Stereoselection at the Steady State in Radical Cyclizations of Acyclic Systems Containing One Radical Acceptor and Two Precursors in 1,5-Relationship under *pseudo*-First Order Conditions[‡]

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Abstract: The first example of a successive kinetic resolution of acyclic diastereomeric radical intermediates in 1,5-relationship under *pseudo*-first order conditions is reported. A mechanistic model involves non-selective generation of the radical intermediates followed by different partitioning of these between two different chemical pathways. The "2,5-*cis*" selectivity in the radical cyclization step arises from transition geometries with the substituents aligned in pseudoequatorial positions.

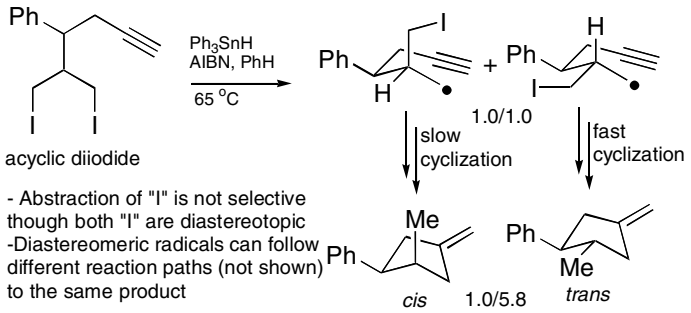
Introduction

The substituted tetrahydrofurans are of interest as building blocks in organic synthesis, chiral auxiliaries, and the structural units of many natural products.[1, 2] The stereoselective approach to this class of compounds is still problematic because of flexible transition states leading to the tetrahydrofuran system.[3] Among the different strategies available free carbon radical cyclizations are of particular interest as an alternative to ionic ones.[4] Especially β-alkoxyacrylates are excellent precursors for stereoselective preparation of *cis* – 2,5-substituted

tetrahydrofurans *via* radical cyclizations.[5] Another radical approach to tetrahydrofurans relies on the addition of electrophilic alkoxy radicals to multiple bonds.[6]

Recently, Curran has proposed a new type of stereoselective process founded on the transiency of radicals and called it "Stereoselection at the Steady State".[7] The most important difference between traditional multistep stereoselective processes and the proposed one seems to be selective partitioning of stereomeric intermediates at the steady state between two different chemical (not stereochemical) pathways to the same stereomeric product.[8] Most of the existing examples of stereoselection at the steady state are diastereoselective and involve bi- and tricyclic systems.[8, 9] Due to lack of rigidity, acyclic systems seem to be more difficult in predicting a stereochemical outcome of the radical cyclizations. However, in most cases the major product(s) can be successfully predicted using the Beckwith-Houk model.[10] So far only one acyclic system containing radical precursors in 1,3-relationship has been subjected to the stereoselection at the steady state (Scheme 1).[11]

Scheme 1. The acyclic model containing precursors in 1,3-relationship



There are relatively few examples of desymmetrizations of *pseudo* C_2-symmetric acyclic systems.[12] All of them are outside radicals. Desymmetrization in such systems requires diastereotopic group selection. However, in the light of the stereoselection at the steady state group selection processes (obviously involved) do not directly control the level of

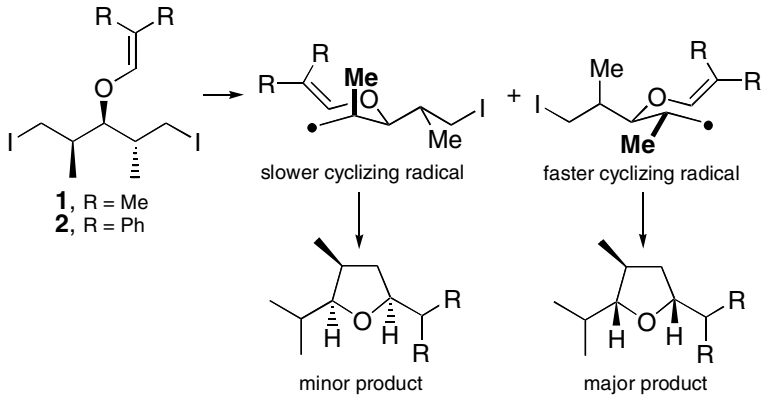
stereoselection as they do in all known processes. The stereocontrol rather results from a complex interplay of reaction paths that diverge and reconverge at various points.

The present study was initiated by our interest in discovering examples of radical-based processes of acyclic *pseudo* C_2-symmetric precursors at the steady state leading to substituted tetrahydrofurans. The possibility of manipulation of stereocontrol by reaction topography prompted us to investigate whether radical cyclizations of acyclic vinyl ethers having two radical precursors in 1,5-relationship will meet the requirements of the stereoselective process. Herein, we wish to describe results of our efforts along these lines.

Results and Discussion

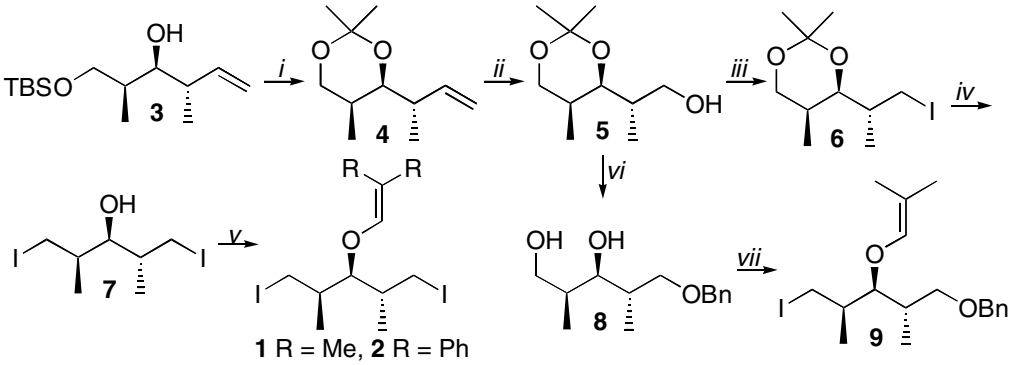
Diiodides **1** and **2** were designed as models representing *pseudo* C_2-symmetric family of compounds having two radical precursors in 1,5-relationship and one radical acceptor. We assumed that transition states of the radical pair of monoiodides obtained after non-selective abstraction of first iodine atom from any of the dioiodides would adopt the chairlike geometry (Scheme 2). The chairlike transition state should favor products derived from intermediates having the substituents in pseudoequatorial positions. On the other hand substituents, which are aligned pseudoaxially, should slow down the cyclizations. In both the radicals derived from **1** or **2** the methyl group adopts either the pseudoaxial or pseudoequatorial position. Therefore one of them was expected to close faster than the other one. We expected that at suitable trapping agent concentrations, the process would converge on the formation of one major product.

Scheme 2. Models having two radical precursors in 1,5 relationship



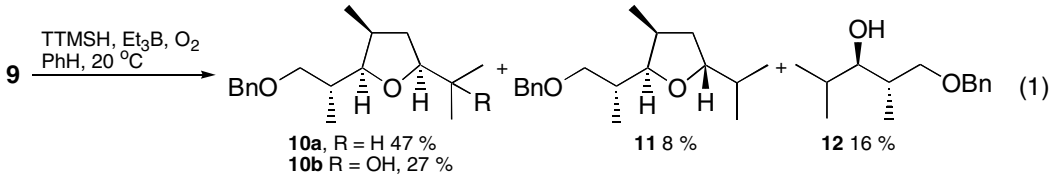
Both model compounds were obtained in a multistep synthesis starting from commercially available (*S*)-(+)-3-hydroxy-2-methylpropionate (Scheme 3). Compound **3** was prepared in four synthetic steps via chiral crotylboronates chemistry.[13] The alcohol thus obtained was converted into acetonide **4** via TBS-deprotection and acetal protection with 2,2-dimethoxypropane. Ozonolysis of **4**, a reductive workup with Me_2S and treatment of the resulting aldehyde with sodium borohydride gave the corresponding alcohol **5** in 67 % yield. Compound **5** was then either reacted with iodine to give iodide **6** or benzylated. Both the acetonides were then hydrolyzed to the corresponding diols, which after conversion to the primary iodides were treated with an excess of either diphenylacetaldehyde dimethylacetal or 1,1-dimethoxy-2-methylpropane in boiling benzene in the presence of an acid catalyst to give the radical precursors **1**, **2** and **9**.

Scheme 3. Synthesis of the radical precursors 1, 2 and 9



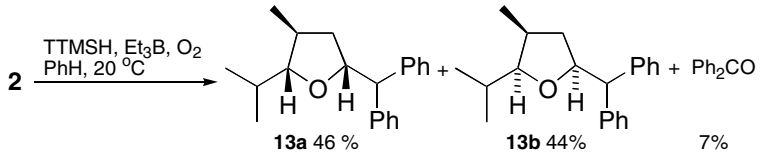
i) TBAF, THF, rt, 3 h 100 %; 2,2-dimethoxypropane, DMF, *p*-TSOH, rt, 24 h, 90 %; *ii)* O_3, MeOH/CH_2Cl_2, -78 °C, 1.5 h, $NaBH_4$, rt, 16 h, 67 %; *iii)* I_2, Im, Ph_3P, THF, 3h, 0 °C, 82 %; *iv)* *p*-TSOH, MeOH, 24 h, rt, 92 %; I_2, Im, Ph_3P, THF,3h, 0 °C, 82 %; *v)* 1,1-dimethoxy-2-methylpropane, PPTS, PhH, reflux, 18 h, 78 % or diphenylacetaldehyde dimethylacetal, *p*-TSOH, reflux, 24 h, 70 %; vi) NaH, BnBr, DMF, 0 °C, 24 h, 86 %; *p*-TSOH, MeOH, 24 h, rt, 96 %; *vii)* *p*-TsCl, Py, CH_2Cl_2, 0 °C, 24 h, 81 %; NaI, acetone, 65 °C, 24 h, 69 %; 1,1-dimethoxy-2-methylpropane, PPTS, PhH, reflux, 18 h, 55 %.

Compound **9** was prepared in order to measure the rate constant of the slower cyclization. Radical cyclizations of **9** with tris(trimethylsilyl)silane (TTMSH) in the presence of Et_3B/O_2 at ~20 °C gave four different products (Eq 1).[14] The calculated rate constant was estimated as 1×10^5 s^{-1} M^{-1}. The value is in agreement with the rate constant of the rearrangement of 6,6-dimethyl-5-hexenyl radical to the isopropylcyclopentyl radical (5×10^5 s^{-1} M^{-1}).[15]



We next studied radical cyclizations of diiodide **1**. A preparative cyclization of **1** was conducted under standard conditions at 0.05 M TTMSH concentration (2.2 equiv.) in benzene at rt. GC/MS analysis of the reaction mixture revealed formation of two major products, presumably the isomeric tetrahydrofurans as concluded from the MS spectra. Due to technical

difficulties we had to abandon the radical cyclizations of **1** and move to **2**.[16] A preparative cyclization of **2** was conducted under the same standard conditions. The reaction provided two major products in a ratio of ~1 : 1 in 90 % yield and benzophenone (7 %). The products were separated by preparative HPLC, and individual pure samples of each were obtained (Eq 2).



(2)

The structures of the cyclic products were derived from the (H, H) (C, H) correlation experiments, and the NOE differential measurements.[17] In order to properly describe the structures of the products of the radical cyclizations of **9** and **2** with TTMSH we decided to assign the ^{1}H NMR signals in spectra of compounds **10a**, **11** and **13a,b**. For this purpose two different NMR techniques, including ^{1}H-^{13}C gradient selected HSQC and HMBC methods were used. Next we employed the results of NOE differential experiments. The results of the ^{1}H and ^{13}C NMR signal assignments for compounds **10a**, **11**, **13a,b** are collected in supporting materials but the chosen NOE results are presented in Figure 1 and 2. At first we decided to determine the structure of the main product obtained after radical cyclization of **9** with TTMSH. In C_6D_6, $CDCl_3$, acetonitrile-d_3, acetone-d_6 and methanol-d_4 signals of the H2, H5 protons as well as H3 and one of the H4 protons of **10a** are very close to each other thus observation of the NOEs is rather complicated. However, basing on the results of the H2-H3, H4-H5, H4-H2 NOEs for **10a** (Fig. 1) the stereochemistry of this compound could be determined with a relatively good probability. Additionally, in the NOESY experiment taken from **10a** we found that dipolar interactions exist between the H2 and H5 protons. Based on

the NOE and NOESY experiments we concluded that the H2, H3 and H5 protons share *cis* relationship.

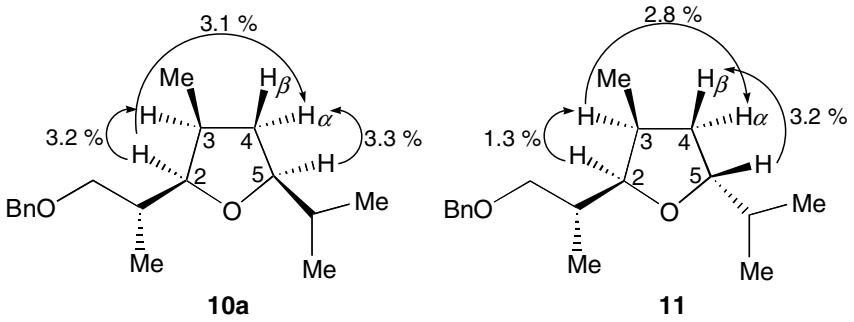


Figure 1. The ^{1}H NMR NOE results of compounds **10a** and **11**.

Contrary to the structure of **10a**, where the H2, H3 and H5 protons are in *cis* position to each other the analysis of NOE differential measurements for **11** suggests that protons H2 and H5 are in *trans* relationship. This suggestion is supported by the NOE effects observed after irradiation of all well separated ^{1}H NMR signals at 3.55 (H5), 3.39 (H2), 2.00 (H3), 1.71 (H4α) and 1.47 (H4β). A careful analysis of the NOE effects for **11**, where weak but measurable NOE effects (Fig. 1) for pairs H3-H4α, H2-H3, H4β-H5 were observed, indicates that this time protons H2, H3 and H4α share *cis* relationship.

The stereochemistry of isomeric tetrahydrofurans **13a,b** was also determined on the basis of the ^{1}H NMR NOE measurements. In the case of **13a,b** almost all signals of the aliphatic protons, including H2 and H5, were well separated (in different solvents) thus the interpretation of the ^{1}H NMR NOE experiments was rather straightforward. The most significant NOEs observed for **13a** and **13b** are presented in Figure 2. At first we decided to determine the structure of the compound obtained with 44 % yield (Eqn 2). Irradiation of the H2 signal (δ = 4.46 ppm) leads to observation of NOE (4.8 %) at H5 (3.20 ppm), and two indistinguishable effects at H3α (1.98 ppm) and H4 (1.96 ppm). When H5 was irradiated one

measurable effect (4.8 %) was observed at H2 (δ = 4.46 ppm) and an additional enhancement at δ = ~1.97 ppm (H3α and H4) was also detected. Irradiation of the signal at δ = 1.26 ppm (H3β) caused another effect (1.9 %) at 0.74 ppm (methyl group at C4). Furthermore, two other enhancements were observed. Proton (CH) of the *iso*-propyl group at 1.77 ppm interacts with the methyl group at C4, and H3β interacts strongly with proton from the benzhydryl group at δ = 4.07 ppm. The above-mentioned effects suggest that the H2, H3α, H4 and H5 protons are in *cis* position to each other and the structure of this compound is **13b**.

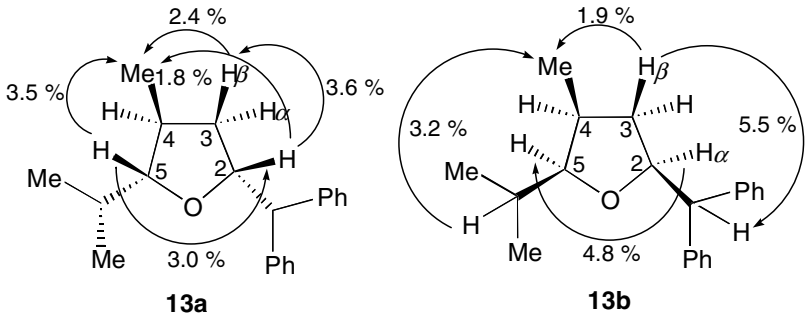
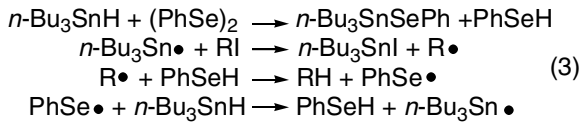


Figure 2. The ^{1}H NMR NOE results of compounds **13a,b**.

In the case of **13a** (46 % yield) a relatively strong effect (3.0 %) between the H2 and H5 protons was observed. Irradiation of the H2 proton at 4.61 ppm provided an additional effect at 1.34 ppm (3.6 %, H3β), whereas irradiation of the H3β proton gives an answer at 4.61 ppm (5.1 %, H2). Medium effects were obtained for the methyl group (C4) at 0.86 ppm, when the H2 (1.8 %) and H5 (3.5 %) protons were respectively irradiated. Similarly to **13b** two other effects were observed. Proton (CH) of the *iso*-propyl group at 1.69 ppm interacts only with the H5 proton, whereas proton from the benzhydryl group (δ = 4.00 ppm) interacts strongly with that at 1.34 ppm. All the NOE enhancements obtained for **13a** suggest that the H2, H3β, H5 and protons of the methyl group (C4) share *cis* relationship.

The two diastereomeric radicals shown in Scheme 2 were expected to cyclize at different rates. The assumption was made on the basis of analysis of the corresponding Beckwith-Houk models. For such a purpose the rate constants of the competing process (reduction of the first and second pair of the radicals) must be between the rate constants of both cyclizations. This was clearly not the case when typical hydrides were used. None of the tested hydrides (TTMSH, *n*-Bu_3SnH, Ph_3SnH) was fast enough to compete with the cyclizations. Even experiments with 5 equivalents of Ph_3SnH at lower temperatures did not alter the ratio of the products. The rate constant of the rearrangement of the 6,6-diphenyl-5-hexenyl radical to the cyclopentyldiphenylmethyl radical has been reported as 4×10^7 s^{-1} M^{-1} at 20 ^oC.[18] We roughly estimated that the rate constant of diiodide **2** could be in the range of $5\times10^7 - 10^9$ s^{-1} M^{-1}.[19]

Recently, Newcomb introduced the use of hydrogen atom abstraction from PhSeH.[20] The rate constant for trapping of radicals at 25 ^oC was determined as 2.1×10^9 $M^{-1}s^{-1}$. However, PhSeH is a very unpleasant substance. It is noxious and must be handled with care.[21] Fortunately, it can be introduced in the form of PhSeSePh and generated by the addition of *n*-Bu_3SnH as reported by Crich (Eq 3).[22] Taking into account that PhSeH reacts with primary alkyl radicals ~20 times faster than PhSH[23] and ~1000 times faster than *n*-Bu_3SnH and its recycling is immediate; PhSeH seems to be the fastest *pseudo*-first order radical trapping agent. The most striking advantage in comparison with other trapping agents is that only a small or even catalytic amount of PhSeH is necessary to establish the conditions for *pseudo*-first order kinetics. Thus, we decided to take advantage of a polarity-matched reaction in radical cyclizations of diiodide **2**.



The appropriate amount of PhSeH was estimated performing three radical experiments with 50, 200 and 500 mol% of PhSeH generated in situ from PhSeSePh and *n*-Bu_3SnH. 500 mol% excess of PhSeH appeared to give the highest **13a/13b** ratio and it was used for further radical cyclizations of diiodide **2** at different PhSeH concentrations (Table 1).

Table 1. Radical cyclizations of 2 with *n*-Bu_3SnH/PhSeH at 70 °C

entry	[PhSeH]	**13a/13b**	**13a** (%)	**13b** (%)	**13a + 13b** (%)	**Ph_2CO** (%)
1	0.05	1.06	48	45	93	2
2	0.10	1.84	59	32	91	4
3	0.13	2.33	63	27	90	6
4	0.20	2.95	69	23	92	3
		1.32[a]	53[a]	40[a]	93[a]	3
		1.84[b]	59[b]	32[b]	91[b]	5
5	0.29	4.33	65	15	80	14
6	0.51	5.90	59	10	69	24
7	1.00	7.66	46	6	52	41

[a] 50 mol% PhSeH, [b] 100 mol% PhSeH

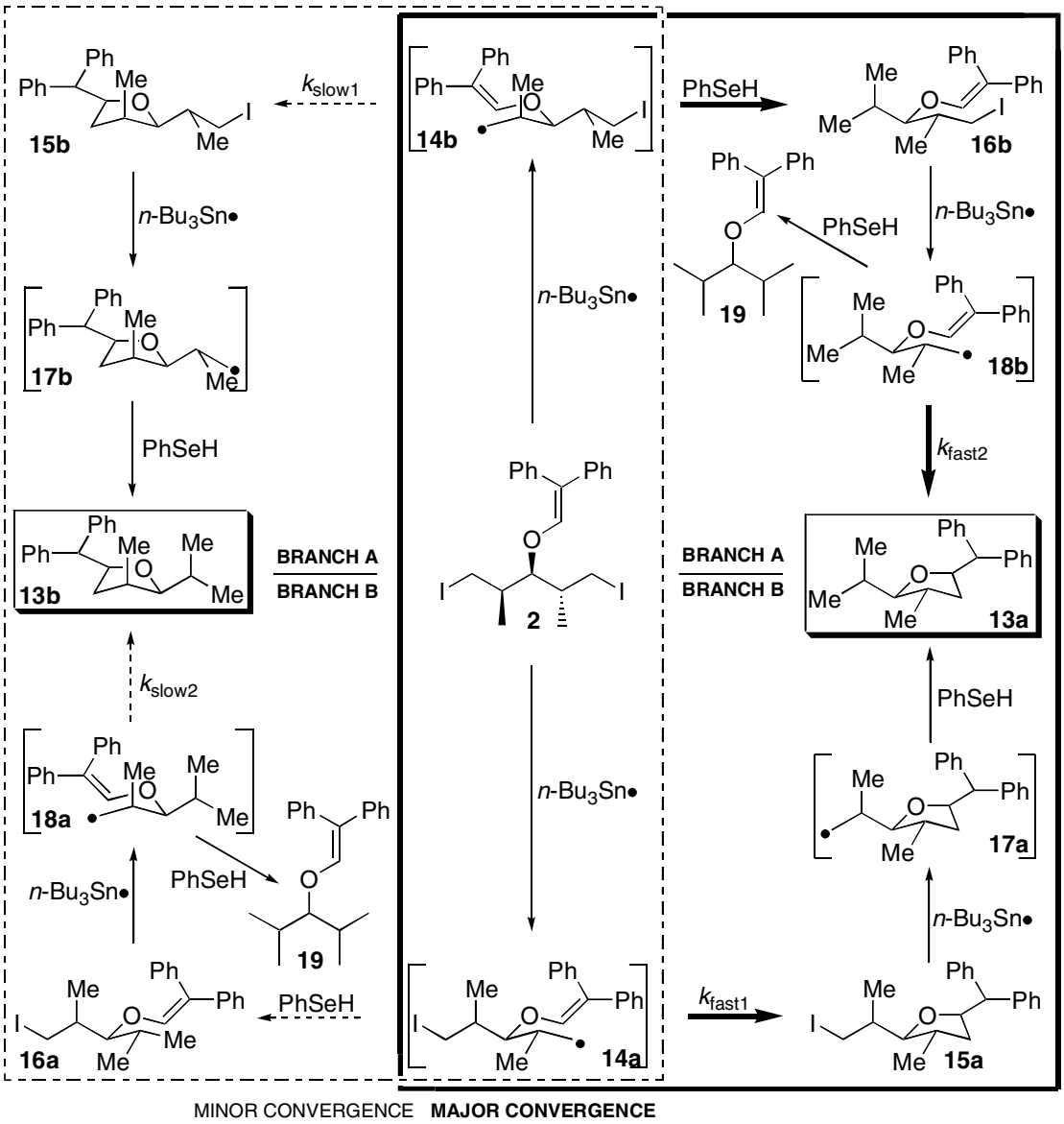
In each experiment a strictly degassed solution of PhSeSePh in benzene was treated with an equimolar amount of the hydride and mixed until the yellow color was discharged. Then the diiodide **2** was added and heated for 2 h during which time a solution of the hydride and AIBN in benzene were added dropwise. After the reaction was completed the solvent was

removed and the reaction mixture passed through a pad of silica gel. The ratio of **13a/13b** was determined using GC/MS with 9-fluorenone as an internal standard.[24] Each of the products was calibrated against the standard. The ratio of **13a/13b** appeared to depend on the concentration of PhSeH. Starting from relatively low PhSeH concentrations the process converged on the formation of **13a**. However, in all the radical experiments the doubly reduced product **19** was not isolated. The absence of **19** is incompatible with the proposed kinetic scheme 4. When an authentic sample of **19**[25] was treated with the tin hydride and AIBN in benzene at 70 ^{o}C for 48 h benzophenone was formed (84 %). We have also observed some unidentified minor products. Thus, the consumption of **19** could be explained in terms of hydrostannylation of the double bond and further radical rearrangements leading mainly to benzophenone. Further investigations concerning the formation of benzophenone are in progress.

Scheme 4 summarizes all the possible reaction pathways, which can be envisioned during the radical cyclization at the steady state of diiodide **2**. The first pair of isomeric radicals **14a**,**b** is formed in a non-selective way.[26] Both the radicals can either cyclize in the 5-*exo* fashion giving **15a**,**b** or be reduced to monoiodides **16a**,**b**. However, the cyclizations occur at different rates due to pseudoequatorial or pseudoaxial position of the methyl group in **14a**,**b**. We propose that at suitable trapping agent concentrations the slower cyclizing **14b** is mostly reduced to **16b** while the faster cyclizing **14a** closes to **15a**. Cyclic monoiodides **15a,b** are reduced *via* radicals **17a,b** to the tetrahydrofurans **13a,b**. The process repeats again in the second stage, where the roles of the radicals **18a,b** are now reversed. Now radical **18a** is preferably reduced to the doubly reduced **19** while **18b** closes to **13a**. The difference in the rates of reduction and cyclization of the first (**14a,b**) and the second (**18a,b**) pair of radicals is crucial, as suggested by Curran for the overall outcome of the radical process at the steady state. Such a difference sets up a concentration gradient that allows the slower cyclizing

radicals **14b** and **18a** to be mostly reduced while the faster cyclizing radicals **14a** and **18b** to cyclize to **13a**. Taking into account that the former pair leads to **13b** and the latter to **13a** further increase of the PhSeH concentration results in the preferable formation of **13a**. Therefore the yield of **13a** can exceed the level of stereoselection in the lowest stereoselective step, i.e. non-selective formation of the first pair of radicals (**14a,b**).

Scheme 4. The overall kinetic framework for stereoselection at the steady state in the radical cyclizations of diiodide 2



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

Conclusions

The radical cyclizations of diiodide **2** provide another efficacious example of manipulation of stereocontrol by reaction topography. At suitable PhSeH concentration high **13a/13b** ratios can be achieved. The yields of the major product are higher than the level of selectivity in the group-selective step. The results clearly support Curran's kinetic model. The 2,5-*cis* selectivity of the products arises from chairlike transition states with the pseudoequatorial substituents. This approach might be of further use wherever functionalized alkyl tetrahydrofurans are needed in organic chemistry. Further efforts towards diastereo- and enantioselective variants of stereoselection at the steady state will be reported in due course.

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Supporting Information Available: The complete experimental details, copies of the ^{1}H and ^{13}C spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[‡] Dedicated to Prof. Dennis P. Curran for his fundamental contribution to the Stereoselection at the Steady State.

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[14] Compounds **10a**,**b** are formed via a chairlike transition state. Compound **11** is presumably formed via a boatlike transition state.

[15] Rate constants for 5-*exo* cyclizations of alkenyl radicals at 25 ^{o}C are in the range of 1-5$\times 10^5$ s^{-1} M^1, see: a) Lusztyk, J.; Maillard, B.; Deycard, S.; Lindsay, D. A.; Ingold, K. U. *J. Org. Chem.* **1987**, *52*, 3509-3514. b) Beckwith, A. L. J.; Easton, C. J.; Lawrence, T.; Serelis, A. K. *Aust. J. Chem.* **1983**, *36*, 545-556. c) Chatgilialoglu, C.; Ferreri, C.; Lucarni, M. *J. Org. Chem.* **1991**, *56*, 6399-6403.

[16] The products could not be separated by chromatography to give the individual pure isomers. Moreover, they appeared to be quite volatile and we were not able to purify them from impurities. The phenyl groups in **2** allowed us to separate the reaction mixture by means of HPLC (UV detection) and added molecular weight so that the products were not volatile.

[17] The ^{1}H NMR NOE enhancements in tetrahydrofurans are usually smaller than in other systems, see: Kadota, T.; Oguro, N.; Yamamoto, Y. *Tetrahedron Letters* **2001**, *42*, 3645-3648.

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[19] One might hope that the relatively slow delivery of hydrogen to the first pair of radicals could be compensated by a huge excess of Ph_3SnH. But the analysis of small quantities of the products in the presence of a large excess of the hydride could be very difficult and give rather inconsistent results. Therefore, we then turned our attention to the use of much faster trapping agents.

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[24] Re-subjected **13a**,**b** to the reaction conditions appeared to be stable and were recovered almost quantitatively (> 96 %).

[25] For the comparison purpose **19** was prepared independently. Commercially available di-isopropyl ketone was reduced with lithium aluminum hydride, and the resulting alcohol was reacted with excess of 1,1-dimethoxy-2,2-diphenylacetaldehyde acetal in the presence of *p*-toluenesulfonic acid.

[26] A reversible iodine transfer does not seem to play a role, 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.

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