26**. This probe is readily synthesized, as shown in eq 7. An authentic sample of the expected Barbier product was prepared by treatment of **26** with *t*-butyllithium in pentane/ether at –78°C. This provided 3/1 mixture of epimeric alcohols **27** in 38% isolated yield.

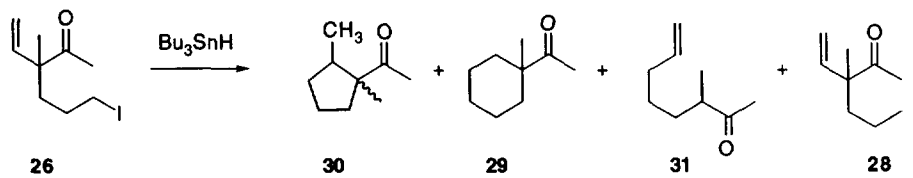
eq 7



26 **27**, 3/1, 38%

The data for the tin hydride reduction of **26** in benzene at 80°C are summarized in Table 4 and interpreted by the mechanism in Scheme 2. Products **28-30** were identified by comparison to independently synthesized samples (see Experimental section), and ratios were determined by GC analysis. Yields were determined by GC intergration against internal standards.

Table 4. Product Ratios for Reduction of 26 with Bu_3SnH at 80°C



26 **30** **29** **31** **28**

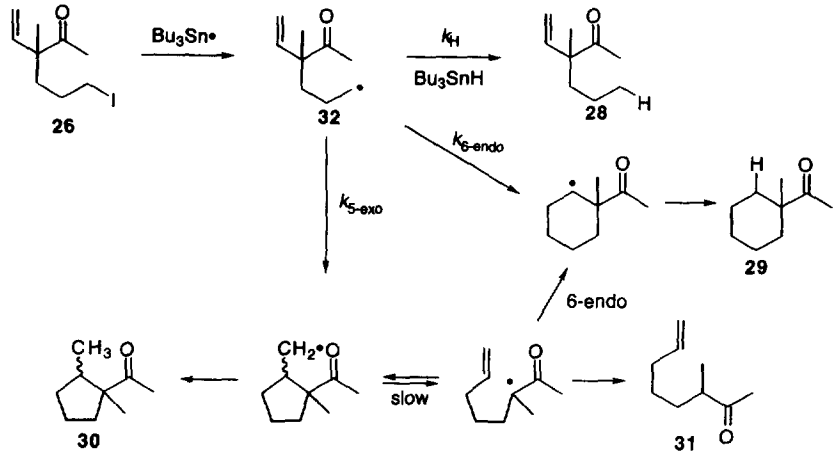
Concentration SnH (M)	Product ratios (%) **30**(*)	**29**	**31**	**28**
1.00	24 (6/1)	2	**	74
0.20	56 (5/1)	4	**	40
0.10	55 (7/1)	3	**	42
0.02	80 (6/1)	7	1	12
0.005	74 (4/1)	17	9	<1

*diastereomer ratio of **30**; **undetectable

At tin hydride concentrations between 0.1M and 1.0M, a normal concentration dependence between the directly reduced product **28** and the products of 5-*exo* (**30**, two epimers) and 6-*endo* (**29**) cyclization was observed. As usual, only small amounts of the 6-*endo* product were observed. However, as the concentration was decreased below 0.01M, the amount of one of the epimers of the

5-*exo* product decreased, a new reduced product **31** appeared, and the amount of 6-*endo* **29** product increased. This suggests that partial equilibration by reverse 5-*exo* cyclization is occurring at the lowest concentrations. Using the data from the cyclization at 0.1M – 1.0 M, we can estimate that k_c 5-*exo* at 80°C = 6 x 10^6 s^{-1}.

Scheme 2



Given that the observed product ratios were so far off from those predicted (see below), careful Arhenius studies of **26** seemed pointless. We therefore simply estimated the rate constant for cyclization of radical **32** under the actual reaction conditions by reducing **26** with 10 equiv tributyltin hydride in benzene (initiation with Et_3B and O_2) at 25°C. From the ratio of cyclized to reduced products, we calculate k_c = 2.5 x 10^5 s^{-1} at 25°C. This rate constant is in a reasonable range based on the expected temperature effect, and is very close to the rate constant for the cyclization of the hexenyl radical.[13]

The expected "ionic addition" mechanism for the intramolecular samarium Barbier reaction of **26** is shown in Scheme 3. As before, a competition between reduction and cyclization at the stage of radical **32** should result in a ratio of Barbier product **27** to "rearranged products" that can be calculated from the known rate constants (k_{Sm} and k_c) and the reaction conditions. A possible point of weakness of this probe is that the nature of the "rearrangement products" (presumably derived from organosamarium reagent **35**) is not known in advance. In the event, this point proved to be moot; there were no "rearranged products".

Scheme 3

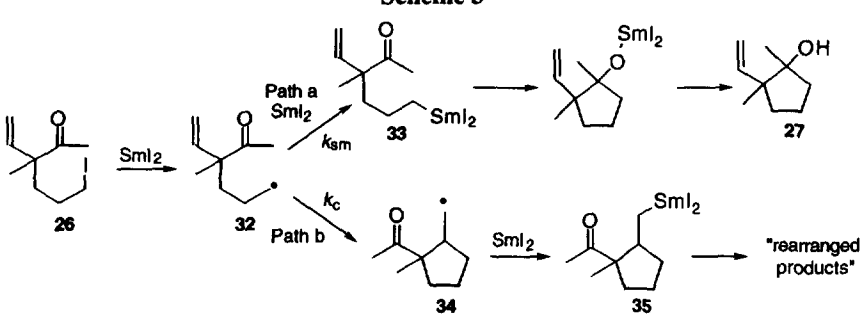
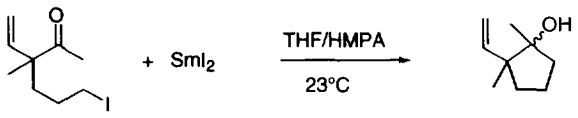


Table 5 collects data from reductions of **26** under several different conditions, and it also shows the predicted ratio of intramolecular Barbier products to (unspecified) rearranged products. In all cases, the only products observed were the epimeric alcohols **27**. These alcohols are formed independent of the reaction concentration and the amount of HMPA, although the amount of HMPA did have a small effect on the ratio of epimeric products. Even the addition of 10 equiv of MeOD or 10 equiv of H_2O prior to the addition of SmI_2 (data not shown) had no effect on the outcome of the reaction. This is in contrast to Molander and McKie's successful trapping in eq 3.[9b]

Table 5. Reduction of 26 with SmI_2



26 **27**

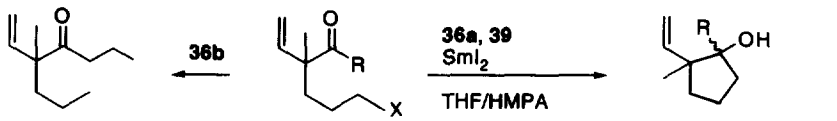
entry	concentration SmI_2 (M)	HMPA equiv vs SmI_2	diastereomer ratio	yield **27**	calc **27**/R[a]
1	0.10	0	—	—[b]	0.2
2	0.10	2.3	57/43	76%	0.2
3	0.10	3.2	62/38	65%	0.2
4	0.10	5.0	71/29	68%	0.2
5	0.03	2.3	57/43	72%	0.6
6	0.01	2.3	57/43	70%	1.8

a) "R" represents unspecified rearranged products (none detected); b) the reaction mixture was stirred at 23°C for 16 h and most of the starting material **26** was recovered.

Isolated yields of **27**, although not quantitative, were reasonable (~70%). No significant side products could be detected by GC-MS analysis in any experiments. Further, the yield of **27** did not vary with conditions and it exceeded the theoretical amount predicted by Scheme 3 (thereby excluding the possibility that "rearranged products" were formed but decomposed by unknown pathways). In short, there is no evidence for formation of "rearranged products" under any conditions. Since substantive amounts of these products are predicted under all conditions (up to 80% in entry 6), we must again conclude that the mechanism is eq 2 as embodied in Scheme 3 is not correct.

Two other attempts in this series were made to side track potential reactive intermediates. The cyclopropylketone **36a** was prepared by a sequence analogous to **26** in order to probe the intermediacy of a ketyl.[15] Reduction of **36a** under the usual conditions (THF/HMPA) cleanly provided a mixture of isomers **37** (63/37) in 74% isolated yield; no other significant products were detected (eq 8). In contrast, reduction of ketone **36b** (lacking the iodide) provided the expected propylketone **38** (60% isolated yield). Thus, if ketyl intermediates are involved in this reaction, their lifetimes must be drastically shortened by the presence of the iodide. The highly crowded ketone **39** was prepared in an attempt to slow down as much as possible the carbon-carbon bond forming reaction. This attempt failed. Cyclization of **39** proceeded normally and gave the alcohol **40** with three adjacent quaternary carbons in 71% isolated yield as a 3/1 mixture of isomers. Whatever the mechanism of this intramolecular Barbier reaction, it is clearly quite efficient—attempts to intercept diverse intermediates all fail!

eq 8



38

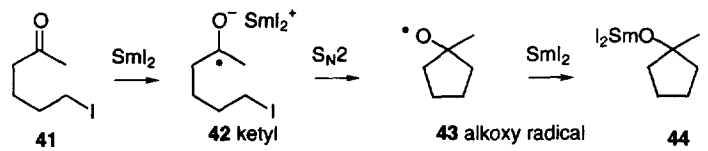
36a X = I, R = cyclopropyl
36b X = H, R = cyclopropyl
39 X = I, R = ^{t}Bu

37 R = cyclopropyl
40 R = ^{t}Bu

The results with probes **18** and **26** are not consistent with the accepted ionic addition mechanism. In ruling out the "unmodified" ionic addition mechanism, we must then step back and reconsider whether the current data are consistent with any of the other mechanisms. Kagan's four mechanisms, as applied to a simple intramolecular samarium Barbier reaction, are shown in eqs 9a-d. These mechanisms are named by the carbon-carbon bond forming step as: 1) S_N2, 2) radical cyclization, 3) ketyl-radical coupling, and 4) ionic addition. We submit that none of these four mechanisms in their unmodified forms is consistent with our observations for this type of intramolecular Barbier cyclization.

eq 9a

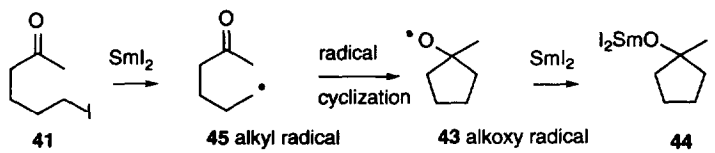
S_N2



41 **42** ketyl **43** alkoxy radical **44**

eq 9b

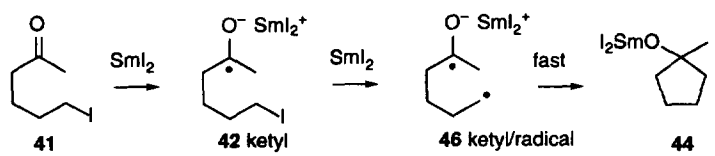
radical cyclization



41 **45** alkyl radical **43** alkoxy radical **44**

eq 9c

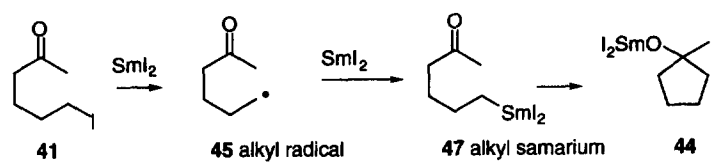
ketyl-radical coupling



41 **42** ketyl **46** ketyl/radical **44**

eq 9d

ionic addition



41 **45** alkyl radical **47** alkyl samarium **44**

Several common intermediates appear in these mechanisms. Although short-lived ketyls **42** cannot be ruled out, attempts to detect the ketyl intermediates **42** that appear in the S_N2 and ketyl-radical coupling mechanisms have failed. Free alkoxy radicals **43**, appearing in the S_N2 and radical cyclization mechanisms, are highly reactive towards fragmentation and 1,5-hydrogen transfer. Since such reactions have never been observed in any kind of samarium Barbier reaction, the intermediacy of free alkoxyl radicals is improbable.[4c] The current study rules out the intermediacy of free alkyl radicals **45** that appear in the radical cyclization and organometallic addition steps. Thus, at least one (sometimes two) intermediates are ruled out in all mechanisms!

Further problems arise when considering individual steps.[5] In the S_N2 mechanism, the conversion of the ketyl **42** to the alkoxy radical **43** by *C*-alkylation is thought to be stereoelectronically disfavored. Intramolecular reaction of ketyls **42** should occur by *O*-alkylation or intramolecular electron transfer, with the electron transfer being more favored in this system (see below).[16] For the radical cyclization mechanism, radical cyclization to ketones simply cannot compete with other processes, so this mechanism was already ruled out before these probe studies. The ketyl-radical coupling mechanism requires an improbable event: the generation of two reactive intermediates—a radical and a ketyl—in the same molecule **46** at the same time. The kinetic problems with this have already been discussed.[5]

Accepting that mechanistic modifications are required, the questions then become which mechanism to modify, and how to modify it? We consider several possible modifications in Scheme 4. In the first, it is suggested that the iodide is reduced by intramolecular electron transfer from the ketyl. There is qualitative evidence that ketones can be reduced to ketyls faster than iodides are reduced to radicals, and recent experimental and theoretical studies suggest that the subsequent intramolecular electron transfer could be very fast[16] (it must be faster than cyclopropylketyl opening[17] to be consistent with the results). We also have some preliminary results from competition experiments that seem consistent with intramolecular electron transfer.[18] However, the postulation of intramolecular ET does not solve any problems; it simply provides a new mechanistic avenue for formation of radical **45**. The key issue remains: what intermediate is involved in the C–C bond formation?

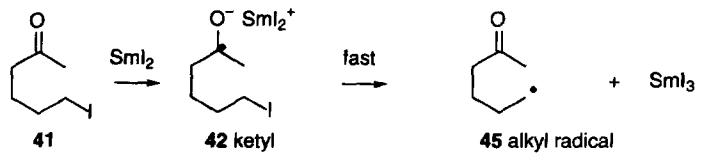
The experimental results suggest that if a radical like **45** is involved, it is either not free, or is not subject to the direct competition between radical cyclization to the alkene and bimolecular reduction by SmI_2. There are at least two ways that the competition can be voided: samarium(III) can accelerate the radical cyclization to the ketone (modification 2), or the samarium species can somehow be oligomeric (modification 3). There is no evidence that Lewis acids like samarium(III) can accelerate radical cyclizations to ketones, although this postulate is not unreasonable based on Frontier Molecular Orbital theory.[19] The postulated acceleration must be quite significant to explain the results, and the coordination must still occur with hindered ketones. Furthermore, this reaction only provides a modified route to an alkoxy radical intermediate so it requires the additional postulate that this alkoxy radical is not free. One can envision a transient intermediate that is either a Sm(III) complexed radical (see **48a**) or a "Sm(IV) alkoxide" (see **48b**).[20]

Modifications involving oligomeric samarium(II) intermediates are also intriguing. For example, consider that samarium ketyls like **49** might be dimeric (or oligomeric).[21] After intramolecular electron transfer, the immediate radical product **50** is still associated to a samarium(II) atom. Intramolecular electron transfer to the new ketone would probably result in immediate C–C bond formation (this is a kind of ketyl–radical coupling), while electron transfer to the radical gives the carbanion (or organosamarium reagent) **52** (this is a kind of nucleophilic or organometallic addition). In either case, these postulates might explain why a direct competition between bimolecular

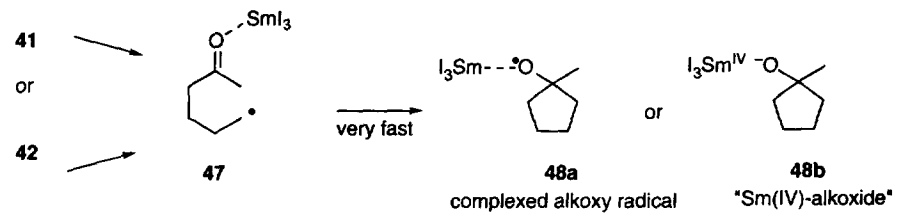
reduction and cyclization of a radical is not observed when the ketone is proximate to the radical. Modifications 2 and 3 look better when paired with modification 1, but this pairing is not required.

Scheme 4

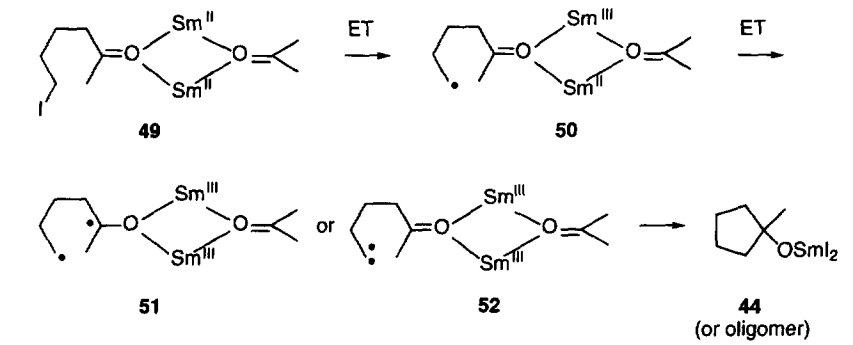
Modification 1 - Intramolecular electron transfer



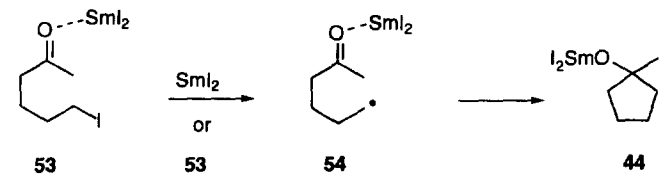
Modification 2 - Complexed ketone with Sm^{III} (Lewis acid)



Modification 3 - Dimeric (oligomeric) Intermediates



Modification 4 Complexed ketone with Sm^{II}



Finally, in modification 4, it is suggested that most ketones are present not free, but as complexes **53** with samarium(II). In this view, reduction of an iodide by free SmI_2 (or by another ketone/SmI_2 complex) provides radical **54**. This can then be subject to rapid coupling to give the product **44** (this reaction resembles ketyl–radical coupling), or undergo rapid intramolecular ET to

give the organosamarium reagent. This further requires that the mechanism of the bimolecular samarium Barbier reaction be modified to include *bimolecular* reduction of a radical by a ketone/SmI_2 complex. This could explain why a normal competition between cyclization/bimolecular reduction of a radical does occur in bimolecular Barbier reactions but not in intramolecular ones, and it is also consistent with the demonstration at the outset of this study that the addition of a ketone alters the rate constant for reduction of radicals by SmI_2. However, this modification is also not without problems. It requires that the ketone–SmI_2 complex **53** be present at high concentrations (otherwise, the mechanism becomes very similar to the ketyl-radical coupling mechanism, and has the same problems). Given that the reaction medium consists largely of THF and HMPA, two excellent ligand for samarium, it is not clear that this postulate is reasonable. Further, altering the HMPA concentration has no effect on the reaction. Finally, the mechanism requires that the ketone–SmI_2 complex **53** and the samarium ketyl **42** be separate intermediates with a real barrier between them, not resonance forms or rapidly equilibrating intermediates. If this condition is not met, then this modification would simply appear to be a minor perturbation on the standard ketyl–radical coupling mechanism.

Conclusions: The previous results of Molander and McKie[9b] provide good evidence that intramolecular samarium Barbier reactions of iodoketone precursors of bridged alcohols occur through organosamarium intermediates. Our iodoketone probes were designed to detect the supposed partitioning of free radicals between cyclization and reduction to an organosamarium intermediate in samarium Barbier reactions to provide fused bicyclic and monocyclic alcohols. The anticipated results were not borne out by experiment, thereby questioning the intermediacy of both free radicals and organosamarium intermediates. These probe substrates suggest a fundamental difference between samarium Grignard reactions, where a standard competition between radical cyclization and bimolecular reduction exists, and intramolecular samarium Barbier reactions, where this competition does not always exist.

At this point, we cannot reconcile the apparent differences between our results and Molander and McKie's. It is possible that the postulate of intramolecular electron transfer is important. The bridged precursors of Molander and McKie may resist intramolecular electron transfer and thereby behave more like bimolecular samarium Barbier substrates. However, as already pointed out, the postulation of intramolecular electron transfer still does not provide an obvious solution to the mechanistic quandary. The intermediate involved in the key carbon–carbon bond forming reaction of the samarium Barbier reaction remains elusive. The results with structure **26** are quite remarkable. If the intermediate is a radical, it cannot be trapped by cyclization, if it is a ketyl, it cannot be trapped by cyclopropylcarbinyl ketyl fragmentation, and if it is an organosamarium species it cannot be trapped by protonation.

EXPERIMENTAL

General: All reactions were conducted under a nitrogen or argon atmosphere. Samarium powder (40 mesh, Aldrich) was used without further purification. Anhydrous solvents were obtained as follows: THF, diethyl ether and benzene were distilled from sodium/benzophenone under argon. Pentane, CH_2Cl_2 and HMPA were distilled from CaH_2. HMPA was stored over 4 Å molecular sieves under argon.

Preparation of 0.1 M SmI_2 in THF.[22] A suspension of samarium powder (1.82 g, 12 mmol) and I_2 (2.54 g, 10 mmol) in dry THF (100 mL) was stirred vigorously at 23°C for at least 2 h, during which time the color changed from purple to yellow-brown to green and finally to prussian blue. This procedure gave a 0.1 M solution of SmI_2, and the titer was checked by titration with a 0.1 M solution of I_2 in THF (the end point is reached when the solution turns yellow and SmI_3 precipitates).

General Procedure for Intermolecular Samarium Barbier Reactions. A mixture of iodide **12** (0.08 g, 0.4 mmol) and ketone **15** (0.05 g, 0.4 mmol) in THF (1.2 mL) was added to a solution of SmI_2 in THF (0.10 M, 8.4 mL) containing HMPA (0.75 g, 4.2 mmol). The reaction was stirred at 23°C for 1 h and then quenched with sat. NH_4Cl and extracted with ether. The organic extracts were washed with water, 3% $Na_2S_2O_3$, and brine and dried over $MgSO_4$. Filtration and concentration gave a crude oil which was analyzed by ^1H NMR spectroscopy. Products were identified by comparison with the authentic samples prepared as described below.

7-Methyl-1-tridec-1-en-7-ol (16). *t*-BuLi in pentane (1.7 M, 0.70 mL) was added dropwise to a solution of **12** (0.11 g, 0.52 mmol) in pentane/ether (3/2, 5 mL) at –78°C and the reaction was stirred at –78°C for 5 min. Ketone **15** (0.07 g, 0.54 mmol) was added. The reaction was then stirred at –78°C for 15 min and at 23°C for 1 h and quenched with water. The aqueous layer was extracted with ether and the ether extracts were washed with water and brine, then dried over $MgSO_4$, filtered and concentrated. The residue oil was chromatographed (Hexane : EtOAc = 8: 1) to give **16** (0.037 g, 34%): ^1H NMR δ 5.88-5.74 (m, 1 H), 5.04-4.92 (m, 2 H), 2.07 (m, 2 H), 1.51-1.10 (m, 19 H), 0.93 (s, 1 H), 0.88 (t, J = 7 Hz, 3 H); ^{13}C NMR δ 139.0, 114.5, 72.9, 42.0, 41.8, 33.8, 32.0, 30.0, 29.6, 27.1, 24.0, 23.5, 22.7, 14.2; IR 3407, 3077, 2930, 2857, 1638, 1458, 1375, 1144, 992, 909; MS (EI) *m/e* 55, 69, 109, 129, 197; HRMS calcd for $C_{13}H_{25}O$ ($M^+ - CH_3$) 197.1905, found 197.1917.

1-Cyclopentyl-2-methyloctan-2-ol (17). *t*-BuLi in pentane (1.7 M, 0.70 mL) was added dropwise to a solution of **12** (0.10 g, 0.48 mmol) in pentane/ether (3/2, 5 mL) at –78°C and the reaction was stirred at –78°C for 5 min. The reaction was then stirred at 23°C for 1 h, then cooled to –78°C, and **15** (0.06 g, 0.47 mmol) was added. The reaction was stirred at –78°C for 1 h, then quenched with water, and extracted with ether. The ether extracts were washed with water, then with brine, dried over $MgSO_4$, filtered and concentrated. The product was chromatographed (Hexane : EtOAc = 8: 1) to give **17** (0.07 g, 74%): ^1H NMR δ 1.91-1.74 (m, 3 H), 1.68-1.02 (m, 22 H), 0.88 (t, J = 6 Hz, 3 H); ^{13}C NMR 73.4, 47.9, 42.8, 36.2, 34.64, 34.59, 32.0, 30.0, 27.5, 25.1, 25.0, 24.0, 22.7, 14.2; IR 3389, 2932, 2859, 1456, 1373, 1148, 924; MS (EI) *m/e* 55, 69, 109, 129, 197; HRMS calcd for $C_{13}H_{25}O$ ($M^+ - CH_3$) 197.1905, found 197.1917.

Kinetic experiment of (1*SR*,3*SR*,4*RS*)-3-(3'-iodopropyl)-1,3,4-trimethylbicyclo[2.2.2]-oct-5-en-2-one (18) with Bu3SnH. Iodide **18** was prepared quantitatively by treatment of (1*SR*,3*SR*,4*RS*)-3-(3'-bromopropyl)-1,3,4-trimethylbicyclo[2.2.2]oct-5-en-2-one[23] with excess NaI in refluxing acetone. Tin hydride reduction of iodide **18** was carried out as follows: Bu_3SnH (270 μL, 1.0 mmol) through a 500 μL microsyringe was rapidly added to a solution of **18** (35.0 mg, 0.11 mmol) and AIBN (1.8 mg, 0.01 mmol) in 2.0 mL of benzene at 40 °C. After 30 min at this temperature, the ratio of cyclization product **20** to direct reduction product **19** was determined by GC analysis. This experiment was repeated at temperatures of 50, 60, 70, and 80 °C. Product ratios are listed in Table 2. Compound **20** has been prepared by an independent method published in earlier papers.[14,23]

Compound **22** is known.[24] An authentic sample of **19** was prepared as follows: a solution of (1*SR*,3*RS*,4*RS*)-1,3,4-trimethylbicyclo[2.2.2]oct-5-en-2-one[23] (50 mg, 0.3 mmol) in THF (0.5 mL) and HMPA (0.5 mL) was added to a stirring 1.5 M LDA solution (0.24 mL, 0.36 mmol) in THF at –78 °C. The temperature of the mixture was allowed to climb to 25 °C and the reaction was stirred at this temperature for 30 min. The reaction mixture was cooled to –30 °C, 1-bromopropane (30.0 mL, 0.33 mmol) was added and the reaction was warmed to 25 °C. The mixture was quenched with 10% aq. NH4Cl solution (1 mL). Flash chromatography (20:1 hexanes-ether) of the crude product after ether workup gave **19** as a colorless oil (23.1 mg, 37%). ^1H NMR ($CDCl_3$) δ 0.76 (t, J = 7.1, 3 H), 0.97 (s, 3 H), 1.13 (s, 3 H), 1.19 (s, 3 H), 0.90–1.85 (8 H), 5.64 (d, J = 8.1, 1 H), 6.16 (d, J = 8.1, 1 H). IR (neat) 1715 (vs, C=O) cm^{-1}. MS *m/e* (rel. intensity) 206 (<1, M+), 135 (5), 108 (100), 93 (44).

Reaction of Compound 18 with SmI_2. To a mixture of 0.1 M SmI_2 (2.5 mL, 0.25 mmol) and HMPA (0.44 mL, 2.5 mmol) in THF was added a solution of **18** (16.6 mg, 0.05 mmol) in 0.2 mL of THF over a period of 0.5 min at 25 °C. After stirring an additional 20 min, a small amount of reaction mixture (~0.2 mL) was taken out and quenched with aqueous NH_4Cl. The relative yields of products were determined by GC analysis. The experiment was repeated with concentrations of SmI_2 at 0.05, 0.03, and 0.01 M. The results are listed in Table 3.

3-(3-Iodopropyl)-3-methylpent-4-en-2-one (26):

2-(3-Chloro-propyl)-2-methylbut-3-enoic acid. A solution of tiglic acid (2.5 g, 25 mmol) in THF (50 mL) was added to a THF solution of LDA (2.0 M, 25 mL) at 0°C.[25] The reaction mixture was stirred at 0°C for 30 min and 1-bromo-3-chloropropane (4.7 g, 30 mmol) was added dropwise. The reaction mixture was then stirred at 23°C for 1 h and quenched with water. A 2 N solution of NaOH was added until the pH of the solution was reached 12. The mixture was then extracted with ether to remove the nonacidic organic residues. The aqueous layer was acidified to pH 3 and extracted with ether. The combined extracts were washed with

water and brine and dried over $MgSO_4$. Removal of the solvent gave the desired α-alkylated acid mixture with the γ-alkylated product (3.9 g, 88%, α/γ = 4/1): ^{1}H NMR δ 11.52 (bs, 1 H), 6.05-5.95 (m, 1 H), 5.19-5.13 (m, 2 H), 3.51 (m, 2 H), 1.82-1.74 (m, 4 H), 1.30 (s, 3 H); ^{13}C NMR δ 182.5, 140.4, 114.8, 48.0, 45.1, 36.0, 27.9, 20.5; IR 3500-2300, 1707, 1639, 1464, 1414, 1377, 1277, 1196, 1119, 999, 925; MS (EI) *m/e* 55, 67, 81, 95, 99, 113, 131, 141, 161, 176; HRMS calcd for $C_8H_{13}ClO$ 176.0604, found 176.0610.

3-(3-Chloropropyl)-3-methylpent-4-en-2-one: General Procedure for Converting a Carboxylic Acid to a Methyl Ketone.[26] An etheral solution of MeLi (1.4 M, 31 mL) was added dropwise to a vigorously stirred solution of 2-(3-chloro-propyl)-2-methyl-but-3-enoic acid prepared above (3.7 g, 21 mmol) in diethyl ether (139 mL) at 0°C. The reaction mixture was stirred at 23°C for 4 h and quenched by addition with stirring to ice cold dilute aqueous HCl. The mixture was extracted with ether and the combined ether layers were washed with aq. Na_2CO_3 and water, and then dried, filtered and concentrated. Flash chromatography (Hexane : EtOAc = 20 : 1) gave the title compound (1.5 g, 40%): ^{1}H NMR δ 5.87 (dd, J = 17, 11 Hz, 1 H), 5.25-5.14 (m, 2 H), 3.53 (t, J = 6 Hz, 2 H), 2.12 (s, 3 H), 1.82-1.56 (m, 4 H), 1.22 (s, 3 H); ^{13}C NMR δ 210.6, 141.0, 115.8, 54.1, 45.4, 34.5, 27.7, 25.8, 19.7; IR 3080, 2961, 1709, 1634, 1454, 1416, 1354, 922, 652; MS (EI) *m/e* 43, 55, 67, 84, 95, 131, 138; HRMS calcd for $C_7H_{12}Cl$ ($M^+ - CH_3CO$) 131.0628, found 131.0632.

3-(3-Iodopropyl)-3-methylpent-4-en-2-one (26): The above chloride was heated with excess NaI in acetone at 55°C for 10 h. Acetone was then removed and the mixture was diluted with water and extracted with ether. The ether layers were washed with aq. $Na_2S_2O_3$, water and dried. Flash chromatography (Hexane : EtOAc = 20 : 1) gave **26** (0.39 g, 85%): ^{1}H NMR δ 5.87 (dd, J = 17, 11 Hz, 1 H), 5.24-5.13 (m, 2 H), 3.16 (m, 2 H), 2.12 (s, 3 H), 1.79-1.66 (m, 4 H), 1.22 (s, 3 H); ^{13}C NMR δ 210.5, 141.0, 115.7, 54.0, 38.0, 28.6, 25.8, 19.8, 6.9; IR 3080, 2975, 1707, 1632, 1462, 1455, 1428, 1416, 1352, 1213, 1001, 922, 650; MS (EI) *m/e* 43, 55, 67, 81, 95, 121, 139, 155, 223, 251; HRMS calcd for $C_7H_{12}I$ ($M^+ - CH_3CO$) 222.9984, found 222.9987.

1,2-Dimethyl-2-vinylcyclopentanol (27).[27] A solution of *t*-BuLi in pentane (1.7 M, 0.24 mL) was added to a solution of **26** (50 mg, 0.19 mmol) in pentane/ether (5 mL, 3/2) at –78°C. After stirring at –78°C for 40 min, the reaction mixture was quenched with water and extracted with ether. The combined ether layers were washed, dried, and concentrated. Flash chromatography (Hexane : EtOAc = 10 : 1) gave a mixture of stereoisomeric alcohols **27** (3/1, 10 mg, 38%): ^{1}H NMR δ 6.02-5.93 (m, 1 H of minor isomer), 5.89-5.80 (m, 1 H of major isomer), 5.21-5.12 (m, 2 H of minor isomer), 5.03-4.95 (m, 2 H of major isomer), 2.18-1.24 (m, 7 H overlaping), 1.17 (s, 3 H of minor isomer), 1.15 (s, 3 H of major isomer), 1.06 (s, 3 H of major isomer), 0.98 (s, 3 H of minor isomer); ^{13}C NMR δ 144.6, 142.6, 115.4, 111.8, 82.4, 82.3, 51.5, 51.0, 38.7, 38.2, 35.7, 35.1, 23.3, 22.7, 22.5, 19.3, 18.9, 18.6; IR 3465, 3083, 2963, 2874, 1634, 1458, 1375, 1123, 1084, 1003, 912; MS (EI) *m/e* 57, 67, 70, 82, 97, 107, 122; HRMS calcd for C_9H_{14} ($M^+ - H_2O$) 122.1096, found 122.1096.

General Procedure for Radical Reactions at 80°C. A mixture of **26** (50.7 mg, 0.191 mmol) and Bu_3SnH (110.9 mg, 0.382 mmol) and AIBN (8.1 mg) was refluxed in benzene (19 mL) until the reaction was complete (8-16 h). After the benzene was removed under vacuum, the residue was dissolved in ether (2 mL) and treated with DBU[28] (29 μl, 2 equiv) to form a white precipitate. Stirring was continued for 10 min and a 0.1 M solution of iodine in ether was added untill the yellow color persisted. The mixture was filtered through a pad of silica gel and $MgSO_4$. Concentration gave the crude oil of products which was then subjected to GC analysis.

General Procedure for Radical Reactions at 23°C.[29] To a solution of **26** (0.051 g, 0.19 mmol) and Bu_3SnH (0.561 g, 1.93 mmol) in benzene (1.41 mL) was added a THF solution of Et_3B (1 M, 48 μl). The mixture was stirred at 23°C for 10 h with a weak O_2 flow passing through, and then worked up as described in general procedure for radical reactions at 80°C.

Preparations of the authentic samples 28-31.

1-(1,2-Dimethylcyclopentyl) ethanone (30).

1-Methyl-2-oxocyclopentanecarboxylic Acid Methyl Ester. Methyl 2-oxocyclopentanecarboxylate (4.0 g, 28 mmol) in THF (5 mL) was added to the suspension of NaH (1.4 g, 34 mmol, 60% suspension in mineral oil) in THF (56 mL). The reaction mixture was stirred at 23°C for 1 h and CH_3I (4.8 g, 34 mmol) was added. After stirring at 23°C for 12 h, the reaction was quenched with water and extracted with ether. The organic layers were washed, dried and concentrated. Flash chromatography (Hexane : EtOAc = 5 : 1) gave the title compound (2.2 g, 50%): ^{1}H NMR δ 3.70 (s, 3 H), 2.51 (m, 1 H), 2.43-2.32 (m, 2 H), 2.03 (m, 1 H), 1.96-1.81 (m, 2 H), 1.31 (s, 3 H); ^{13}C NMR δ 215.8, 172.8, 55.8, 52.5, 37.6, 36.1, 19.5, 19.4; IR 3461, 2959, 1760, 1727, 1455, 1435, 1406, 1375, 1318, 1273, 1194, 1157, 1065, 980, 939; MS (EI) *m/e* 55, 69, 82, 97, 101, 113, 128, 156; HRMS calcd for $C_7H_{12}O_2$ ($M^+ - CO$) 128.0837, found 128.0830.

1-Methyl-2-methylidenecyclopentanecarboxylic Acid Methyl Ester. Solid *t*-BuOK (2.26 g, 20.1 mmol) was added at 23°C to a solution of Ph_3PCH_3Br (7.20 g, 20.1 mmol) in THF (17 mL). The mixture was stirred at 40°C for 2 h and cooled to 23°C. To the resulting yellow solution was added 1-methyl-2-

oxocyclopentanecarboxylic acid methyl ester prepared above (1.05 g, 6.7 mmol) and the mixture was stirred at 23°C for 12 h. The reaction was quenched with water and extracted with ether. The ether was then evaporated and the residue was dissolved in pentane. The solid was filtered and the filtrate was concentrated. The crude oil was purified by chromatography (Hexane : EtOAc = 35 : 1) to give the title compound (0.35g, 35%): ^{1}H NMR δ 4.98 (t, J = 2 Hz, 1 H), 4.95 (t, J = 2 Hz, 1 H), 3.67 (s, 3 H), 2.47-2.40 (m, 2 H), 2.39-2.29 (m, 1 H), 1.81 (m, 1 H), 1.71-1.54 (m, 2 H), 1.32 (s, 3 H); ^{13}C NMR δ 177.0, 156.5, 106.9, 52.4, 52.2, 39.0, 33.7, 25.1, 23.9; IR 3079, 2957, 2876, 1730, 1651, 1462, 1433, 1374, 1269, 1192, 1153, 1098, 1080, 986, 893.

1,2-Dimethylcyclopentanecarboxylic Acid. Compound 1-methyl-2-methylidene-cyclopentanecarboxylic acid methyl ester from the prior step (0.33 g, 2.1 mmol) was added to a suspension of palladium on active carbon (50 mg) in MeOH (21 mL). The reaction mixture was stirred under hydrogen atmosphere for 8 h and then filtered through a pad of Celite. The filtrate was concentrated to give a crude oil. Without purification, the oil was heated with NaOH (0.21 g, 5.3 mmol) in MeOH-H_2O at 55°C for 10 h. The reaction mixture was cooled and washed with ether. The aqueous layers were acidified with 2 N HCl, and extracted with ether. The ether layers were washed with water and brine and dried over $MgSO_4$. Concentration under vacuum gave the title compound as a pair of diastereomers (1.25/1, 0.16 g, 54% for two steps): ^{1}H NMR δ 2.38-1.26 (m, 7 H), 1.24 (s, 3 H, minor isomer), 1.07 (s, 3 H, major isomer), 0.99 (d, J = 7 Hz, 3 H, minor isomer), 0.96 (d, J = 7 Hz, 3 H, major isomer); ^{13}C NMR δ 185.2, 183.7, 52.5, 51.2, 46.1, 41.9, 38.4, 36.8, 33.4, 32.6, 23.9, 22.7, 22.4, 17.2, 15.7, 14.7; IR 3500-2500, 2963, 1700, 1458, 1373, 1286, 1200, 970; MS (EI) *m/e* 40, 55, 87, 97, 127, 142; HRMS calcd for $C_8H_{14}O_2$ 142.0994, found 142.0999.

1-(1,2-Dimethylcyclopentyl)ethanone (30). By following the general procedure for converting a carboxylic acid to a methyl ketone, 1,2-dimethylcyclopentanecarboxylic acid from the prior step (0.16 g, 1.1 mmol) was treated with MeLi (0.98 M, 2.32 mL, 2.3 mmol). Flash chromatography (pentane : Et_2O = 15: 1) gave **30** as a colorless oil (0.09 g, 56%): ^{1}H NMR δ 2.25 (m, 1 H), 2.14 (s, 3 H, major isomer), 2.12 (s, 3 H, minor isomer), 2.01 (m, 1 H), 1.93-1.29 (m, 5 H), 1.27 (s, 3 H, minor isomer), 1.02 (s, 3 H, major isomer), 0.91 (d, J = 7 Hz, 3 H, major isomer), 0.86 (d, J = 7 Hz, 3 H, minor isomer); ^{13}C NMR δ 213.7 (major isomer), 213.5 (minor isomer), 58.8 (minor isomer), 57.5 (minor isomer), 44.5, 40.1, 37.5, 33.4, 32.8, 32.7, 28.0, 25.6, 24.3, 22.5, 21.7, 17.2, 16.8, 14.8; IR 2961, 2874, 1701, 1456, 1379, 1356, 1154, 960; MS (EI) *m/e* 43, 55, 97, 125, 140; HRMS calcd for $C_9H_{16}O$ 140.1201, found 140.1193

1-(1-Methylcyclohexyl)ethanone (29). Methyl cyclohexanecarboxylate (1.0 g, 7.0 mmol) was added to a THF solution of LDA (1.0 M, 7.0 mL) at –78°C. The reaction mixture was stirred at this temperature for 40 min and CH_3I (1.2 g, 8.4 mmol) dissolved in HMPA (1.2 mL, 7.0 mmol) was added. After stirring for 30 min, the mixture was treated with aq. NH_4Cl and extracted with ether. The ether layers were washed with water and brine and dried over $MgSO_4$. Concentration under vacuum gave a crude oil. This crude oil was heated with NaOH in MeOH-H_2O by following the same hydrolysis procedure for preparing 1,2-dimethyl-cyclopentanecarboxylic acid. After aqueous workup, an oil was obtained which was then treated with MeLi according to the general procedure for converting a carboxylic acid to a methyl ketone. Aqueous workup afforded a crude oil which was purified by flash chromatography (Hexane : EtOAc = 15: 1) to give **29** (0.35 g, 36% for three steps): ^{1}H NMR δ 2.12 (s, 3 H), 1.95-1.90 (m, 2 H), 1.57-1.23 (m, 8H), 1.07 (s, 3 H); ^{13}C NMR δ 214.4, 48.5, 34.8, 25.9, 24.9, 23.0; IR 2932, 2857, 1705, 1458, 1358, 1152, 1130; MS (EI) *m/e* 43, 55, 69, 81, 84, 97, 125, 140; HRMS calcd for $C_9H_{16}O$ 140.1201, found 140.1219.

3-Methyloct-7-en-2-one (31).

2-Acetyl-2-methylhept-6-enoic Acid Ethyl Ester. Ethyl 2-methylacetoacetate (2.4 g, 17 mmol) was added to a suspension of NaH (0.8 g, 20 mmol, 60% suspension in mineral oil) in THF (50 mL). The mixture was stirred at 23°C for 1 h and then treated with 5-bromo-1-pentene (3.0 g, 20 mmol). The resulting mixture was refluxed for 8 h. The reaction was quenched by water and extracted with ether. The ether layers were washed, dried and concentrated to give the title compound (2.2 g, 62%): ^{1}H NMR δ 5.86-5.71 (m, 1 H), 5.04-4.95 (m, 2 H), 4.20 (q, J = 6 Hz, 2 H), 2.14 (s, 3 H), 2.06 (m, 2 H), 1.95-1.71 (m, 2 H), 1.33 (s, 3 H), 1.30-1.20 (m, 5 H); ^{13}C NMR δ 205.8, 173.1, 138.1, 115.1, 61.3, 60.0, 34.3, 33.9, 26.2, 23.6, 18.9, 14.1; IR 3095, 2982, 2940, 1738, 1715, 1644, 1462, 1454, 1377, 1356, 1254, 1186, 1150, 1105, 1024, 912; MS (EI) *m/e* 43, 49, 55, 67, 74, 84, 96, 102, 115, 123, 144, 170, 184, 213; HRMS calcd for $C_{10}H_{18}O_2$ (M^+ – C_2H_2O) 170.1307, found 170.1302.

3-Methyloct-7-en-2-one (31). A mixture of LiI•$2H_2O$ (0.73 g, 3.9 mmol) and 2,6-lutidine (3.5 mL) was heated to reflux. As soon as the solid dissolved, a solution of 2-acetyl-2-methyl-hept-6-enoic acid ethyl ester from the prior step (0.60 g, 2.8 mmol) in 2,6-lutidine (2 mL) was added. The reaction mixture was refluxed for 20 h and then cooled to 0°C. 6 N HCl (6 mL) was added with vigorous stirring. The aqueous layer was extracted with ether and the ether extracts were washed with 6 N HCl, water, sat. $NaHCO_3$, water and brine and dried, filtered, and concentrated. The oil was purified by flash chromatography (Hexane : EtOAc = 20 : 1) to give **31** (0.20 g, 89% based on unrecovered starting material): ^{1}H NMR δ 5.83-5.69 (m, 1 H), 5.02-4.92 (m, 2 H), 2.49 (m, 1 H), 2.10 (s, 3 H), 2.03 (m, 2 H), 1.63 (m, 1 H), 1.39-1.31 (m, 3 H), 1.07 (d, J = 7Hz, 3 H); ^{13}C NMR δ 212.8, 138.4, 114.8, 47.0, 33.7, 32.3, 28.0, 26.4, 16.2; IR 3076, 2996, 2973, 2933,

2878, 1713, 1641, 1460, 1440, 1357, 1200, 1170, 1140, 996, 952, 912; MS (EI) *m/e* 43, 49, 55, 67, 72, 84, 97, 107, 112, 125, 140.

3-Methyl-3-propylpent-4-en-2-one (28). Iodoketone **26** (0.20 g, 0.75 mmol) was added to a suspension of LAH (0.06 g, 1.5 mmol) in THF (5 mL). The reaction mixture was stirred at 23°C for 1 h and then quenched with water. The THF solution was decanted, dried and concentrated to give a crude oil (0.07 g, 65%): ^{1}H NMR δ 5.79-5.68 (m, 1 H), 5.22-4.99 (m, 2 H), 3.53 (m, 1 H), 1.55 (bs, 1 H), 1.38-1.15 (m, 4 H), 1.13 (d, *J* = 6 Hz, 3 H), 0.98 (s, 3 H of one isomer), 0.92 (s, 3 H of the other isomer), 0.91-0.86 (m, 3 H). This crude oil (0.07 g, 0.49 mmol) was then added to PCC (0.24 g, 1.13 mmol) suspended in CH_2Cl_2 at 23°C. After the oxidation was complete, the reaction mixture was diluted with ether. The solvent was decanted, the resulting black solid was washed with ether. The organic extracts were filtered through Florisil and concentrated to afford **28** (0.03 g, 44%): ^{1}H NMR δ 5.90 (dd, *J* = 18, 11 Hz), 5.19-5.09 (m, 2 H), 2.10 (s, 3 H), 1.69-1.50 (m, 2 H), 1.31-1.09 (m, 2 H), 1.19 (s, 3 H), 0.91 (t, *J* = 7Hz, 3 H); ^{13}C NMR δ 211.3, 141.9, 114.9, 54.8, 39.8, 25.9, 19.7, 17.7, 14.8. MS (EI) *m/e* 43, 55, 82, 97, 122, 140, 149; HRMS calcd for C_7H_{13} ($M^+ - COCH_3$) 97.1017, found 97.1007.

General Procedure for Intramolecular Barbier Reactions. To a solution of SmI_2 in THF (0.093 M, 7.14 mL) containing HMPA (various amount, see Table 5) was added a THF solution (0.8 mL) of **26** (0.084 g, 0.32 mmol). The resulting mixture was stirred at 23°C for 1 h, and then quenched with sat. NH_4Cl and extracted with ether/pentane (1/1). The organic extracts were washed with water, 3% $Na_2S_2O_3$, and brine and dried over $MgSO_4$. Filtration and concentration gave the crude oil of **27** which was then analyzed by GC. Flash chromatography (hexane:EtOAc = 10: 1) gave **27** in yields ranging from 65% to 76%.

1-Cyclopropyl-2-(3-iodopropyl)-2-methylbut-3-en-1-one (36a).

2-(3-Chloropropyl)-2-methylbut-3-enoyl chloride. Oxalyl chloride (2.69 g, 21.2 mmol) was added over 1 min to a solution of the mixture of 2-(3-chloro-propyl)-2-methyl-but-3-enoic acid (prepared as shown in the synthesis of **26**) and its γ-alkylated isomer (4/1, 0.32 g, 1.8 mmol) in benzene (18 mL) while stirring at reflux. The mixture was refluxed for an aditional 15 min and the solution was allowed to stand at 23°C for 2 h. It was then evaporated to dryness under vacuum at 30°C-40°C. The residue was dissolved in benzene (2.5 mL) and evaporated to dryness again. A crude oil was obtained and used immediately in the next step.

2-(3-Chloropropyl)-1-cyclopropyl-2-methylbut-3-en-1-one. To a stirred solution of cyclopropyl bromide (0.33 g, 2.7 mmol) in dry THF (11 mL) at –78°C was added dropwise a solution of *t*-BuLi in pentane (1.7 M, 2.0 mL). The resulting solution was stirred at –78°C for 2 h. Solid PhSCu (0.47 g, 2.7 mmol) was added and the resulting slurry was diluted with THF (3 mL). The mixture was then warmed to –20°C, stirred at this temperature for 30 min and recooled to –78°C. To the clear brown solution was added the crude 2-(3-chloropropyl)-2-methyl-but-3-enoyl chloride from the prior step in THF (5 mL) and the reaction mixture was stirred at –78°C for 10 min, at –25°C for 1 h, and at 23°C for 1 h. The solution was treated with sat. aqueous NH_4Cl (0.7 mL) and ether (20 mL) and stirred for 20 min. Anhydrous $MgSO_4$ was added and the mixture was filtered through a pad of Florisil layered over anhydrous $MgSO_4$. Removal of the solvent from the combined filtrates gave an oil, which upon chromatography (Hexane : EtOAc = 20 : 1) afforded the title compound (0.19 g, 66% for two steps): ^{1}H NMR δ 5.97 (dd, *J* = 18, 11 Hz, 1 H), 5.26-5.16 (m, 2 H), 3.53 (t, *J* = 6 Hz, 2 H), 2.13 (m, 1 H), 1.94-1.85 (m, 1 H), 1.81-1.62 (m, 3 H), 1.26 (s, 3 H), 0.99-0.94 (m, 2 H), 0.87-0.82 (m, 2 H); ^{13}C NMR δ 212.2, 141.3, 115.5, 54.1, 45.1, 34.6, 27.8, 20.2, 17.1, 11.5; IR 3080, 2961, 1694, 1634, 1447, 1377, 1057, 1009, 922, 799, 652; MS (CI) *m/e* 69, 165, 201, 269.

1-Cyclopropyl-2-(3-iodopropyl)-2-methyl-3-buten-1-one (36a). The chloroketone from the prior step (0.19 g, 0.94 mmol) was treated with NaI (0.43 g, 2.80 mmol). Upon flash chromatography (Hexane : EtOAc = 35 : 1), **36a** was obtained (0.20 g, 73%): ^{1}H NMR δ 5.96 (dd, *J* = 17, 11 Hz, 1 H), 5.26-5.16 (m, 2 H), 3.17 (t, *J* = 6 Hz, 2 H), 2.12 (m, 1 H), 1.92-1.64 (m, 4 H), 1.26 (s, 3 H), 0.99-0.94 (m, 2 H), 0.87-0.81 (m, 2 H); ^{13}C NMR δ 212.2, 141.2, 115.6, 54.0, 38.2, 28.7, 20.4, 17.1, 11.6, 7.2; IR 3085, 2973, 1694, 1462, 1455, 1416, 1377, 1254, 1198, 1044, 1011, 922; MS (EI) *m/e* 69, 165, 197, 223, 277, 292; HRMS calcd for $C_{11}H_{17}O$ ($M^+ - I$) 165.1279, found 165.1277.

1-Cyclopropyl-2-methyl-2-vinylcyclopentanol (37). By following the general procedure for intramolecular Barbier reaction, **36a** (0.07 g, 0.24 mmol) was treated with a THF solution of SmI_2 (0.10 M, 5.0 mL, 0.50 mmol) containing HMPA (0.44 g, 2.5 mmol). Flash chromatography (Hexane : EtOAc = 10 : 1) gave **37** (0.024 g, 61%) as a pair of diastereomers (63/37): ^{1}H NMR δ 6.09-5.96 (m, 1 H), 5.20-4.96 (m, 2 H), 2.23-1.19 (m, 7 H), 1.10 (s, 3 H, major isomer), 1.08 (s, 3 H, minor isomer), 0.98-0.88 (m, 1 H), 0.39-0.22 (m, 4 H); ^{13}C NMR δ 144.8, 143.2, 115.1, 111.4, 83.0, 82.7, 52.9, 52.1, 35.9, 35.3, 35.2, 35.1, 22.9, 19.2, 19.1, 15.7, 14.9, 1.5, 0.9, 0.4, 0.1; IR 3492, 3083, 2961, 2874, 1636, 1458, 1374, 1005, 970, 911; MS (EI) *m/e* 67, 79, 91, 105, 133, 148; HRMS calcd for $C_{11}H_{16}$ ($M^+ - H_2O$) 148.1252, found 148.1255.

1-Cyclopropyl-2-methyl-2-propylbut-3-en-1-one (36b). Compound **36b** was prepared by treating **36a** (0.067 g, 0.23 mmol) with neat Bu_3SnH (0.133 g, 0.46 mmol) and AIBN (8 mg). The mixture was heated at 80°C for 4 h and subjected to standard DBU workup described in the general procedure for the radical reaction with Bu_3SnH. Flash chromatography (Hexane : EtOAc = 45 : 1) gave **36b** (0.020 g, 58 %):

^{1}H NMR δ 5.99 (dd, *J* = 17, 11 Hz, 1 H), 5.20-5.12 (m, 2 H), 2.17-2.10 (m, 1 H), 1.81-1.55 (m, 2 H), 1.31-1.14 (m, 5 H), 0.97-0.87 (m, 5 H), 0.83-0.78 (m, 2 H); ^{13}C NMR δ 212.7, 142.2, 114.7, 54.7, 39.9, 20.2, 17.8, 17.0, 14.8, 11.3, 11.2; IR 3097, 2961, 1700, 1636, 1458, 1375, 1063, 1005, 905.

3-Methyl-3-propylhept-1-en-4-one (38). Compound **36b** (0.020 g, 0.12 mmol) was treated with a THF solution of SmI_2 (0.10 M, 2.56 mL) containing HMPA (0.106 g, 0.59 mmol) following the general procedure for the intramolecular Barbier reaction. Flash chromatography (Hexane : EtOAc = 50 : 1) gave **38** (0.012 g, 60%): ^{1}H NMR δ 5.89 (dd, *J* = 17, 11 Hz, 1 H), 5.17-5.07 (m, 2 H), 2.40 (m, 2 H), 1.70-1.47 (m, 4 H), 1.29-1.03 (m, 5 H), 0.93-0.84 (m, 6H); ^{13}C NMR δ 213.1, 142.0, 114.7, 54.4, 39.8, 39.7, 19.6, 17.7, 17.4, 14.8, 13.8; IR 3086, 2962, 2932, 2874, 1708, 1632, 1464, 1410, 1373, 1114, 1004, 917; MS (EI) *m/e* 82, 89, 97, 125, 139, 168; HRMS calcd for $C_{11}H_{20}O$ 168.1514, found 168.1512.

4-(3-Iodopropyl)-2,2,4-trimethylhex-5-en-3-one (39).

4-(3-Chloropropyl)-2,2,4-trimethylhex-5-en-3-one. *t*-BuLi (1.6 M, 1.56 mL) was added to PhSCu (0.435 g, 2.52 mmol) suspended in THF (18 mL) at –25°C immediately forming a clear brown solution immediately. After 10 min, the solution was cooled to –78°C, and the mixture of 2-(3-chloropropyl)-2-methylbut-3-enoyl chloride and its γ-alkylated isomer (prepared as shown in the synthesis of **36a**) (4/1, 0.351 g, 1.80 mmol) was added. The reaction mixture was stirred at –78°C for 1 h, quenched by absolute MeOH (1.8 mL), and warmed to 23°C. The mixture was then added to sat. NH_4Cl (90 mL) and stirred for 15 min. After removing the solid by filtration, the organic products were extracted into ether. The ether layers were dried and concentrated to give a yellow oil which was purified by flash chromatography (Hexane : EtOAc = 30 : 1) to afford the title compound (0.155 g, 49% for two steps): ^{1}H NMR δ 6.08 (dd, *J* = 18, 11 Hz, 1 H), 5.22-5.10 (m, 2 H), 3.50 (t, *J* = 7 Hz, 2 H), 1.87-1.58 (m, 4 H), 1.29 (s, 3 H), 1.18 (s, 9H); ^{13}C NMR δ 216.1, 141.7, 114.9, 54.7, 46.3, 45.5, 37.0, 28.3, 28.0, 22.2; IR 3356, 3087, 2961, 2874, 1686, 1634, 1482, 1414, 1395, 1366, 1046, 989, 920; MS (CI) *m/e* 85, 95, 125, 161, 181, 217.

4-(3-Iodopropyl)-2,2,4-trimethylhex-5-en-3-one (39). The chloride from last step (0.045 g, 0.23 mmol) was heated with NaI (0.104 g, 0.70 mmol) in acetone. Flash chromatography (Hexane : EtOAc = 30 : 1) gave **39** (0.040 g, 56%): ^{1}H NMR δ 6.08 (dd, *J* = 18, 11 Hz, 1 H), 5.23-5.11 (m, 2 H), 3.14 (t, *J* = 7Hz, 2 H), 1.78-1.65 (m, 4 H), 1.30 (s, 3 H), 1.19 (s, 9H); ^{13}C NMR δ 216.1, 141.7, 114.9, 54.7, 46.3, 40.7, 29.0, 28.3, 22.3, 7.1; IR 3090, 2959, 1686, 1632, 1479, 1458, 1366, 1179, 1044, 988, 918; MS (CI) *m/e* 85, 95, 125, 181, 223, 253, 291, 309.

1-*t*-Butyl-2-methyl-2-vinylcyclopentanol (40). By following general procedure of intramolecular Barbier reactions, **39** (0.030g, 0.10 mmol) was treated with SmI_2/THF solution (0.1 M, 2.14 mL) containing HMPA (0.085 g, 0.47 mmol). Flash chromatography (Hexane : EtOAc = 15 : 1) gave **40** as a pair of diastereomers (75/25) (0.013 g, 71%): ^{1}H NMR δ 6.22 (dd, *J* = 17, 11 Hz, 1 H, minor isomer), 6.09 (dd, *J* = 17, 11 Hz, 1 H, major isomer), 5.13-5.07 (m, 2 H, minor isomer), 5.01-4.85 (m, 2 H, major isomer), 2.32-1.41 (m, 6 H), 1.24 (s, 3 H, major isomer), 1.19 (s, 3 H, minor isomer), 1.01 (s, 9H); ^{13}C NMR δ 146.5, 145.0, 113.4, 109.2, 88.0, 87.8, 53.5, 53.2, 41.3, 39.5, 38.8, 38.7, 33.8, 32.8, 28.3, 27.9, 24.7, 19.3, 18.7, 18.4; IR 3524, 3090, 2957, 2874, 1640, 1466, 1394, 1368, 1109, 1071, 1051, 1009, 986, 960, 907; MS (EI) *m/e* 97, 107, 125, 149, 182; HRMS calcd for $C_{12}H_{22}O$ 182.1671, found 182.1667.

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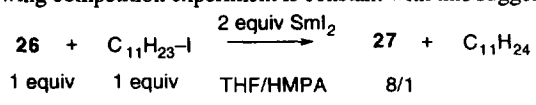
17. This assumes that ketyl opening is not reversible.
18. The postulate of intramolecular electron transfer suggests that iodoketones might to more reactive than alkyl iodides. The following competition experiment is constant with this suggestion.



19. However, it is known that Lewis acids can influence the outcome of radical reactions. For recent examples, see a) Sibi, M. P.; Ji, J. G.; Wu, J. H.; Gurtler, S.; Porter, N. A. *J. Am. Chem. Soc.* **1996**, *118*, 9200. b) Guindon, Y.; Guerin, B.; Rancourt, J.; Chabot, C.; Mackintosh, N.; Ogilvie, W. W. *Pure Appl. Chem.* **1996**, *68*, 89. c) Renaud, P.; Moufid, N.; Kuo, L. H.; Curran, D. P. *J. Org. Chem.* **1994**, *59*, 3547.

20. Either of the intermediates could also be used to resurrect S_N2-based mechanisms with ketyls, but this type of nucleophilic substitution is supposed to be strongly disfavored with respect to electron transfer. See reference 16.

21. Alternatively, the ketyls may be monomeric yet serve as ligands for SmI_2.

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