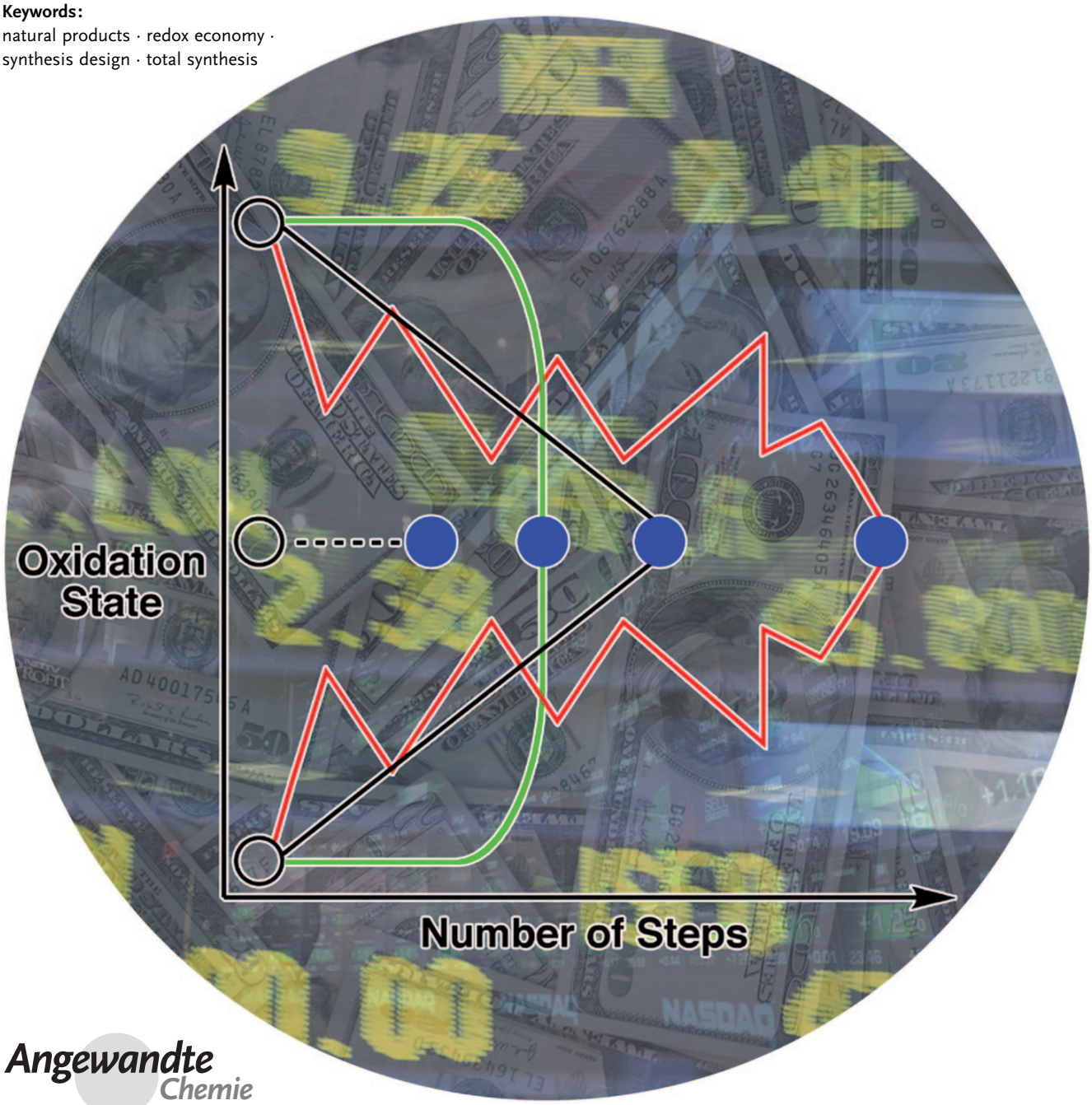
DOI: 10.1002/anie.200806086

Synthetic Methods

Redox Economy in Organic Synthesis

Noah Z. Burns, Phil S. Baran, and Reinhard W. Hoffmann**

Keywords:
natural products · redox economy · synthesis design · total synthesis



"Economy" is referred to as the thrifty and efficient use of material resources, as the principle of "minimum effort to reach a goal." More illuminating is: "the aim to portion one's forces in order to use as little as possible of them to reach a goal." Such statements certainly apply when the goal is to synthesize a complex target molecule. Redox economy then implies the use of as few redox steps as possible in the synthetic conquest of a target compound. While any sort of economy will help to streamline the effort of total synthesis, redox economy addresses a particularly weak area in present-day total synthesis. It is not enough to point out the present deficiencies, rather the purpose of this Review is to serve as a teaching tool for all practitioners of the field by giving and illustrating guidelines to increase redox economy in multistep organic synthesis.

From the Contents

1. Introduction

Synthesis in the 21st century is addressing more and more complex target structures. In order to attain a rapid increase in complexity during a synthesis, the overall efficiency of the synthetic sequence gains heightened attention. The most efficient synthesis, the "ideal synthesis," has been defined by Hendrickson:[1] "*The ideal synthesis creates a complex skeleton … in a sequence only of successive construction reactions involving no intermediary refunctionalizations, and leading directly to the structure of the target, not only its skeleton but also its correctly placed functionality.*"

Hendrickson realized that the only indispensable steps in a synthesis are those that form the molecular skeleton. The later introduced concepts of atom economy[2] and step economy[3] have provided important conceptual tools in the planning and analysis of a target-oriented synthesis. Minimizing the total number of steps as well as the use of superfluous atoms lays a foundation for achieving overall efficiency. Unnecessary steps could be avoided if one succeeds in the skeleton-forming reactions to generate the functionality required to carry out the next step or to have such functionality already present. The introduction and later removal of protecting groups could be rendered obsolete if all the skeleton-forming reactions could be carried out in a chemoselective fashion. In line with these considerations, protecting group free synthesis has been put on the agenda of organic synthesis in the 21st century.[4,5] Attention then turns to the avoidance of the remaining refunctionalization steps, which for the most part are oxidation and reduction reactions. This requires one to address *redox economy*[6] in synthesis planning, an aspect that is less well appreciated. In addition to the seminal work of Hendrickson, Evans has been a pioneer in this conceptual arena and has pointed out in several lectures the benefits of a regular increase in oxidation state during a convergent assemblage process.[7] Redox economy refers to the endeavours to reduce the number of non-strategic (those that do not set stereochemistry or are not skeleton-building) or corrective oxidation and reduction steps in synthesis, not only because these steps lower the overall efficiency of a synthesis,[8] but also since many redox reactions are difficult to scale up in industrial settings and are frequently the source of noxious byproducts and environmental problems. In addition, traditional redox reactions such as the $LiAlH_4$-reduction or chromate oxidations are in many instances not chemoselective. This high reactivity can impair a variety of functional groups, requiring additional protection prior to their use. It becomes immediately clear that avoidance of chemo-unselective reactions allows for the reduction in the number of unnecessary redox or protecting group manipulation steps in synthesis.

Along these lines, one could postulate a synthesis sequence that is in the extreme devoid of any redox steps. Such synthesis schemes have been called *isohypsic*.[1,9] In fact there is a wealth of skeleton-forming reactions that do not change the oxidation state of the growing molecule. These encompass most transition metal catalyzed coupling reactions, olefin metathesis, most pericyclic reactions (cycloadditions and sigmatropic or electrocyclic rearrangements), traditional transition metal catalyzed or free-radical rearrangements, as well as hydration or dehydration reactions, to name some of the most pertinent. Thus, this toolbox offers many opportunities to attain isohypsic synthesis. Yet isohypsic synthesis may, as an extreme variant, not necessarily be the

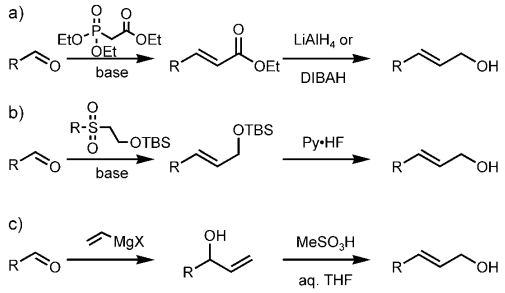
[*] N. Z. Burns, Prof. Dr. P. S. Baran
Department of Chemistry, The Scripps Research Institute
10650 N. Torrey Pines Road, La Jolla, CA 92037 (USA)
E-mail: pbaran@scripps.edu
Prof. Dr. R. W. Hoffmann
Fachbereich Chemie der Philipps Universität
35032 Marburg (Germany)
E-mail: rwho@chemie.uni-marburg.de

optimum solution. There are redox steps in a synthesis that are strategic, serving the priority goal of setting stereogenic centers; examples are the Noyori hydrogenation[10] or the Corey–Bakshi–Shibata reduction of ketones,[11] or the Sharpless dihydroxylation reaction.[12] It would be unwise not to take advantage of the potential that these reactions offer to generate a rapid increase in complexity during a synthesis. Accordingly, the concept of isohypsic synthesis provides an important reference point towards which syntheses should be optimized, but it is equally important to find the compromise with respect to other criteria for synthesis such as convergency or high stereoselectivity. Hence, redox economy searches for an acceptable optimum on the way to the utopian isohypsic extreme.

As the basic concepts of redox economy already exist in the literature, this Review does not purport the *invention* of such an idea. Rather, the purpose of this review is to bring to light these concepts within a framework that will be of utility to and stimulate discussion among practitioners of the field.

2. Tactics to Achieve Redox Economy

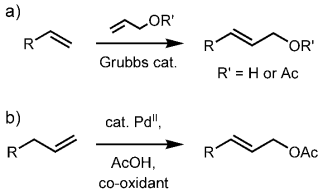
What are the situations that call for an improvement in redox economy? Consider—case (1)—an ubiquitous sequence in synthesis involving a redox step: the generation of terminal allylic alcohols by Horner–Wadsworth–Emmons olefination and reduction (Scheme 1a).



Scheme 1. Skeleton-extending routes to allylic alcohols. A list of abbreviations is provided at the end of this Review.

Are there redox-neutral[13] alternatives? At first one may turn to a carbonyl olefination reaction at the correct oxidation level (Scheme 1b).[15] Then, one can consider a vinylation followed by a rearrangement of the internal allylic alcohol to a terminal one,[16] a reaction related to the Meyer–Schuster reaction (Scheme 1c). While these alternatives are devoid of redox steps, neither of them reduces the number of steps as compared with the reaction of Scheme 1a. The absence of a $LiAlH_4$- or related reduction, though, may allow for the avoidance of protecting groups or refunctionalization elsewhere in the substrate.

Complete rethinking of the situation leads to a better way to access terminal allylic alcohols. Hendrickson[1] teaches us to introduce a functional group together with the skeleton-forming reaction. But the advantage gained in doing this will be lost when this functional group has to be protected and later deprotected during the subsequent course of the synthesis. It may therefore be advantageous (although not perfect) to construct the skeleton first and then to introduce the functional group in a separate step at a stage of the synthesis where protection of this functional group or other moieties may no longer be required. Following this line of thought two possible alternative exists: 1) alkene cross-metathesis[17] of a terminal olefin with allyl alcohol or allyl acetate (Scheme 2a); or 2) direct synthesis of terminal allylic acetates by palladium-catalyzed allylic oxidation (Scheme 2b).[18]



Scheme 2. Chemoselective routes to allylic alcohols.

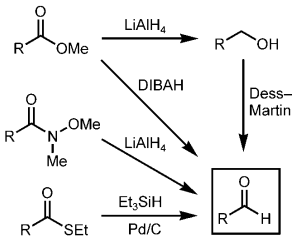
The importance of these transformations arises from their high functional-group tolerance. It is exactly in the context of streamlining syntheses that the significance of these works is established.[18c]

Redox steps accumulate in synthesis when—case (2)—accessing aldehydes, the preferred starting points for skel-

Reinhard W. Hoffmann studied chemistry from 1951 to 1958 at the University of Bonn, finishing with a doctorate under the guidance of Professor B. Helferich. Two years of postdoctoral studies at the Pennsylvania State University were followed by a second postdoctorate with Professor G. Wittig at the University of Heidelberg. There he started his independent research that led to his habilitation in 1964. Three years later he was appointed as Dozent at the Technische Hochschule Darmstadt. Since 1970 he has held a position as professor of organic chemistry at the Universität Marburg (emeritus status since 2001).

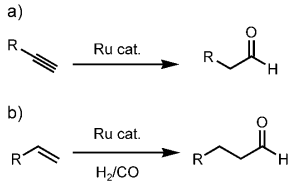
Phil S. Baran was born in New Jersey in 1977 and received his undergraduate education from New York University with Professor David I. Schuster in 1997. After earning his PhD with Professor K. C. Nicolaou at The Scripps Research Institute in 2001 he pursued postdoctoral studies with Professor E. J. Corey at Harvard until 2003 at which point he began his independent career at Scripps, rising to the rank of Professor in 2008. His laboratory is dedicated to the study of fundamental organic chemistry through the auspices of natural product total synthesis.

eton-forming reactions such as the Wittig reaction, aldol addition, or organometallic additions. Because of its high reactivity, the aldehyde function is usually generated immediately preceding the above skeleton forming reactions by either oxidation of primary alcohols or 1,2-diols or by transformation of an ester group, that is, by redox reactions. Conversion of an ester into an aldehyde is most common, but not without problems (Scheme 3). Direct conversion by a limited amount of DIBAH[19] is capricious to the point that this route is rarely used. Rather it is customary to reduce the ester with $LiAlH_4$ to a primary alcohol and to oxidize the latter in a subsequent step. This constitutes a sequence of two redox steps just to get the aldehyde function one needs!



Scheme 3. Generating aldehydes by refunctionalization.

In contrast to esters, Weinreb amides[20] or thioesters[21] can be readily reduced directly to aldehydes. Provided the Weinreb amide or thioester can be incorporated with the starting material, it is advisable to plan a synthesis with these acid derivatives instead of simple esters as latent aldehydes. But to enhance redox economy further it is attractive to consider other aldehyde precursors than acid derivatives. Here, the anti-Markovnikoff-hydration of alkynes[14,22] stands out (Scheme 4a). Likewise, the hydroformylation of alkenes[23] assumes a prominent position (Scheme 4b). Both reactions are compatible with a variety of functional groups.

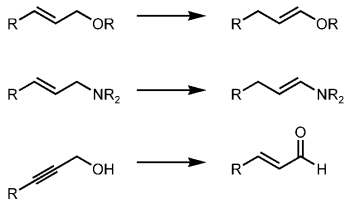


Scheme 4. Generating aldehydes by functionalization.

Noah Z. Burns received a BA in chemistry from Columbia University in 2004, performing research under the supervision of Professor James L. Leighton. He is currently a graduate student in the group of Professor Phil S. Baran at The Scripps Research Institute pursuing the total synthesis of marine alkaloids.

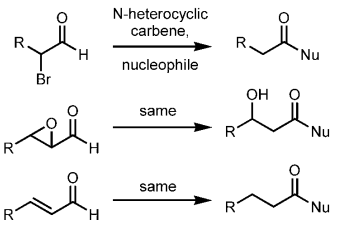
Moreover, hydroformylation reactions may frequently be carried out in tandem with the follow-up reaction of the aldehyde (such as Wittig reaction or imine formation), reducing the step count of a synthesis even further.

Coming back to redox economy, the above case studies illustrate how the number of redox steps in a synthesis may be reduced by proper choice of reactions or by proper choice of the sequence of reaction steps. Another way to reduce the number of oxidation or reduction steps in a synthesis is to turn to systems that may undergo refunctionalization by isomerization equivalent to internal redox reactions. Examples are olefin isomerizations that generate (latent) aldehyde functions, referred to as "redox isomerizations" by Trost (Scheme 5).[24]



Scheme 5. Isomerizations equivalent to internal redox reactions.

Such isomerizations complement the possibilities to resolve the problems associated with case (2) above. Internal redox reactions involving N-heterocyclic carbenes also open attractive routes for refunctionalization as seen in the examples in Scheme 6.[25] The details of such a process[26] are delineated in Scheme 7.

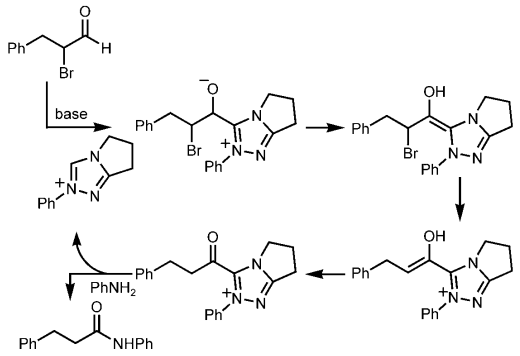


Scheme 6. N-heterocyclic carbene catalyzed internal redox reactions.

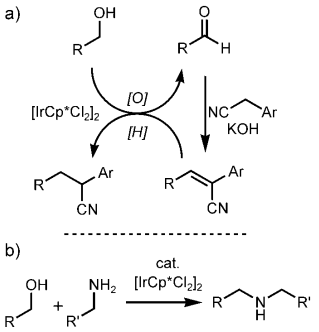
The two participating functional groups do not necessarily have to be conjugated. It suffices when a catalyst can reach them both as in a rhodium-catalyzed reduction–oxidation process (Scheme 8a).[27] Likewise, ruthenium-catalyzed intermolecular transfer hydrogenative coupling reactions are redox-neutral skeleton forming reactions (Scheme 8b).[28,29]

The Tishchenko reaction[30a] (Scheme 9a) as well as the Evans–Tishchenko reaction[30b] (Scheme 9b) are also examples of redox-neutral reactions for they couple either two aldehydes or an aldehyde with a β-hydroxy ketone by an internal hydride transfer.

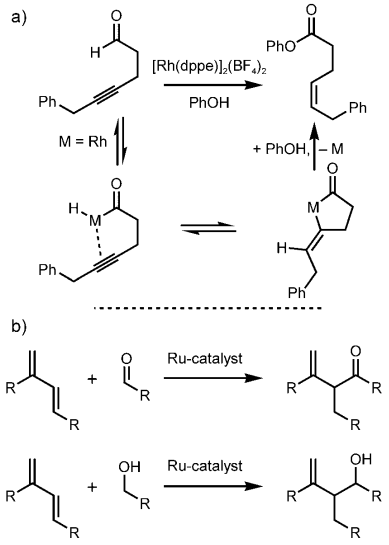
Equivalent to internal redox reactions are tandem reactions, in which oxidation and reduction steps are coupled. This



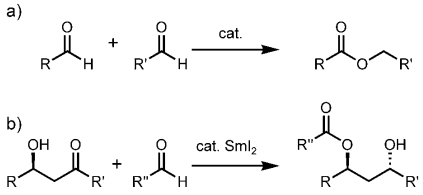
Scheme 7. Mechanism of an N-heterocyclic carbene catalyzed internal redox reaction.



Scheme 10. "Borrowing hydrogen" to avoid explicit redox steps.



Scheme 8. Transition-metal-catalyzed redox-neutral reactions.



Scheme 9. The redox-neutral Tishchenko and Evans–Tishchenko reactions.

is exemplified by the concept of "borrowing hydrogen"[31] as shown in the reaction between an alcohol and a nitrile to give a reduced and coupled product (Scheme 10a).[32a] This reaction involves the iridium-catalyzed oxidation of an alcohol to an aldehyde, base-mediated condensation to give an α,β-unsaturated nitrile, and subsequent reduction to the saturated compound catalyzed by the same iridium complex. The reaction sequence proceeds without a stoichiometric oxidation or reduction reagent because the redox steps are coupled by means of the iridium catalyst. The same catalyst and concept has been applied to the coupling of alcohols with amines, proceeding along a coupled oxidation–reductive amination pathway (Scheme 10b).[32b,33]

These transformations are distinctly isohypsic, yet their incorporation into a synthetic sequence does not automatically render that sequence redox-economic because one has to take into account all the redox steps that are necessary to generate the starting structures. Thus, it would be inappropriate to refer to a redox-neutral reaction (or any singular method) as redox-economic. Any particular reaction can either involve redox steps or be devoid of it. Redox economy is applied only in relation to a *multistep synthetic sequence*. There is a wealth of non-redox-neutral *construction* reactions that can introduce considerable complexity from simpler starting materials that could be applied in a redox-economic synthesis. This directly reflects advancement within the field of organic synthesis that has occurred over the past several decades. For example, Hendrickson made the statement that "*oxidative and reductive couplings … are rarely useful in synthesis since they are only effective for creating symmetrical dimers in intermolecular reactions.*"[1] While this may have been accurate in 1975, such a statement is far from the truth today. Redox coupling reactions have seen considerable improvement in recent years; there are countless examples of such reactions and their application in synthesis that clearly have not been covered in this Review, many of which could be or are topics of entire books (see Section 7). The purpose of this Review is not to comprehensively cover them or any methodology in particular, but rather to provide guidelines for increasing redox economy in the construction of molecules.

To summarize, a redox-neutral step (constructively powerful as it may be) does not necessarily make a synthesis redox-economic, nor does the application of redox steps render a synthesis non-redox-economic; both kinds of reactions can be utilized in a highly redox-economic synthesis assuming a non-circuitous derivation of starting materials and a judicious choice of complexity increasing disconnections. Redox economy is therefore achieved at the strategic and tactical level in multistep synthesis wherein the overall sequence is scrutinized with such considerations. This is illustrated in the discussion of complex molecular construction below.

3. Redox-Economic Syntheses

Note: In the synthesis examples traditional oxidation or reduction steps are highlighted in red while strategic oxidation or reduction steps are highlighted in blue.

Most complex target structures for organic synthesis contain carbon atoms at various levels of oxidation. Therefore, oxidation-state adjustment is likely to occur at some point in any synthesis. This will preclude a completely isohypsic synthesis. Redox economy in turn allows for a one-time oxidation-state adjustment of a carbon atom and frowns upon subsequent changes. This leads to the insight that "*the overall oxidation level of intermediates should linearly escalate during assembly of the molecular framework.*"[5,7] Inversely, a linear decrease in oxidation level (while more rare of a case) could be just as efficient. Such approaches should lead to the most redox-economic synthesis of complex target structures. A graphical representation of these ideas is shown in Figure 1 for a hypothetical synthesis from starting materials of varying oxidation state to a target of specified oxidation state.

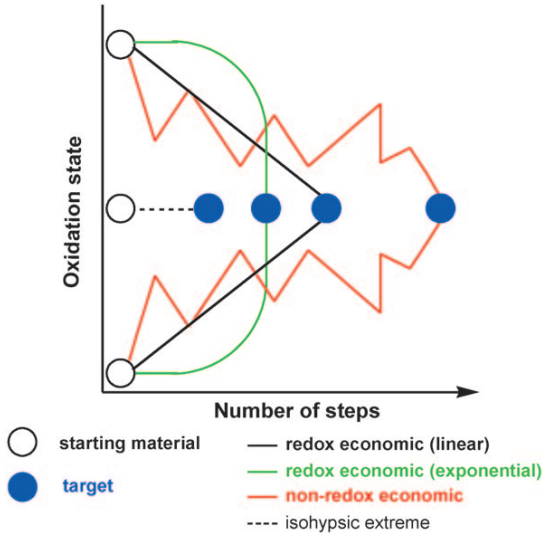
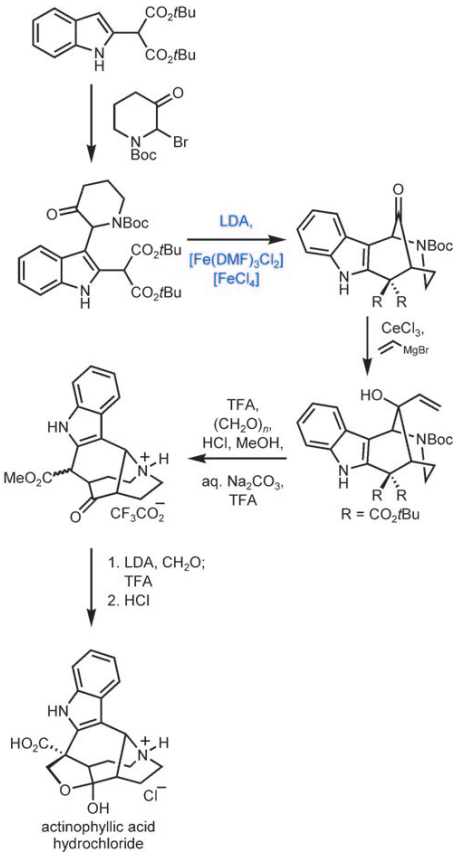


Figure 1. A schematic view of redox economy in a synthetic sequence inspired by Evans' lectures on the topic.[7]

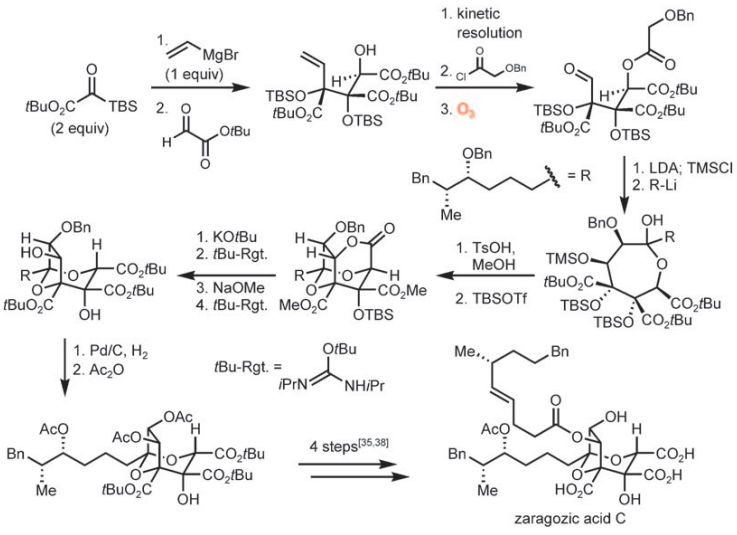
The benefit of applying the concepts of redox economy is to streamline syntheses of complex target molecules to an optimal point, approaching the ideal synthesis as defined by Hendrickson.[1] It is easy to demonstrate that efficient and short syntheses have a high level of redox economy as demonstrated by the near-isohypsic synthesis of actinophyllic acid by Overman et al. (Scheme 11).[34] In this synthesis, nearly every step is skeleton-building—the use of an oxidative intramolecular enolate coupling and aza-Cope–Mannich cascade are powerfully simplifying disconnections.

While it may be more difficult to document that adherence to redox economy will necessarily shorten a synthesis, an exemplary and nearly isohypsic example is



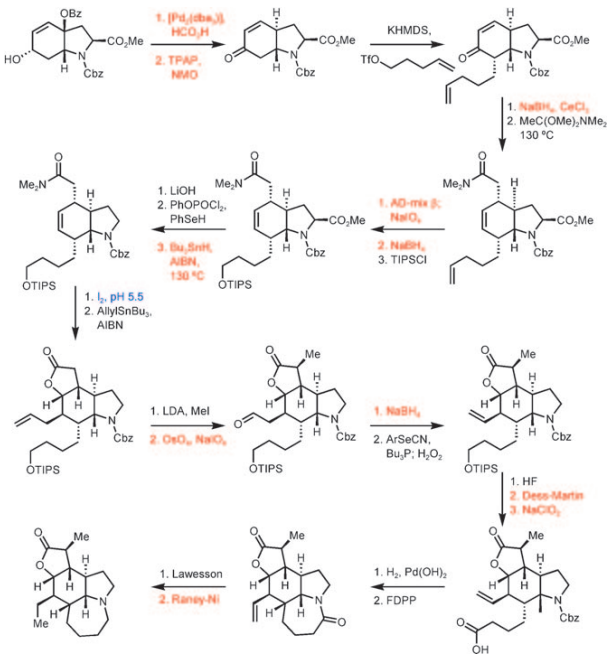
Scheme 11. A highly redox-economic synthesis of actinophyllic acid.

Johnson's recent synthesis of zaragozic acid C[35] (Scheme 12) that explicitly seeks to minimize oxidation state variance. It nicely demonstrates the hard-to-reach situation in which the oxidation level of the starting materials is chosen such that



Scheme 12. A virtually isohypsic synthesis of zaragozic acid C.

they can be carried over without additional redox interconversions into the product. Ultimately it occurs with *one* redox operation and in 18 steps overall. In comparison, three other syntheses of zaragozic acid C occur in 22 steps with eight redox operations,[36] 30 steps with 11 redox operations (one of which is strategic),[37] and 36 steps with 13 redox operations (two of which are strategic);[38] a synthesis of zaragozic acid A (which differs only in the side chains) occurs in 33 steps with eight redox operations (three being strategic).[39] This is additionally impressive in the case of such a highly oxidized target.

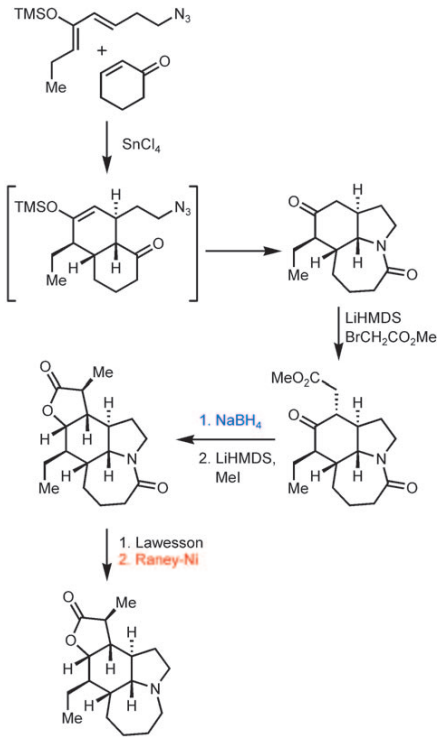


Scheme 13. The first synthesis of stenine.

Another convincing case for the advantage of adhering to the principles of redox economy is given by two syntheses of the alkaloid stenine. The first successful synthesis[40] shown in Scheme 13 had to break new ground. One can see how it sets up the substituent pattern of the central six-membered ring carefully layer by layer. In addressing each subtask in a separate manner the synthesis amasses a large number of redox adjustment steps.

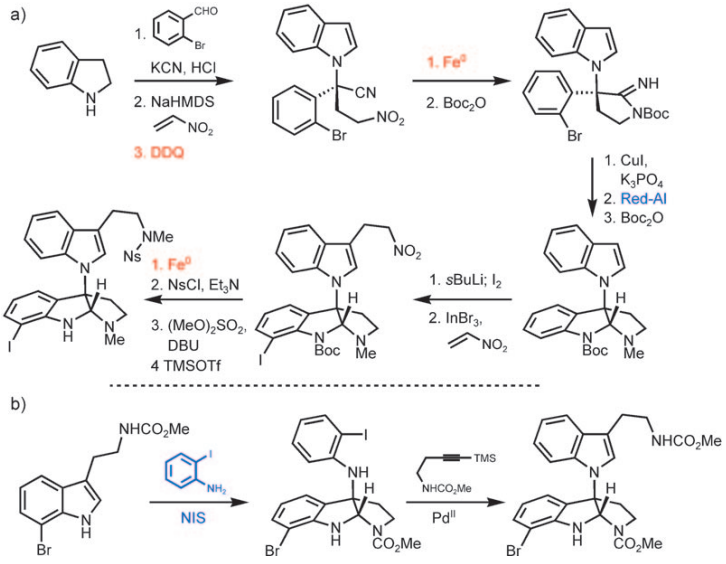
Ten years later in the 21st century it is the aim to carry out synthesis in a much more focused fashion, utilizing cascade reactions, and capitalizing on atom-, step-, and redox economy as well as protecting group free synthesis. All these attributes apply to the stenine synthesis[41] shown in Scheme 14. This recent synthesis of stenine succeeded with just two reduction operations, one of which was strategic.

The advantage of redox-economic synthesis also becomes clear on comparing two syntheses



Scheme 14. A 21st century synthesis of stenine.

that target a unique structural motif in strategically similar ways. This is shown for the case of similarly advanced psychotrimine precursors in Scheme 15. Both Takayama et al. (Scheme 15a)[42] and Baran (Scheme 15b)[43] chose to introduce the hallmark (indole N1)–(indole C3) bond in the first step of their total syntheses. However, the large number of redox manipulations in the former case renders this route far less efficient.

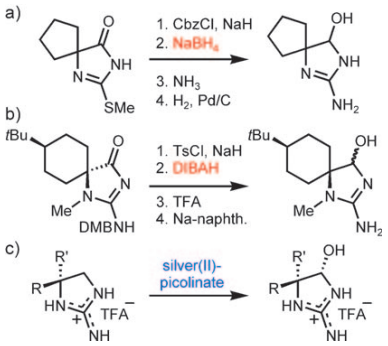


Scheme 15. Key steps from two psychotrimine syntheses.

4. Guidelines: Linear Increase/Decrease in Oxidation Level

Any overshooting in the oxidation level of a functional group (as in Scheme 1) requires a redox-adjustment immediately or at a later stage. To avoid this, it is advisable to change the oxidation level of a carbon atom only gradually to just reach the desired oxidation level but not more or less. Moreover, it is advisable to effect this oxidation as late as possible in the synthesis sequence because this offers the chance to prevent the necessity of having to protect this (or another) functional group during the subsequent steps. Such an approach is illustrated by comparing the routes to the spiro-hydroxyimidazoline ring in the axinellamines.

In the first approach by Overman and Lanman (Scheme 16a)[44] the starting point is an imidazolinone, a moiety in which the oxidation level has to be reduced. In

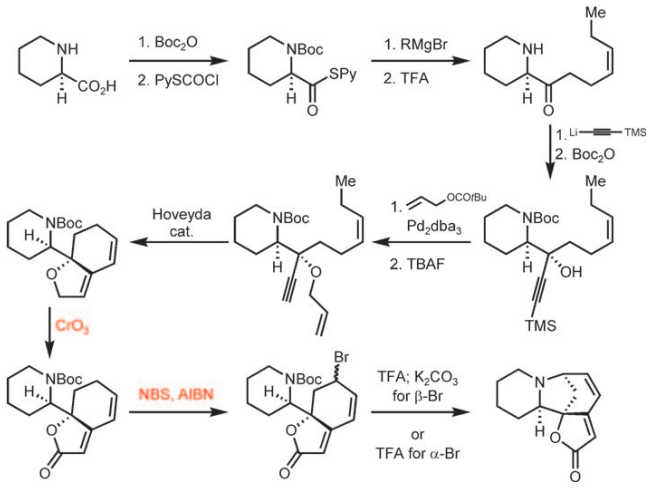


Scheme 16. Approaches to the spiro-hydroxyimidazoline ring of the axinellamines.

order to achieve this, a protecting group (benzyloxycarbonyl) had to be introduced and subsequently removed. In the subsequent approach by Romo and Tang (Scheme 16b)[45] again an N-protected amino-imidazolinone served as the starting point. To effect the required reduction, the other nitrogen had to be blocked by a tosyl group. All in all, what appeared initially as a simple reduction required three additional protecting group management steps!

Scheme 16c refers to the actual axinellamine synthesis by Baran et al.[46a] Here the oxidation level of the imidazoline ring was kept low throughout the major part of the synthesis. Only three steps before the end, the imidazoline was oxidized to the spiro-hydroxyimidazoline. The success depended on the fortuitous discovery of the proper oxidizing agent, silver picolinate, which neither led to overoxidation, nor did it require any protecting groups elsewhere in the axinellamine structure.[46b]

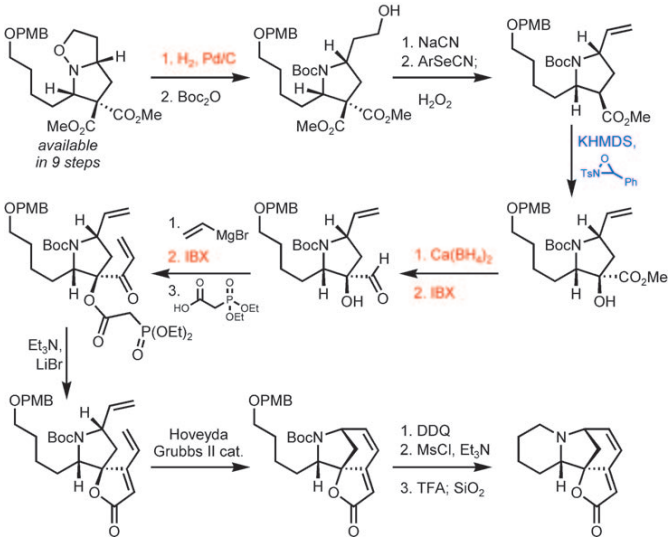
The introduction of a functional group by a separate oxidation step does not meet the Hendrickson criteria of an ideal synthesis, rather it reflects a compromise with respect to the present state of the art of organic synthesis; it is thus certainly preferable to introduce a functional group late in the synthesis by a separate step as opposed to having it generated in a skeleton-building step early in the synthesis and subsequently posing chemoselectivity issues. Two syntheses, one of allosecurinine and the other of its naturally occurring enantiomer, viroallosecurinine, illustrate the advantage of a late placement of oxidation steps. The first one of viroallosecurinine (Scheme 17)[47] assembles major parts of the skeleton first with the two sole oxidation steps preceding the final ring closure reaction.



Scheme 17. Total synthesis of viroallosecurinine.

The second synthesis (Scheme 18)[48] builds on a longer method-oriented route to the starting point. It then enters a sequence of refunctionalization steps to access first a vinyl ketone and then the butenolide substructure. The synthesis is concluded by ring-closing metathesis followed by traditional closure of the piperidine ring.

The comparison of the two syntheses emphasizes the greater focus of the first approach, allowing for a rapid increase in complexity by the enyne-metathesis before linearly increasing to the correct oxidation state. The second

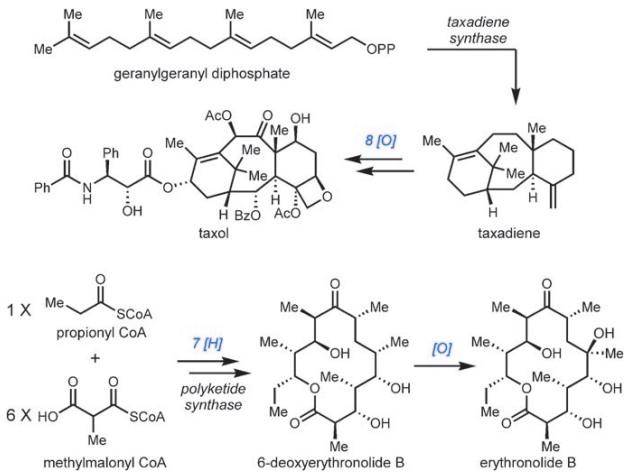


Scheme 18. Total synthesis of allosecurinine.

approach, in contrast, runs through a sequence of redox reactions. The attendant lower redox economy detracts from this synthetic approach to the securina alkaloids.

5. Guidelines: Biomimetic Approaches

Nature exhibits near perfect redox economy in its selective synthesis of natural products while not necessarily adhering to the isohypsic extreme. Two representative biosyntheses of the natural products taxol and erythronolide B are shown in Scheme 19. In the case of taxol, geranyl-

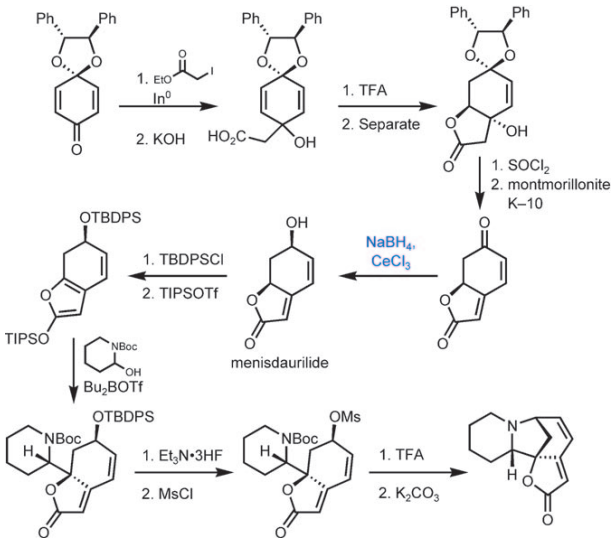


Scheme 19. Comparative linear increase or decrease of oxidation state in natural-product biosynthesis.

geranyl diphosphate is converted by taxadiene synthase to the tricycle taxadiene.[49] This core is then linearly oxidized at eight carbons by a number of cytochrome P450-dependant enzymes to taxol. Erythronolide B provides an example of the inverse case wherein propionyl CoA and six methylmalonyl CoA units are joined together by a polyketide synthase in a sequence involving carbon–carbon bond formation steps interspersed with seven reductions to produce 6-deoxyerythronolide B.[50] In polyketide synthesis, nature thus uses a sequence of linear reduction to set the correct oxidation state as well as the relative stereochemistry. A further cytochrome P450-dependant hydroxylation sets the C-6 oxidation state stereospecifically.

Applying known (or implied) biosynthetic lessons towards natural products in the laboratory (i.e. biomimetic total synthesis) should therefore be redox-economic at least for that part of the synthesis that is patterned after nature's precedent.

Staying with the syntheses of allosecurinine, this is demonstrated by a recent biomimetic synthesis[51] shown in Scheme 20 that proceeds via menisdaurilide, the presumed biogenetic precursor of allosecurinine. The synthesis of menisdaurilide starts from quinone as a cheap building block.[51a] Accordingly one carbon atom

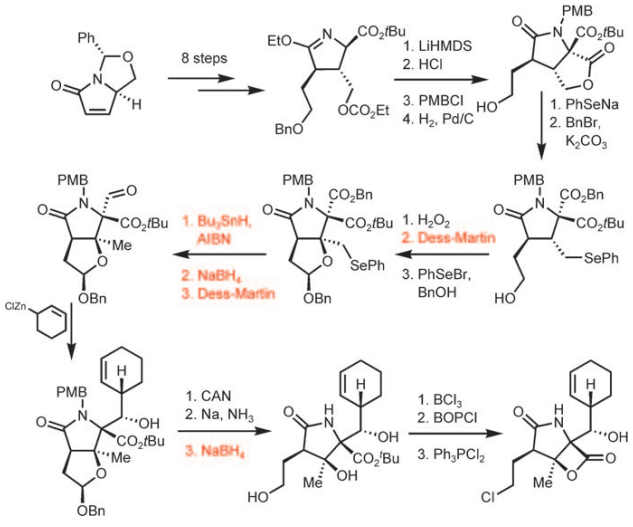


Scheme 20. Biomimetic total synthesis of allosecurinine.

was too high in oxidation level and had to be reduced in the last step towards menisdaurilide. The subsequent biomimetic conversion of menisdaurilide into allosecurinine[51b] did not require any further redox operations. This synthesis is thus equally effective as the one shown in Scheme 17.

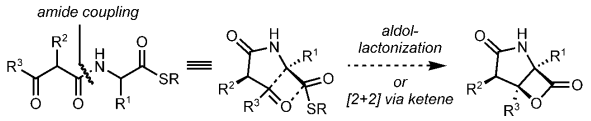
A further example is given by the syntheses of salinosporamide A, a compound that is challenging because of its high level of oxygenation, the presence of five contiguous stereogenic centers (two of them quaternary), and the presence of the sensitive β-lactone functionality. Initial synthetic efforts towards salinosporamide A focused on the stereochemical issues. An impressive solution to generate the two adjacent quaternary stereocenters is presented in Scheme 21.[52]

This synthesis is characterized by five skeleton-forming steps, seven redox operations, and nine protecting group



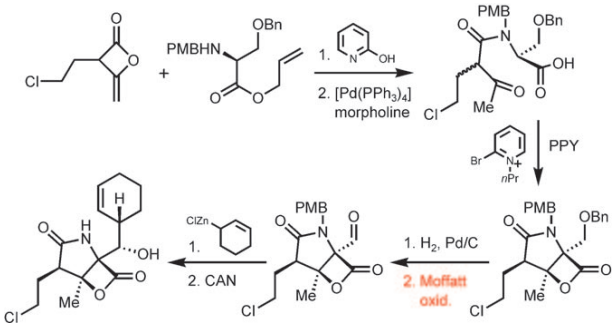
Scheme 21. An impressive stereochemical solution to salinosporamide A.

management steps. However, nature appears to generate salinosporamide and related structures in a more straightforward manner, as the proposed[53] biosynthesis pathway implies (Scheme 22).



Scheme 22. Proposed biogenesis of salinosporamide A.

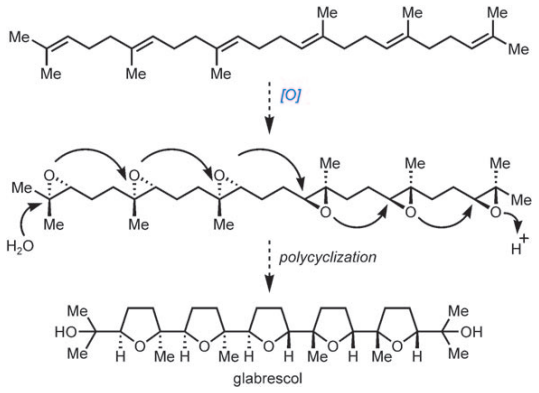
This scheme served as a guideline to devise a biomimetic synthesis of salinosporamide A, resulting in a suprisingly direct synthesis of this target (Scheme 23)[53] that has only a single controlled oxidation step and manages with just three protecting-group operations.



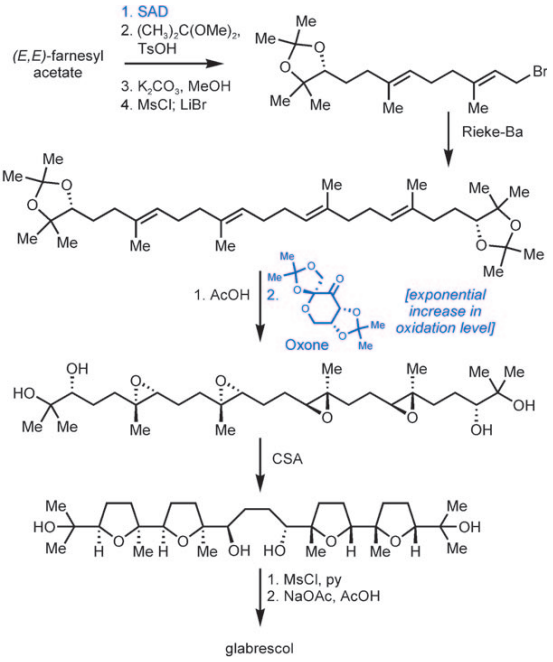
Scheme 23. Biomimetic total synthesis of salinosporamide A.

A further interesting case is given by the syntheses of glabrescol, whose biosynthesis may occur[54] by a hexaepoxidation of squalene to give a distinct stereoisomer (Scheme 24). A cyclase may then convert this intermediate in one operation into glabrescol.

A synthesis following this lead by Corey et al. managed to reach the goal with just two oxidation steps[55] (Scheme 25), one of which may be viewed as an *exponential* increase in oxidation level.



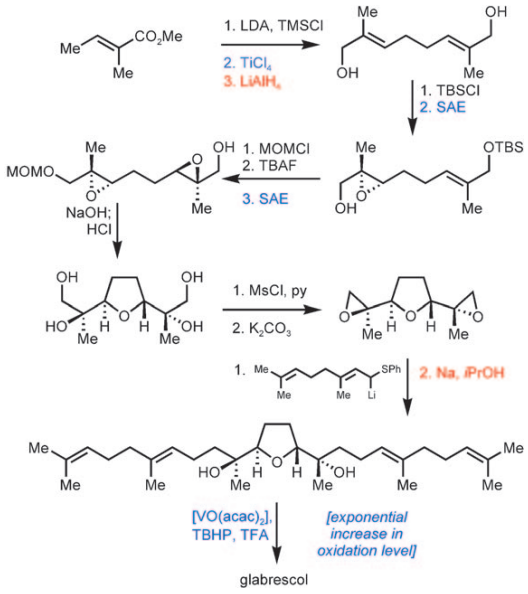
Scheme 24. Proposed biogenesis of glabrescol.



Scheme 25. Biogenesis-inspired synthesis of glabrescol.

A synthesis of glabrescol which adhered less to the proposed biogenesis turned out to be substantially longer (Scheme 26) requiring two reduction and three oxidation steps.[56]

The examples shown in Schemes 20, 23, and 25 demonstrate that a biomimetic synthesis offers the chance of achieving a high level of redox economy.

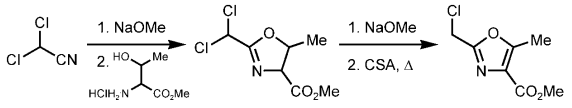


Scheme 26. A second total synthesis of glabrescol.

6. Redox Economy in Process Research

Arguably the greatest practitioners of redox economy are process chemists who, often in the quiet of the patent literature, develop remarkably elegant syntheses of small molecules. While medicinal chemistry routes tend to focus more on diversification and speed in order to find potential leads, the process chemist must take these routes (or start over from scratch) and develop one based on atom, step, and redox economy.

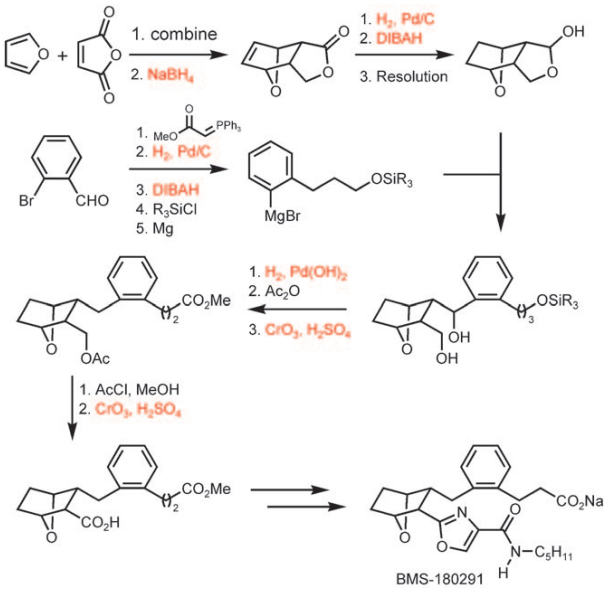
In process studies on GW475151, a creative isohypsic approach to a functionalized oxazole was developed. As opposed to synthesizing the heterocycle by redox methods, the researchers had the required oxidation state within the starting materials and then performed an "oxidation state transfer" through the molecular skeleton (Scheme 27).[57]



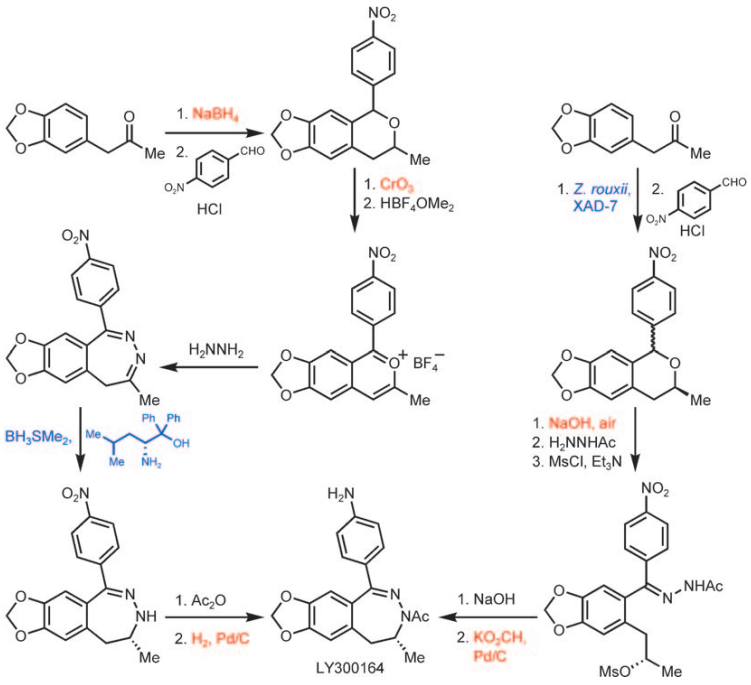
Scheme 27. A transfer of oxidation state in oxazole synthesis.

Researchers at Eli Lilly required a process-scale synthesis of LY300164, a drug candidate for the treatment of epilepsy and neurodegenerative disorders. The modified discovery route (Scheme 28, left) circuitously sets up the oxidation state of the benzodiazepine, twice readjusting that of the carbonyl carbon of the starting material. After its reduction and oxidation, a chiral auxiliary-mediated reduction, while strategic in setting the sole stereocenter, then reduces this same carbon. The process route (Scheme 28, right) stereoselectively reduces the carbonyl in the first step, obviating further adjustment. This avoidance of unnecessary redox manipulations allowed the process chemists to raise the yield from 14% to 55% overall.[58]

The original synthesis of an intermediate en route to BMS-180291, a thromboxane A2 receptor antagonist, is shown in Scheme 29.[59] The excessive use of redox manipulations (8 shown) resulted in an unacceptable 3% overall yield. The oxidation state of the carboxylic acid in the final intermediate is of particular note, for while it is already at the correct level in the starting maleic anydride the initial route carried it through the synthesis at the alcohol oxidation level.



Scheme 29. Original synthesis of a BMS-180291 intermediate.



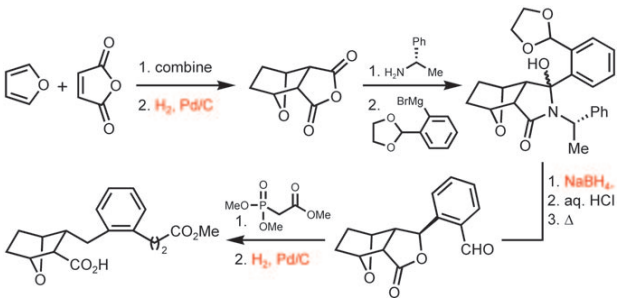
Scheme 28. Modified discovery (left) and process routes (right) to LY300164.

The process route is able to reduce the number of redox steps to three by chemoselectively manipulating only one of the anhydride carbonyls and performing a simultaneous olefin and benzylic alcohol hydrogenation in the final step (Scheme 30).

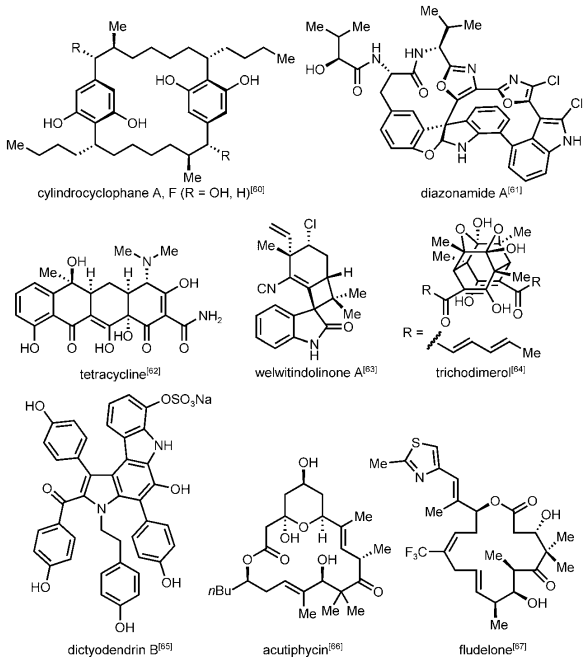
7. Suggested Further Reading

As the purpose of this Review is to serve as a teaching tool rather than as an encyclopaedic coverage of all redox-economic methodology and synthesis, numerous examples have clearly been overlooked. The reader is encouraged to further critically analyze the literature through the redox economy filter presented here. Selected targets of redox-economic total synthesis are shown in Scheme 31.

In the realm of transition metal catalyzed cross coupling, direct bond formation without the need for prior functionalization (i.e. by halogenation or stoi-



Scheme 30. Process synthesis of a BMS-180291 intermediate.



Scheme 31. Suggested further total-synthesis reading.

chiometric metalation) is redox-neutral,[68] as is the entire burgeoning field of C H activation[69] as well as directed metalation.[70] The application of gold catalysis is predicated on the metal's reluctance to participate in oxidative addition and reductive elimination cycles and is clearly of high utility in skeleton-building reactions.[71] Redox-economic syntheses could clearly result from the appropriate incorporation of such reactions.

8. Putting Redox Economy to Practice

How does one put the ideas of redox economy to use in the planning and execution of a total synthesis? According to Corey: "*Cycles of perception and logical analysis applied reiteratively to a target structure and to the 'data field' of chemistry lead to the development of concepts and ideas for solving a synthetic problem.*"[72] In order to have such a solution turn out to be redox-economic, four specifics should be considered and iteratively applied in such a cycle:

- One should seek to use redox-neutral *reagents* to accomplish reaction(s) on the same starting material, such as choosing the Ir-catalyzed transfer reductive amination of an alcohol[32b] mentioned earlier as opposed to a traditional two-step oxidation followed by reductive amination. Each redox step in a planned synthesis should then be analyzed as to whether reagents exist that could make the redox step unnecessary.
- Redox economy should be applied *tactically* by examining slight changes in the starting materials. The result would not be a drastic rewriting of the synthetic analysis. For example, this could mean the application of cross-metathesis or allylic oxidation methodology as mentioned previously to obtain a terminal allylic alcohol without starting from an aldehyde.
- *Choreography* must be scrutinized in order to optimally introduce functionality and avoid chemo-unselective reactions that may require protection or oxidation state adjustment. The glabrescrol example showcases intelligent choreography in the polyepoxidation step that reduces the number of epoxidation steps to one.
- The most drastic maximization of redox economy (and most difficult to plan a priori) can occur through examining *connectivity* and choosing challenging and unprecedented retrosynthetic disconnections that drastically simplify the forward plan without superfluously altering the oxidation state of starting materials or products. The invention of a direct indole–aniline coupling for the total synthesis of psychotrimine[43] is an example of such an approach.

9. Summary and Outlook

The pursuit of redox economy will have a considerable impact on the practice of organic synthesis. The economics of synthesis planning and analysis can be simultaneously examined from the vantage point of atom, step, and redox manipulations. In atom economy[2] the goal is to minimize wasteful steps and encourage the use of catalysis to efficiently generate molecular frameworks. In step economy,[3] a more "macroscopic" view of the entire synthesis is taken and a general reduction in the number of steps is encouraged through the use of powerful reactions and strategies that build up complexity as rapidly as possible. The goals of redox-economic syntheses are to minimize unnecessary non-strategic redox manipulations within a synthesis. When the oxidation state of intermediates changes, it should do so in a linear (or exponential) fashion and steadily increase or decrease throughout the course of the synthesis without overshooting the goal and requiring an extra redox step. An ideal synthesis should benefit from the concepts and principles espoused by all three economies. A conscious adherance to these principles in the planning stages of a synthesis will foster an innovative and invention-driven approach to total synthesis.

Abbreviations

Ac	acetyl
acac	acetylacetonyl
AIBN	2,2′-azobis(2-methylpropionitrile)
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bz	benzoyl
CAN	cerium(IV) ammonium nitrate
cat.	catalytic
Cbz	benzyloxycarbonyl
CoA	coenzyme A
Cp	cyclopentadienyl
CSA	camphorsulfonic acid
dba	1,5-diphenyl-1,4-pentadien-3-one
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
Dess–Martin	1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1*H*)-one
DIBAH	diisobutylaluminum hydride
DMB	3,4-dimethoxybenzyl
dppe	1,2-bis(diphenylphosphino)ethane
FDPP	pentafluorophenyl diphenylphosphinate
HMDS	hexamethyldisilazine
IBX	*o*-iodoxybenzoic acid
KHMDS	potassium hexamethyldisilazide
Lawesson	2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
Ms	methanesulfonyl
NaHMDS	sodium hexamethyldisilazide
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMO	4-methylmorpholine-*N*-oxide
Ns	nitrobenzenesulfonyl
PMB	*para*-methoxybenzyl
Py	pyridine
Red-Al	sodium bis(2-methoxyethoxy)aluminum hydride
SAD	Sharpless asymmetric dihydroxylation
SAE	Sharpless asymmetric epoxidation
TBAF	tetra-*n*-butylammonium fluoride
TBHP	*tert*-butyl hydroperoxide
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMS	trimethylsilyl
TPAP	tetra-*n*-propylammonium perruthenate
Ts	4-toluenesulfonyl

Received: December 13, 2008
Revised: January 29, 2009
Published online: March 17, 2009

[1] J. B. Hendrickson, *J. Am. Chem. Soc.* **1975**, *97*, 5784 – 5800.
[2] a) B. M. Trost, *Science* **1991**, *254*, 1471 – 1477; b) B. M. Trost, *Angew. Chem.* **1995**, *107*, 285 – 307; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259 – 281.
[3] P. A. Wender, M. P. Croatt, B. Witulski, *Tetrahedron* **2006**, *62*, 7505 – 7511.
[4] For reviews , see: a) R. W. Hoffmann, *Synthesis* **2006**, 3531 – 3541; b) I. S. Young, P. S. Baran, *Nat. Chem.* **2009**, in press.
[5] P. S. Baran, T. J. Maimone, J. M. Richter, *Nature* **2007**, *446*, 404 – 408.
[6] J. M. Richter, Y. Ishihara, T. Masuda, B. W. Whitefield, T. Llamas, A. Pohjakallio, P. S. Baran, *J. Am. Chem. Soc.* **2008**, *130*, 17938 – 17954.
[7] D. A. Evans, for example, oral presentation at The Scripps Research Institute, 12 February 2004.
[8] a) The oft-cited synthesis of tropinone by Robinson[8b] seems to have introduced the above concepts as well as those of biomimetic synthesis and retrosynthetic analysis nearly one hundred years ago. It is thus clearly pertinent to bring such ideas to light in order to more critically analyze and further the art and science of synthesis; b) R. Robinson, *J. Chem. Soc.* **1917**, 762 – 768.
[9] J. B. Hendrickson, *J. Am. Chem. Soc.* **1971**, *93*, 6847 – 6854.
[10] a) R. Noyori, *Acta Chem. Scand.* **1996**, *50*, 380 – 390; b) "Carbonyl Hydrogenation": T. Ohkuma, R. Noyori in *Transition Metals for Organic Synthesis*, *Vol. 2* (Eds.: M. Beller, C. Bolm), Wiley-VCH, Weinheim, **2004**, pp. 29 – 112.
[11] E. J. Corey, R. K. Bakshi, S. Shibata, *J. Am. Chem. Soc.* **1987**, *109*, 5551 – 5553.
[12] a) A. B. Zaitsev, H. Adolfsson, *Synthesis* **2006**, 1725 – 1776; b) "Asymmetric Dihydroxylation": H. C. Kolb, K. B. Sharpless in *Transition Metals for Organic Synthesis*, *Vol. 2* (Eds.: M. Beller; C. Bolm), Wiley-VCH, Weinheim, **2004**, pp. 275 – 297.
[13] The term "redox-neutral" appears in the title of ref. [14].
[14] A. Labonne, L. Zani, L. Hintermann, C. Bolm, *J. Org. Chem.* **2007**, *72*, 5704 – 5708.
[15] J. Pospísil, I. Markó, *Org. Lett.* **2006**, *8*, 5983 – 5986.
[16] R. R. Leleti, B. Hu, M. Prashad, O. Repic, *Tetrahedron Lett.* **2007**, *48*, 8505 – 8507.
[17] a) "Olefin Cross Metathesis": A. K. Chatterjee in *Handbook of Metathesis*, *Vol. 2* (Ed.: R. H. Grubbs), Wiley-VCH, Weinheim, **2003**, pp. 246 – 295; b) A. K. Chatterjee, T.-L. Choi, D. P. Sanders, R. H. Grubbs, *J. Am. Chem. Soc.* **2003**, *125*, 11360 – 11370; c) V. A. Keller, I. Kim, S. D. Burke, *Org. Lett.* **2005**, *7*, 737 – 740.
[18] a) M. S. Chen, M. C. White, *J. Am. Chem. Soc.* **2004**, *126*, 1346 – 1347; b) T. Mitsudome, T. Umetami, N. Nosaka, K. Mori, T. Mizugaki, K. Ebitani, K. Kaneda, *Angew. Chem.* **2006**, *118*, 495 – 499; *Angew. Chem. Int. Ed.* **2006**, *45*, 481 – 485; c) K. J. Fraunhoffer, D. A. Bachovchin, M. C. White, *Org. Lett.* **2005**, *7*, 223 – 226.
[19] E. Winterfeldt, *Synthesis* **1975**, 617 – 630.
[20] J. Singh, N. Satyamurthi, I. S. Aidhen, *J. Prakt. Chem.* **2000**, *342*, 340 – 347.
[21] T. Fukuyama, S.-C. Lin, L. Li, *J. Am. Chem. Soc.* **1990**, *112*, 7050 – 7051.
[22] L. Hintermann, A. Labonne, *Synthesis* **2007**, 1121 – 1150.
[23] I. Ojima, C.-Y. Tsai, M. Tzamarioudaki, D. Bonafoux, *Org. React.* **2000**, *56*, 1 – 354.
[24] a) "Isomerization of Carbon–Carbon Double Bonds": S. Akutagawa in *Comprehensive Asymmetric Catalysis*, *Vol. 2* (Eds.: E. N. Jacobsen; A. S. Pfaltz; H. Yamamoto), Springer, Heidelberg, **1999**, pp. 813 – 830; b) B. M. Trost, R. C. Livingston, *J. Am. Chem. Soc.* **2008**, *130*, 11970 – 11978.
[25] a) K. Zeitler, *Angew. Chem.* **2005**, *117*, 7674 – 7678; *Angew. Chem. Int. Ed.* **2005**, *44*, 7506 – 7510; b) H. U. Vora, T. Rovis, *J. Am. Chem. Soc.* **2007**, *129*, 13796 – 13797.

[26] N. T. Reynolds, J. Read deAlaniz, T. Rovis, *J. Am. Chem. Soc.* **2004**, *126*, 9518 – 9519.
[27] a) K. Tanaka, G. C. Fu, *Angew. Chem.* **2002**, *114*, 1677 – 1679; *Angew. Chem. Int. Ed.* **2002**, *41*, 1607 – 1609; b) L.-L. Wei, L.-M. Wei, W.-B. Pan, M.-J. Wu, *Synlett* **2004**, 1497 – 1502.
[28] a) S. Omura, T. Fukuyama, J. Horiguchi, Y. Murakami, I. Ryu, *J. Am. Chem. Soc.* **2008**, *130*, 14094 – 14095; b) F. Shibahara, J. F. Bower, M. J. Krische, *J. Am. Chem. Soc.* **2008**, *130*, 14120 – 14122.
[29] For an insightful review on both internal and external transfer hydrogenative couplings, see: J. F. Bower, I. S. Kim, R. L. Patman, M. J. Krische, *Angew. Chem.* **2009**, *121*, 36 – 48; *Angew. Chem. Int. Ed.* **2009**, *48*, 34 – 46.
[30] a) O. P. Törmäkangas, A. M. P. Koskinen, *Recent Res. Dev. Org. Chem.* **2001**, *5*, 225 – 255; b) D. A. Evans, A. H. Hoveyda, *J. Am. Chem. Soc.* **1990**, *112*, 6447 – 6449.
[31] P. J. Black, G. Cami-Cobeci, M. G. Edwards, P. A. Slatford, M. K. Whittlesey, J. M. J. Williams, *Org. Biomol. Chem.* **2006**, *4*, 116 – 125.
[32] a) C. Löfberg, R. Grigg, M. A. Whittaker, A. Keep, A. Derrick, *J. Org. Chem.* **2006**, *71*, 8023 – 8027; b) K. Fujita, Z. Li, N. Ozeki, R. Yamaguchi, *Tetrahedron Lett.* **2003**, *44*, 2687 – 2690.
[33] For another example, see: F. Shibahara, J. F. Bower, M. J. Krische, *J. Am. Chem. Soc.* **2008**, *130*, 6338 – 6339.
[34] C. L. Martin, L. E. Overman, J. M. Rohde, *J. Am. Chem. Soc.* **2008**, *130*, 7568 – 7569.
[35] D. A. Nicewicz, A. D. Satterfield, D. C. Schmitt, J. S. Johnson, *J. Am. Chem. Soc.* **2008**, *130*, 17281 – 17283.
[36] D. A. Evans, J. C. Barrow, J. L. Leighton, A. J. Robichaud, M. Sefkow, *J. Am. Chem. Soc.* **1994**, *116*, 12111 – 12112.
[37] S. Nakamura, Y. Hirata, T. Kurosaki, M. Anada, O. Kataoka, S. Kitagaki, S. Hashimoto, *Angew. Chem.* **2003**, *115*, 5509 – 5513; *Angew. Chem. Int. Ed.* **2003**, *42*, 5351 – 5355.
[38] a) E. M. Carreira, J. Du Bois, *J. Am. Chem. Soc.* **1994**, *116*, 10825 – 10826; b) E. M. Carreira, J. Du Bois, *J. Am. Chem. Soc.* **1995**, *117*, 8106 – 8125.
[39] a) K. C. Nicolaou, E. W. Yue, Y. Naniwa, F. De Riccardis, A. Nadin, J. E. Leresche, S. La Greca, Z. Yang, *Angew. Chem.* **1994**, *106*, 2306 – 2309; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2184 – 2187; b) K. C. Nicolaou, A. Nadin, J. E. Leresche, S. La Greca, T. Tsuri, E. W. Yue, Z. Yang, *Angew. Chem.* **1994**, *106*, 2309 – 2312; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2187 – 2190; K. C. Nicolaou, A. Nadin, J. E. Leresche, E. W. Yue, S. La Greca, *Angew. Chem.* **1994**, *106*, 2312 – 2313; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2190 – 2191.
[40] P. Wipf, Y. Kim, D. M. Goldstein, *J. Am. Chem. Soc.* **1995**, *117*, 11106 – 11112.
[41] Y. Zeng, J. Aubé, *J. Am. Chem. Soc.* **2005**, *127*, 15712 – 15713.
[42] Y. Matsuda, M. Kitajima, H. Takayama, *Org. Lett.* **2008**, *10*, 125 – 128.
[43] T. Newhouse, P. S. Baran, *J. Am. Chem. Soc.* **2008**, *130*, 10886 – 10887.
[44] B. A. Lanman, L. E. Overman, *Heterocycles* **2006**, *70*, 557 – 570.
[45] L. Tang, D. Romo, *Heterocycles* **2007**, *74*, 999 – 1008.
[46] a) D. P. O'Malley, J. Yamaguchi, I. S. Young, I. B. Seiple, P. S. Baran, *Angew. Chem.* **2008**, *120*, 3637 – 3639; *Angew. Chem. Int. Ed.* **2008**, *47*, 3581 – 3583; b) S. Su, I. B. Seiple, I. S. Young, P. S. Baran, *J. Am. Chem. Soc.* **2008**, *130*, 16490 – 16491.
[47] T. Honda, H. Namiki, M. Watanabe, H. Mizutani, *Tetrahedron Lett.* **2004**, *45*, 5211 – 5213.
[48] A. B. Leduc, M. A. Kerr, *Angew. Chem.* **2008**, *120*, 8063 – 8066; *Angew. Chem. Int. Ed.* **2008**, *47*, 7945 – 7948.
[49] S. Jennewein, C. D. Rithner, R. M. Williams, R. B. Croteau, *Proc. Natl. Acad. Sci. USA* **2001**, *98*, 13595 – 13600.
[50] J. Staunton, B. Wilkinson, *Chem. Rev.* **1997**, *97*, 2611 – 2630.
[51] a) F. Busqué, M. Cantó, P. de March, M. Figueredo, J. Font, S. Rodríguez, *Tetrahedron: Asymmetry* **2003**, *14*, 2021 – 2032; b) G. G. Bardají, M. Cantó, R. Alibés, P. Bayón, F. Busqué, P. de March, M. Figueredo, J. Font, *J. Org. Chem.* **2008**, *73*, 7657 – 7662.
[52] A. Endo, S. J. Danishefsky, *J. Am. Chem. Soc.* **2005**, *127*, 8298 – 8299.
[53] G. Ma, H. Nguyen, D. Romo, *Org. Lett.* **2007**, *9*, 2143 – 2146.
[54] M. Suzuki, Y. Matsuo, S. Takeda, T. Suzuki, *Phytochemistry* **1993**, *33*, 651 – 656.
[55] a) E. J. Corey, M. C. Noe, S. Lin, *Tetrahedron Lett.* **1995**, *36*, 8741 – 8744; b) Z. Xiong, E. J. Corey, *J. Am. Chem. Soc.* **2000**, *122*, 9328 – 9329.
[56] a) Y. Morimoto, T. Iwai, T. Kinoshita, *J. Am. Chem. Soc.* **2000**, *122*, 7124 – 7125; b) T. Lindel, B. Franck, *Tetrahedron Lett.* **1995**, *36*, 9465 – 9468.
[57] S. A. Hermitage, K. S. Cardwell, T. Chapman, J. W. B. Cooke, R. Newton, *Org. Process Res. Dev.* **2001**, *5*, 37 – 44.
[58] B. A. Anderson, M. M. Hansen, J. T. Vicenzi in *Process Chemistry in the Pharmaceutical Industry* (Ed.: K. G. Gadamasetti), Marcel Dekker, New York, **1999**, pp. 263 – 282.
[59] R. H. Mueller in *Process Chemistry in the Pharmaceutical Industry* (Ed.: K. G. Gadamasetti), Marcel Dekker, New York, **1999**, pp. 37 – 55.
[60] A. B. Smith III, S. A. Kozmin, C. M. Adams, D. V. Paone, *J. Am. Chem. Soc.* **2000**, *122*, 4984 – 4985.
[61] A. W. G. Burgett, Q. Li, Q. Wei, P. G. Harran, *Angew. Chem.* **2003**, *115*, 5111 – 5116; *Angew. Chem. Int. Ed.* **2003**, *42*, 4961 – 4966.
[62] M. G. Charest, D. R. Siegel, A. G. Myers, *J. Am. Chem. Soc.* **2005**, *127*, 8292 – 8293.
[63] P. S. Baran, J. M. Richter, *J. Am. Chem. Soc.* **2005**, *127*, 15394 – 15396.
[64] a) K. C. Nicolaou, K. B. Simonsen, G. Vassilikogiannakis, P. S. Baran, V. P. Vidali, E. N. Pitsinos, E. A. Couladouros, *Angew. Chem.* **1999**, *111*, 3762 – 3766; *Angew. Chem. Int. Ed.* **1999**, *38*, 3555 – 3559; b) D. Barnes-Seeman, E. J. Corey, *Org. Lett.* **1999**, *1*, 1503 – 1504.
[65] A. Fürstner, M. M. Domostoj, B. Scheiper, *J. Am. Chem. Soc.* **2005**, *127*, 11620 – 11621.
[66] R. M. Moslin, T. F. Jamison, *J. Am. Chem. Soc.* **2006**, *128*, 15106 – 15107.
[67] A. Rivkin, F. Yoshimura, A. E. Gabarda, T. Chou, H. Dong, W. P. Tong, S. J. Danishefsky, *J. Am. Chem. Soc.* **2003**, *125*, 2899 – 2901.
[68] D. Alberico, M. E. Scottt, M. Lautens, *Chem. Rev.* **2007**, *107*, 174 – 238.
[69] *Handbook of C-H Transformations* (Ed.: G. Dyker), Wiley-VCH, New York, **2005**.
[70] V. Snieckus, T. Macklin in *Handbook of C H Transformations* (Ed.: G. Dyker), Wiley-VCH, New York, **2005**, pp. 106 – 118.
[71] For reviews, see: a) A. S. K. Hashmi, *Chem. Rev.* **2007**, *107*, 3180 – 3211; b) D. J. Gorin, B. D. Sherry, F. D. Toste, *Chem. Rev.* **2008**, *108*, 3351 – 3378.
[72] E. J. Corey, X.-M. Cheng, *The Logic of Chemical Synthesis*, Wiley, New York, **1989**.