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Stereoselection at the Steady State within Radicals – How far can we go?*

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Stereoselection at the steady state is a process, which results from a complex interplay of reaction pathways that diverge and reconverge at various points. Therefore, it can be considered as a manipulation of stereocontrol mainly by reaction topography. The advantages of this process are at least twofold: First, stereoconvergence allows the system to exceed the yield of the initial stereoconvergent event, where stereomeric transition states compete. Second, a successive resolution of the reactive intermediates by chemoselective events allows the system to generate high stereomeric excess, practically without any stereoselective competition. While illustrated with radicals, the process may prove useful in other fields of chemistry.

Key words: stereoselection, steady state, radicals

1. Introduction

The use of free radical chemistry in organic synthesis has witnessed a fast development in recent years. Its continued success seems to be dependent on further advances of control of stereochemical configuration in such reactions [1]. While the majority of asymmetric radical cyclizations, in the transformation of sp^2 to sp^3 center, involves diastereotopic face selection [2] – diastereotopic group selectivity has only recently been applied to radical reactions [3,4]. The group selectivity in radical transformations can be classed either as under chiral auxiliary control or under substrate control. In the latter case the selectivity is not caused by either a simple stereoselective competition or the cumulation of many stereoselective competitions, but by reaction topography. Although elementary stereoselective processes like group selection are involved, these do not directly control the level of stereoselection as they do in all known processes. Instead, stereocontrol results from complex orchestration of reaction pathways, that diverge and reconverge at various points. If the process can be realized at the steady state, where the relative concentration of two stereomeric reactive intermediates remains constant, the orchestration of reaction pathways can lead to the same product by choosing appropriate reaction conditions. Therefore, this strategy offers a unique possibility of providing a yield of a major product, that exceeds the level of selectivity in any stereoselective event in a kinetically controlled process.

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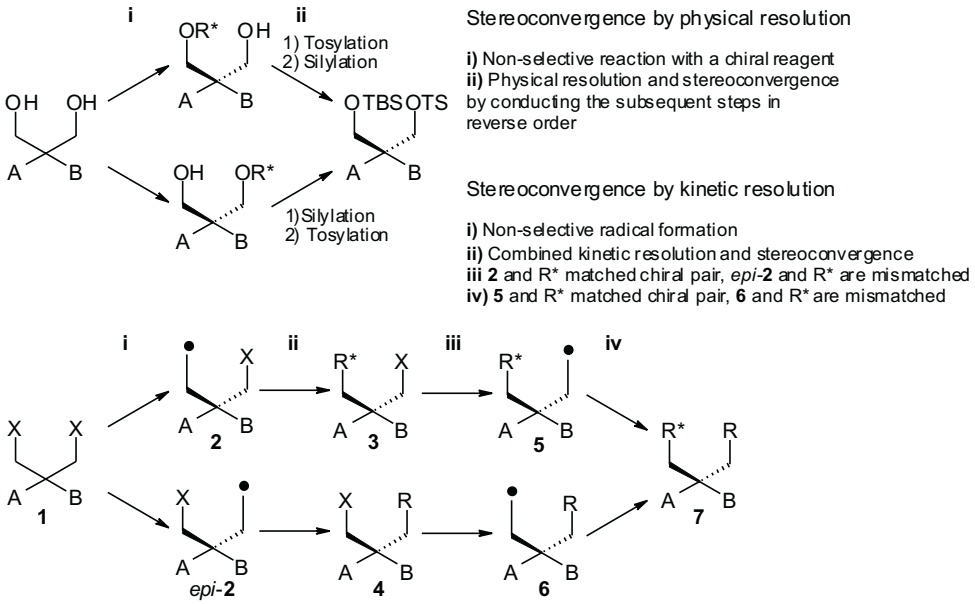
* Dedicated to Professor Mieczysław Mąkosza on the occasion of his 70th birthday.

Recently, the conceptual and mathematical framework of a new strategy called "Stereoselection at the steady state" has been proposed [5,6]. The basic process of it is akin to the process of "stereoconvergent synthesis", except that a kinetic resolution replaces a physical resolution. Both processes are illustrated side-by-side in Scheme 1. In a stereoconvergent synthesis, a molecule with two enantiotopic functional groups is reacted in a non-selective fashion with one equivalent of an enantiopure reagent (R*) [7]. This provides a mixture of diastereomers, which is separated by physical means (crystallization, chromatography, *etc*.). These diastereomers are then processed separately to the same enantiomer by conducting subsequent steps in opposite order. Scheme 1 shows a hypothetical example where an achiral diol is converted to a single enantiomer of a mono-tosyl, mono-silyl derivative.



Scheme 1. Stereoconvergence by physical and kinetic resolutions.

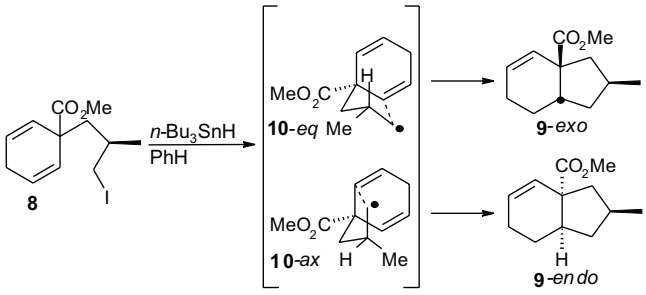
Prior to conducting any experiments, one can imagine a single reaction scheme, whose topology contained a stereoconvergent process, in which a kinetic resolution replaced the physical resolution [8,9]. While not unique to radicals, the process is illustrated with radicals. Isomeric radicals **2**/*epi*-**2** are generated at equal rates from dihalide **1** [10]. These are then allowed to compete for two different processes, at least one of which must be stereoselective. In the idealized case in Scheme 1, the matched stereoselective reactions (of **2** or **6** with R*) occur much faster than the mismatched ones (of *epi*-**2** or **5** with R*, products not shown), and the non-stereoselective reactions occur at a rate in between the rates of the faster and the slower stereoselective reactions. If the rate differences are large enough, the remarkable result is a

stereoconvergent process, in which **1** is converted into **7** independent of the level of group selectivity in the initial group selective step! This stereoconvergence can be directly attributed to the steady state. In the absence of the achiral component R, the different reaction rates of **2** and *epi*-**2** with the chiral reagent R* establish a concentration gradient between these two species. For example, if **2** reacts with R* 100 times faster than *epi*-**2**, then *epi*-**2** will be present at the steady state at 100 times higher concentration than **2**. This concentration gradient then dictates that *epi*-**2** will react preferentially with R at the first stage even though the rate constants for reaction of **2** and *epi*-**2** with R are identical. In reality, the idealized process with complicated scenarios results. Nonetheless, in practice, high levels of stereoselection can be obtained.

2. Group selective radical cyclizations

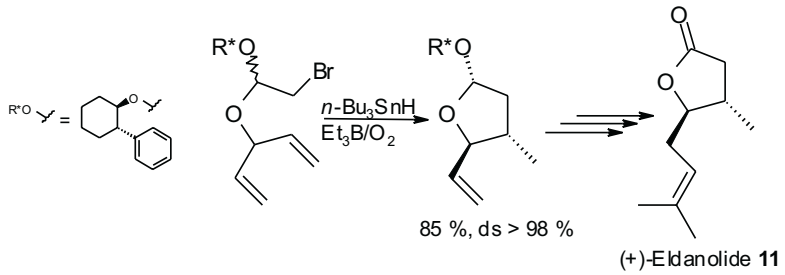
Most of the reported examples of stereochemical control of radical cyclizations have focused on face selectivity [11]. Group selective ones are less common [12]. Two types of group selective radical transformations can be envisioned: either there can be two radical acceptors and one radical precursor (class I) or there can be two radical precursors and one acceptor (class II). The outcome of such reactions can be anticipated by applying the Beckwith-Houk model [13,14].

2.1. Two radical acceptors and one radical precursor. There are only a few examples of this class of group selective radical transformations. Most of them rely on the attack of radicals (formed from cyclic or acyclic radical precursors) onto double bonds (radical acceptors). In such cases the stereoselection does not result from orchestration of all possible pathways. The only thing that counts is the relative energy of the competing transition states. For example, cyclization of **8** with tributyltin hydride gives preferentially bicyclic product **9**-*exo* (Scheme 2) [15]. The selectivity is established at the stage of radical **10**, which chooses between a chairlike transition structure (**10**-*eq*) involving one double bond and an isomeric chairlike structure (**10**-*ax*) involving the other. Both the closures are intramolecular, therefore the selectivity cannot be varied by changing the tin hydride concentration (although the ratio of directly reduced to cyclized products is of course affected by the tin hydride concentration).



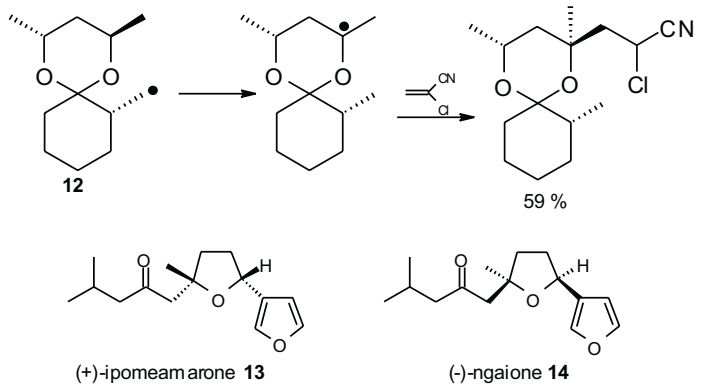
Scheme 2. Two acceptors and one radical precursor.

Another example is a desymmetrization of 1,4-dien-3-ols *via* Ueno-Stork radical cyclization [16,17]. The utility of this method has been demonstrated by achieving a short synthesis of (+)-eldanolide **11**, the pheromone of the male African sugarcane stem borer *Eldana saccharina* (Scheme 3) [18]. The stereochemistry of the cyclization is controlled by the acetal center. Namely, the system adopts a conformation, where the anomeric effect at the acetal center is maximized [19].



Scheme 3. Synthesis of (+)-Eldanolide.

Besides radical cyclizations also radical transfers may be considered as another example of the group selective process. Sugimura and co-workers reported, that intramolecular hydrogen shift of β-radical ketal **12** was found in the reduction of optically active β-mercuro ketal (Scheme 4) [20]. The addition of olefins to the hydrogen transferred radical proceeded regio and diastereo differentiatingly and afforded optically active *sec-tert*-1,3-diols. This strategy was then applied for total syntheses of (+)-ipomeamarone **13** and (–)-ngaione **14** [21], enantiomeric constituents of fatal toxins for domestic animals [22].



Scheme 4. The stereoselective hydride transfer/olefin addition process.

2.2. Two radical precursors and one radical acceptor. This class of group selective radical transformations seems to be more interesting from conceptual point of view. Namely, the isomer ratio resulting from one stereoselective event can be changed by concurrent events in the reaction scheme. All the reported examples have two radical precursors and double or triple bonds as radical acceptors. Therefore, they can be classed as group selective radical cyclizations. In this class stereoconvergence [23] can be made to occur if two conditions exist:

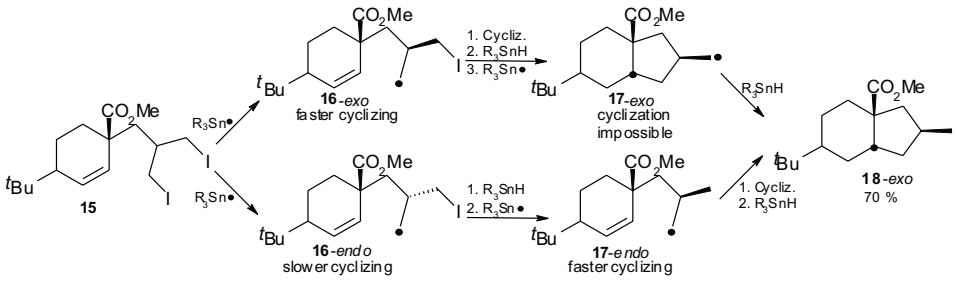
1) At least one of the competing processes must be stereoselective (Scheme 1, reactions of **2** and *epi*-**2** with R*).
2) The other possible processes must have rates of reaction, that are in competition with the two rates of the first process (Scheme 1, reactions with R). It means, that the rate of the other processes must be between the stereoselective ones.

Ideally: $\nu_{\text{fast stereoselective event}} > \nu_{\text{the other processes}} > \nu_{\text{slow stereoselective event}}$

Taking into account, that radical cyclizations are at stake, the most obvious competing process seems to be reduction, because there is always a competition between cyclization and reduction there. Said another way, the ratio of directly reduced to cyclized products can be varied by changing the used hydride concentration (not amount!). Therefore, there is a topological way to improve or erode the stereoselection.

2.2.1. Cyclic systems. So far only diastereoconvergent processes have been reported, in which the stereoselective reaction was cyclization and the competing non-stereoselective reaction was reduction by tin hydride. The stereochemistry of the process depends directly on tin hydride concentration, despite the fact that the radical reactions with tin hydride are not selective. Non-selective halogen abstraction from **15** generates two diastereomeric radicals **16**-*exo* and **16**-*endo*, which cyclize at different rates [6]. At (infinitely) low tin hydride concentration, both cyclizations are faster than reduction, and even though the cyclizations occur at different rates, there is no stereoselection because the two radicals are generated in equal ratios. At (infinitely) high tin hydride concentrations, both radicals are reduced and no cyclization occurs. In between these extremes is the interesting area. The different rates of cyclization of the stereomeric radicals set up a concentration gradient, that allows the slower cyclizing radical **16**-*endo* to react selectively with tin hydride, while the faster cyclizing radical **16**-*exo* forms the bicyclic radical product. The process repeats again in the second stage, where the roles of radicals **17**-*exo* and **17**-*endo* are now reversed. Scheme 5 shows only the major pathways and not the full competition. In the experiment, there is a competition at every stage between cyclization and reduction, and at suitable tin hydride concentrations the process converges on the formation of **18**-*exo*.

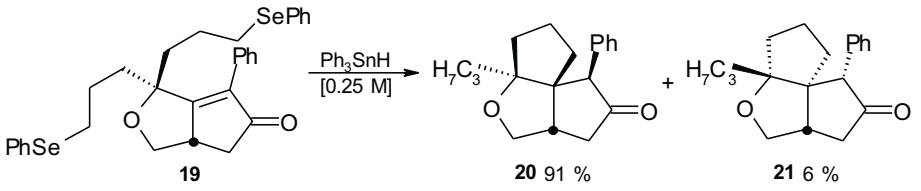
This process seems to be a fundamentally new branch of stereoselection, that has been heretofore unrecognized. Prior multi-step, stereoselective processes are "composites" of all their individual stereoselective steps. In no case can the yield of a major product exceed the level of stereoselection in the lowest stereoselective step in



Scheme 5. One acceptor and two radical precursors.

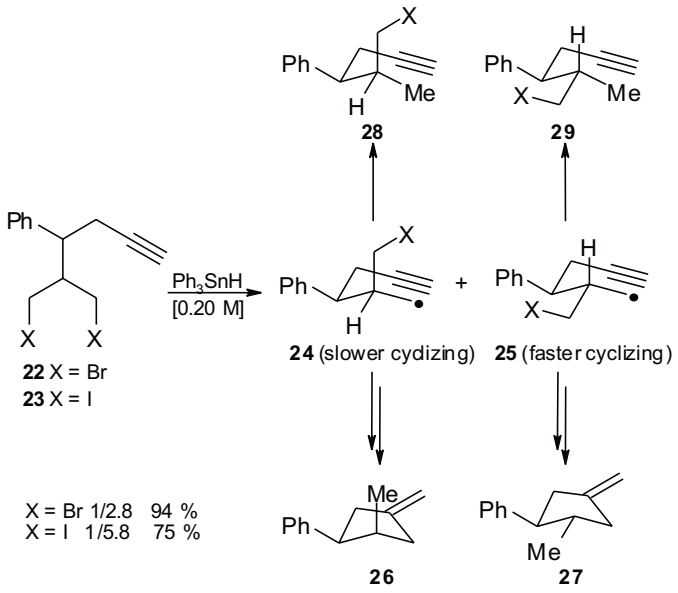
the composite. On the other hand, stereoselection at the steady state is fundamentally different; a 50% level of group selection can result in > 70% yield of a major isomer. The advantages of this process are at least twofold: First, stereoconvergence allows the system to exceed the yield of the initial stereoconvergent event, where stereomeric transition states compete. Second, a successive resolution of the reactive intermediates by chemoselective events allows the system to generate high stereomeric excess, practically without any stereoselective competition. Therefore, selectivity can be easily optimized by simply manipulating the rates of the two component transformations.

Even more impressive appeared to be the reduction of **19**, containing the radical precursors (SePh) in a 1,7-relationship with triphenyltin hydride [24]. It provided mixtures of *cis,cis*- (**20**) and *cis,trans*- (**21**) angular triquinane products, in yields that varied from 50/50 to 91/6 (%), depending on the tin hydride concentration (Scheme 6). The initial abstraction of the PhSe group from **19** by a triphenyl tin radical is the only traditional diastereotopic-group-selective step, but the level of group selectivity in this step is zero. At no other juncture the stereomeric intermediates compete directly against each other. At the lowest Ph_3SnH concentration, this group selective step determines the product ratio. As the Ph_3SnH concentration is raised, the cyclization of one diastereomeric radical remains faster than the bimolecular hydrogen transfer. On the other hand, the trapping of the second radical gradually becomes more efficient. Thus, raising the Ph_3SnH concentration opens a new pathway, that increases the yield of **20** at the expense of the yield of **21**.



Scheme 6. Reduction of the bis-radical precursor (**19**) with Ph_3SnH.

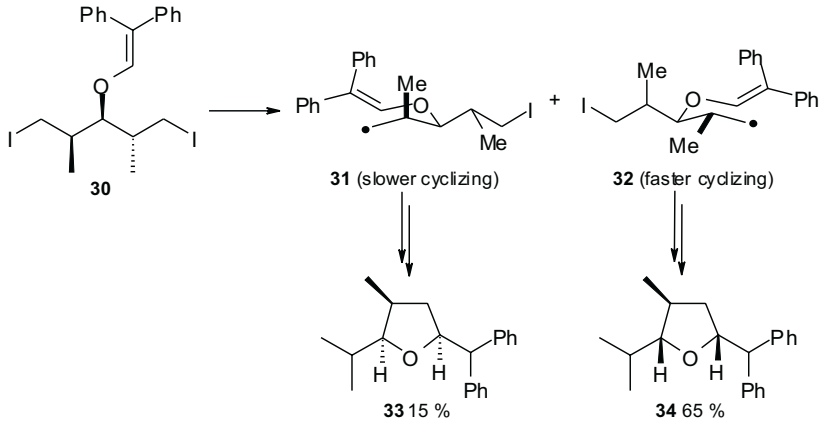
2.2.2. Acyclic systems. Cyclic systems provide a rigidity to reduce options for intermediate radicals, but there is no reason bi- and tricyclic systems are needed. So far two acyclic radical systems have been successfully subjected to stereoselection at the steady state. In the first case, the radical precursors (**22** X = Br, **23** X = I) were in a 1,3-relationship [25]. On the basis of the Beckwith-Houk model, the two diastereomeric radicals **24** and **25** were expected to cyclize at different rates, because stereoselection at the steady state required such a rate difference (Scheme 7). Even though reduction of these intermediates with tin hydrides is not a selective process. The overall stereoselection depends crucially on the tin hydride concentration. The first key step, that helps to determine the final ratio of **26**/**27**, is reduction of radicals **24** and **25** to monoreduced products **28** and **29**, which occurs in competition with cyclization to **26** and **27**. Careful monitoring of the radical cyclizations of **22** revealed the presence of acyclic monobromides **28** and **29**. The structure of the major reduced monobromide appeared to be **28**, what was in agreement with the slower rate of cyclization of radical **24**. Also 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 attributed to differing rates of cyclization at the monohalo stage [26].



Scheme 7. Acyclic model having two radical precursors in 1,3-relationship.

There are relatively few examples of desymmetrizations of *pseudo* C_2-symmetric acyclic systems [27]. All of them are outside radical reactions. Desymmetrization in such systems requires diastereotopic group selection. However, in the light of stereoselection at the steady state group selection processes (obviously involved) do

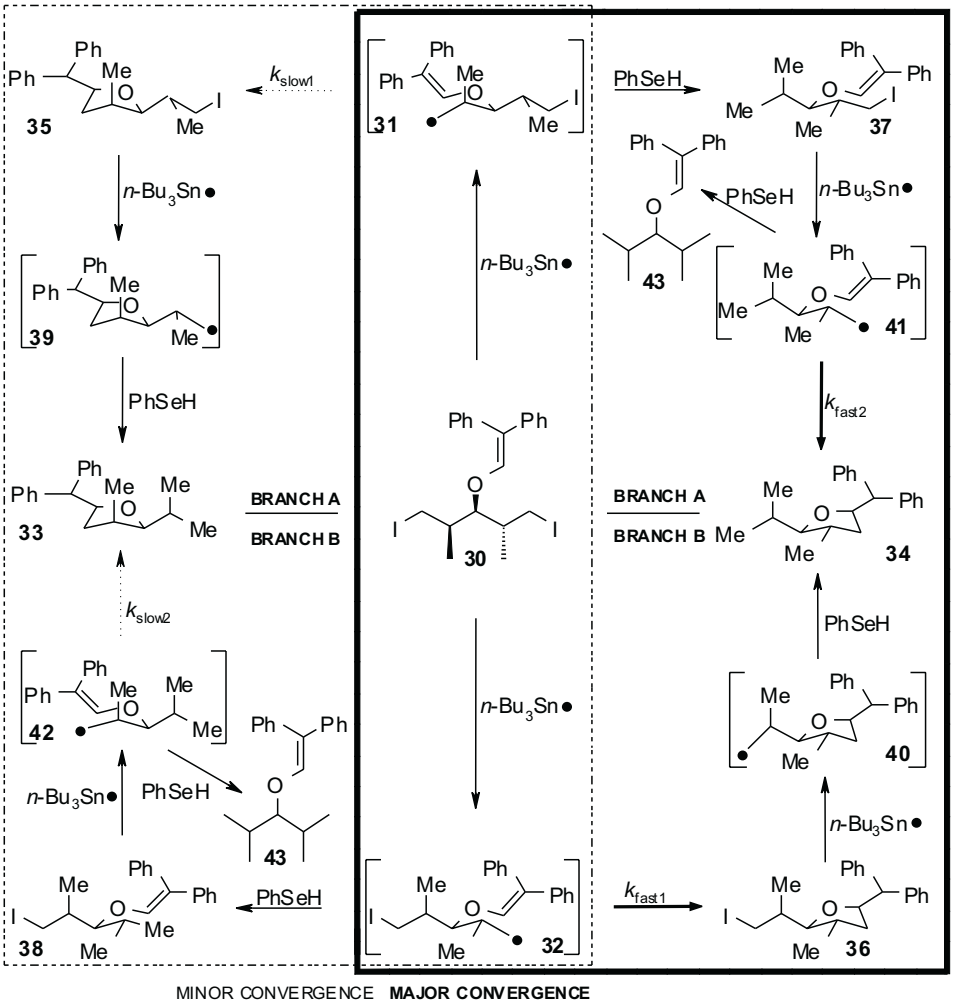
not directly control the level of stereoselection, as they do in all known processes. The stereocontrol rather results from a complex interplay of reaction pathways, that diverge and reconverge at various points. The first example of a successive kinetic resolution of acyclic diastereomeric radical intermediates in a 1,5-relationship, leading to substituted tetrahydrofurans, has been experimentally verified [28]. The substituted tetrahydrofurans are of interest as building blocks in organic synthesis, chiral auxiliaries, and the structural units of many natural products [29]. The stereoselective approach to this class of compounds is still problematic, because of flexible transitions states leading to the tetrahydrofuran system [30]. Among the different strategies available, free carbon radical cyclizations are of particular interest as an alternative to ionic processes [31]. Especially β-alkoxyacrylates are excellent precursors for stereoselective preparation of *cis*-2,5-substituted tetrahydrofurans *via* radical cyclizations [32]. Acyclic vinyl ether **30** having two radical precursors met the requirements of the stereoselective process. The "2,5-*cis*" selectivity in the radical cyclization step arises from transition geometries with the substituents aligned in pseudoequatorial positions (Scheme 8).



Scheme 8. Acyclic vinyl ether having two radical precursors in 1,5-relationship.

Scheme 9 summaries all the possible reaction pathways, that can be envisioned during the radical cyclization at the steady state of diiodide **30**. The first pair of isomeric radicals **31** and **32** is formed in a non-selective way. Both the radicals can either cyclize in the 5-*exo* fashion giving **35** and **36** or be reduced to monoiodides **37** and **38**. However, the cyclizations occur at different rates, due to a pseudoequatorial or pseudoaxial position of the methyl group in **31** and **32**. At suitable trapping agent concentrations, the slower cyclizing **31** is mostly reduced to **37**, while the faster cyclizing **32** closes to **36**. Cyclic monoiodides **35** and **36** are reduced *via* radicals **39** and **40** to the tetrahydrofurans **33** and **34**. The process repeats again in the second stage, where the roles of the radicals **41**,**42** are now reversed. Radical **42** is preferably reduced to the doubly reduced **43**, while **41** closes to **34**. The difference in the rates of

reduction and cyclization of the first (**31**,**32**) and the second (**41**,**42**) pair of radicals is crucial, as suggested by Curran for the overall outcome of the radical process at the steady state. The difference sets up a concentration gradient, that allows the slower cyclizing radicals **31** and **42** to be mostly reduced, while the faster cyclizing radicals **32** and **41** to cyclize to **34**. Taking into account, that the former pair leads to **33** and the latter to **34**. A further increase of the PhSeH concentration results in the preferable formation of **34** [33]. Therefore, the yield of **34** can exceed the level of stereoselection in the lowest step, *i.e.* non-selective formation of the first pair of radicals (**31** and **32**).

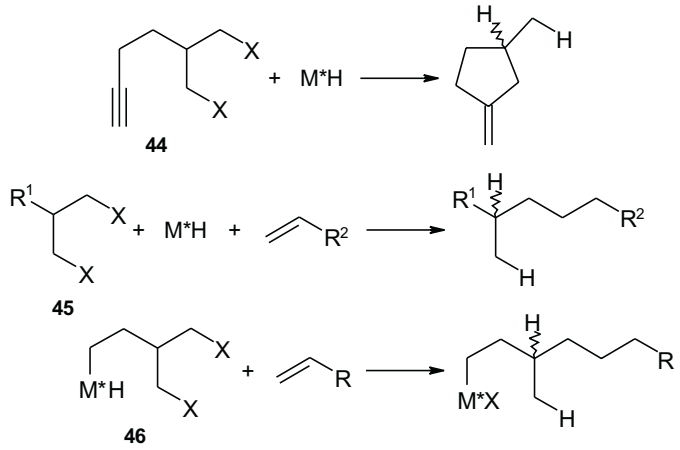


Bold arrows represent faster reactions. Dashed arrows represent slower reactions. Standard arrows represent nonselective reactions.

Scheme 9. The overall kinetic framework for stereoselection at the steady state in the radical cyclizations of diiodide **30**.

3. Envisioned enantioselective systems

Up to date all the experimentally verified examples of stereoselection at the steady state are diastereoselective, in which the stereoselective reaction is a cyclization and the competing reaction is a reduction. None of these features is a prerequisite for stereoselection at the steady state. Now it is time to move toward new types of examples within and outside chemistry. Especially interesting seem to be enantioselective variants of stereoselection at the steady state. Recently, knowledge of enantioselective radical reactions has increased significantly [34]. In theory, it is possible to design competing radical reactions, in which enantiomeric radical precursors generate enantiomeric radicals, which cyclize at the same rate but are trapped by chiral traps at different rates. Scheme 10 presents some hypothetical enantioselective variants of stereoselection at the steady state. If a chiral metal hydride (M*H) were available, that would differentiate between the enantiomeric radicals derived from, for example dihalides **44**–**46**, then an enantioselective cylization could be conducted. It requires developing of efficient routes to new chiral hydrides [35]. They are of high interest, because they could be used catalytically to deliver hydrogen to radicals; they are the synthetic equivalents of "chiral hydrogen atom" [36].



Scheme 10. Envisioned examples of enantioselective variants at the steady state.

4. Conclusions

Stereoselection at the steady state is a unique and fascinating process. Over the past several years, major strides forward in expanding the concepts, solidifying the mathematical foundation of the kinetics, and developing new experimental systems within radicals have been taken. But it would be naive to assume that the phenomenon has relinquished all its secrets. Too many questions still remain to be answered, even if some progress has been done. For instance, what other radical systems could be

applied? Preliminary studies seem to indicate, that other precursors are equally capable of sustaining the same type of radical chain reactions, but further work is necessary to ascertain, whether they offer any special advantages. What other fields of chemistry beyond radicals could prove useful in this area too? The transition-metal chemistry offers many opportunities for speculation. How important is stereoselection at the steady state from synthetic point of view? More fundamentally, the kinetics of the overall process needs to be deeper determined, in order to gain a greater mastery of the system.

Acknowledgment

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