1,2-Asymmetric Induction in Reactions of Nonconjugated Acyclic Radicals: A New Model for Highly Selective Atom-Transfer Reactions of Alkyl-Substituted Radicals

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Received March 29, 1993

Abstract: The iodine-transfer addition of methyliodomalonodinitrile (**1**) to several dialkyl-substituted olefins is reported. The iodine-transfer reaction to the acyclic nonconjugated radical intermediates often results in selective product formation due to 1,2-asymmetric induction. The level of diastereoselectivity depends on the size of the alkyl substituent on the radical. Tertiary alkyl groups give high syn selectivity, secondary groups lead to a moderate syn selectivity, and primary groups show completely unselective reactions. To explain the stereochemical outcome, a new steric model of the ^{t}Bu-substituted radical **5e** is introduced on the basis of AM1 calculations and EPR data. This transition-state model is unusual in that it postulates attack of the reagent on the radical between the medium and large groups and anti to the small group.

Introduction

Stereocontrol in radical reactions is a vibrant research topic. Asymmetric radical cyclizations[1] and asymmetric reactions of cyclic radicals[2] are now reasonably well understood, and recent work has focused on acyclic molecules.[3] A variety of stereoselective radical bond-forming reactions can now be achieved by employing strategies based on either chiral auxiliary[4] or substrate control. Within the domain of substrate control, the vast majority[5-7] of stereoselective transformations are 1,2-asymmetric induction reactions of conjugated radicals. In a representative example, addition of iodomalonodinitrile **1** to β-methylstyrene (**2a**) (R^1 = Me; R^2 = Ph) under our thermal iodine-transfer conditions[8] gives an 85/15 syn/anti mixture of adducts **3a** (Scheme I and Table I, entry a).[9] In the accepted mechanism, malonodinitrile radical **4** is trapped by olefin **2** to produce adduct radical **5a** (step 1). In turn, radical **5a** abstracts iodine from **1** (or perhaps also I_2[8a]) with modest syn selectivity to give the product **3a** and propagate the chain (step 2).[9] For less reactive alkenes, a combination of radicals **4** to give **6** (step 3) competes with the chain addition.

The stereochemical outcome of this reaction can be explained by the A-strain model[5a,b] that describes the behavior of phenyl-,[6g,9] carbonyl-,[5e,f] and nitrogen-substituted[6f,g] radicals. Oxygen-[6a-e] and sulfur-substituted[6g] radicals follow a Felkin–Ahn model. Conjugating substituents at the radical center are a key underlying theme in all of the reactions.

Recently, we reported that the addition of iodide **1** to ^{t}Bu-substituted olefin **2e** (R^1 = Me; R^2 = ^{t}Bu) leads to a 98/2 syn/anti mixture of products **3e** at 60 °C.[6g] As far as we know, this is the first example of very high 1,2-asymmetric induction in any reaction of a simple alkyl radical. We now describe an expanded study of a series of iodine- and hydrogen-transfer reactions to 1,2-dialkyl-substituted olefins **2**. On the basis of EPR measurements and AM1 calculations of the ground-state conformations of several intermediate radicals and on AM1 calculations of the geometry of the transition state of the iodine transfer to one intermediate radical, we suggest a new model for 1,2-induction reactions of alkyl radicals. This model is not related to any of the existing models for asymmetric reactions of conjugated radicals.

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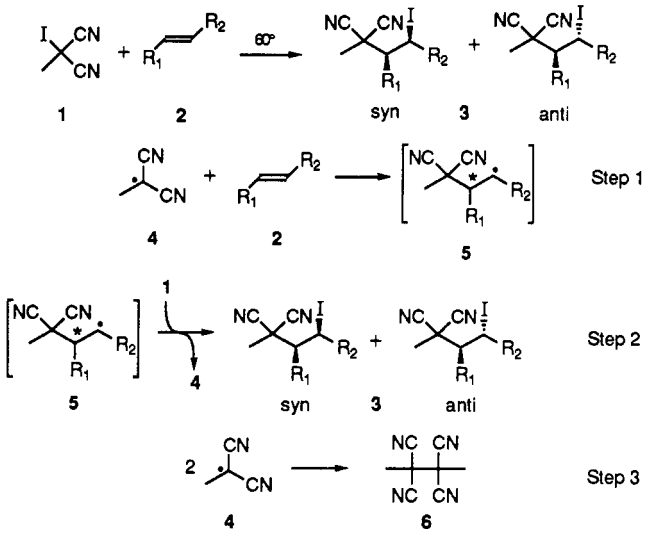
Scheme I[a]



[a] **a**, R^1 = Me, R^2 = Ph; **b**, R^1 = R^2 = Me; **c**, R^1 = R^2 = ^{n}Pr; **d**, R^1 = Me, R^2 = ^{i}Pr; **e**, R^1 = Me, R^2 = ^{t}Bu; and **f**, R^1 = Me, R^2 = adamantyl.

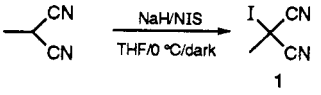
Table I. Addition of Iodide **1** to 1,2-Disubstituted Olefins **2**

entry	R^1	R^2	equiv of **2**	% yield of **3**[a]	% yield of **6**[b]	syn/anti
a	Me	Ph	2	98		85/15
b	Me	Me	20	75	10	~50/50
c	^{n}Pr	^{n}Pr	2 (15)	10 (80)	80 (15)	~50/50
d	Me	^{i}Pr	3 (15)	40 (88)	55 (10)	75/25
e	Me	^{t}Bu	6 (20)	40 (83)	55 (15)	98/2
f	Me	Ad	3	14	80	>98/2

[a] Isolated yield; values in parentheses are yields with 15–20 of equiv **2**. [b] Yield estimated by ^{1}H NMR; values in parentheses are yields with 15–20 equiv of **2**.

Results and Discussion

Iodomalonodinitrile **1** was prepared from readily available methylmalonodinitrile.[10] Deprotonation with sodium hydride in the presence of NIS (*N*-iodosuccinimide) gave the radical precursor **1** in 72% isolated yield.[8] When protected from light, this iodide is surprisingly stable. It can be handled at ambient temperature in the air and stored in the refrigerator over several months without any decomposition.



(1)

The addition reactions were carried out by simply heating iodide **1** and 1,2-dialkyl-substituted olefins **2b–f** in chloroform at 60 °C. After concentration of the mixture, the crude products were purified by flash chromatography. The results are summarized in Table I, entries b–f. At low alkene concentrations (2–3 equiv), the yields of addition products **3** were poor to moderate (10–75%). A combination of initially formed malonodinitrile radicals **4** to give tetracyanobutane **6** competes successfully with addition to the double bond (Scheme I, step 3). We were able to enhance the isolated yields up to 80–88% by adding 15–20 equiv of alkene. All the reactions were very clean. Tetracyanobutane **6** was the only detectable side product in the crude ^{1}H NMR spectrum, and the dark color of the reactions indicated that the product accompanying formation of **6** was molecular iodine.

The stereochemical outcome of the additions to 1,2-dialkyl-substituted olefins **2b–f** was monitored by ^{1}H NMR spectroscopy of the crude reaction mixtures until **1** was consumed. In all cases, the product ratio remained unchanged over the course of the reaction, and we conclude that the syn/anti ratios are kinetically controlled.[11] Primary substituents on the alkene (R^1, R^2 = Me or ^{n}Pr; Table I, entries b and c) gave no significant selectivity: the syn/anti ratios of products **3b,c** were nearly 50/50. Alkenes containing one methyl group and one secondary or tertiary alkyl group exhibited high regioselectivity and modest to high stereoselectivity in their reactions with **1**. An isopropyl substituent (Table I, entry d) led to modest syn selectivity: products **3d** were obtained in a 75/25 syn/anti ratio. The ^{t}Bu-substituted olefin **2e** gave a highly selective reaction leading to a 98/2 syn/anti mixture of products **3e** (Table I, entry e). Only the syn product **3f**-syn formed when the adamantyl-substituted alkene **2f** was used (Table I, entry f). We could not detect **3f**-anti.

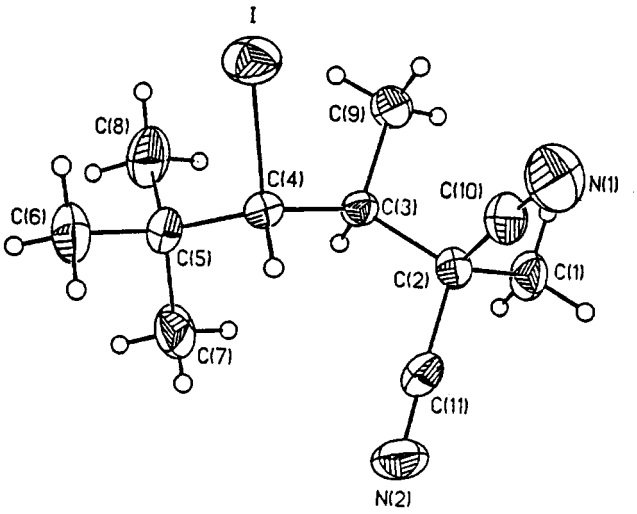
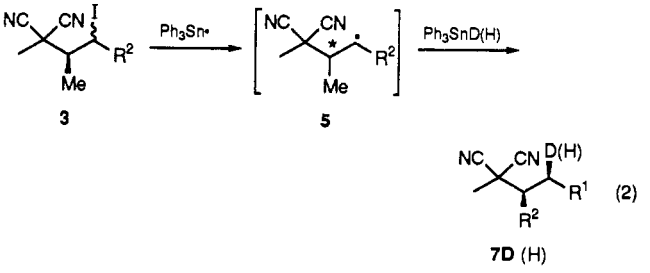


Figure 1. X-ray crystal structure of **3e**-syn.

We relied on a combination of techniques to assign configurations of **3d–f**. The major isomer of product **3e** crystallized from ether/pentane, and the X-ray crystal structure of this product is shown in Figure 1. The relative configuration is syn. The structure of adamantyl-substituted product **3f**-syn was assigned by the similarity of the ^{1}H NMR spectra of **3e**-syn and **3f**-syn (see Experimental Section). Direct assignment of the configurations of ^{i}Pr adducts **3d** was not straightforward, so we relied on analogy to the tin hydride reductions described below.

In a series of experiments conducted in NMR tubes, iodides **3a**, **3d**, and **3e** were heated with triphenyltin deuteride and AIBN in benzene-d_6 at 80 °C (eq 2). In all three cases, syn-selective deuterium transfer was observed (**a**, R^2 = Ph, 80/20; **d**, R^2 = ^{i}Pr, 70/30; **e**, R^2 = ^{t}Bu; estimated ≥90/10[12]), and the levels of selectivity were comparable to those of the iodine-transfer reactions.



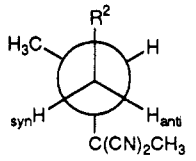
(2)

Fully protiated products **7H** showed resolved signals of H_{syn} and H_{anti}, and the vicinal coupling constants $J_{H,Hsyn}$ (10.0–11.5

(10) Hosmane, R. S.; Bakthavachalam, V.; Leonard, N. J. *J. Am. Chem. Soc.* **1982**, *104*, 235.

(11) In the case of products **3b** and **3c**, the isolated syn/anti mixtures after chromatography on silica gel differ considerably from the initially formed product ratio. See Experimental Section for details.

(12) Stereoselectivity in the deuterium-transfer reactions of the ^{t}Bu-substituted radicals was difficult to determine precisely due to overlapping of key resonances; however, it was qualitatively clear that the syn isomer was formed and that the selectivity was high.



$J_{H,Hsyn}$ = 10.0-11.5 Hz

$J_{H,Hanti}$ = 2.9-3.2 Hz

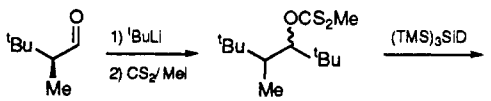
7H

[a] **a**, R^2 = Ph; **d**, R^2 = ^{i}Pr; and **e**, R^2 = ^{t}Bu

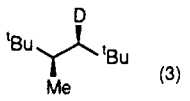
Figure 2. Newman projection of the preferred rotamers of the reduction products **7H**.[a]

Hz) and $J_{H,Hanti}$ (2.9–3.2 Hz) differed characteristically (Figure 2). MM2 calculations confirmed expectations that the preferred conformations of **7** are those where the R^2 substituent and the large dicyanoethyl group are anti. On the basis of this conformation, H_{syn} and H_{anti} are readily assigned from the large differences in vicinal coupling constants. Configurations of isomers **7D** are then assigned on the basis of peak heights in the ^{2}H NMR spectra.

To help identify the role of the dicyanoethyl group in the asymmetric atom-transfer reactions of radicals **5**, we prepared model **8** where this group is replaced by a ^{t}Bu group (eq 3).[13] Reduction of **8** with $(TMS)_3SiD$ as above gave mostly **9**-syn (≥90/10[12]). Because reductions of **3e** and **8** give comparable selectivities, we conclude that the dicyanoethyl group in radicals **5** simply functions as a very large substituent in the atom-transfer reactions.



8



9-syn (3)

The selectivities of the reactions are clearly associated with the size of the alkyl substituents: larger substituents on the radical center give higher syn selectivities. The levels of stereoselectivity in the formation of **3e,f** are some of the highest yet observed in substrate-controlled asymmetric radical reactions. The results are even more remarkable because the reactions were conducted at relatively high temperatures (60 °C), iodine-transfer reactions of **1** occur at very high rates,[8,9] and the radical centers of **5** bear no conjugating substituents. To gain insight into the structure of reactive intermediates **5**, we carried out a series of AM1 calculations on the ground states of **5b** (R^1 = Me; R^2 = Me), **5d** (R^1 = Me; R^2 = ^{i}Pr), and **5e** (R^1 = Me; R^2 = ^{t}Bu). Since radical reactions have early transition states, the ground-state geometry of the radical provides a good starting point for a transition-state analysis. Figure 3 shows the calculated conformational energy values of radicals **5** as a function of the torsional angle of the C–C bond between the radical and the stereocenter.

The energy profile of the Me-substituted radical **5b** shows an extremely broad minimum and a low rotation barrier of 3 kcal/mol. The formation of a preferred transition-state conformation that could lead to a stereoselective reaction is unlikely. Indeed, iodine transfer from iodide **1** gave a 50/50 syn/anti mixture of products **3b**. The energy profile of the ^{i}Pr-substituted radical **5d** also shows only one very broad minimum (180–270°), but the calculated rotation barrier is higher compared to that of **5b** (4.5 kcal/mol). In the iodine-transfer reaction to **5d**, we observed a modest (75/25) syn selectivity.

(13) We are very grateful to Mr. Shunneng Sun (University of Pittsburgh) for conducting the experiments shown in eq 3.

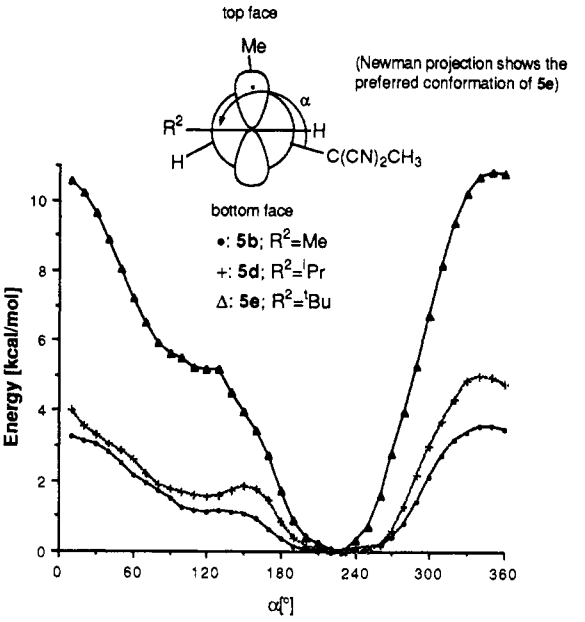


Figure 3. AM1-calculated conformational energies of alkyl-substituted radicals **5**.

The calculated profile of the ^{t}Bu-substituted radical **5e** is significantly different. The profile shows a sharper, deeper minimum (190–240°) with a calculated rotation barrier of 11 kcal/mol. The Newman projection in Figure 3 indicates the preferred conformation of radical **5e** in which the ^{t}Bu and the 1,1-dicyanoethyl groups are almost anti to each other. This must be due to steric repulsion of the two large substituents. Attack of the iodine donor **1** from the top face leads to **3e**-syn, whereas attack from the bottom face gives **3e**-anti (Figure 3). Experimentally, the addition of iodide **1** to ^{t}Bu-substituted olefin **2e** gave a 98/2 syn/anti product mixture. These calculations demonstrate that a preferred conformation of radical **5** is more likely with increasing bulk of the R^2 group and suggest that the existence of this preferred conformation is coupled with high syn selectivity.

To support these ground-state calculations, we recorded the EPR spectra of the radicals **5b,d,e**. The ^{t}Bu-substituted radical **5e** gave a well-resolved EPR spectrum (Figure 4). Unfortunately, radicals **5b** and **5d** led to weak signals, but these spectra could be simulated, and coupling constants could be obtained nonetheless. We believe that combination processes decrease the concentration of primary and secondary alkyl-substituted radicals **5b,d**; radical **5e** may actually be somewhat persistent. The H_α-coupling constant was determined to be 21.3 G in all three cases. Hyperfine coupling constants for H_β are listed in Table II. The H_β-coupling of radical **5e** showed no temperature dependence. This result is in good agreement with the single minimum and the high calculated rotation barrier of **5e** (Figure 3). By using the energy profiles of radicals **5b,d,e** (Figure 3), we also calculated EPR H_β-coupling constants.[14] Table II compares theoretical and experimental EPR data. Though the values differ considerably, the β-coupling constants decrease with increasing bulk of the R group. Both calculated and measured β-splittings show similar trends.

Given the difficulties in accurately calculating EPR coupling constants,[15] we consider that the calculated hyperfine couplings

(14) Nelson, S. F. *J. Chem. Soc., Perkin Trans. II* **1988**, 1005.

(15) The deviations of the calculated β-splittings from the experimental values are probably due to strong simplifications that were made to calculate both the torsion potentials and the coupling constants. Especially in the case of the ^{t}Bu-substituted radical **5e**, even small changes in the energy profile led to considerably smaller theoretical coupling constants. For example, a 10° shift of the torsion potential of **5e** to higher values gave a 4.9-G β-splitting instead of a 7.9-G β-splitting.

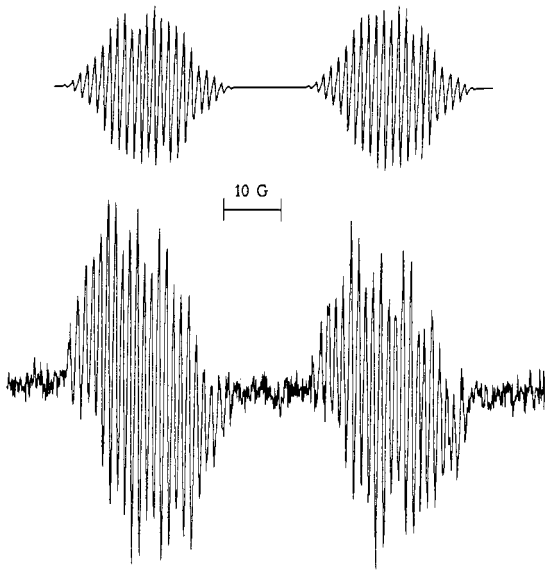


Figure 4. ESR spectrum obtained by photolyzing **3e**-syn with hexabutylditin at 243 K. The upper spectrum is a simulation generated by using the coupling constants listed in Table II.

Table II. Calculated and Experimental EPR H_β-Coupling Constants of Radicals **5**[15]

5	R^1	R^2	H_β(calcd) (G)	H_β(exp) (G)
b	Me	Me	12.5	12.2
d	Me	^{i}Pr	9.4[16]	8.1
e	Me	^{t}Bu	7.9[16]	3.9

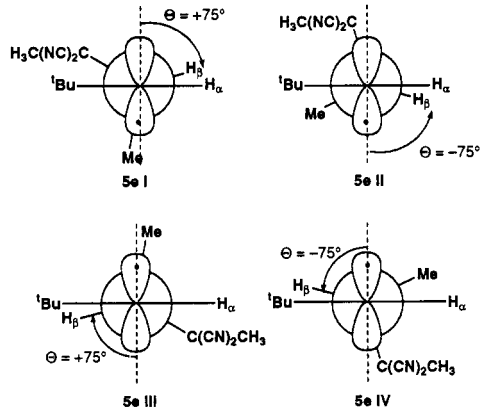


Figure 5. Preferred conformations of **5e** according to the EPR H_β-coupling constants.

are consistent with the measured ones. The extremely small value of 3.9 G for the ^{t}Bu-substituted radical **5e** is especially revealing. A preferred conformation is indicated in which the rotation about the C–C bond between the radical center and the stereocenter is hindered.[16] By using the Heller–McConnell equation,[17] we estimated that the angle θ between the SOMO of the radical and the C–H_β bond was approximately ±75°. Figure 5 shows the four possible conformations that adopt this angle. We exclude **5e I** and **5e II** from consideration because the ^{t}Bu substituent is staggered between the methyl and the dicyanoethyl substituents. This leaves as candidates closely related conformations **5e III** or **5e IV** in which H_β and the ^{t}Bu substituent are almost eclipsed. The AM1 calculations suggest that both of these could be important in the ground state, though there is a slight preference for **5e III**, which is essentially the calculated minimum. This probably arises because the ^{t}Bu substituent in **5e III** is slightly staggered toward the methyl group, whereas in **5e IV**, it is slightly staggered toward the dicyanoethyl group.

Inspection of the ground-state conformations **5e III**/**IV** (Figure 5) does not convincingly explain the very high syn selectivity that this radical exhibits in its atom-transfer reactions. Attack of the top face of both **5e III** and **5e IV** forms the syn product. In our original communication,[6g] we tentatively suggested a model conformation similar to **5e IV** that followed from the prevailing A-strain model for π-conjugated radicals. However, this model was not satisfying, in part because the related ester- and phenyl-substituted radicals[5b,9] on which the model is based give much lower selectivities than radical **5e** (compare Table I, entries a and e).[18]

A key difference between alkyl-substituted and π-conjugated radicals is their respective ability to pyramidalize. Alkyl radicals pyramidalize readily with little energy cost.[19] Fischer has recently suggested that ease of pyramidalization is a key factor that controls rates of radical additions.[20] Alkyl-substituted radicals pyramidalize easily and add readily to alkenes if the electronic pairing is favorable. In contrast, benzyl radicals are reluctant to pyramidalize and add slowly to alkenes even if the electronic pairing is favorable. We thus began to suspect that the ability to pyramidalize might be an important feature that distinguishes the atom-transfer reactions of **5** from its π-conjugated counterparts.

To address this question, we conducted transition-state calculations at the AM1 semiempirical level. We managed to locate five of the six possible transition states (TS)[21] for the iodine-transfer reaction between **5** and **1**. Figure 6 shows the bottom and top attack upon radical conformation **5e III** and the resulting transition states TS A and TS B which are lowest in energy.[22] The transition structure TS C resulting from the top attack upon radical **5e IV**, which was the proposed one in our original work, was not located as a transition state, and it is about 8 kcal/mol higher in energy than TS A. Consistent with the experimental results, the transition structure TS A leading to the syn product is significantly lower in energy than all the other transition structures. Figure 6 also shows energies for different conformations of the products. Interestingly, the immediate product of TS A is the calculated ground-state (GS) minimum of the syn rotamer, while all other syn rotamers are at least 7 kcal/mol higher in energy. The immediate product from TS B is the least favored GS conformer of the anti isomer. Furthermore, all other located anti minima are at least 3 kcal/mol higher in energy than the lowest energy syn rotamer **3e**. Full details of all five located transition states and all six ground-state minima are provided in the supplementary material. The excellent geometric correlation between the calculated minimum of **3e**-syn (Figure 6) and its crystal structure (Figure 1) lends credence to the ground-state calculations.

The energy differences between these transition states are not dominated by steric interactions between the radical substituents and the incoming reagent; in the favored transition state A, the

(16) Krusic, P. J.; Kochi, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 846.
(17) Heller, C.; McConnell, H. M. *J. Chem. Phys.* **1960**, *32*, 1535.

(18) This difference might be rationalized by suggesting that minor products from the ester-substituted radicals can come from "Me-inside" conformations, while such conformations are prohibited with **5e** due to the large ^{t}Bu group. See ref 5d.
(19) Kochi, J. K. *Adv. Free Rad.* **1975**, *5*, 175.
(20) Heberger, K.; Walbiner, M.; Fischer, H. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 635.
(21) These correspond to the six possible staggered conformations of the products: three syn and three anti.
(22) We also calculated the transition states of the H transfer from SiH_4 to the radical obtained from **8**. The transition-state analog to TS A was favored by 3 kcal/mol over any other transition state. Since the AM1 method was parameterized on ground states of small unstrained molecules, care must be taken in the use of this method on transition-state calculations with UHF wave functions. In hydrogen-transfer reactions, we have found similar geometries and energies of transition states calculated by UAM1 and by *ab initio* methods (to be published). The large calculated energy differences between the transition-state conformations found in the hydrogen-abstraction reaction of **8** and the iodine abstraction of **5e** strengthen our conclusions about transition-state geometries.

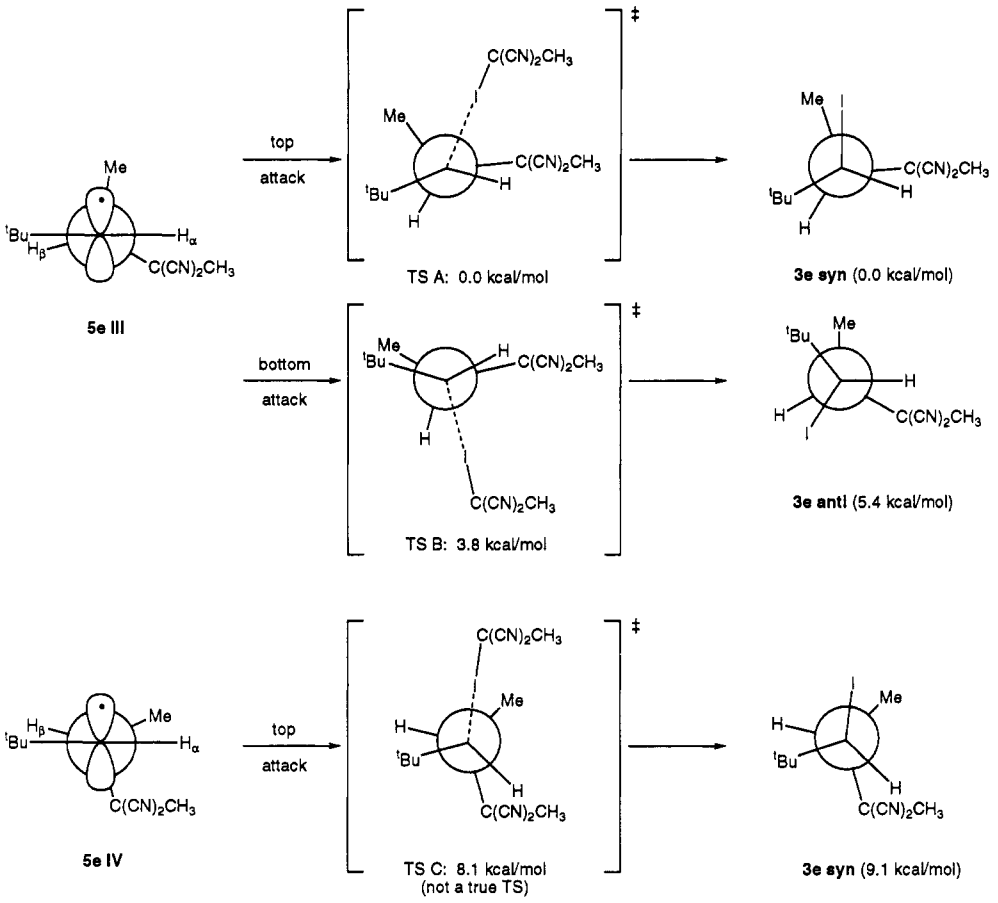


Figure 6. AM1-calculated transition-state energies and geometries.

reagent actually approaches between the two largest groups. Further, even though the lowest energy rotamer of the syn conformer is the immediate product of TS A, the relative stabilities of the products cannot account for the stereoselectivity. This is because deuterium transfer from Ph_3SnD gives similar stereoselectivity to the iodine transfer; yet the syn and anti products from TSs A and B are now the same (except for isotopic substitution, **3e**, I = D).

We suggest that the key energetic differences between the TSs lie in the interactions between the ^{t}Bu group and its vicinal neighbors (torsional strain[23]), as enforced by the direction of pyramidalization of the radical during atom transfer. The energetic preference for the ^{t}Bu group to stay as far away as possible from both the methyl and dicyanoethyl groups is clearly shown by the AM1 calculations of the radical **5e**. Postulated TS C (Figure 6) is related to the higher energy conformer **5e IV**, and it pays a further energetic price in the transition state as the ^{t}Bu pyramidalizes toward the large dicyanoethyl group. The TS calculations suggest that this energetic cost far outweighs any discount that might arise by attack of the iodine between the medium (Me) and small (H) groups. TSs A and B are both related to the likely radical GS minimum **5e III**, but the different facial attack has a large effect on the resulting TS geometries and energies. In the higher energy TS B, the ^{t}Bu group is pyramidalized toward the methyl group. Relief of this torsion strain by bond rotation begins to eclipse the C–H bond of the stereocenter with the incoming iodide. In contrast, the ^{t}Bu group of TS A pyramidalizes away from the methyl group. Though the iodide approaches between the medium and large groups, it can do so in a staggered fashion in which the large groups on the radical and the stereocenter are interacting only with vicinal C–H bonds.

A very consistent picture emerges for the syn-selective reactions of large-alkyl-substituted radicals: intermediates with GS conformation **5e III** pass thorugh TS A to give syn products **3e** as the most favored rotamers. This picture is essentially based on steric repulsion between the large substituents, which dominate in a related way the conformations of the ground state of the reactant, the transition state, and the ground state of the product. We therefore suggest that TS model A realistically rationalizes the high selectivities of such radicals. We feel that pyramidalization is a key feature that diffeentiates TSs A and B. If radicals **5** were planar in the transition state, then key interactions between the Me and ^{t}Bu groups in TS B would be reduced. Under such circumstances, TS B might even be lower in energy than TS A since the attack of the iodide occurs between the large and small (rather than large and medium) groups.

Transition-state model A is significantly different from all existing TS models[3,5,6] for radical reactions. Beyond that, it breaks with two widely held tenets of transition-state analysis[24] of all types of stereoselective reactions: (1) the reagent approaches anti to a hydrogen atom (rather than a larger group) and (2) the reagent approaches between the two largest groups. We believe that these unusual features arise due to the need to pyramidalize into roughly staggered conformations that avoid gauche interactions between large groups. We suggest that our analysis will be useful in interpreting existing results and designing substrates that exhibit high stereoselectivities both within and beyond the domain of radical chemistry.

Experimental Section

Calculations. All calculations were done with the AM1 method using the MOPAC 6.0 package. Radicals were calculated with UHF wave functions, and all geometry optimizations were done with the keywords

(23) Torsional strain is often cited as a key feature in stereoselective reactions of cyclic radicals. See: Damm, W.; Giese, B.; Hartung, J.; Hasskerl, T.; Houk, K. N.; Zipse, H. *J. Am. Chem. Soc.* **1992**, *114*, 4067.

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EF HESS = 1 PRECISE. Optimizations to the transition state were carried out with TS DMAX = 0.01 HESS = 1 PRECISE.

The conformation analysis of the transition states was first calculated with a fixed forming C–I bond length of 2.3 Å. For the nonsymmetrical substituents (two $-C(CN)_2Me$ and the stereocenter), all possible orientations (27 for each diastereomer) were tested for their energy via geometry optimization.[25] The pseudo-transition-state conformers lowest in energy with different orientations of the stereocenter were then optimized to the transition states by leaving the C–I bond free. These final transition states were tested via frequency calculations. In the conformation analysis of the products, all orientations of the two nonsymmetrical substituents were tested for their energy and therefore 18 conformers of each diastereomer were optimized.

General. Nuclear magnetic resonance (NMR) spectra were obtained on a Bruker Model WH-300 spectrometer (300 MHz for ^1H and 75 MHz for ^{13}C NMR). Chemical shift values are in parts per million (δ) downfield from tetramethylsilane as an internal reference at 0.00 ppm. Infrared spectra (cm^{-1}) were obtained on a Perkin-Elmer Model IR/32 (FT-IR) spectrometer using NaCl plates. Low-resolution mass spectra were obtained on an LKB-9000 instrument and high-resolution mass spectra by peak matching on a Varian MATCH-5DF instrument. EPR spectra were recorded on a Bruker ESP-300 spectrometer. EPR hyperfine coupling constants were refined by simulation of the manually evaluated EPR spectra with the simulation program integrated in the Bruker software. The values of g were determined with the help of a microwave frequency counter (Hewlett-Packard 5350B) and an NMR field measuring unit (Bruker ER 035M). Flash column chromatography was performed with Kieselgel 60 (230–400 mesh ASTM) using distilled solvents. THF and benzene were freshly distilled from sodium/benzophenone. Commercially available reagents were used without further purification. Air-sensitive operations were conducted under an argon atmosphere.

Methyliodomalonodinitrile (1). Oil-free sodium hydride (10.0 mmol; prepared from 0.60 g, 60% dispersion) and NIS (4.05 g; 15.0 mmol) were suspended under argon in 50 mL of THF. A solution of methylmalonodinitrile[10] (0.80 g; 10.0 mmol) in 50 mL of THF was added in one portion at 0 °C. After 1 h, the mixture was diluted with 100 mL of ether and filtered through silica gel (3 cm). Flash chromatography on silica gel (hexanes/ethyl acetate, 9/1) afforded 1.48 g (72%) of pure iodide **1** as a yellow oil which crystallized in the refrigerator: IR (neat) 2245; ^1H NMR ($CDCl_3$) δ 2.56 (s); ^{13}C NMR ($CDCl_3$) δ 115.0, 32.6, –21.5; MS m/z 206 (M^+); HRMS calcd for $C_4H_3IN_2$ 205.9341, found 205.9341.

***trans*-1-Adamantylprop-1-ene (2f).** Under argon, a solution of AIBN (0.10 g; 0.61 mmol) in 5 mL of benzene was added over 58 h via syringe pump to a refluxing solution of 1-adamantyl bromide (1.00 g; 4.65 mmol) and allyltributyltin (2.00 g; 6.05 mmol) in 15 mL of benzene. After complete consumption of the bromide (GC monitoring), the solvent was removed and the residue dissolved in ether. Water (1 mL) and KF (3 g) were added, and the mixture was stirred for 3 h at room temperature. Chromatography on silica gel (hexanes) followed by Kugelrohr distillation (150 °C/12 Torr) gave 465 mg (57%) of 3-adamantylprop-1-ene as a colorless oil: ^1H NMR ($CDCl_3$) δ 5.85 (1 H, m), 4.95 (2 H, m), 1.94–1.47 (17 H, m); ^{13}C NMR ($CDCl_3$) δ 134.9, 116.5, 49.1, 42.4, 37.2, 28.7. 3-Adamantylprop-1-ene (400 mg, 2.27 mmol) and rhodium(III) chloride trihydrate (50 mg) in dry ethanol were heated at reflux for 1 h. The solvent was removed, and the residue was dissolved in 30 mL of hexanes and filtered through silica gel (2 cm). Kugelrohr distillation (150 °C/12 Torr) yielded 360 mg (90%) of **2f**: IR (neat) 3020, 2980, 2940, 1465, 1025, 985; ^1H NMR ($CDCl_3$) δ 5.32 (1 H, d, J = 15.6 Hz), 5.25 (1 H, dq, J = 15.6, 5.6 Hz), 1.96–1.45 (15 H, m), 1.65 (3 H, d, J = 5.6 Hz); ^{13}C NMR ($CDCl_3$) δ 143.2, 119.2, 42.5, 37.0, 28.6, 18.2; MS m/z 176 (M^+), 135, 119, 91; HRMS calcd for $C_{13}H_{20}$ 176.1558, found 176.1558.

Additions of Methyliodomalonodinitrile (1) to Olefins 2. *syn/anti*-(1,2-Dimethyl-3-iodo-3-phenylpropyl)malonodinitrile (3a).[9] A solution of iodide **1** (25 mg; 0.121 mmol) and *trans*-1-phenylprop-1-ene (**2a**) in 2 mL of chloroform was heated at reflux for 3 h. Following removal of the solvent, flash chromatography on silica gel (hexanes, then hexanes/ether, 5/1) gave 15.5 mg (40%) of pure **3a**-syn, 8.0 mg (20%) of a 1/1 mixture of **3a**-syn and **3a**-anti, and 15.0 mg (38%) of a 1/8 syn/anti mixture of **3a**. The course of the reaction was monitored in a separate ^1H NMR experiment. The initially formed 85/15 syn/anti mixture of **3a** changed to an approximately 1/1 ratio after complete consumption of **1**. **3a-syn**: IR (neat) 3030, 2940, 2870, 2250, 1500, 1450, 1400, 1300, 1190, 1170, 1090, 1060; ^1H NMR ($CDCl_3$) δ 7.51–7.27 (5 H, m), 5.39 (1 H, d, J = 6.0 Hz), 2.06 (1 H, br quint, J = 6.5 Hz), 1.78 (3 H, s), 1.53 (3 H, d, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 141.1, 129.5, 128.9 (2 C), 128.8 (2 C), 115.0 (2 C), 47.0, 35.7, 34.7, 24.5, 17.8; MS m/z 197 (M^+ – I), 118; HRMS calcd for $C_{13}H_{13}N_2$ 197.1079, found 197.1083. **3a-anti**: IR (neat) 3030, 2940, 2870, 2250, 1500, 1450, 1400, 1300, 1190, 1170, 1090, 1055; ^1H NMR ($CDCl_3$) δ 7.55–7.31 (5 H, m), 5.83 (1 H, d, J = 3.9 Hz), 2.65 (1 H, dq, J = 3.9, 7.0 Hz), 1.75 (3 H, s), 1.65 (3 H, d, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 137.3, 129.5 (2 C), 129.4, 128.8 (2 C), 115.7, 113.6, 49.5, 34.7, 30.3, 24.5, 13.0; MS m/z 197 (M^+ – I), 118; HRMS calcd for $C_{13}H_{13}N_2$ 197.1079, found 197.1064.

***syn/anti*-(1,2-Dimethyl-3-iodobutyl)malonodinitrile (3b).** At –20 °C, 10 mL of *trans*-2-butene (**2b**) was condensed in an autoclave. A solution of iodide **1** (0.80 g; 3.88 mmol) in 30 mL of chloroform was added. The mixture was held at 60 °C for 20 h. The ^1H NMR spectrum of the crude products showed an approximately 50/50 syn/anti ratio. Chromatography on silica gel (hexanes, then hexanes/ether, 5/1) led to the isolation of 0.76 g (75%) of only one product **3b** as a colorless solid, mp 55–56 °C: IR (neat) 2970, 2930, 2250, 1460, 1440, 1405, 1395, 1220, 1105, 1050; ^1H NMR ($CDCl_3$) δ 4.91 (1 H, dq, J = 2.7, 7.1 Hz), 2.52 (1 H, dq, J = 2.7, 6.9 Hz), 1.96 (3 H, d, J = 7.1 Hz), 1.86 (3 H, s), 1.49 (3 H, d, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 115.3, 115.2, 48.7, 34.1, 24.7, 24.1, 21.9, 11.4; MS m/z 262 (M^+), 183, 155, 135; HRMS calcd for $C_8H_{11}IN_2$ 261.9945, found 261.9945. **Second Diastereomer**: ^1H NMR ($CDCl_3$) δ 4.54 (1 H, br q, J = 7.0 Hz), 2.01 (3 H, d, J = 7.0 Hz), 1.99 (1 H, m), 1.89 (3 H, s), 1.34 (3 H, m); the other signals overlap with the other diastereomer.

***syn/anti*-(1,4-Dimethyl-2-(1-methylethyl)-3-iodopentyl)malonodinitrile (3c).** A solution of iodide **1** (50 mg; 0.243 mmol) and *trans*-4-octene (**2c**) in 3 mL of chloroform was heated at reflux for 4 h. The ^1H NMR spectrum of the crude products showed an approximately 50/50 syn/anti ratio. Following the removal of the solvent, flash chromatography on silica gel (hexanes, then hexanes/ether, 10/1) gave 62 mg (80%) of an inseparable 4/1 mixture of products **3c**: ^1H NMR ($CDCl_3$) δ 4.59 (1 H, dt, J = 11.8, 2.6 Hz), 2.33 (1 H, sx, J = 2.6 Hz), 1.90–1.40 (8 H, m), 1.88 (3 H, s), 1.02 (3 H, t, J = 7.2 Hz), 0.95 (3 H, t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 116.0, 115.5, 49.0, 42.1, 37.2, 36.2, 34.2, 23.8, 22.8, 22.5, 14.3, 13.0. **Second diastereomer**: ^1H NMR ($CDCl_3$) δ 4.37 (1 H, ddd, J = 10.1, 4.2, 2.1 Hz), 1.90–1.40 (9 H, m), 1.90 (3 H, s), 1.02 (3 H, t, J = 7.2 Hz), 0.97 (3 H, t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 115.9, 115.7, 52.6, 35.5, 31.6, 25.3, 22.9, 14.1, 12.9 (missing signals are concealed by major diastereomer); HRMS m/z 191 (M^+ – I), 175, 164, 149, 135, 122, 121, 108, 95; HRMS calcd for $C_{12}H_{19}N_2$ 191.1543, found 191.1449. An analogous experiment in deuteriochloroform was monitored by ^1H NMR spectroscopy. The product ratio remained constant in the course of the reaction and was determined to be approximately 50/50.

***syn/anti*-(1,2,4-Trimethyl-3-iodopentyl)malonodinitrile (3d).** A solution of iodide **1** (40 mg; 0.194 mmol) and olefin **2d** (300 mg; 3.57 mmol) in 3 mL of chloroform was heated at reflux for 3 h. The ^1H NMR spectrum of the crude products showed an approximately 75/25 syn/anti ratio. Following the removal of the solvent, the diastereomers were separated by flash chromatography (hexanes, then hexanes/ether, 5/1) to yield 15 mg (26%) of **3d**-anti and 38 mg (67%) of **3d**-syn. **3d-anti**: IR (neat) 2970, 2875, 2245, 1455, 1390, 1370, 1315, 1185, 1160, 1055; ^1H NMR ($CDCl_3$) δ 4.74 (1 H, dd, J = 4.1, 2.3 Hz), 2.54 (1 H, dq, J = 7.2, 4.1 Hz), 1.89 (3 H, s), 1.53 (3 H, d, J = 7.2 Hz), 1.34 (1 H, m), 1.02 (3 H, d, J = 6.2 Hz), 1.00 (3 H, d, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 115.4 (2 C), 48.9, 48.0, 35.7, 30.2, 25.7, 25.1, 22.9, 14.6; MS m/z 290 (M^+), 195, 163, 121, 83, 41. **3d-syn**: IR (neat) 2970, 2875, 2245, 1455, 1390, 1370, 1315, 1180, 1160, 1090; ^1H NMR ($CDCl_3$) δ 4.22 (1 H, dd, J = 7.6, 2.3 Hz), 1.87 (3 H, s), 1.84 (1 H, m), 1.68 (1 H, dq, J = 6.7, 2.3 Hz), 1.36 (3 H, d, J = 6.7 Hz), 1.15 (3 H, d, J = 6.5 Hz), 1.04 (3 H, d, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$) δ 115.5, 115.3, 46.8, 42.4, 37.8, 35.9, 23.8, 23.4, 20.7, 16.3; MS m/z 290 (M^+), 195, 163, 121, 83, 41; HRMS calcd for $C_8H_{11}N_2$ 163.1235, found 163.1239. An analogous experiment in deuteriochloroform was monitored by ^1H NMR spectroscopy. The syn/anti ratio of products **3d** remained constant in the course of the reaction and was determined to be approximately 75/25.

***syn/anti*-(1,2,4,4-Tetramethyl-3-iodopentyl)malonodinitrile (3e).** A solution of iodide **1** (10 mg; 0.048 mmol) and olefin **2e** (100 mg; 1.02 mmol) in 0.5 mL of deuteriochloroform was heated at 60 °C for 6 h. The course of the reaction was monitored by ^1H NMR spectroscopy. The syn/anti ratio remained constant and was determined to be 98/2. After complete consumption of **1**, the solvent was removed. Flash chroma-

(25) Fixing the C–I bond length at 2.3 Å for the preliminary conformational analysis is justified because the largest deviation in the calculated transition states from this value is only 0.05 Å and the energy differences between the actual transition states (with the forming C–I bond free) and the "pseudo-transition states" (with a C–I bond length fixed to 2.3 Å) are less than 0.5 kcal/mol.

tography of the residue (hexanes, then hexanes/ether, 5/1) gave 12.1 mg (83%) of **3e**-syn as colorless crystals. The minor diastereomer could not be isolated even when the reaction was conducted on a larger scale. **3e-syn**: mp 92–93 °C; IR (neat) 2970, 2930, 2870, 2250, 1480, 1460, 1440, 1250, 1190, 1140; ^{1}H NMR ($CDCl_3$) δ 4.40 (1 H, d, J = 0.9 Hz), 1.86 (3 H, s), 1.85 (1 H, dq, J = 0.9, 6.5 Hz), 1.39 (3 H, d, J = 6.5 Hz), 1.16 (9 H, s); ^{13}C NMR ($CDCl_3$) δ 115.9, 115.6, 52.6, 39.8, 37.6, 36.9, 29.2 (3 C), 22.2, 20.4; MS m/z 289 (M^+ – Me), 209, 177, 97; HRMS calcd for $C_{11}H_{17}N_2$ 177.1372, found 177.1370. **3e-anti**: ^{1}H NMR ($CDCl_3$) δ 4.32 (1 H, d, J = 3.1 Hz), 1.96 (3 H, s), 1.20 (9 H, s).

***syn*-(3-Adamantyl-1,2-dimethyl-3-iodopropyl)malonodinitrile (3f).** A solution of iodide **1** (10 mg; 0.048 mmol) and olefin **2f** (200 mg; 1.14 mmol) in 0.5 mL of deuteriochloroform was heated at 60 °C. Every 24 h, a 10-mg portion of **1** was added to the reaction mixture. After addition of 90 mg of **1**, the mixture was heated for an additional 24 h. The solvent was removed, and the residue was chromatographed on silica gel (hexanes, then hexanes/ether, 10/1) to yield 25 mg (14%) of **3f**-syn as a colorless solid. The course of the reaction was monitored by ^{1}H NMR spectroscopy. The formation of a second diastereomer could not be detected. **3f-syn**: mp 143–144 °C; IR (neat) 2970, 2900, 2890, 2850, 2250, 1445, 1390, 1260, 1140, 860; ^{1}H NMR ($CDCl_3$) δ 4.26 (1 H, br s), 2.02–1.90 (4 H, m), 1.86 (3 H, s), 1.72–1.55 (12 H, m), 1.39 (3 H, d, 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 116.0, 115.8, 55.9, 41.7, 37.9, 37.8, 37.6, 36.5, 29.7, 28.7, 22.1, 21.4; MS m/z 255 (M^+ – I), 135; HRMS calcd for $C_{17}H_{23}N_2$ 255.1868, found 255.1868.

Reductions of 3a, 3d, and 3e were conducted by heating small samples (10–35 mg, 0.2 M) with 1.1 equiv of Ph_3SnH(D) in benzene at 80 °C. Xanthate **8** was reduced under similar conditions with $(TMS)_3SiH$(D).

7aH: ^{1}H NMR ($CDCl_3$) δ 7.56–7.16 (5 H, m), 3.21 (H_{anti}, dd, J = 13.1, 2.9 Hz), 2.47 (H_{syn}, dd, J = 13.1, 11.4 Hz), 2.18 (1 H, m), 1.81 (3 H, s), 1.07 (3 H, d, J = 6.6 Hz).

7dH: ^{1}H NMR ($CDCl_3$) δ 1.97 (1 H, ddq, J = 10.0, 3.2, 6.7 Hz), 1.73 (3 H, s), 1.70 (1 H, m), 1.42 (H_{syn}, m, J_{vic} = 10.7 Hz), 1.34 (H_{anti}, m, J_{vic} = 3.8 Hz), 1.16 (3 H, d, J = 6.7 Hz), 0.98 (3 H, d, J = 6.7 Hz), 0.89 (3 H, d, J = 6.7 Hz).

7eH: ^{1}H NMR ($CDCl_3$) δ 2.00 (1 H, br dq, J = 8.2, 7.0 Hz), 1.74 (3 H, s), 1.59 (H_{anti}, d, J = 14.2 Hz), 1.31 (H_{syn}, dd, J = 14.2, 8.2 Hz), 1.27 (3 H, d, J = 7.0 Hz), 0.97 (9 H, s).

9H: ^{1}H NMR ($CDCl_3$) δ 1.39 (H_{anti}, d, J = 14.0 Hz), 1.20 (1 H, m), 0.88 (9 H, s), 0.84 (3 H, d, J = 7.3 Hz), 0.82 (9 H, s), 0.79 (H_{syn}, dd, J = 14.0, 6.3 Hz).

EPR Measurements of Radicals 5. Radicals were generated at 243 K by UV irradiation of solutions in Suprasil quartz tubes (o.d. 5.0 mm) with the filtered light (water-cooled Schott Filter UG-5) of a Hanovia 977-B1 1-kW Hg–Xe high pressure lamp. The lamp housing and the optical equipment were identical to those described by Fischer.[26] The EPR solutions were prepared by dissolving iodides **3b,d,e** (*ca.* 50 mg) and hexabutylditin (0.1 mL) in dry fluorobenzene (0.4 mL). Oxygen was removed from the solutions by purging with dry argon for 30 min. **5b**: g = 2.0024; a (1 H)$_a$ = 21.3 G, a (3 H)$_b$ = 25.7 G, a (1 H)$_b$ = 12.2 G, a (3 H)$_g$ = 0.5 G. **5d**: g = 2.0024; a (1 H)$_a$ = 21.3 G, a (1 H)$_b$ = 21.1 G, a (1 H)$_b$ = 8.1 G, a (3 H)$_g$ = 1.5 G, a (6 H)$_g$ = 0.3 G. **5e**: g = 2.0024; a (1 H)$_a$ = 21.3 G, a (1 H)$_b$ = 3.9 G, a (3 H)$_g$ = 3.0 G, a (9 H)$_g$ = 0.6 G.

Acknowledgment. This work was supported by the National Institutes of Health and the Swiss National Science Foundation. G.T. thanks the Deutsche Forschungsgemeinschaft for a postdoctoral fellowship.

Supplementary Material Available: Details of the X-ray crystal structure of **3e** and geometrical details of all calculated transition states and product conformations (13 pages); table of observed and calculated structure factors (9 pages). Ordering information is given on any current masthead page.

(26) Fischer, H.; Paul, H. *Helv. Chim. Acta* **1973**, *56*, 1575.