Stereocontrol at the Steady State in Radical Cyclizations of Acyclic Dihalides†

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The first examples of manipulating stereocontrol solely by reaction topography in radical cyclizations starting from acyclic precursors are reported. The kinetic model for acyclic compound stereoselection is verified experimentally by conducting a series of radical cyclizations of 1,3-dihalo-2-(1-phenyl-3-butynyl)propanes with triphenyltin hydride and measuring the ratios of the products. Monohalide intermediates are observed for the first time, and evidence that bromide- and iodide-substituted radicals have different cyclization rate constants is provided.

1. Introduction

The study of stereoselection in radical reactions has been a major focus of the synthetic radical community over the past decade or so.[1] Like their ionic and pericyclic counterparts, stereoselective radical transformations often involve reactions of stereoheterotopic[2] faces of sp^2-hybridized radicals or radical acceptors. Stereoselection can be dictated by nearby stereocenters (substrate control), by chiral auxiliaries, by chiral additives, and even by chiral catalysts.[1] A few examples of traditional stereotopic group selective radical cyclizations are also known.[3] In the example shown in Figure 1[3a] (upper part), two alkenes compete directly against each other (through diastereomeric transition states) for a single radical. As in many radical cyclizations, the major product of this reaction is readily predicted by the Beckwith−Houk model.[1e,4]

Beyond offering new options for traditional types of face and group selective reactions, the transiency of radicals also offers unique opportunities for stereocontrol in nonequilibrium situations. For example, Rychnovsky has shown that reactions of tetrahydropyranyl radicals can be faster than ring flip,[5] and we have shown that aryl radical cyclizations of acrylanilides can be faster than rotation of the N−aryl bond.[6] Giese has found that closures of diradicals can be faster than standard σ bond rotations.[7] In each of these reactions, the short lifetimes and high reactivity of radicals avoid racemizations or conformational changes that many other types of intermediates would undergo.

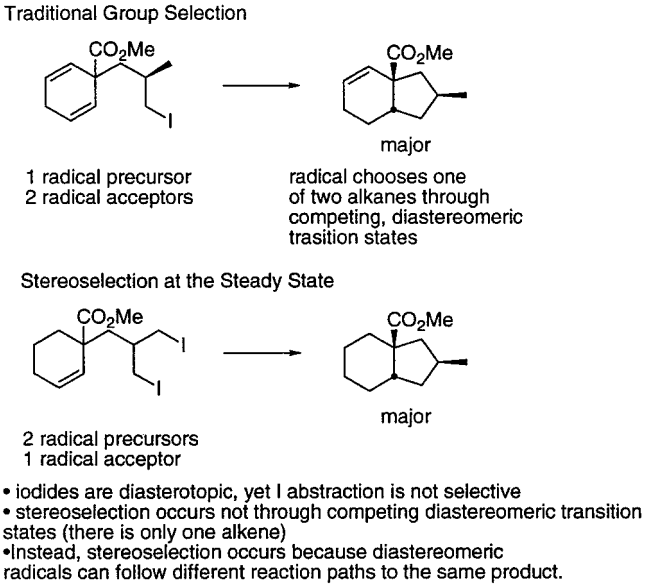

Figure 1. Traditional and steady-state stereoselection in radical cyclizations to make bicyclic rings.

Recently, we have put forth a new type of stereoselective process founded on the transiency of radicals and called "stereoselection at the steady state".[4,8] As illustrated by Figure 1b (lower part), existing examples of this process include competition of two radical precursors for a single radical acceptor in a multistep process. We have advanced the notion that stereoselection at the steady state is fundamentally different from existing multistep stereoselective processes, which are "composites" of individual steps.[8a] Stereoselection at the steady state is not a composite process, and unlike other existing stereoselective processes, stereoselection can be accomplished without ever pitting stereoisomeric transition

† Dedicated to the memory of Dr. Emmanuil Troyansky.

(1) (a) Sibi, M. P.; Porter, N. A. *Acc. Chem. Res.* **1999**, *32*, 163−171. (b) Guindon, Y.; Guérin, B.; Rancourt, J.; Chabot, C.; Mackintosh, N.; Ogilvie, W. W. *Pure Appl. Chem.* **1996**, *68* (1), 89−96. (c) Renaud, P.; Gerster, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2563−2579. (d) Curran, D. P.; Giese, B.; Porter, N. A. *Acc. Chem. Res.* **1991**, *24*, 296−304. (e) Curran, D. P.; Giese, B.; Porter, N. A. *Stereochemistry of Radical Reactions: Concepts, Guidelines, and Synthetic Applications*; VCH: Weinheim, Germany, 1996.

(2) Eliel, L.; Wilen, S. *Stereochemistry of Organic Compounds*; Wiley-Interscience: New York, 1994.

(3) (a) Curran, D. P.; Qi, H. Y.; Demello, N. C.; Lin, C. H. *J. Am. Chem. Soc.* **1994**, *116*, 8430. (b) Qi, H. Ph.D. Thesis, University of Pittsburgh, Pennsylvania, 1994. (c) Villar, F.; Equey, O.; Renaud, P. *Org. Lett.* **2000**, *2*, 1061.

(4) (a) Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959. (b) Beckwith, A. L. J.; Lawrence, T.; Serelis, A. K. *J. Chem. Soc., Chem. Commun.* **1980**, 482. (c) Beckwith, A. L. J.; Easton, C. J.; Serelis, A. K. *J. Chem. Soc., Chem. Commun.* **1980**, 484.

(5) (a) Buckmelter, A. J.; Kim, A. I.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2000**, *122*, 386. (b) Buckmelter, A. J.; Powers, J. P.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1998**, *120*, 5589.

(6) Curran, D. P.; Liu, W. D.; Chen, C. H.-T. *J. Am. Chem. Soc.* **1999**, *121*, 11012.

(7) Giese, B.; Wettstein, P.; Stahelin, C.; Barbosa, F.; Neuburger, M.; Zehnder, M.; Wessig, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 2586.

(8) (a) Curran, D. P.; DeMello, N. C. *J. Am. Chem. Soc.* **1998**, *120*, 329−341. (b) Curran, D. P.; DeMello, N. C.; Junggebauer, J.; Lin, C.-H. *J. Am. Chem. Soc.* **1998**, *120*, 342−351.

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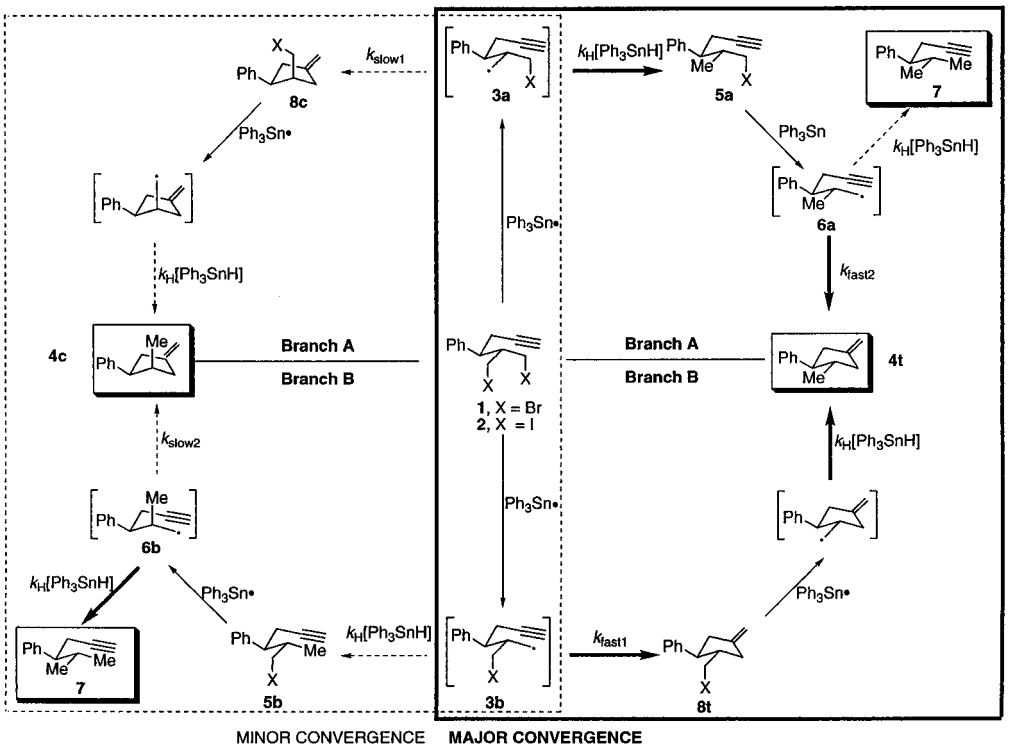
Scheme 1. Stereoselection at the Steady State[a]



[a] Bold arrows represent faster reactions. Dashed arrows represent slower reactions. Standard arros represent nonselective reactions.

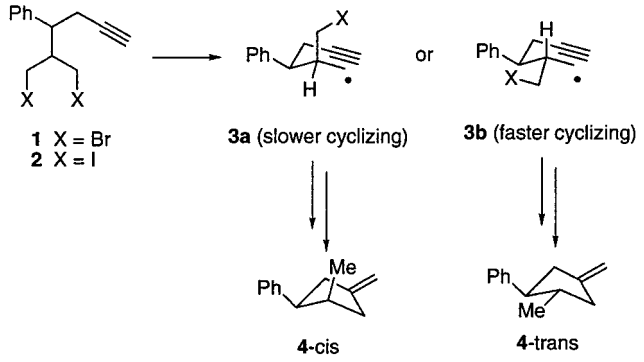


Figure 2. Designing substrates after the Beckwith−Houk model.

states in direct competition with each other. Instead, stereoselection is achieved when stereoisomeric intermediates at the steady state partition selectively between two different chemical (not stereochemical) pathways[9] to the same stereoisomeric product.

All existing examples of stereoselection at the steady state are diastereoselective and involve bicyclic systems.[3,8] These systems have provided a rigidity to reduce options for intermediate radicals, but there is no reason bicyclic systems are needed. The goal of this work was to identify and study an acyclic radical precursor that would be subject to stereoselection at the steady state. We report herein the design, synthesis, and detailed study of the cyclizations of radicals derived from **1** and **2** (Figure 2). Results consistent with stereoselection at the steady state are observed, and postulated monohalide intermediates are identified for the first time. Differences in the results between the dibromide **1** and the dihalide **2** suggest a substituent effect on the initial radical cyclization.

2. Results and Discussion

Dihalides **1** and **2** were selected for this study on the basis of a number of criteria. First and foremost, on the basis of the Beckwith−Houk model,[1e,4] the two diastereomeric radicals **3a** and **3b** shown in Figure 2 were expected to cyclize at different rates. Stereoselection at the steady state is a kinetic resolution that is predicated on this rate difference. In addition to providing the bias needed for stereoselection, the phenyl group adds molecular weight so that products *trans*/*cis*-**4** are not volatile and provides for a ready assignment of the relative configuration of the products due to anisotropic shielding of the methyl protons of the cis isomer by the phenyl group.

The proposed kinetic framework for stereoselection at the steady state in the radical cyclizations of precursors **1** and **2** is shown in Scheme 1.[10] The abstraction of the first halide from **1** or **2** produces two diastereomeric radicals, **3a** and **3b**. This step irreversibly partitions these and all subsequent intermediates into two different branches, hereafter called A (upper paths) and B (lower paths). Nevertheless, the radicals are not irreversibly committed to any product since the two branches converge on the final cyclic (**4t**/**4c**) and reduced (**7**) products. The first key step that helps to determine the final ratio of stereoisomers is reduction of radicals **3a,b** to monoreduced products **5a,b**, which occurs in competition with cyclization to **8t** and **8c**. Stereoselection at the steady

(9) Kagan, H. *Tetrahedron* **2001**, *47*, 2449.

(10) Bold and dotted arrows represent fast and slow stereoselective processes, respectively. Standard arrows represent nonselective reactions. The major and minor convergences are shown in the bold and dotted boxes.

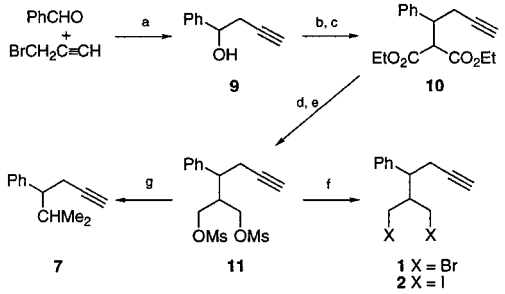
state capitalizes on different partitioning of **3a** and **3b** between these two competing chemical transformations (reduction and cyclization). Under suitable conditions, the majority of both initial radicals **3a** and **3b** can be partitioned into the major convergence toward **4t**.

Even though reduction of intermediate radicals **3a,b** with tin hydride is not a selective process, the overall stereoselection depends crucially on the tin hydride concentration. At low tin hydride concentrations, reduction of radicals **3a,b** does not compete with cyclization and the ratio of **4t** to **4c** depends only on the ratio of the rate constants for halogen abstraction to form **3b** (which partitions exclusively through the major convergence to **4t**) and **3a** (which partitions exclusively through the minor convergence to **4c**).[11] As the tin hydride concentration increases, reduction of **3a** to **5a** starts to compete with cyclization and radicals **3a** set to enter the minor convergence are derailed from the path to **4c** and sent into the major convergence on the path to **4t**. A similar partitioning occurs for **3b**. However, at the steady state, the concentration of the slower cyclizing radical **3a** is higher than that of its faster cyclizing diastereomer **3b** so more of radical **3a** is rerouted to the major convergence than **3b** to the minor convergence. This results in stereoselection by enhancement of the yield of the major product **4t**. In contrast, multistep composite processes generally provide increased stereoselection by decreasing the yield of the minor product. A similar partitioning between reduction and cyclization occurs at radicals **6a** and **6b**; however, now the radicals are irrevocably committed toward one or the other cyclized product, and enhanced stereoselection here arises because the slower cyclizing radical **6b** is derailed to the doubly reduced product **7** more efficiently than the faster cyclizing radical **6a**.

After radical generation, there is no point in the process where two stereoisomeric transition states compete directly with each other to influence the product ratio. Instead, the stereoselection arises from the reaction topography, which offers multiple routes to the same products. Despite the absence of a direct competition, differences in the rate constants for cyclizations are crucial since these establish the concentration gradient of isomeric radicals **3a,b** at the steady state; higher rate constant ratios (k_{fast1}/k_{slow1}) enforce higher gradients, and that allows higher yields of the major stereoisomer **4t**. The addition of the tin hydride harvests the concentration gradient by forcing radicals **3a** present in higher concentrations down a reduction pathway while radicals **3b** present in lower concentration can still cyclize.

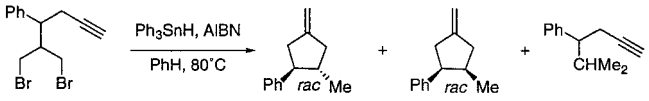
To experimentally verify the expected behavior for this type of topological group selective process, compounds **1** and **2** were designed as models having two radical precursors and one radical acceptor. The compounds are readily available (Scheme 2) by mesylation of **9** followed by standard malonate alkylation to give **10**.[12] Reduction and mesylation gave **11**, which was readily converted to the bromide **1** or iodide **2**. The synthesis can be carried out on a multigram scale. Reduction of the dimesylate **11** with LAH provided a standard sample of the doubly reduced product **7** in high yield.

Scheme 2[a]



[a] Reagents and conditions: (a) Al, $HgCl_2$, THF, ~30 °C for 2 days, 50%; (b) MsCl/Et_3N, CH_2Cl_2, 0 °C for 10 min, ~100%; (c) NaH/$CH_2(CO_2Et)_2$, THF, 70 °C for 2 days, 75%; (d) LAH, Et_2O, 0 °C for 4 h, 60%; (e) MsCl/Et_3N, CH_2Cl_2, 0 °C for 2 h, ~100%; (f) LiBr or NaI, acetone, reflux for 12 h, 95−99%; (g) LAH, Et_2O, 0 °C for 2 h, 74%.

Table 1. Preliminary Cyclizations of Dibromide 1 with Ph_3SnH



entry	[Ph_3SnH] (M)	**4t** (%)	**4c** (%)	**7** (%)	**4t** + **4c** (%)	**4t**/**4c**
1[a]	0.05	57	36	0	93	1.6
1	0.05	53	37	0	90	1.4
2	0.10	44	32	0	76	1.4
3	0.20	48	20	0	68	2.4
4	0.25	41	22	0	63	1.9
5	0.40	32	27	0	59	1.2

[a] With Bu_3SnH.

Preparative cyclization of **1** with triphenyltin hydride (5 equiv, 0.05 M) provided a mixture of **4t** and **4c** in over 74% isolated yield. These isomeric products could not be separated by chromatography to give the individual pure isomers, so they were characterized as a mixture. The assignment of the relative configuration of these products was made by ^1H NMR spectroscopy on the basis of the chemical shifts of a methyl group; the resonance from the cis isomer **4c** resonates at higher field than that of the trans isomer **4t** due to anisotropic shielding of the phenyl ring.

A preliminary series of cyclizations with bromide **1** was first conducted with 10 equiv of triphenyltin hydride at 80 °C. All reactions were performed in benzene with a catalytic amount of AIBN to ensure initiation. Biphenyl was added as an internal standard for GC/MS analyses, and each of the products was calibrated against this standard. The results of this series of experiments are shown in Table 1.

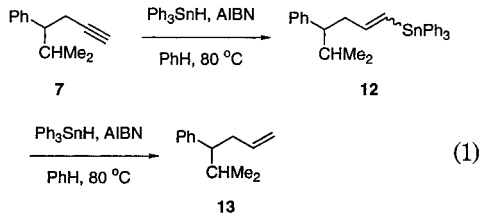
The expected cyclized products **4t**/**4c** were produced in up to 93% yield. Disconcertingly, we did not detect any of the doubly reduced product **7** in any of the experiments by comparison of retention times with that of the authentic sample. Also, the ratio of **4t**/**4c** varied in an unexpected manner as the concentration of Ph_3SnH was changed. Initially, the trans/cis ratio increased as the concentration increased up to 0.2 M Ph_3SnH, but then it began to decrease on further concentration increase. These results are inconsistent with the model in Scheme 1, which predicts that the yield of **7** should increase as the yield of **4** decreases and that the **4t**/**4c** ratio should

(11) However, in practice this ratio might not be exactly 50/50 because one of the diastereomeric radicals should cyclize faster than the second one.

(12) Katzenellenbogen, J. A.; Sofia, M. J. *J. Med. Chem.* **1986**, *29*, 230−238.

continue to increase even as the total yield of these two products falls (because the yield of **4c** falls faster than that of **4t**).

The absence of the doubly reduced product **7** suggested that hydrostannylation of its triple bond might have taken place.[13] To verify this, we treated an authentic sample of **7** with excess (10 equiv) Ph_3SnH in benzene at 80 °C. The reaction was monitored by GC/MS. After 36 h, **7** was consumed, and the reaction was worked up. The crude product was chromatographed to provide a single compound (60%) identified as alkene **13** (eq 1). This presumably results from protodestannylation of the hydrostannylated product **12**, so hydrostannylation does indeed explain the absence of **7**.



(1)

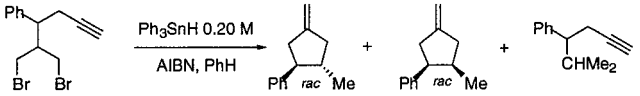
That the change in the **4t**/**4c** ratio did not follow the kinetic model also suggests that a side reaction, possibly again hydrostannylation, consumes **4t** faster than **4c**. To identify conditions that minimized side reactions, four experiments were conducted at different temperatures with the same concentration of the tin hydride (0.2 M). The results of these experiments are summarized in Table 2. The optimum temperature was 65 °C. At that temperature, the combined yield of the products, including the doubly reduced **7**, was almost quantitative (99%).

Having identified conditions that minimized secondary product formation, we next performed a series of experiments at increasing Ph_3SnH concentrations following a standard protocol. A benzene solution containing **1**, Ph_3SnH (10 equiv), and a catalytic amount of AIBN was heated at 65 °C until the reaction was complete, and the products were analyzed by GC. Reaction times varied from 30 min for the highest concentration experiment to >8 h for the lowest. The results of these experiments are summarized in Table 3, entries 2−12. A syringe pump addition experiment was also conducted (entry 1), and this presumably has the lowest tin hydride concentration even though the nature of the experiment precludes an accurate measure of that concentration.

In the syringe pump addition experiment (entry 1), the ratio **4t**/**4c** is close to 1/1. This confirms that the selectivity in the initial abstraction of bromine by the tin radical is negligible. As the tin hydride concentration increases, the yield of **4t** begins to increase and the yield of **4c** declines. After reaching a maximum in the vicinity of 70% (entries 6 and 7), the yield of **4t**/**4c** begins to decline, but the yield of **4c** declines more steeply, so the **4t**/**4c** ratio increases as the combined yield of **4** decreases. Concomitantly, the doubly reduced product **7** begins to grow in (entries 2−9). However, the yields of this product only increase to 14% (entry 9), and then slowly decrease (entries 10−12). At very high tin hydride concentrations the total yield of **4** and **7** begins to fall from quantitative as well. Apparently, hydrostannylation of the products cannot be avoided at high concentrations even at 65 °C.

(13) Nozaki, K.; Oshima, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 2547−2549.

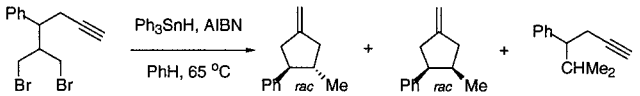
Table 2. Reduction of Dibromide 1 with Ph_3SnH at Different Temperatures



1 **4t** **4c** **7**

entry	*t* (°C)	**4t** (%)	**4c** (%)	**7** (%)	**4t** + **4c** (%)	**4t**/**4c**
1	80	48	20	0	68	2.4
2	70	63	22	3	85	2.9
3	65	70	24	5	94	2.9
4	60	59	31	2	90	1.9

Table 3. Reductions of Dibromide 1 with Ph_3SnH at 65 °C



1 **4t** **4c** **7**

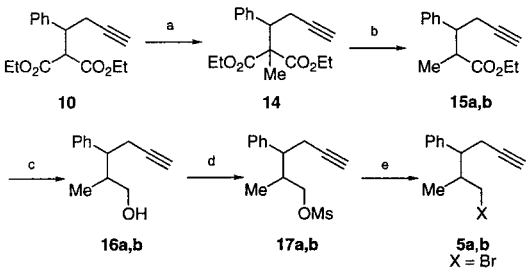
entry	[Ph_3SnH] (M)	**4t**/**4c**	**4t** (%)	**4c** (%)	**4t** + **4c** (%)	**7** (%)	total (%)
1	*a*	1.1	51	48	99	0	99
2	0.025	1.4	57	41	98	1	99
3	0.05	1.6	60	37	97	2	99
4	0.075	1.8	62	35	97	2	99
5	0.10	2.1	65	31	96	3	99
6	0.15	2.4	67	27	94	4	98
7	0.20	2.8	70	24	94	5	99
8	0.30	3.2	67	21	88	10	98
9	0.40	3.7	59	16	75	14	89
10	0.50	3.9	49	13	61	11	72
11	0.60	4.2	40	10	50	8	58
12	1.00	4.5	18	4	22	6	28

[a] Syringe pump addition.

Interestingly, careful monitoring of the radical cyclizations of **1** by GC/MS revealed the presence of several intermediates with retention times between those of the dibromide **1** and the collection of hydrocarbons **4t**, **4c**, and **7** (see the experimental details in the Supporting Information) which grew in and then disappeared during the course of the reaction. Two overlapping, shorter-retained peaks were assigned as acyclic monobromides (**5a,b**, X = Br, Scheme 1) by comparison with authentic samples (see below). The remaining two longer-retained peaks were tentatively assigned as cyclic monobromides (**8t,c**, X = Br, Scheme 1) on the basis of GC/MS data. The ratio **8t**/**8c** at intermediate states of the experiments was very similar to the final **4t**/**4c** ratio, providing further support for this assignment.

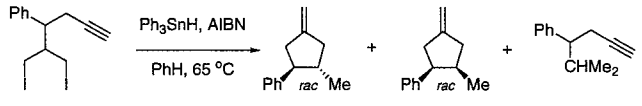
This discovery gave us an opportunity to confirm a heretofore untested feature of stereoselection at the steady state. According to the model in Scheme 1, the rates of cyclization of the first pair of radicals (**3a,b**) should be different on the basis of the Beckwith−Houk model;[4] radical **3b** cyclizes preferentially while radical **3a** is preferentially reduced. This predicts that the structure of the major reduced monobromide should be **5a** (X = Br). To prove this hypothesis, we first needed authentic samples of **5** for structure assignment. These were prepared in a straightforward, nonstereoselective fashion, as shown in Scheme 3. Methylation of **10** gave **14**, which was decarboxylated to give a mixture of **15a,b**. Reduction with LAH gave alcohols **16a,b**. These alcohols were separable, and the isomers were carried on to **5a,b**. The isomers of **5** were readily assigned by conducting

Scheme 3[a]



[a] Reagents and conditions: (a) NaH/MeI, THF, 50 °C for 6 h, 85%; (b) $NaCl/H_2O$, DMSO, 160−170 °C for 2 days, 92%; (c) LAH, Et_2O, 0 °C for 2 h, 60−75%; (d) $MsCl/Et_3N$, CH_2Cl_2, 0 °C for 2 h, ~100%; (e) LiBr or NaI, acetone, reflux for 12 h, 85−96%.

Table 4. Reductions of Diiodide 2 with Ph_3SnH at 65 °C



entry	[Ph_3SnH] (M)	4a/4b	4a (%)	4b (%)	4a + 4b (%)	7 (%)	total (%)
1	*a*	1.0	50	50	99	0	99
2	0.025	1.3	56.5	42.5	99	0	99
3	0.05	2.0	66	33	99	0	99
4	0.075	2.6	70	26	96	3	99
5	0.10	3.3	71	21	92	7	99
6	0.15	5.5	69	12	81	16	97
7	0.20	5.8	64	11	75	21	96

[a] Syringe pump addition.

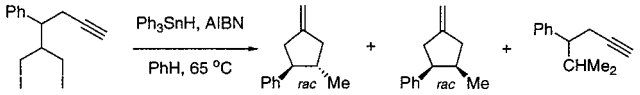
cyclizations: **5a** gave **4t,** and **5b** gave **4c** (see the experimental details in the Supporting Information).

Radical cyclizations of **1** with a small amount of Ph_3SnH (2.2 equiv) provided a complex mixture of unreacted dibromide **7** (about one-third), monobromides **5a,b** (about one-third) and **8t,c** (about one-third), and hydrocarbons **4t,c** and **7**. Co-injection of a sample from the reaction mixture with the authentic samples of monobromides **5a** and **5b** showed that **5a** is the major diastereoisomer. Quantitation is difficult because the peaks are close together (see the GC chromatograms in the Supporting Information), but we estimate that the ratio **5a**/**5b** was at least 90/10. This verifies the hypothesis that **3a** is reduced to **5a** faster than **3b** is reduced to **5b**. This must be due to the increased concentration of **3b** of the steady state.

We next studied the tin hydride mediated cyclization of the diiodide **2**. In limited prior studies, diiodides and dibromides have provided similar results even though the first pairs of radicals **3a,b** are different (X = Br or I).[8] Similar results are expected if the first pairs of radicals **3a,b** bearing iodine or bromine have identical or similar rate constants for cyclization.

Using the standard protocol, we cyclized diiodide **2** at different Ph_3SnH concentrations, and the data for these experiments are summarized in Table 4. The reaction times for **2** (<15 min) were much shorter, presumably because iodine is a better radical precursor than bromine. We were not able to detect any monoiodide intermediates even with careful monitoring by GC/MS. The short reaction times also minimized the problem of hydrostannylation, and high total yields (95−100%) were observed in all experiments. Cyclopropane formation can occur in

Table 5. Reduction of 2 at Different Concentrations



entry	[2] (M)	4t/4c	4t (%)	4c (%)	4t + 4c (%)	7 (%)	total (%)
1	0.007	5.8	63	11	74	4	78
2	0.02	5.6	63	11	74	21	95
3	0.03	5.4	64	12	76	13	89
4	0.06	5.9	68	12	80	9	88

reactions of 1,3-diiodopropanes, but the high total yield of products (96−99%) rule out such a competition in this case.[14]

Surprisingly, the results with the iodide (Table 4) did not match those with the bromide (Table 3). With the exception of the initial syringe pump experiment (entry 1, 50/50 ratio), the ratios of the cyclic products as a function of starting tin hydride concentration are approximately twice as high as those of dibromide **1** at any given concentration. We considered three possible explanations for this behavior: (1) equilibration of intermediate radicals, (2) reactions of intermediate radicals **3a,b** (X = Br) and **3a,b** (X = I) with Ph_3SnH at different rates (Br versus I), or (3) cyclizations of the intermediate bromide- and iodide-substituted radicals **3a,b** with different rate constants. The first of these possible explanations is a radical precursor effect, while the second and third are radical substituent effects. The third explanation seems most likely, but is also most difficult to test because the ratios of monoreduced products as a function of time cannot be measured.

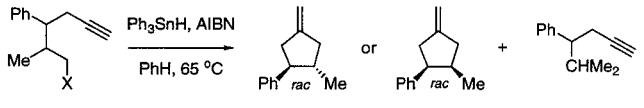
Equilibration by iodine transfer seems unlikely since the relative rates of iodine transfer (k_I[RI]) are small compared to those of cyclization (k_c; see below for values) and reduction.[15] Iodine transfer is a bimolecular process, and cyclization is unimolecular, so experiments with different ratios of **2** to Ph_3SnH at a set Ph_3SnH concentration (0.2 M) were undertaken. As shown in Table 5, the product ratio **4t/4c** was constant within experimental error, thus further suggesting that reversible iodine transfer does not play a role when diiodides are used as precursors.

To rule out any other unusual radical precursor effects, we measured the rate constants for cyclization of the diastereomeric radicals derived from monohalides **5a,b** (X = Br or I). The same radical **6a** or **6b** is generated from both the iodide and the bromide, and these are the second set of radicals that partition between reduction and cyclization in Scheme 1. Accordingly, these experiments directly measure k_{fast2} and k_{slow2} in Scheme 1. Kinetic experiments using the standard protocol were conducted on diastereomerically pure compounds, and the results of these experiments are shown in Table 6. Rate constants were calculated from the raw data in the usual way.[16] The iodide and bromide precursors provided

(14) Curran, D. P.; Gabarda, A. E. *Tetrahedron* **1999**, *55*, 3327.

(15) Rate constants for iodine transfer between primary alkyl radicals are more than an order of magnitude lower than those from Ph_3SnH, and Ph_3SnH is also used in large excess. See: (a) Newcomb, M.; Sanchez, R. M.; Kaplan, J. *J. Am. Chem. Soc.* **1987**, *109*, 1195−1199. (b) Newcomb, M.; Curran, D. P. *Acc. Chem. Res.* **1988**, *21*, 206−214. (c) Drury, R. F.; Kaplan, L. *J. Am. Chem. Soc.* **1972**, *94*, 3982−3986. (d) Chatgilialoglu, C.; Newcomb, M. In *Advances In Organometallic Chemistry*; West, R., Hill, A. F., Eds.; Academic Press: San Diego, 1999; Vol. 44; p 67.

Table 6. Rate Constant Measurements of Radicals Derived from 5a,b (X = Br, I)

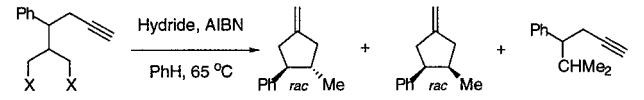


5a, b **4t** **4c** **7**

compd	X	[Bu_3SnH] (M)	**4** (%)[a]	**7** (%)	k_c (M^{-1} s^{-1})
5a	Br	0.7	85.7	14.3	2.52×10^7
		1.0	77.0	23.0	2.09×10^7
	I	0.2	94.8	5.2	2.19×10^7
		0.5	88.1	11.9	2.21×10^7
5b	Br	0.7	31.4	68.6	1.92×10^6
		1.0	25.0	75.0	2.00×10^6
	I	0.5	38.0	61.9	1.84×10^6

[a] **5a** provided **4t**, and **5b** provided **4c.**

Table 7. Reduction of 1 with Four Different Hydrides at a Constant H-Transfer Rate



1 X = Br **4c** **4t** **7**

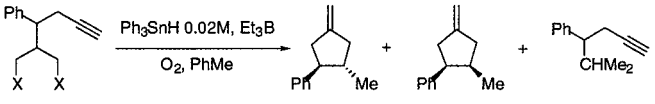
entry	hydride	[hydride] (M)	**4t**/**4c**	**4t** (%)	**4c** (%)	**4t** + **4c** (%)	**7** (%)
1	Ph_3SnH	0.025	1.4	57	41	98	1
2	$^nBu_3SnH$	0.088	1.6	61	38	99	0
			1.6	61	37	98	0
3	$(Me_3Si)_3SiH$	0.42	1.4	57	42	99	0
			1.4	58	41	99	0
4	$^nBu_3GeH$	1.42	1.4	52	38	90	0
			1.4	53	37	90	0

the same rate constants for the slow and fast cyclizations. This strongly suggests that the differences between the dibromide **1** and the diiodide **2** emanate from radical substituent effects, not radical precursor effects. The cyclization of the radical derived from **5a** (2×10^7 m^{-1} s^{-1}) is about 10 times faster than that of the radical derived from its diastereomer **5b** (2×10^6 $m^{-1}s^{-1}$).

Turning to differential effects of bromine and iodine as substituents in one of the component reactions, we postulated that substituent effects on hydrogen-transfer reactions were unlikely because most primary radicals react with a given metal hydride with similar rate constants[16] and because the bromine/iodine substituent is three atoms removed from the reacting radical. To probe the involvement of differential hydrogen transfer, we performed a series of experiments in which the concentrations of a series of metal hydrides were selected so k_H[hydride] would be the same within experimental error (Table 7). This was done by adjusting the concentration of every reaction to offset the difference in relative reactivity between that hydride and the others.[16] The reactivity of the tested hydrides follows the order Ph_3SnH > Bu_3SnH > $(Me_3Si)_3SiH$ > Bu_3GeH. The experiments afforded very similar ratios of the products in all the investigated cases, and this suggests that there are no usual substituent effects on hydrogen transfer.

(16) The rate constants for hydrogen abstraction from these hydrides by primary radicals at 25 °C are reported as 5×10^6, 2.4×10^6, 3.8×10^5, and 1×10^5 M^{-1} s^{-1}, respectively. The rate constants for hydrogen abstraction from the hydrides at 65 °C by primary radicals were calculated from the reported temperature-dependent Arrhenius equation. See: Newcomb, M. *Tetrahedron* **1993**, *49*, 1151−1176 and ref 14d therein.

Table 8. Temperature Effects on Dihalide Cyclizations



1 X = Br
2 X = I
4t **4c** **7**

X	*t* (°C)	**4t**/**4c**	**4t** (%)	**4c** (%)	**4t** + **4c** (%)	**7** (%)	yield (%)
Br, **1**	0	6.9	44	6	50	0	50
Br, **1**	−20	10.0	30	3	33	0	33
I, **2**	0	11.1	56	5	61	11	72
I, **2**	−20	17.0	34	2	36	27	63

Thus, while the conclusion is not definitive, we feel that the most likely reason for the differences in product ratios between the iodide and the bromide is that the k_{fast}/k_{slow} ratio for cyclization of radical **3a,b** with X = I is about 2 times higher than that for radical **3a,b** with X = Br.

It was also of interest to check the influence of temperature on the **4t**/**4c** ratio from dibromide **1** and diiodide **2**. Experiments were performed at two different temperatures, 0 and −20 °C, using Et_3B/O_2 to initiate radical chains. The results of these experiments are summarized in Table 8. Experiments were conducted at a 0.2 M concentration of Ph_3SnH so the data can be compared with the relevant experiments conducted at 65 °C (Tables 3 and 4, entry 7).

The temperature-dependent selectivities range from 7/1 and 11/1 at 0 °C to 10/1 and 17/1 at −20 °C for **1** and **2**, respectively. Again the ratios **4t**/**4c** resulting from **2** were higher than those resulting from **1**. The modest overall yields (33−72%) are apparently connected to the hydrostannylation of the triple bond, which competes effectively due to the long reaction times at lower temperatures. Furthermore, the reduced yields of **4** (33−61%) indicate that tin hydride reduction competes more favorably with radical cyclization as the temperature is lowered and that better preparative results could be obtained by reducing the tin hydride concentration. Nevertheless, the highest **4a**/**4b** ratio (17) suggests that the process could be important not only from a theoretical but also from a preparative point of view.

3. Conclusions

The results described in this paper expand and solidify our understanding of stereoselection at the steady state with radical reactions. It should be generally possible to design such processes by extending the well established Beckwith−Houk model for stereoselection to encompass substrates with two radical precursors and one radical acceptor, as illustrated in Figure 2. Intermediate monohalide products have been observed for the first time. And while their behavior was difficult to quantitate because they appear and disappear, it was consistent with the kinetic model for steady-state stereoselection. Clear, if small, differences in the results as a function of the radical precursor (diiodide better than dibromide) have been observed for the first time, and these have been tentatively attributed to differing rates of cyclization at the monohalo stage. In the big picture, kinetic theory[8a] in this area still far outpaces experiments. With a solid understanding on one type of steady-state stereoselection process in hand, the challenge now becomes discovering examples of other types of radical-based processes that have been modeled as well as nonradical examples.

Acknowledgment. We thank the National Science Foundation for funding this work.

Supporting Information Available: Complete experimental details, copies of ^{1}H and ^{13}C NMR spectra for all new compounds, and copies of GC chromatograms from experiments to identify dibromides **5** and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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