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A Sleeping Beauty Finally Kissed to Life

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Markovnikov Free Radical Addition Reactions, a Sleeping Beauty Kissed to Life

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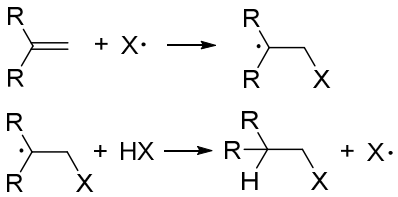
This review covers free radical additions, that are initiated by the formal addition of a hydrogen atom to a C=C double bond. These reactions originated in the realms of inorganic chemistry, polymer chemistry, and organic chemistry, whereby barriers between these disciplines impeded the rapid implementation of the findings.

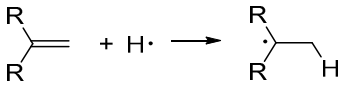
Introduction

Progress of science is sometimes frantic and hectic; sometimes it drags on over decades. The latter applies to the hydrogen atom additions to C=C-double bonds. Addition to C=C-double bonds are standard operations in organic synthesis in order to expand or functionalize a molecular skeleton. Examples constitute the edifice of teaching organic chemistry, comprising polar additions as well as free radical chain reactions. The addition of H-X (e.g. X = Br, SPh) to a C=C-double bond in a free radical chain reaction is carried by an X· radical and results in an anti-Markovnikov addition of H-X.[1]



Scheme 1 Anti-Markovnikov addition of H-X to alkenes

When one would consider the opposite regioselectivity, a Markovnikov addition, one would have to effect the addition of a hydrogen atom to the C=C-double bond [2] in a free radical chain reaction.



Scheme 2 Hydrogen atom addition to alkenes

Yet there was no need to develop such a reaction, given the classical polar addition of H-X to C=C-double bonds. It was therefore left to chance, that such a reaction was uncovered.

The Beginning out of the Blue Sky

Hydrogen atom transfer to a C=C-double bond was discovered in the context of studying transition

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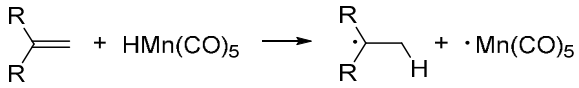
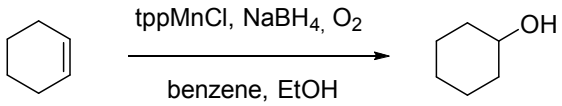
metal hydrides as catalysts in the hydrogenation of C=C-double bonds. In the late sixties it was speculated that hydrogenation of alkenes catalyzed by $Co(CN)_5^{3-}$ could involve the transfer of a hydrogen atom to the alkene.[3] Definite proof of a hydrogen atom transfer in the hydrogenation of α-methylstyrene catalyzed by $HMn(CO)_5$ was provided in 1977 by CIDNP studies by J. Halpern.[4] For a review see 5



Scheme 3 Hydrogen atom addition to alkenes effected by transition metal hydrides

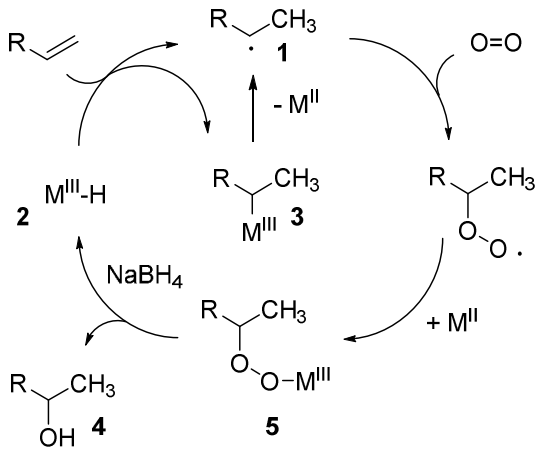
This finding, was noted by inorganic and polymer chemists, though, but did not draw attention from organic chemists.

Another entry into H-atom transfer reactions originated from studies to model NADH-dependent heme-containing dioxygenases. Thus in 1979 a system containing tppMnCl, $NaBH_4$, and oxygen was reported by Tabushi and Koga[6] to convert cyclohexene in 80 % yield to cyclohexanol.



Scheme 4 Catalytic oxidation/reduction hydration of cyclohexene; tpp = tetraphenylporphyrin

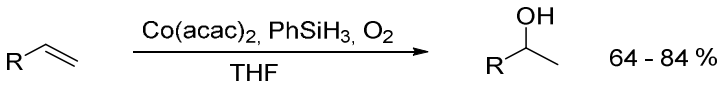
These conversions were extended in the early eighties from tppMnCl[7] to tppCo [8, 9] and to tppFeCl[10] showing the generality of this transformation. The reaction is triggered by a transition metal hydride (**2**) that either transfers a hydrogen atom directly to the alkene to generate the radical **1** in a single step, or via hydrometallation to **3** followed by homolysis of the weak metal-carbon bond.[9] The formation of an organometallic intermediate **3** has been postulated and observed in several instances.[11, 12] In any case, the overall transformation of the alkene to the radical **1** amounts to the addition of a hydrogen atom to the alkene. The subsequent transformation of **1** to the alcohol **4** corresponds to a standard autoxidation process.



Scheme 5 Mechanism of the catalytic oxidation/reduction hydration of alkenes

The Hibernating Phase

These results led to further studies in the steroid field.[13] Since organic chemists had very little overlap with the community of bioinorganic chemists, it was quite fortuitous that Teruaki Mukaiyama embarked on a systematic study of the catalytic oxidation/reduction hydration of alkenes.[14] Mukaiyama chose $Co(acac)_2$ as the metal component and used initially isopropanol[15] and later $PhSiH_3$ as hydride donors.[16] The resulting procedure has been applied to a variety of terminal alkenes.

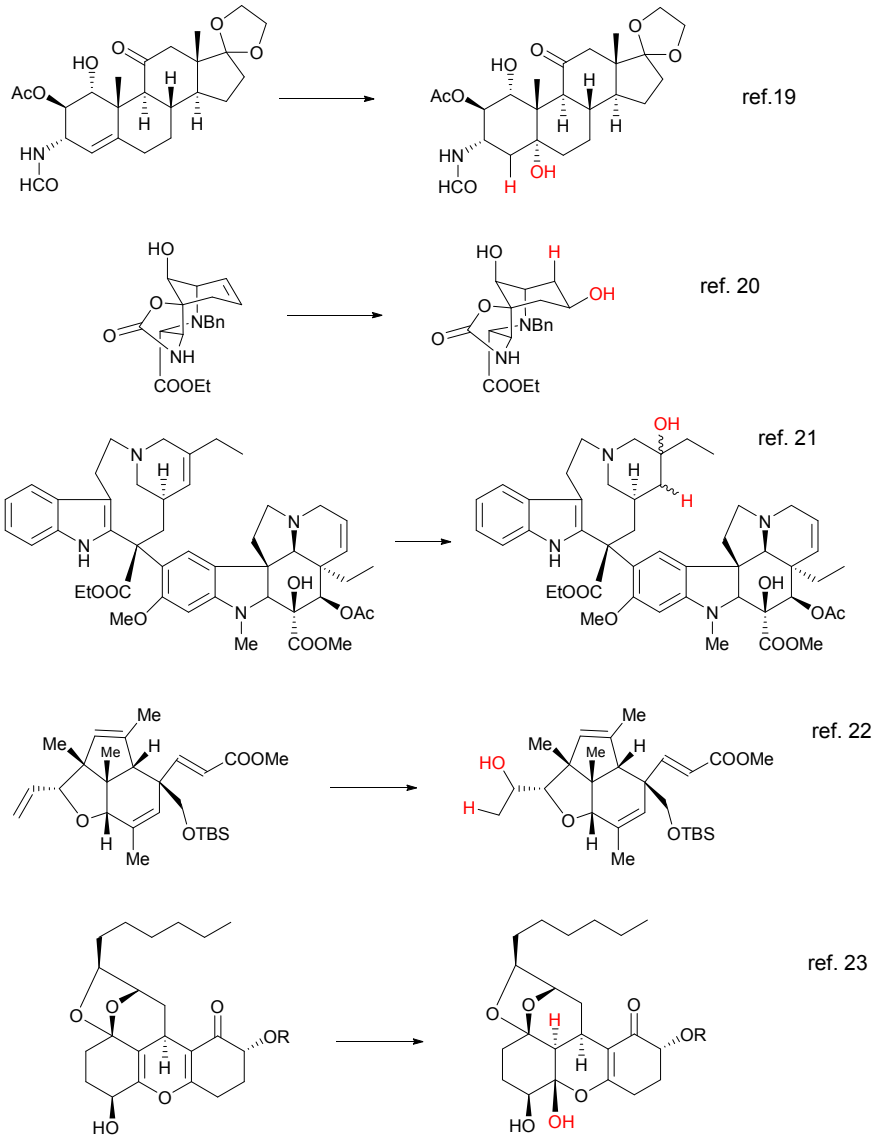


Scheme 6 Catalytic oxidation/reduction hydration of alkenes; acac = acetonylacetonato

The reaction has later been dubbed “Mukaiyama hydration of alkenes” demonstrating that its preceding chemistry had not been adequately recognized and acknowledged in the community. The reaction has been studied further in detail,[17] and additional variants have been developed during the early nineties.[11, 18] Yet, in the eyes of most organic chemists this reaction remained a not very exciting variant of the classical Markovnikov hydration of alkenes.

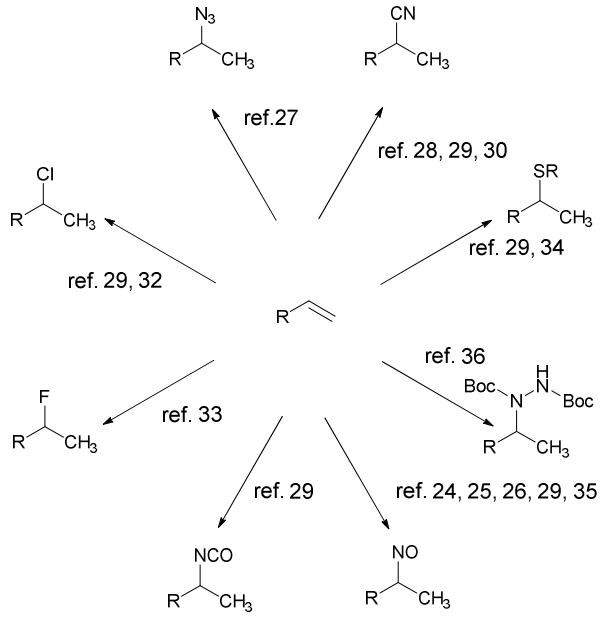
The Rise from Obscurity

While classical Markovnikov hydration requires quite harsh conditions, the catalytic oxidation/reduction hydration of alkenes proceeded under mild conditions and was compatible with a large variety of functional groups. It was this asset, that finally (by 2005) led to the adoption of this reaction by organic chemists in the late stages of complex natural product synthesis, cf. Scheme 7.



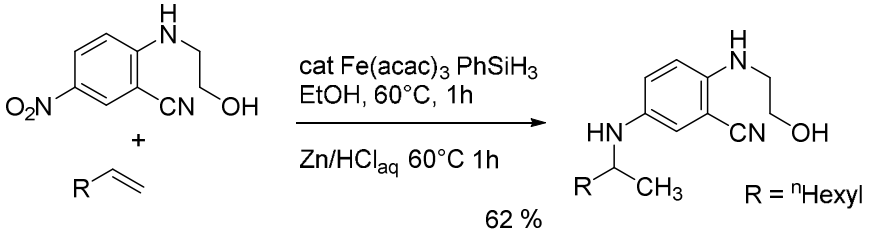
Scheme 7 Oxidation/reduction hydration of alkenes in natural product syntheses

The initiating step depicted in Scheme 2 opens up many more possibilities to functionalize an alkene beyond the hydration reactions in Scheme 6 and 7. Mukaiyama himself didn't explore these possibilities except for a hydronitrosation reaction.[24, 25, 26] The opportunities were rather used by each and every of the research groups that used the oxidation/reduction hydration of alkenes in natural product syntheses. These groups in rapid succession explored diverse hydro-functionalization reactions of terminal alkenes. In this vein hydroazidation[27] as well as hydrocyanation,[28, 29] – reactions without precedent – were developed cf. Scheme 8; for further examples see [30, 31].



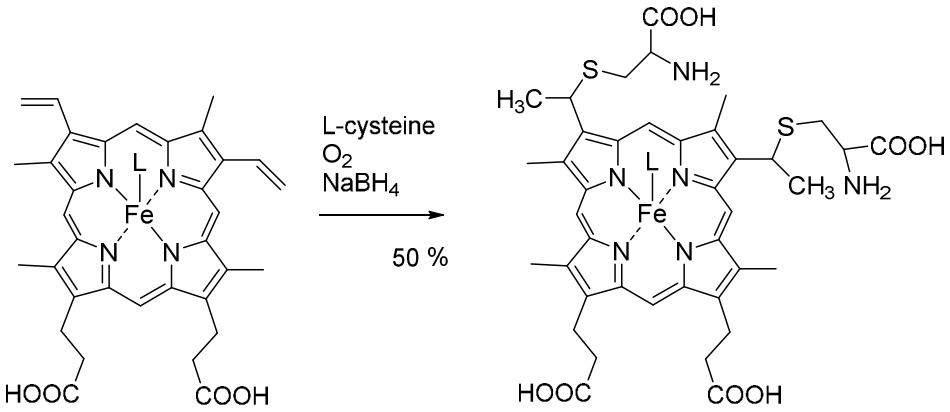
Scheme 8 Markovnikov hydrofunctionalization of alkenes

A spectacular case of a Markovnikiov hydroamination[37] is given in Scheme 9.



Scheme 9 Markovnikov hydroamination of alkenes by nitro compounds

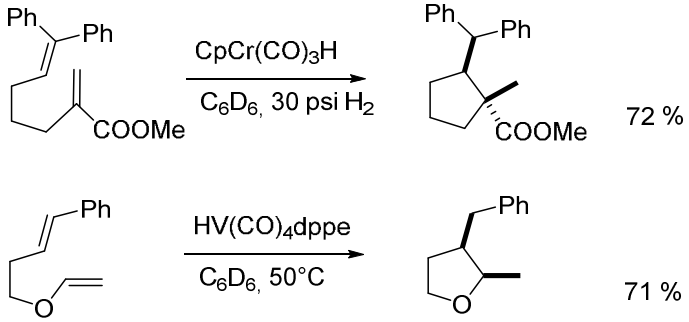
With respect to the historic side of these reactions, the paper by Kojo and Sano[38] merits special mention. The authors realized the transformation shown in Scheme 10, in which the substrate apparently served also as the catalyst.



Scheme 10 Hydrothiolylation of protohemin

The authors provided an interpretation, which is by and large the one presently accepted, cf. Scheme 5. The authors thereby essentially preempted in 1981 the later developments collected in Scheme 8. They published their findings with the programmatic title “A Markownikoff-type Radical Addition Reaction” in a mainstream journal of organic chemistry. All the more, it is shocking that this work drew only eight citations in the 33 years that followed.

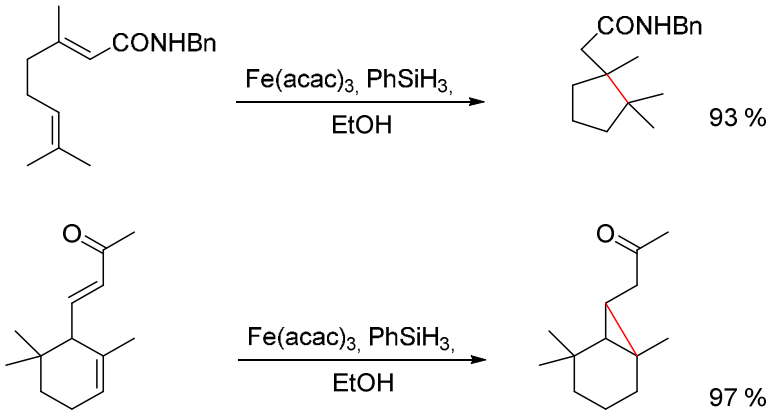
The free radicals that are generated by H-atom transfer to a C=C-double bond (Scheme 2) may not only add to heteroatom-radicophiles (cf. Scheme 8). Intramolecular addition to nearby placed double bonds may result in cyclization reactions. These have been studied initially by the Norton group.[39, see also 40, 41]



Scheme 11 Ring formation initiated by H-atom transfer to C=C-double bonds; dppe = bis-diphenylphosphino-ethane

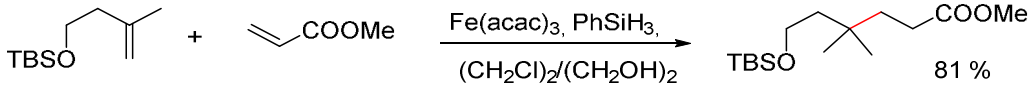
As the substrates for these cyclizations have two C=C-double bonds, proper initiation requires chemoselective transfer of the H-atom to a distinct double bond. The necessary basic information regarding rates of H-atom transfer from different H-atom donors and to different H-atom acceptors had been collected by the Norton group early on.[5, 42]

The addition of carbon-centered radicals to a C=C-double bond has an early transition state in which the forming bond is still being long.[43] These additions therefore allow the formation of bonds between quaternary centers, as illustrated in Scheme 12, i.e. of strained ring systems. Here the initiation via H-atom transfer comes especially handy. [41, 44]



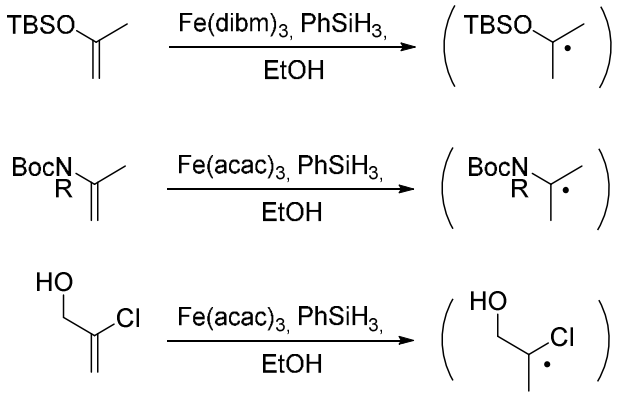
Scheme 12 Formation of strained rings initiated by H-atom transfer to C=C-double bonds

*Intra*molecular addition to C=C-double bonds of the radicals generated by H-atom transfer was soon followed by the *inter*molecular counterpart;[44] Scheme 13.



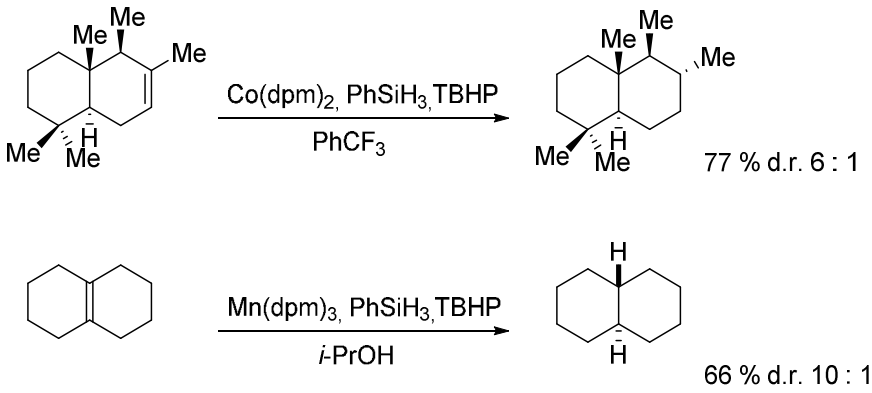
Scheme 13 Formation of quaternary centers by H-atom transfer initiated radical addition reactions

At this point, the generality of this reaction scheme to address fundamental skeleton building steps in organic synthesis becomes obvious. There comes a bonus along: C=C-double bonds carrying heteroatom substituents may serve as H-atom acceptors. Enol ethers, enamides, or vinyl halides thereby become precursors to nucleophilic α-substituted radicals. This transformation is equivalent to an umpolung of the enol ethers or enamides facilitating in the end by addition to α,ß-unsaturated carbonyl compounds the formation of 1,4-difunctionalized molecular skeletons,[45] a substitution pattern not readily attained otherwise; Scheme 14.



Scheme 14 Generation of nucleophilic radicals by H-atom transfer to hetero-substituted double bonds; dibm = diisobutyrylmethane

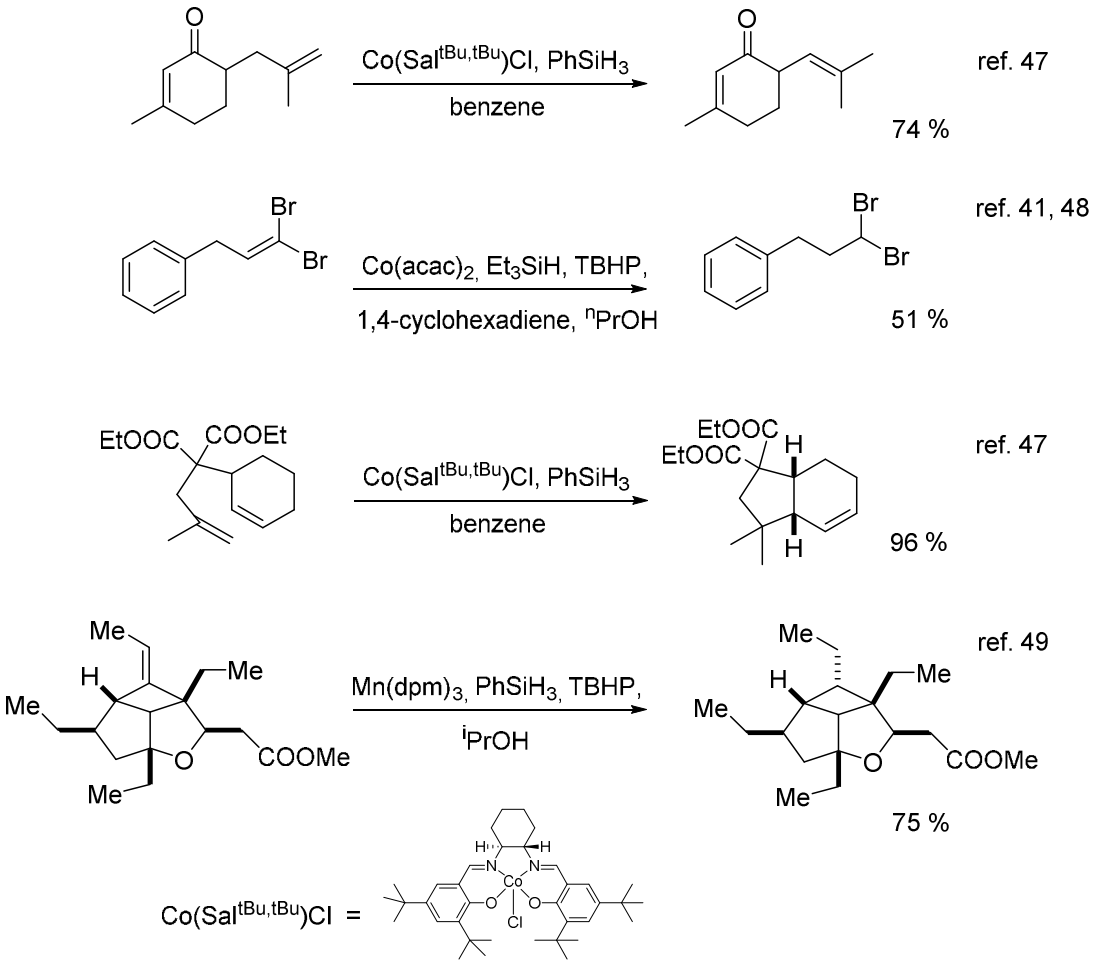
A novel reaction such as H-atom transfer to C=C-double bonds becomes invaluable to chemistry if it allows transformations which could not otherwise be attained in a simple manner. This holds for certain features of the hydrogenation of C=C-double bonds initiated by H-atom transfer.[41] Consider an endocyclic C=C-double bond. H-atom transfer to this double bond generates a carbon-centered radical (cf. Scheme 2), which is configurationally undefined. It adopts a configuration, in which all substituents take up the thermodynamically most stable conformation, before a second hydrogen atom is attached. Overall, a diastereoselective hydrogenation of an endocyclic double bond is realized that provides predominantly the thermodynamically more stable diastereomer. This means, that on hydrogenation of a methyl-cyclohexene substructure, the methyl group will end up in the equatorial position. This means that a $\Delta^{9,10}$-octalin substructure will be hydrogenated to a *trans*-decaline. Moreover, this type of hydrogenation does not touch carbon-iodine-, carbon-sulfur-, or benzylic-heteroatom bonds;[41] Scheme 15.



Scheme 15 Diastereoselective H-atom transfer initiated hydrogenation of double bonds

Hydrogen-atom transfer to generate carbon-centered radicals, the sleeping beauty, has now been kissed to full life. These reactions have become an actively pursued area of research,[46] the frontiers

of which constantly expand. This can be taken from the recently published applications to the specific translocation of terminal C=C-double bonds,[47] to the selective hydrogenation of vinylic halides to haloalkanes,[41, 48] to the cycloisomerizations of 1,6- and 1,7-dienes,[47] or to stereoselective hydrogenation;[49] Scheme 16.



Scheme 16 Recent applications of H-atom transfer initiated reactions; dpm = dipivaloylmethane

Epilogue

Looking back at the development of the Markovnikov Free Radical Addition Reactions one cannot avoid noticing a decades-long induction period. Induction periods in chemical reactions may be caused by the (intended or coincidental) presence of an inhibitor. Are there material or immaterial inhibitors responsible for an induction period in the progress of science? Progress of science is fostered by a flux of information between individual scientists. Unfortunately, there are barriers, which inhibit such exchange of information. Such barriers result e.g. from man-made compartmentalization of scientists, called specialization!

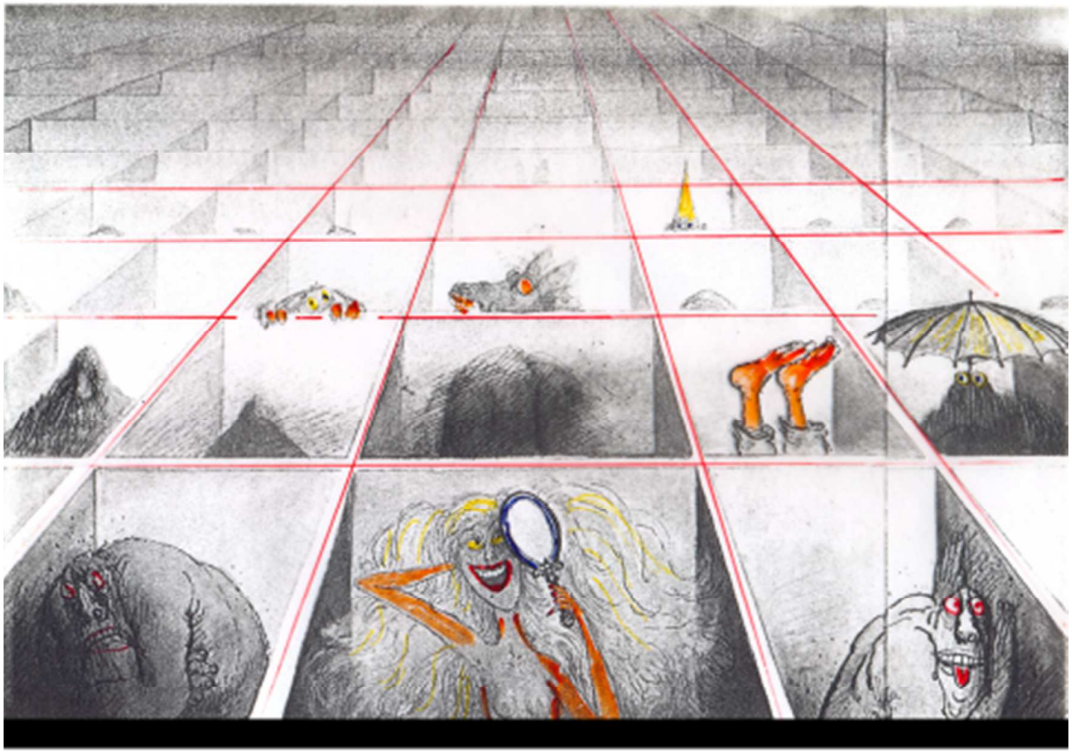


Fig. 1 Detail from **Ronald Searle**: “People”, reprinted by kind permission of The Ronald Searle Cultural Trust and The Sayle Literary Agency © 1978.

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