Conformational Memory in Enantioselective Radical Reductions and a New Radical Clock Reaction

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Abstract: The radical decarboxylation of acid **1** led to tetrahydropyran **3** with significant optical activity. This transfer of chirality is an example of a conformational memory effect and derives from the slow ring inversion of the atropisomer **2** and its enantiomer **2′**. A similar conformational memory effect was observed in the reductive decyanation and reductive lithiation of cyanohydrin **4**. We propose that the racemization of radicals with chiral conformations such as **2** could be used as new radical clocks. The rate of racemization of **2** was evaluated and used to determine the rate of H atom transfer to **2** by different H atom donors. The rate of racemization of **2** is 5.7×10^8 s^{-1} at 22 °C, which is about five times faster than ring opening of a cyclopropylmethyl radical.

The field of enantioselective radical reactions is rapidly advancing with the emergence of both auxiliary-based and chiral Lewis acid-based strategies.[1] Our recent investigation of nonequilibrium radical reactions made us aware of a third strategy for introducing chirality in radical reactions: the retention of stereochemical information due to slow equilibration of chiral conformations.[2] A similar effect has been observed in the alkylation of certain enolates and has been described as a "memory of chirality".[3] A demonstration of memory of chirality in radical reactions is described herein.

The reactions of radicals are very rapid, and it has long been recognized that in certain situations these reactions may be competitive with conformational isomerizations. The recombination of radical pairs often shows a memory effect. Our primary interest, however, is in the reaction of free radicals with bulk reagents. Although most alkyl radicals have very low barriers to inversion, there are a few structures such as cyclopropyl radicals,[4] 1,3-dioxolan-2-yl radicals,[5] and some vinyl radicals[6] that have modest barriers to inversion.[7] These radicals can react with partial or complete retention of configuration, depending upon the conditions and trapping reagents used in the reaction. Less common are systems where the radical inverts rapidly but the conformation of the rest of the molecule imposes a barrier to complete equilibration. The 9-decalyl radical is the most prominent example of this type.[8] The slow conformational interconversion of cyclohexyl radicals has also been invoked to explain the stereoselectivity in radical additions to substituted cyclohexenes.[7,9] The present investigation examines a system of the later type, where a slow conformational interconversion was found to impose a barrier to equilibration despite a very low barrier to radical inversion.

The reaction of an optically pure substrate with a single stereogenic center was envisioned to proceed through a radical intermediate in which the only stereogenic center was destroyed. Could an optically active product be produced in such a reaction? The radical decarboxylation of carboxylic acid **1** to give radical **2** (Scheme 1) is an example. Radical **2** does not contain a stereogenic center, and a cursory inspection might classify it as achiral. However, radical **2** is chiral by virtue of its three-dimensional structure and only behaves as an achiral molecule when in equilibrium with its enantiomer, **2′**. Interconversion of **2** and **2′** involves a radical inversion with a very low inversion barrier estimated at ≤ 0.5 kcal/mol[10] and a chair−chair ring inversion with a more substantial barrier estimated to be between 5 and 10 kcal/mol.[11] Because the key ring inversions of **2** and **2′** involves rotations around single bonds, they can be classified as rapidly interconverting atropisomers. When the reaction of the chiral radical **2** is fast compared with the ring inversion and when the addition reaction of **2** is stereoselective, an optically active product will be produced.

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(11) Cyclohexane and tetrahydropyran have ring-inversion barriers of about 10 kcal/mol, but the cyclohexyl radical has a ring-inversion barrier of only 5.5 kcal/mol. (a) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994; pp 740−742. (b) Roberts, B. P.; Steel, A. J. *J. Chem. Soc., Perkin Trans. 2* **1992**, 2025−2029.

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Scheme 1

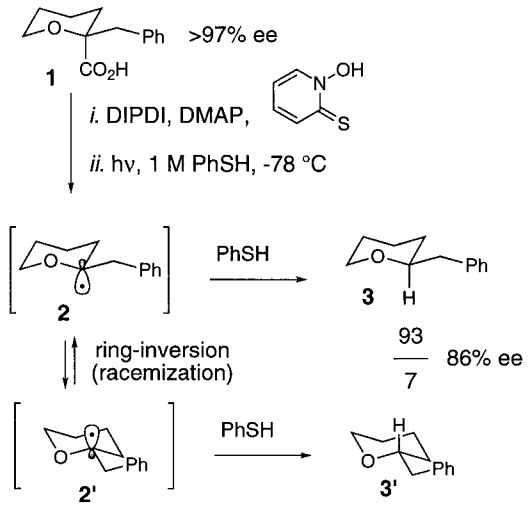
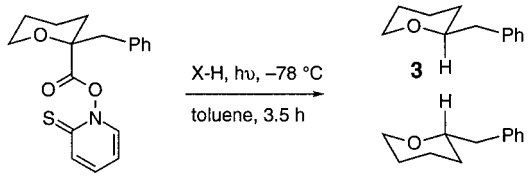


Table 1. Enantioselective Reduction of **5** in the Presence of Different H Atom Donors



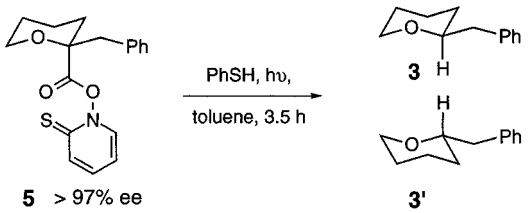
entry	donor	[X-H] (M)	% yield	ratio **3**:**3′**	% ee
1	Bu_3SnH	1.0	70	51.4:48.6	2.6
2	Bu_3SnH	0.5	78	50.7:49.3	1.5
3	Bu_3SnH	0.05	77	50.0:50.0	0.0
4	*t*-BuSH	2.0	29	67.1:32.9	34.3
5	*t*-BuSH	1.0	83	62.9:37.1	25.8
6	*t*-BuSH	0.5	31	61.7:38.3	23.0
7	*t*-BuSH	0.05	30	51.1:48.9	2.3
8	**PhSH**	**1.0**	**92**	**93.2:6.8**	**86.5**
9	PhSH	0.5	75	84.8:15.2	69.7
10	PhSH	0.05	58	61.5:38.5	23.0
11	PhSH	0.01	67	52.2:47.8	4.3
12	PhSeH	0.05	28	67.3:32.7	34.6

In such a reaction, the memory of the chirality is held by the conformation of the radical, even though the original stereogenic center has been destroyed. Radical decarboxylation of **1** is an example of memory of chirality in a radical reaction.

Carboxylic acid **1** (Scheme 1) was prepared in optically pure form[12] and converted to its corresponding *N*-hydroxypyridine-2-thione ester **5**. Photolysis of the ester in toluene at −78 °C with 1 M PhSH as a hydrogen atom donor led to the expected product **3** and its enantiomer **3′** in a 93:7 ratio. Thus, in the presence of a very efficient hydrogen atom trap, reduction of **2** is competitive with ring inversion and an optically active product is produced. The radical reduction of **1** is an unusual example of a self-regenerating stereocenters (SRS) reaction as designated by Seebach,[13] although in this case the added chiral element is the ring conformation rather than an added stereogenic center.

The efficiency of the chiral memory effect will depend on the relative rates of racemization and productive coupling. Table 1 shows the results of decarboxylations of **5** with different H atom donors at −78 °C in toluene. Tributyltin hydride leads to a nearly racemic product (entries 1−3) at each concentration, as expected from its relatively slow reaction with electron-rich radicals such as **2**/**2′**. The electron-deficient H atom donor *t*-BuSH reacts rapidly with **2**/**2′** to give optically active product **3** (entries 4−7). The optical purity of the product decreases with decreasing *t*-BuSH concentration. The reaction of *t*-BuSH should be first order in radical and first order in thiol; reduced thiol concentrations allow more time for the racemization of radical **2**. Benzenethiol is a more efficient H atom donor than *t*-BuSH and leads to tetrahydropyran **3** in 86% ee when present at 1 M concentration (entry 8). Benzeneselenol is an even more efficient H atom donor,[14] and it produces **3** in 32% ee when present at a nominal concentration[15] of 0.05 M, compared with 23% ee when PhSH was present at the same concentration (entries 10 and 12). The optical purity of **3** also depends on the temperature of the decarboxylation reaction. Table 2 shows the results from decarboxylation of **5** at different temperatures and with different concentrations of PhSH. As the temperature increases, the maximum enantiomeric excess decreases until the enantiomeric excess of **3** is only 8% with 0.5 M PhSH at 22 °C. The efficiency of the chiral memory effect in the decarboxylation of **5** depends on the concentration, temperature, and identity of the H atom donor.

Table 2. Enantioselectivity of the Reduction of **5** in PhSH As a Function of Concentration and Temperature



entry	temp (°C)	[X-H] (M)	% yield	ratio **3**:**3′**	% ee
1	−40	0.5	50	69.9:30.1	39.8
2	−40	0.15	46	59.7:40.3	19.4
3	−40	0.01	41	50.6:49.4	1.2
4	0	0.5	77	57.6:42.4	15.2
5	0	0.15	79	53.0:47.0	6.0
6	0	0.01	54	50.3:49.7	0.5
7	22	0.5	72	54.2:45.8	8.4
8	22	0.15	62	51.2:48.8	2.4
9	22	0.01	60	50.7:49.3	1.4

Cyanohydrins can be reduced to give configurationally stable alkyllithium reagents.[16] The reduction of cyanohydrin **4** by lithium di-*tert*-butylbiphenylide (LiDBB) is outlined in Scheme 2 and Table 3. Reduction of **4** to alkyllithium **6**, followed by protonation with methanol, gave reduced tetrahydropyran **3** of low to moderate optical purity. Inverse addition led to products with low optical purity, whereas direct addition of the substrate to 0.63 M LiDBB gave products with ca. 40% ee. Optically active alkyllithium reagent **6**, prepared using 0.63 M LiDBB, was trapped with CO_2 and esterified with CH_2N_2 to give the methyl ester **7** in 42% yield and 49% ee. Trapping of α-alkoxylithium reagents with CO_2 proceeds with retention of configuration.[17] Ester **7** was shown by direct correlation to have the same absolute configuration as **4**. In addition, the same major enantiomer of tetrahydropyran **3** was produced by each of the

(12) Details for the preparation and resolution of **1** are provided in the Supporting Information.

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(17) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481−1487.

Scheme 2

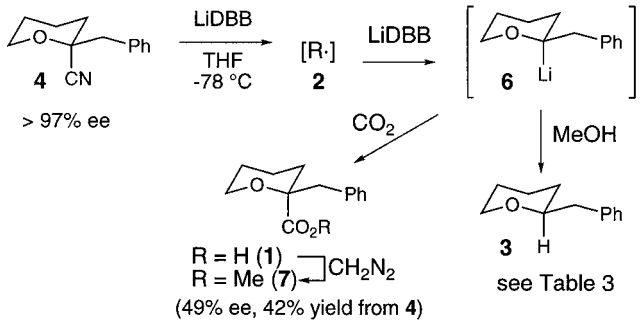
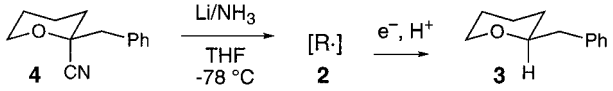


Table 3. Reductive Decyanations of **4** with LiDBB in THF

conditions[a]	optical purity of **3**
0.12 M LiDBB, −78 °C	26% ee
0.31 M LiDBB, −78 °C	30% ee
0.47 M LiDBB, −78 °C	39% ee
0.63 M LiDBB, −78 °C	40% ee
Inverse addition, −78 °C	9% ee

[a] The nitrile in THF was added to the solution of Li in NH_3 unless otherwise noted.

Table 4. Results of the Reduction of **4** with Li/NH_3



entry	conditions[a]	optical purity of **3**
1	Li (ca. 1 M)/NH_3, −78 °C[b]	7% ee
2	Li (ca. 1 M)/NH_3, −33 °C[c]	16% ee
3	Na (1.8 M)/NH_3, −78 °C[c]	16% ee
4	Li (0.8 M)/NH_3, −78 °C[c]	30% ee
5	Li (3.5 M)/NH_3, −78 °C[c]	30% ee
6	Li (4.3 M)/NH_3, −78 °C[d]	10% ee
7	Li (5.4 M)/NH_3, −78 °C[d]	54% ee
8	Li (6.4 M)/NH_3, −78 °C[d]	90% ee

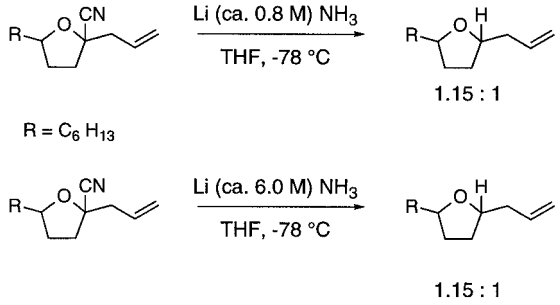
[a] The nitrile in THF was added to a solution of metal in NH_3. [b] Inverse addition: lithium was added to the nitrile in NH_3. [c] The Li/NH_3 solution was blue in color. [d] The Li/NH_3 solution had a metallic gold appearance.

routes described, so we conclude that all of the radical reductions discussed herein proceed with retention of configuration. Retention of configuration is expected for the memory of chirality phenomena outlined in Scheme 1.

A memory effect also was observed in the reductive decyanation of optically active nitrile **4** (Table 4). Reductive decyanations of nitriles are stepwise reactions that proceed via a radical intermediate.[18] Reduction of **4** by addition to a 0.8 M Li/NH_3 solution at −78 °C gave tetrahydropyran **3** in 30% ee (entry 4). However, the optical purity of the product is very sensitive to conditions. Addition of lithium metal to the nitrile (inverse addition) gave the product in only 7% ee (entry 1). Presumably, the concentration of the lithium in the reaction was low and thus the lifetime of the intermediate radical **2**/**2′** was long enough to allow significant racemization. When the reduction was carried out with lithium at −33 °C, the product was produced in only 16% ee because ring inversion takes place faster at higher temperatures (entry 2). Reduction of **4** with sodium at −78 °C gave a product with 16% ee (entry 3). Sodium is a less powerful reducing agent than lithium, and the slower reduction of the radicals **2**/**2′** with this reagent allows more time

(18) Rychnovsky, S. D.; Powers, J. P.; Lepage, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 8375−8384.

Scheme 3



for ring inversion. The most intriguing example is the reduction of **4** by high concentrations of lithium in NH_3. The optical purity of the product is not a simple function of Li concentration. Above 4 M, Li solutions in ammonia have a metallic gold appearance, and these gold-colored solutions lead to a rapid increase in the % ee of the product with further increases in Li concentration. At 6.4 M, the product **3** was obtained in 90% ee (entry 8). Evidently, the highly concentrated solution of lithium reduces the radical **2** much faster than the ring inversion. Although reductive decyanations are sensitive to reaction conditions, they can show a nearly complete memory of chirality.

An alternative explanation for the optical activity of the products at high lithium concentrations is that the reaction mechanism has changed and a two-electron reduction of the nitrile is taking place with retention of configuration. This possibility can be excluded by the following result (Scheme 3): reduction of a single diastereomer of the tetrahydrofuran nitrile[19] at −78 °C gave essentially the same 1.15:1 ratio of tetrahydrofuran products at lithium concentrations of 0.8 and 6.4 M. Ring inversion of the five-membered ring radical is much faster than with the six-membered ring radical, and the chiral ring conformation cannot be intercepted under these conditions. Under conditions where the six-membered ring shows nearly complete retention of configuration, *vide supra*, the five-membered ring shows pronounced stereochemical scrambling. Assuming both substrates react through a common mechanism, stereospecific two-electron reductions can be excluded.

Results and Discussion

Racemization as a Radical Clock Reactions. In the decarboxylation of **5**, the optical purity of the product is a reflection of the lifetime of the radical. The first-order racemization reaction competes with other radical processes, much like the 5-hexenyl radical cyclization or the opening of cyclopropylmethyl radicals. The rate of racemization (k_R) and the rate of H atom transfer (k_H) are related to the enantiomeric ratio of the products **3** and **3′** by eq 1.[20]

$$k_R = k_H[\mathrm{PhSH}]2[\mathbf{3'}]/([\mathbf{3}] - [\mathbf{3'}]) \qquad (1)$$

One can calculate the approximate rate of H atom transfer to **2** by extrapolating Arrhenius data for the rate of H atom transfer

(19) Rychnovsky, S. D.; Dahanukar, V. H. *J. Org. Chem.* **1996**, *61*, 7648−7649.

(20) Eq 1 was derived by assuming that **2** and **2′** react with perfect axial selectivity and that the product ratios are controlled by simple partitioning of radical **2** between the optically pure product [**3**] and the racemic product [$\mathbf{3}_{rac}$]. These assumptions leads to the following equation, which simplifies to eq 1 when evaluated in terms of the observed products [**3**] and [**3′**]: $[\mathbf{3}]/[\mathbf{3}_{rac}] = k_H/k_R[\mathrm{RSH}]$.

from *t*-BuSH to a secondary α-alkoxy radical.[21] The estimated rate constant k_H is 1.1×10^6 M^{-1} s^{-1} at −78 °C. From the enantiomeric ratio of **3** produced at different concentrations of *t*-BuSH (Table 1, entries 4−7), one can calculate that the rate of racemization (k_R) for **2** as $1.9-4.3 \times 10^6$ s^{-1} with an average value of 3.9×10^6 s^{-1} at −78 °C, based on 12 experiments.[22] The rate of racemization of **2** should be relatively invariant to most reaction parameters except temperature. We suggest that the racemization of **2** and related conformationally chiral radicals could be used as radical clocks. The absolute rate for racemization of **2** is much faster than for the 5-hexenyl radical and significantly faster than for the cyclopropyl methyl radical but slower than for the *trans*-(2-phenylcyclopropyl)carbinyl radical.[23] Racemization reactions have several advantages over more conventional radical-clock reactions. First, a racemization reaction is by its very nature irreversible. Second, the downstream radical reactions of the initial radical **2** and the rearranged radical **2′** will have identical rates because they are enantiomers.[24] Finally, the enantiomeric ratio of **3** can be measured directly by GC using a chiral column, and the ratio of **3**/**3′** is unlikely to be affected by isolation and purification procedures. The rate of racemization of radical **2** suggests that it could function as a very rapid radical-clock reaction with unique advantages over more conventional radical clocks.

The rates of H atom transfer from different H atom donors can be determined using the racemization of **2** as a radical clock reaction. In the case of PhSH, the enantiomeric ratios of reduced product **3** as a function of concentration (Table 1, entries 8−11) lead to H atom transfer rates of $1.8-2.5 \times 10^7$ M^{-1} s^{-1} at −78 °C with an average value of 2.0×10^7 M^{-1} s^{-1}. These values compare favorably with the rate of 1.8×10^7 M^{-1} s^{-1} calculated from Arrhenius parameters for the PhSH reduction of a secondary radical.[25] The rate of H atom trapping with Bu_3SnH can be calculated from the data in Table 1, although the low optical purity of the product compromises the precision of the determination. The rate of H atom transfer from Bu_3SnH comes to 1.1×10^5 M^{-1} s^{-1} at −78 °C based on entries 1 and 2. This rate is faster than the estimated rate of 1.4×10^4 M^{-1} s^{-1} at −78 °C that comes from analysis of the reported Arrhenius parameters for reduction of an α-alkoxy radical.[26] The difference could be due to the difference in substrates but is in part a consequence of the disparity in rates between the racemization and the rate of the H atom transfer. Measuring precise H atom transfer rates requires products with significant optical enrichment, and these arise from similar rates of racemization and H atom transfer.

The enantiomeric enrichment of **3** found in the reduction of **5** shows a strong temperature dependence. Table 2 lists the optical purity of product **3** as a function of temperature and PhSH concentration. One can calculate the k_R/k_H ratio for each example; the average value of k_R/k_H at each temperature is 0.7 at −40 °C, 2.5 at 0 °C, and 6.5 at 22 °C. Thus, the rate of racemization increases faster than the rate of H atom transfer with increasing temperature. In theory one could use these data to calculate Arrhenius parameters for the racemization of **2**, but unfortunately we are not aware of reliable H atom transfer rates for the reaction of PhSH with a radical similar to **2**. Arrhenius parameters have been reported for the reaction of secondary radicals with PhSH, and one can use these parameters to estimate an approximate rate of racemization for radical **2** of 5.7×10^8 s^{-1} at 22 °C. Thus, the racemization of **2** is about five times faster than the ring opening of a cyclopropylmethyl radical.[23,27] The rate of racemization for radical **2** should be established with higher precision, but it is apparent from the estimated rates reported above that it can function as a very fast radical clock reaction.

It must be emphasized that in each of the enantioselective radical reactions described, the radicals themselves are configurationally unstable. Two features are necessary for retention of configuration: slow ring inversion and a pronounced preference for reactions at one face of the radical. All of the present examples make use of 2-tetrahydropyranyl radicals because the radicals have a significant facial bias and there is a significant barrier to ring inversions in six-membered rings. The racemization of radical **2** can be used as a fast radical clock reaction, with an estimated rate of 5.7×10^8 s^{-1} at 22 °C. Conformational interconversions can be very fast, and the use of conformational interconversions in other ring systems has the potential to produce new ultrafast radical clock reactions.

Experimental Section[28]

Procedure for Preparation and Reduction of *N*-Hydroxypyridine-2-thione Ester 5 in the Presence of an H Atom Donor: 2-Benzyltetrahydropyran (3). All reactions were performed under an inert atmosphere. To a 0.01 M solution of optically pure 2-benzyltetrahydropyran-2-carboxylic acid (1 equiv) in freshly distilled solvent were added DMAP (cat.), 2-mercaptopyridine *N*-oxide (1.5 equiv), and dodecane (1.0 equiv). The mixture was shielded from light then cooled to 0 °C. Diisopropylcarbodiimide (1.5 equiv) was then slowly added to the reaction flask. The reaction was allowed to warm to room temperature and stirred for 2.5 h. Then a 1−2 mL aliquot from this stock solution was added to individual reaction flasks, which were shielded from light. These reaction flasks were then cooled to the appropriate temperature under argon and the appropriate H atom transfer agent was added. The mixture was exposed to a 120 V (60 Hz) lamp at a distance of 30−50 cm from the reaction flask. The reaction mixture was then photolyzed for 3.5 h at the appropriate temperature. A precooled (0 °C) solution of potassium trimethylsiloxide (0.5 equiv) was added to destroy the ester **5**, followed by the addition of a saturated aqueous $NaHCO_3$ solution. The organic layer was extracted with Et_2O and washed with brine then dried with $MgSO_4$. The solution was filtered through a silica gel plug and then analyzed by GC using a CHIRALDEX β-cyclodextrin permethylated hydroxylpropyl (B-PH) chiral column (20 m × 0.25 mm) to determine % yield and % ee. The yields were determined relative to a dodecane internal standard. The GC oven began at 100 °C and was ramped to 150 °C at 0.3 deg/min. The two enantiomers **3** and **3′** showed retention times of 37.3 and 38.4 min, respectively.

Procedure for Reductive Decyanation of 4 Using Li/NH_3: 2-Benzyltetrahydropyran (3). Anhydrous ammonia (5.0 mL, distilled

(21) The Arrhenius function for the reaction of *t*-BuSH with a secondary α-alkoxy radical was determined to be $\log(k_tMS) = (8.4 \pm 0.3) - (2.1 \pm 0.4)/2.3RT$. Johnson, C. C.; Horner, J. H.; Tronche, C.; Newcomb, M. *J. Am. Chem. Soc.* **1995**, *117*, 1684−7.

(22) The decarboxylations of **5** in the presence of *t*-BuSH at −78 °C were repeated three times at each concentration. The average value of for k_R was 3.9×10^6 with a standard deviation of 2.2×10^6. The standard deviation was smaller for reactions run simultaneously in the same cooling bath, suggesting that some of the scatter can be attributed to imprecise temperature control.

(23) (a) Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 317−323. (b) Newcomb, M. *Tetrahedron* **1993**, *49*, 1151−1176. (c) Newcomb, M.; Manek, M. B. *J. Am. Chem. Soc.* **1990**, *112*, 9662−9663.

(24) This assumes that the trapping agents are achiral. Chiral trapping agents would lead to diastereomeric transition states. However, most trapping agent of interest are achiral.

(25) The Arrhenius function for the reaction of PhSH with a secondary radical was determined to be $\log(k_tMS) = (8.4 \pm 0.6) - (3.8 \pm 0.9)/2.3RT$. Franz, J. A.; Bushaw, B. A.; Alnajjar, M. S. *J. Am. Chem. Soc.* **1989**, *111*, 268−275.

(26) The Arrhenius function for the reaction of Bu_3SnH with a secondary α-alkoxy radical was determined to be $\log(k_tMS) = (9.26 \pm 0.13) - (1.78 \pm 0.26)/2.3RT$. See ref 21.

(27) Newcomb, M.; Glenn, A. G. *J. Am. Chem. Soc.* **1989**, *111*, 275−277.

(28) The general experimental section is included in the Supporting Information.

from sodium) was condensed into a flame-dried two-neck flask equipped with a coldfinger and glass stirbar under Ar at −78 °C. To make a concentrated (6.4 M Li/NH_3) solution, Li wire (221 mg, 31.8 mmol) was cut directly into the ammonia, forming the characteristic metallic gold color of a Li/NH_3 solution (Li/NH_3 solutions of concentrations ≤4.0 M generated a deep blue color). This solution was stirred for 30 min at −78 °C, and **4** (typically 10 mg) was added via cannula as a solution in THF (1.0 mL). The mixture was stirred for 15 min and then NH_4Cl(s) was added through the coldfinger until the reaction was quenched (as evidenced by a complete dissipation of color). The ammonia was allowed to evaporate, Et_2O and water were added, and the mixture was extracted twice with Et_2O. The crude product was dried ($MgSO_4$), filtered, concentrated, and taken up in benzene. A small amount of DDQ (typically 10 mg) was then added, and the yellow-orange reaction mixture was stirred overnight. The mixture was loaded directly onto a column and flashed (SiO_2, 10% EtOAc/hexanes) to afford the product as a pale yellow oil (consistently isolated in >80% yield). IR (neat) 3027, 2936, 2843, 1454, 1088 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34−7.24 (m, 5 H), 4.04−4.00 (m, 1 H), 3.53 (dddd, J = 10.8, 6.5, 6.5, 2.1 Hz, 1 H), 3.45 (td, J = 11.7, 2.5 Hz, 1 H), 2.93 (dd, J = 13.6, 6.6 Hz, 1 H), 2.69 (dd, J = 13.6, 6.5 Hz, 1 H), 1.65−1.61 (m, 1 H), 1.54−1.32 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.8, 129.3, 128.1, 126.0, 78.7, 68.6, 43.1, 31.4, 26.0, 23.4. HRMS (EI-GC-MS) m/z calcd for $C_{12}H_{16}O$ (M^+) 176.1201, found 176.1196.

Procedure for Reductive Lithiation of 4 Using LiDBB, Trapping with CO_2, and Esterification with CH_2N_2: 2-Benzyl-2-carbomethoxytetrahydropyran (7) and 2-Benzyltetrahydropyran (3). A 0.47 M solution of LiDBB was made by dissolving 4,4′-di-*tert*-butylbiphenyl (500 mg) in THF (4.0 mL) at 0 °C, adding a crystal of 1,10-phenanthroline, and titrating with *n*-BuLi. Excess Li wire was added to the THF solution, and the deep green mixture was stirred for 5 h. The LiDBB solution was cooled to −78 °C, and (*S*)-(−)-**4** (65.1 mg, 0.32 mmol, >95% ee) was added as a solution in THF (1.0 mL) via cannula. The mixture was stirred for 10 min at −78 °C, and then CO_2(g) was bubbled through the solution for 30 min (the solution color goes from malachite green to orange). The reaction (and unreacted lithium) was quenched with MeOH, warmed to room temperature, basified with 2 N NaOH, and extracted with CH_2Cl_2 (2×). From the basic extracts, 2-benzyltetrahydropyran (**3**) could be isolated (19.6 mg, 0.11 mmol, 34% yield, 41% ee). The aqueous layer was acidified with 6 N HCl, extracted with CH_2Cl_2 (3 ×), and dried (Na_2SO_4). The crude acid was taken up in Et_2O, cooled to 0 °C, and treated with excess of an ethereal solution of CH_2N_2. The yellow mixture was quenched with HOAc, neutralized with saturated $NaHCO_3$, extracted with Et_2O (3 ×), and dried ($MgSO_4$). Chromatography (SiO_2, 10% EtOAc/hexanes) afforded **7** as a yellow oil (31.9 mg, 0.14 mmol, 42% yield, 49% ee).

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Supporting Information Available: The synthesis and resolution of **1**, **4**, and **7** are described as well as the absolute configuration of these compounds by X-ray analysis of a diastereomeric derivative. This material is available free of charge via the Internet at http://pubs.acs.org.

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