Stereoselection at the Steady State: The Design of New Asymmetric Reactions[**]

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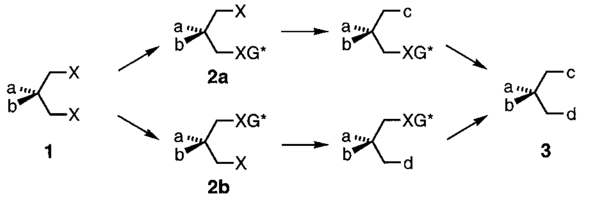
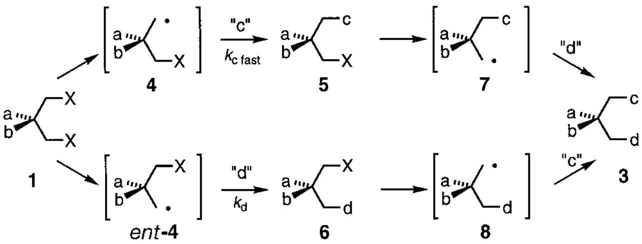
A reaction leading to an optically pure product in quantitative yield is the dream of every chemist working in the field of asymmetric synthesis. If only catalytic amounts of a chiral compound are needed to achieve this goal, then it is like paradise. But only very few asymmetric reactions have been developed thus far. Compounds with asymmetric centers can be obtained from prochiral starting molecules by either face-selective reactions (stereoheterotopic facial addition) or group-selective reactions (stereoheterotopic ligand substitution). The transition states of these selective stereodivergent reactions must be diastereomeric, and the kinetics are the same as those of parallel reactions with different products (enantiomers or diastereomers). The selectivity in the stereoselective event leading to the different transition states can never be exceeded by the final yield of the major stereoisomer.

In two recent publications Curran et al. described the theoretical as well as the mathematical background of stereoconvergent reactions.[1] They give further evidence for their analysis by providing some examples from the field of radical chemistry to demonstrate this strategy called "complex stereoselection". The process of stereoconvergent synthesis was already proposed by Fischli et al. in 1975.[2] The first step in this process is the nonselective monoprotection of a reactive group (X in **1**) by a chiral agent (G*, Scheme 1). After separation of the diastereomers **2a** and **2b**, the still reactive groups are converted into "c" and "d". These derivatives generate **3** with a theoretical enantiomeric excess of 100 % and without destroying any material. The ratio **2a**:**2b** has no influence on the outcome of the reaction.



Scheme 1. General progress of a stereoconvergent synthesis.

Although the subsequent discussion describes the stereoselection at the steady state through the example of radical reactions, the analysis and principles are general for any reaction profile that fits into the scheme of complex stereoselective reactions. In the process proposed and analyzed by Curran et al., the activation of compounds of type **1** is done, for example, by radical formation. The group selectivity in this first step has again no effect on the stereomeric nature of the product. To obtain a stereoconvergent process it is crucial, however, that the reaction is operating at the steady state. This means that the concentrations of the radical intermediates (compounds in brackets in Scheme 2) are low and stationary, while their absolute concentrations are determined by the different rates of reaction.



Scheme 2. Stereoselection at the steady state with the example of a radical reaction.

The radicals **4** and *ent*-**4** formed in the first reaction must have competing reaction rates for c and d: The second process must have a reaction rate in competition with the two rates of the first process ($k_{c\,fast} > k_d > k_{c\,slow}$). This means that radical **4** reacts much faster with c than with d yielding product **5**. Radical *ent*-**4**, however, will react faster with d than with c, and **6** will be produced. Compounds **5** and **6** are then activated again by conversion into **7** and **8**. Radical **7** is mismatched for the reaction with c ($k_{c\,slow} < k_d$), and reaction with d provides product **3**. Radical **8** is converted also into **3** as shown in Scheme 2. The achiral products (disubstitution of X with either c or d) result from a leakage out of one convergence and are only minor products because of the reaction rates. Furthermore, it is necessary for the stereoconvergence at the steady state that at least one of these processes (reaction with either c or d) is stereoselective.

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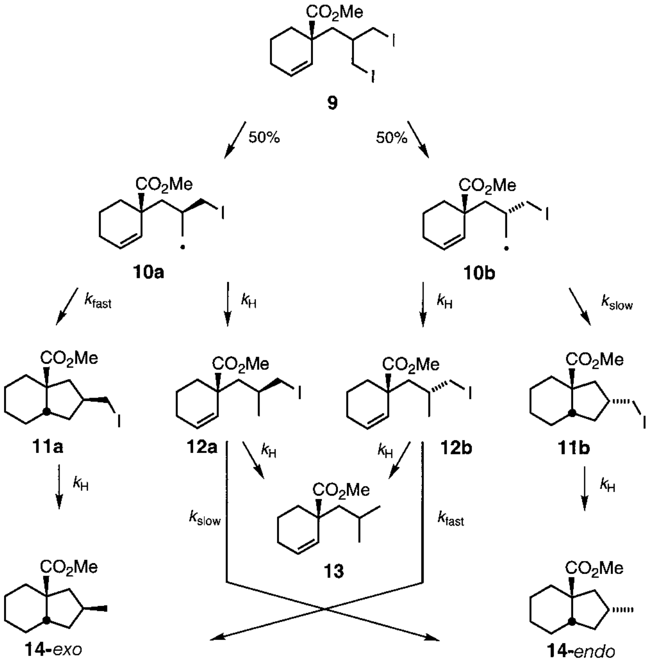
The mathematical description of this and related reaction schemes are complex and will not be discussed here. To verify the analysis of the stereoselection at the steady state experimentally, diastereoselective radical cyclization reactions were selected. Although face-selective radical cyclizations are much more common than the group-selective counterparts,[3] several model compounds were suggested by Curran et al.[1] Molecules which have two radical precursors and one radical acceptor group such as **9** were selected to provide experimental verification (Scheme 3). This choice also seems wise from a different point of view: Because the intermediates are radicals, the two competing reactions are an intramolecular cyclization and an intermolecular hydrogen-transfer reaction. The latter is dependent upon the tin hydride concentration. In other words, by varying the tin hydride concentration it is possible to influence the stereochemical outcome of the reaction.



Scheme 3. Diastereoselective synthesis of **14**-*exo* and **14**-*endo* from **9**.

At low tin hydride concentrations the product ratio of **14**-*exo*:**14**-*endo* is approximately 1:1; this ratio confirms that there is no selectivity in the first abstraction of iodine by the tin radical. The radicals **10a** and **10b** are formed in equal amounts. Product **13** is not detected. The rate for the subsequent cyclization reaction is, however, different for **10a** and **10b**. Cyclization of radical **10a** to the *exo*-derivative **11a** is faster than the generation of the *endo*-derivative **11b** from **10b**. With increasing tin hydride concentration the competing hydrogen-transfer reaction is opening new paths on the reaction topography. If the faster cyclizing radical **10a** is reduced to **12a** before cyclization occurs, most of the product **12a** will end up as the doubly reduced compound **13**. When the slower cyclizing radical **10b** is reduced, however, most of the resulting product **12b** follows the pathway to the major product **14**-*exo*. The yield of **14**-*exo* is, therefore, both eroded (**12a**→**13**) and supplemented (**12b**→**14**-*exo*). However, because the concentration of the slower cyclizing radical **10b** always exceeds the concentration of the faster cyclizing radical **10a**, the yield of **14**-*exo* is supplemented faster than it is eroded (Scheme 3).[4] This situation is visualized in Figure 1.

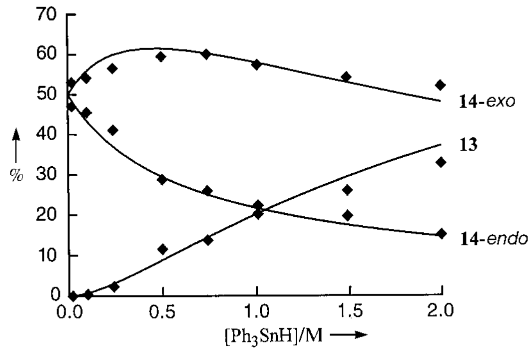


Figure 1. The effect of the tin hydride concentration on the formation of **13**, **14**-*exo*, and **14**-*endo* (selectivity approximately five). The experimental results (◆) are compared with the calculated ones (lines).[5]

The data fits nicely to a k_{fast}:k_{slow} ratio of about five. With this selectivity between the major and the minor stereoconvergence, the maximum yield of **14**-*exo* is about 60 %. The importance of this concept, however, becomes appearent when a selectivity of 500 is assumed. Figure 2 shows the calculated curves for this scenario, whereby an increase in the tin hydride concentration leads to a large *exo*:*endo* ratio.

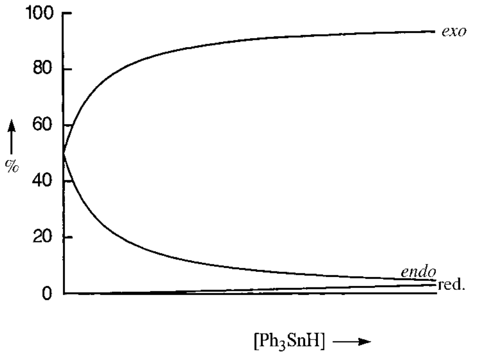


Figure 2. Calculated curves showing the effect of the tin hydride concentration on the formation of **13**, **14**-*exo*, and **14**-*endo* when a selectivity of 500 is assumed.

The reaction of **9** to products **14** is one simple example of a complex stereoselective reaction. Other reactions based on radical chemistry have been suggested by Curran et al., but these reactions with a stereoselection at the steady state are by no means restricted to radical chemistry. Organometallic reactions can also involve transient intermediates which may fulfil the crucial need for competing reactions with different rates, with the rate of the nonselective reaction lying between the rates of the two selective ones. In this context catalytic enantioselective reactions are especially challenging and could have a high preparative value. The stage is now set for the discovery of new stereoconvergent reactions orchestrated by stereoselection at the steady state.

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[1] a) N. C. DeMello, D. P. Curran, *J. Am. Chem. Soc.* **1998**, *120*, 329–341. b) D. P. Curran, C.-H. Lin, N. DeMello, J. Junggebauer, *J. Am. Chem. Soc.* **1998**, *120*, 342–351.
[2] A. Fischli, M. Klaus, H. Meyer, P. Schönholzer, R. Rüegg, *Helv. Chim. Acta* **1975**, *58*, 564–584.
[3] a) D. P. Curran, S. J. Geib, C. H. Lin, *Tetrahedron: Asymmetry* **1994**, *5*, 199–202. b) D. P. Curran, W. Shen, J. Zhang, S. J. Gieb, C.-H. Lin, *Heterocycles* **1994**, *37*, 1773–1788.
[4] The pairs of fast and slow rate constants are assumed to be equal to simplify the theoretical analysis.
[5] The following rate constants were used for the calculation: $k_{\mathrm{fast}} = 4.6 \times 10^7\ \mathrm{s}^{-1}$; $k_{\mathrm{slow}} = 1.0 \times 10^7\ \mathrm{s}^{-1}$; $k_{\mathrm{H}} = 2.0 \times 10^7\ \mathrm{s}^{-1}$.

Phosphanides of the Heavier Alkali Metals

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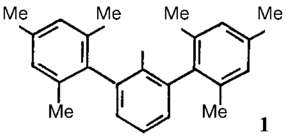
Much of the fascination of inorganic chemistry lies in the study of trends in the periodic table, up and down groups, across periods, and diagonally. Compounds of the same stoichiometry are compared, similarities noted, and attempts made to understand subtle differences. It has been commonplace in teaching inorganic chemistry to cover the marked changes from carbon to lead or from nitrogen to bismuth in considerable detail, and to pass rather quickly over some of the other groups—for example, the alkali metals, alkaline earths, or halogens—because the variation from the top to the bottom of the periodic table is much smaller. In these groups near the sides of the table the chemistry is dominated by one oxidation state, but it is rash to assume that the chemistry of those elements which have been less fully studied will simply mirror that of the compounds that are well known. Factors other than oxidation state, for example size and polarizability, have to be considered, and these may give much greater variety in the chemistry of, for example, elements from Groups 1, 2, 3, or 17 than is sometimes acknowledged.

This point is illustrated for the chemistry of the Group 1 elements in the recent paper by Rabe et al.[1] on the structure of the rubidium and cesium phosphanides MPHR (M = Rb, Cs, R = 2,6-dimesitylphenyl (**1**)). General interest in the reactions of alkali metals with phosphanes comes from their widespread use in the synthesis of phosphorus-containing ligands. The lithium phosphanides of general formula LiPHR or $LiPR_2$ show a wide variety of structures that were summarized recently by Becker et al.[2] A few compounds—especially those in which the lithium atom is complexed by large ligands, for example, [12]crown-4—are ionic,[2, 3] that is, $[LiL_n][PR_2]$. Monomeric molecular structures are rare. More commonly, the molecules associate to give ladder or helical structures which may be oligomeric or polymeric[2, 4] (Figure 1) like the corresponding amido compounds.[5] Information on the structures of sodium and potassium phosphanides is sparse, but the few examples that have been reported show that they fit into the same overall pattern. Polymeric ladder structures, based on alkali metal–phosphorus bonds, predominate.[6]



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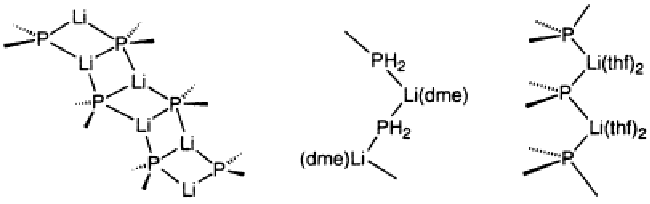

Figure 1. Some structures of lithium phosphanides (taken from reference [4]). dme = 1,2-dimethoxyethane.

The general principles underlying this pattern of structures were defined in a seminal paper[7] many years ago, and they apply to most groups of oligomeric compounds containing an element from Groups 1–3 (M) and one from Groups 15–17 (E). Firstly, for the formation of higher from lower oligomers, the enthalpy change associated with the formation of additional M–E bonds must be sufficient to overcome the unfavorable entropic contribution to the free energy. Secondly, the oligomerization or polymerization is curtailed by the attachment of large groups to either element. In the last few years very bulky aryl groups such as **1** have been used for this purpose, and a range of main group compounds showing highly unusual structural features have been obtained.[3, 8]

Rabe et al.[1] studied the reactions of the heavier alkali metals rubidium and cesium with the very bulky 2,6-dimesi-

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