Theilheimer's

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of Organic Chemistry

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Theilheimer's Synthetic Methods of Organic Chemistry

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Preface

Completing fifty years of *Theilheimer*, this yearbook is the last in the Tenth Series and contains abstracts and supplementary data from papers published in the field of synthetic organic chemistry in the latter half of 1994 and the first half of 1995. Being the fifth volume of the series, it also contains a cumulation of the reaction titles (including key supplementary references) published in Volumes *46–49*. These are presented with Volume 50 abstracts according to the familiar Systematic Classification (Survey s. p. XXVI) so that the reader can browse the significant developments in any particular method during the last five years. Data on epoxidation, for example, can be found within the section OC⇓CC (pp. 60–71), the title order being dependent on the reagents. The latter are arranged in each section according to the Periodic Table (Groups I to VIII) so that alkali metal bases, for example, appear at the beginning and Group VIII complexes at the end.

In order to maintain the size (and cost) of this volume on a par with Volume *49*, we have opted to forgo the customary five-yearly cumulation of the Subject Indexes. Hence, for a subject index search through the Tenth Series, the reader should refer to the indexes in Volumes *50*, *49*, *48*, and *47* (the latter having a cumulation of the indexes for Volumes *46* and *47*).

To assist in locating the Subject Index nomenclature, the reader is referred to the Formula Index of Complex Functional Groups (last cumulated in Volume *48*), and the rules governing the Systematic Classification (symbol notation) are outlined on p. IX. However, for the more important reaction types, such as epoxidation, aldol condensation, O-desilylation, and Michael addition, the corresponding reaction symbols can be located in the Subject Index under such entries as **Aldol condensation** (CC⇓OC). For browsing, the reader should then refer to the Systematic Survey (p. XXVI) for the appropriate page reference.

The *Trends* section (p. XII) contains references to data published up to March 1996, and the *Reviews* section (p. 458) contains data published up to December 1995.

It must be a particular pleasure for the founder of these yearbooks, Dr. Theilheimer, to realise that the series which he pioneered has reached its 50th anniversary. His encouragement through the last fifteen years has been very much appreciated, as also that of my colleagues at Karger in Basel and at Derwent Information, London, whose *Journal of Synthetic Methods* provides the data for inclusion in these volumes. A word of thanks also to Mrs. Cook, librarian of the Chemistry Department at Cambridge University, for permitting my access to the current literature.

April 1996 *A.F. Finch*, Editor

"Theilheimer" Celebrates Its 50th Anniversary

The pioneering editor of *Synthetic Methods of Organic Chemistry* from 1946–1981, William Theilheimer, laid the foundations of this series in Basel, Switzerland, during the early 1940s. The ingenious concept developed by William Theilheimer was recognized by my father, Heinz Karger, head of S. Karger Publishers at the time, and together they brought into existence what has become an archival source and powerful retrieval tool in the sphere of synthetic organic chemistry. Its unique, all-embracing, systematic classification of reactions and their encapsulation in the form of succinct, stylized abstracts have remained essentially unchanged during these last 50 years, and the development of consistent nomenclature and cross-referencing has been the cornerstone of the most sophisticated subject index in this field. Since 1982, the name Theilheimer has been incorporated into the title to honor the achievements of its founder.

On this occasion, I would like to express my thanks to Dr. Theilheimer for his continued interest and support throughout the years, for which the publishing house is very grateful. I would also like to take this opportunity to thank Dr. A.F. Finch for his enthusiasm and untiring efforts on behalf of the series which have made the continuation of the yearbooks possible. I am pleased that the preparation of Volume 51 is already underway and that *Theilheimer*, as it is commonly referred to today, will continue to be a practical tool and source of ideas for all organic chemists as Dr. Theilheimer envisaged 50 years ago.

The concept developed by William Theilheimer half a century ago has proven to be so successful that we are now considering publishing *Theilheimer* twice yearly as of 1997. Its more frequent appearance would make *Theilheimer* even more valuable as users could benefit from having more detailed information at their fingertips, more quickly. As ever, each volume of *Theilheimer* is ideal for browsing as it brings together under one cover the very latest data normally found scattered throughout the literature.

May 1996 *Thomas Karger*

Advice to the User

General Remarks

New methods for the synthesis of organic compounds and improvements of known methods are being recorded continuously in this series.

Reactions are classified on a simple though purely formal basis by symbols, which can be arranged systematically. Thus searches can be performed without knowledge of the current trivial or author names (e.g., 'Oxidation' and 'Friedel-Crafts reaction').

Users accustomed to the common notations will find these in the subject index. By consulting this index, use of the classification system may be avoided. It is thought that the volumes should be kept close at hand. The books should provide a quick survey, and obviate the immediate need for an elaborate library search. Syntheses are therefore recorded in the index by starting materials and end products, along with the systematic arrangement for the methods. This makes possible a subclassification within the reaction symbols by reagents, a further methodical criterion. Complex compounds are indexed with cross reference under the related simpler compounds. General terms, such as synthesis, replacement, heterocyclics, may also be brought to the attention of the reader.

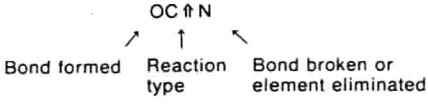
A brief review, *Trends in Synthetic Organic Chemistry*, stresses highlights of general interest and calls attention to developments too recent to be included in the body of the text.

The abstracts are limited to the information needed for an appraisal of the applicability of a desired synthesis. In order to carry out a particular synthesis it is therefore advisable to have recourse to the original papers or, at least, to an abstract journal. In order to avoid repetition, selections are made on the basis of most detailed description and best yields, whenever the same method is used in similar cases. Continuations of papers already included will not be abstracted, unless they contain essentially new information. They may, however, be quoted at the place corresponding to the abstracted papers. These supplementary references (see page 506) make it possible to keep abstracts of previous volumes up-to-date.

Syntheses that are divided into their various steps and recorded in different places can be followed with the help of the notations *startg. m. f.* (starting material for the preparation of ...) and *prepn. s.* (preparation, see).

Method of Classification

Reaction Symbols. As summarized in the Systematic Survey (p. XXVI), reactions are classified firstly according to the bond formed in the synthesis, secondly according to the reaction type, and thirdly according to the bond broken or the element eliminated. This classification is summarized in the reaction symbol, e.g.



The first part of the symbol refers to the chemical bond formed during the reaction, expressed as a combination of the symbols for the two elements bonded together, e.g. HN, NC, CC. The order of the elements is as follows:

H, O, N, Hal (Halogen), S, Rem (Remaining elements), and C.

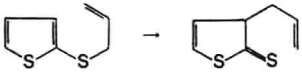
Thus, for the formation of a hydrogen-nitrogen bond, the notation is HN, not NH.

If two or more bonds are formed in a reaction, the 'principle of the latest position' applies. Thus, for the reduction

in which both hydrogen-oxygen and hydrogen-carbon bonds are formed, the symbol is HC ⇓ OC and not HO ⇓ OC.

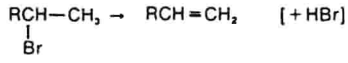
The second part of the symbol refers to the reaction type. Four types are distinguished: addition (⇓), rearrangement (∩), exchange (⇵), and elimination (⇑), e.g.

OC ⇓ CC



CC ∩ SC

CC ⇵ Hal



CC ⇑ Hal

Monomolecular reactions are either rearrangements (∩), where the molecular weight of the starting material and product are the same, or eliminations (⇑), where an organic or inorganic fragment is lost; bimolecular and multicomponent reactions are either additions (⇓), where

the combined molecular weight of the starting materials is the same as that of the product,[1] or exchanges (⇵), such as substitutions and condensations, where an organic or inorganic fragment is lost.

The last part of the symbol refers to the essential bond broken or, in the case of exchange reactions and eliminations, to a characteristic fragment which is lost. While the addition symbol is normally followed by the two elements denoting the bond broken, in the case of valency expansion, where no bonds are broken, the last part of the symbol indicates the atom at which the addition occurs, e.g.

$R_2S \rightarrow R_2SO$ OS⇓S

$RONO \rightarrow RONO_2$ ON⇓N

For additions, exchanges, and eliminations, the 'principle of the latest position' again applies if more than one bond is broken. However, for rearrangements, the most descriptive bond-breakage is used instead.[2] Thus, for the thio-Claisen rearrangement depicted above, the symbol is CC∩SC, and not CC∩CC.

Deoxygenations, quaternizations, stable radical formations, and certain rare reaction types are included as the last few methods in the yearbook. The reaction symbols for these incorporates the special symbols El (electron pair), Het (heteropolar bond), Rad (radical), Res (resolutions), and Oth (other reaction types), e.g.

$R_2S{=}O \rightarrow R_2S{:}$ EIS⇑O

$R_3N + R'Cl \rightarrow R_3\overset{+}{N}R'\ Cl^-$ Het⇓N

The following rules simplify the use of the reaction symbols:

1. The chemical bond is rigidly classified according to the structural formula without taking the reaction mechanism into consideration.

2. Double or triple bonds are treated as being equivalent to two or three single bonds, respectively.

3. Only stable organic compounds are usually considered: intermediates such as Grignard compounds and sodiomalonic esters, and inorganic reactants, such as nitric acid, are therefore not expressed in the reaction symbols.

Reagents. A further subdivision, not included in the reaction symbols, is based on the reagents used. The sequence of the reagents usually follows

[1] Exceptions being additions of organometallics, e.g.

$RCH{=}O + R'MgBr \rightarrow RCH(R')-OH$ CC⇓OC

$RCH{=}CHCOOR + LiCuR'_2 \rightarrow RCH(R')-CH_2COOR$ CC⇓CC

[2] Similarly, the formation of a peroxy function is classified under OO⇓CC, instead of OC⇓CC.

that of the periodic system. Reagents made up of several components are arranged according to the element significant for the reaction (e.g., $KMnO_4$ under Mn, NaClO under Cl). When a constituent of the reagent forms part of the product, the remainder of the reagent, which acts as a carrier of this constituent, is the criterion for the classification; for example, phosphorus is the carrier in a chlorination with PCl_5 and sodium in a nitrosation with $NaNO_2$.

High-Coverage Searches

A search through *Synthetic Methods* provides a selection of key references from the journal literature. For greater coverage, as for bibliographies, a supplementary search through the following publications is suggested:

Derwent Reaction Service[3]. Designed for both current awareness and retrospective retrieval. Its monthly publication, the *Journal of Synthetic Methods*, covers the journal and patent literature, and provides 3,000 abstracts of recently published papers annually, together with 3,000 supplementary references.

On-line access is available to over 80,000 reactions, including the data in all the abstracts in *Synthetic Methods*.

Science Citation Index[4]. For which *Synthetic Methods* serves as a source of starting references.

Chemical Abstract Service[5]. References may not be included in *Synthetic Methods* (1) to reactions which are routinely performed by well known procedures; (2) to subjects which can be easily located in handbooks and indexes of abstract journals, such as the ring system of heterocyclics or the metal in case of organometallic compounds, and (3) to inadequately described procedures, especially if yields are not indicated.

References to less accessible publications such as those in the Chinese or Japanese language are usually only included if the method in question is not described elsewhere.

[3] Derwent Information Ltd., 14 Great Queen Street, London WC2B 5DF, England.
[4] Institute for Scientific Information, Philadelphia, Pa., USA.
[5] Chemical Abstracts Service, Columbus, Ohio, USA.

Trends in Synthetic Organic Chemistry 1996

From the development of the Merrifield resin for peptide synthesis in 1963 (Synth. Meth. *19*, 33), polymer-supported ['solid-phase'] organic synthesis has been an important facet of chemistry during the last 30 years. Simplification of work-up by filtration of soluble reagents and by-products is an obvious advantage over the corresponding homogeneous conversion, and aspects such as 'site isolation' (illustrated in Synth. Meth. *45*, 415; *50*, 81) have been utilized more recently to prevent unwanted side-reactions. Today, however, the technique has acquired a totally new meaning in the context of 'combinatorial chemistry': a discipline in itself which promises to aid the discovery of new drugs by offering simultaneous or parallel syntheses of huge libraries of compounds in a short space of time. The recent overviews[1a] and reviews[1b] speak volumes and there is little to add, save, perhaps, one or two cautionary notes: a level of iteration from interim bioassays as the synthesis develops could effect optimization from only a handful of the theoretically possible combinations at one's disposal[2]. But, more importantly, there may be inherent disadvantages in, for example, the scale which is limited to the loading capacity of the resin. The need to design compatible spacer linkers and capping strategies places further constraints, and the adaptation of orthogonal chemistries for substrate attachment and product detachment may present insurmountable obstacles. Hence the emergence of *solution-phase* syntheses of combinatorial libraries. Here, intermediates and products are isolated from unwanted material by *conventional* extractive methods, as in the generation of a peptidomimetic library from a multifunctionalized bicyclic template[3]. Digression to combinatorial biosynthesis has also been highlighted[4], and recently we read of optimization of catalyst combinations by parallel assay on microtiter plates[5].

We have witnessed through the years the development of transition metal catalysis as a cornerstone of synthetic organic chemistry. The particular characteristics of the central metal, and the seemingly limitless tailoring of reactivity by ligand design have introduced powerful variables for studying key

[1a] S. Borman, Chem. Eng. News. *74*, No. 7, 28–54 (1996); C.D. Floyd et al., Chem. Britain *32*, No. 3, 31–5 (1996).

[1b] L.A. Thompson, J.A. Ellman, Chem. Rev. *96*, 555–600 (1996); Special Issue on Combinatorial Chemistry s. Acc. Chem. Res. *29*, 112–70 (1996) (6 papers); survey of polymer-based reactions s. P.H.H. Hermkens et al., Tetrahedron *52*, 4527–54 (1996); f. reviews s. Synth. Meth. *50*. 555s*50* (p. 463).

[2] J. Singh et al., J. Am. Chem. Soc. *118*, 1669–76 (1996).

[3] D.L. Boger et al., J. Am. Chem. Soc. *118*, 2109–110, 2567–73 (1996).

[4] Overview s. J. Rohr, Angew. Chem. Intern. Ed. *34*, 881–6 (1995).

[5] K. Burgess et al., Angew. Chem. Intern. Ed. *35*, 220–2 (1996).

functional group conversions, many of which – such as oxygen-transfer reactions with porphyrin and Schiff base complexes[6] – are modelled on enzymatic processes. Transition metal-catalyzed syntheses by carbon-carbon bond formation, however, has been inspired more by man's intuition than natural parallels – none more so than 'atom economical' additions and isomerizations [note key sections under CC ⇓ CC (pp. 309–16), CC ∩ HC (p. 320), CC ∩ CC (pp. 330–1)] where by-product formation is theoretically zero[7]. Here, we have only scratched the surface, not only in the design of more efficient ways of conducting established reactions, but also in the procurement of totally new chemistry. Palladium- or ruthenium-catalyzed reactions, such as cycloisomerization of enynes, cycloaddition[8], and intramolecular ene reactions, are archetypal and have paved the way to such recent developments as regiospecific addition of pro-nucleophiles to unsaturated systems[9]. Ruthenium-catalyzed addition of electron-deficient alkenes to simple olefins is notable in that reaction involves oxidative insertion of Ru(0) into a β-vinylic carbon-hydrogen bond[10], while ruthenium π-allyl species are implicated in a novel isomerization of allyl and homoallyl alcohols[11]. Reference might also be given to Pd-catalyzed Michael-type addition of terminal alkynes to α,β-acetylenecarboxylic acid esters[12], and the highly regioselective co-dimerization of alkenes with styrenes (under Ni-catalysis[13]) and with 1,3-dienes (under Co-catalysis[14]).

Contrasting with 'atom-economical' chemistry, transition metal-catalyzed condensations are more familiar, notable developments having been made in Heck chemistry[15], C-α-allylation[16], and in Suzuki- and Stille-coupling[17]. Polymer-supported variants are welcomed[18], as also novel procedures with high catalytic turnover. In this respect, palladacyclics merit particular attention following the report that Heck arylation can be conducted with a turnover as high as 200,000 using as little as 0.005 mol% of the catalyst[19].

[6] Review s. Synth. Meth. *46*, 106s*50* (p. 461).
[7] Review s. Synth. Meth. *48*, 691s*50* (p. 462).
[8] Review s. M. Lautens et al., Chem. Rev. *96*, 49–92 (1996).
[9] Addition to 1,3-enynes s. Y. Yamamoto et al., Chem. Commun. *1996*, 17–8; to allenes s. Synth. Meth. *50*, 423.
[10] B.M. Trost et al., J. Am. Chem. Soc. *117*, 5371–2 (1995).
[11] C.-J. Li et al., J. Am. Chem. Soc. *117*, 12867–8 (1995).
[12] B.M. Trost, M.C. McIntosh, J. Am. Chem. Soc. *117*, 7255–6 (1995).
[13] A.L. Monteiro et al., Tetrahedron Letters *37*, 1157–60 (1996).
[14] Synth. Meth. *50*, 416.
[15] Reviews s. Synth. Meth. *27*, 871s*50* (p. 459); recent application to macrocyclization by polymer-based intramolecular Heck arylation s. M. Hiroshige et al., J. Am. Chem. Soc. *117*, 11590–1 (1995).
[16] Review of asym. allylation s. B.M. Trost, D.L. Van Vranken, Chem. Rev. *96*, 395–422 (1996); recent method s. Angew. Chem. Intern. Ed. *34*, 2386–8 (1995).
[17] Reviews s. Synth. Meth. *37*, 902s*50* (p. 460).
[18] Synth. Meth. *50*, 556 and *50*, 555, respectively.
[19] W.A. Herrmann et al., Angew. Chem. Intern. Ed. *34*, 1844–8 (1995).

Suzuki- and Stille-coupling may also be achieved *in situ*[20] (thereby avoiding prior synthesis of boron derivatives and stannanes), and inexpensive variants under nickel catalysis have been reported[21], as well as an application of Stille-coupling to the preparation of functional polymers[22]. The aspect of carbopalladation inherent in Heck chemistry[23] has been extended and adapted in a variety of tandem fashions, as in ring closures via intramolecular carbopalladation-nucleophile capture[24], but the chemoselectivity of the initial oxidative addition of Pd(0) has been largely unexplored. This introduces the novel element of 'molecular queueing' where competition of the catalyst for two different electrophiles determines the course of reaction, as in a recent 4-component spirolactone synthesis[25]. Events other than oxidative addition may also initiate such intramolecular carbometalation. One of the latest is nickel-catalyzed conjugate addition to an enone, the intermediate σ-alkyl or π-allyl species being captured by an appended acetylene group prior to reductive elimination of the catalyst[26]. Nor is termination restricted to α-elimination of the metal or β-hydride elimination: in halopalladation-carbopalladation, for example, the catalyst is regenerated by protonolysis[27], while a recent Pd-catalyzed oxidative dimerization of terminal alkynes is thought to involve nucleophilic displacement of a π-allyl ligand *at carbon*[28]. The first syntheses via oxidative addition of a metal complex to the phosphorus-hydrogen bond has also been reported[29], along with Pd-catalyzed amination of aryl halides, now achievable *without* the use of toxic stannanes[30]. In the latter reaction, the catalytic cyclic is completed by reductive elimination from an arylpalladium amide complex in the presence of a hindered base (NaOBu-*t*).

The involvement of transition metal carbene chemistry in organic synthesis has been particularly notable in recent years, due, in part, to developments of the Dötz reaction[31] and, in part, to the close parallel between α,β-unsatu-

[20] *in situ*-Suzuki coupling s. M.S. Passafaro, B.A. Keay, Tetrahedron Letters *37*, 429–32 (1996); F. Naso et al., J. Chem. Soc. Chem. Commun. *1995*, 2523–4; Synth. Meth. *50*, 494; *in situ*-Stille coupling s. S.A. Hitchcock et al., Tetrahedron Letters *36*, 9085–8 (1995).

[21] Suzuki coupling with mesylates s. V. Percec et al., J. Org. Chem. *60*, 1060–5 (1995); Stille-type synthesis of 1,4-enynes via nickel π-allyl complexes s. S. Ikeda et al., ibid. 5752–6.

[22] L. Yu et al., J. Am. Chem. Soc. *117*, 12426–35 (1995).

[23] Review of ring closure by carbopalladation s. E. Negishi et al., Chem. Rev. *96*, 365–94 (1996).

[24] Methodology s. Synth. Meth. *49*, 829; recent examples with allenes s. E. Negishi, S. Ma, J. Am. Chem. Soc. *117*, 6345–57 (1995); R. Grigg et al., J. Chem. Soc. Chem. Commun. *1995*, 1903–4; under Ni-catalysis cf. Synth. Meth. *50*, 521.

[25] R. Grigg et al., Tetrahedron Letters *37*, 695–9 (1996).

[26] J. Montgomery, A.V. Savchenko, J. Am. Chem. Soc. *118*, 2099–100 (1996).

[27] Z. Wang, X. Lu, Chem. Commun. *1996*, 535–6.

[28] M. Vlassa et al., Tetrahedron *52*, 1337–42 (1996).

[29] L.-B. Han, M. Tanaka, J. Am. Chem. Soc. *118*, 1571–2 (1996).

[30] Overviews s. M. Beller, Angew. Chem. Intern. Ed. *34*, 1316–7 (1995); with aryl iodides s. J.P. Wolfe, S.L. Buchwald, J. Org. Chem. *61*, 1133–5 (1996).

[31] Review of transition metal carbene-alkyne-alkene cyclization s. D.F. Harvey, D.M. Sigano, Chem. Rev. *96*, 271–88 (1996).

rated carbene complexes and the corresponding α,β-unsaturated carboxylic acid derivs. In the context of cycloaddition, for example, a new 2-azepinone [4+3]-annelation with α,β-acetylene(alkoxy)carbene complexes is worthy of note[32], as also an iron-catalyzed [2+2+1+1]-cycloaddition to provide benzo-condensed N-heterocyclics from azadienes[33]. It is, however, the *catalytic* role of transition metal carbene complexes which perhaps commands the greatest attention, with particular reference to ring closing metathesis[34] as a development of the pioneering work of Grubbs (with molybdenum carbene complexes) and Schrock (with ruthenium carbene complexes). The stitching of polyolefins into poly(cyclopentenes) is one such application[35], another being the formation of cyclic enolethers by Tebbe methylenation-ring closing metathesis, which is of clear potential for generating the complex polyether frameworks of marine biotoxins[36]. Ruthenium carbene complexes, generated *in situ* from diazo compds., are also featured in a novel synthesis of trisubstituted ethylene derivs. via π-allyl complexes[37], while the more familiar rhodium carbenoids are central to progress in asym. cyclopropanation[38] and [courtesy of Padwa et al.] a multitude of polyheterocyclizations via carbonyl ylids[39]. One such is a triple ring closure to form the aspidospermine skeleton with incorporation of *five* contiguous chiral centres[40]. Cycloaromatization to the key indolo[3,2-c]carbazole system is a further bonus[41], as also Rh-catalyzed aziridination of olefins[42], cycloheptadiene ring closure by intramolecular homo-Diels-Alder reaction[43], and carbonylative [4+1]-cycloaddition for the preparation of alkylidenecyclopentenones[44].

The involvement of a rhodacyclopentoid in the last two-mentioned conversions is an illustration of the central role of 5-membered metallacyclics in transition metal-catalyzed syntheses. Oxidative addition of palladium and ruthenium to enynes also generates such species, considered pivotal in Trost-type cycloisomerization[45]. Syntheses via addition of low-valent zircono-

[32] J. Barluenga et al., J. Am. Chem. Soc. *118*, 695–6 (1996).
[33] M. Mori et al., Chem. Letters *1995*, 615–6.
[34] Review s. Synth. Meth. *48*, 988s*50* (p. 462); overview s. H.-G. Schmalz, Angew. Chem. Intern. Ed. *34*, 1833–6 (1995).
[35] G.W. Coates, R.H. Grubbs, J. Am. Chem. Soc. *118*, 229–30 (1996).
[36] K.C. Nicolaou et al., J. Am. Chem. Soc. *118*, 1565–6 (1996); review of synthesis of *trans*-fused polyether toxins s. Synth. Meth. *33*, 145s*50* (p. 459).
[37] T. Braun et al., J. Am. Chem. Soc. *117*, 7291–2 (1995).
[38] Methodology s. Synth. Meth. *23*, 819s*46*, *48*, *49*.
[39] Review of such cascade processes s. A. Padwa, M.D. Weingarten, Chem. Rev. *96*, 223–70 (1996).
[40] A. Padwa, A.T. Price, J. Org. Chem. *60*, 6258–9 (1995).
[41] J.L. Wood et al., J. Am. Chem. Soc. *117*, 10413–4 (1995).
[42] P. Müller et al., Tetrahedron *52*, 1543–8 (1996).
[43] Overview s. G. Dyker, Angew. Chem. Intern. Ed. *34*, 2223–4 (1995).
[44] M. Murakami et al., Angew. Chem. Intern. Ed. *34*, 2691–4 (1995).
[45] Recent applications s. C. Kibayashi et al., J. Am. Chem. Soc. *118*, 1054–9 (1996); B.M. Trost, ibid. 233–4.

cenes are even more prominent, following the development of zirconacyclopentoids from the Negishi reagent[46]. However, cheaper low-valent titanium equivalents, such as titanocene η^2-olefin complexes, are now fashionable, as evident in ring closure of dienynes via titanacyclopent-1-enes[47]. Here, isocyclics are formed with an appended σ-allyltitanium functionality for subsequent manipulation, the same initiating process taking place with 3,4-dienol carbonates to secure polyfunctionalized γ-lactones via titanacyclopent-3-enes[48]. Titanium(II) η^2-propene complexes also add oxidatively to unsaturated imines to yield aminoisocyclics via 1,2-azatitanacyclopentanes[49], whereas $Cp_2Ti(PMe_3)_2$ reacts with unsaturated oxo compounds to yield condensed γ-lactones via unprecedented carbonylation of 1,2-oxatitanacyclopentanes[50]. The latter also feature in a novel cyclopropylamine ring closure via elimination of TiO_2[51], as well as in the intramolecular version of the Kulinkovich cyclopropanol[52] synthesis and in a vinylcyclopropane ring closure from 1,3-bis(arylthio)ethylenes[53].

A perusal of the systematic classification under HC ⇓ OC (pp. 21–4), HC ⇓ CC (pp. 28–31), and OC ⇓ CC (pp. 67–71) will reveal what depth and variety of transition metal complexes are available for simple reductive and oxidative processes, especially in the sphere of asymmetric synthesis. Noteable, of course, are developments of Noyori-type ruthenium[54] and Brintzinger-type titanocene[55] complexes for asym. hydrogenation, but among more recent offerings is an inexpensive catalytic alternative to $NaBH_4$ (in the form of $RuCl_2(PPh_3)_3/H_2NCH_2CH_2NH_2/KOH$) for large-scale selective hydrogenation of unsaturated oxo compounds[56]. The development of asym. dihydroxylation with chiral osmium complexes[57], and asym. epoxidation by catalyzed oxygen atom transfer[58] needs no further comment; nor the catalyzed incorporation of molecular oxygen[59], or the widespread usage of titanium and vanadium silicates in oxidation with H_2O_2[60], which have all been well reviewed. Transition metal-catalyzed nitrogen atom transfer, however,

[46] Review s. Synth. Meth. *49*, 939s*50* (p. 463).
[47] F. Sato et al., Tetrahedron Letters *37*, 1253–6 (1996); methodology s. Synth. Meth. *49*, 663.
[48] F. Sato et al., Chem. Commun. *1996*, 197–8; s.a. J. Am. Chem. Soc. *118*, 2208 (1996).
[49] F. Sato et al., Chem. Commun. *1996*, 533–4.
[50] W.E. Crowe, A.T. Vu, J. Am. Chem. Soc. *118*, 1557–8 (1996).
[51] V. Chaplinski, A. de Meijere, Angew. Chem. Intern. Ed. *35*, 413–4 (1996).
[52] J.K. Cha et al., J. Am. Chem. Soc. *118*, 291–2 (1996).
[53] T. Takeda et al., Tetrahedron Letters *36*, 8835–8 (1995).
[54] Developments s. Synth. Meth. *42*, 45s*49*, *50*; *43*, 51s*46–9*.
[55] Synth. Meth. *49*, 54; *50*, 15.
[56] R. Noyori et al., J. Am. Chem. Soc. *117*, 10417–8 (1995).
[57] Developments s. this volume (p. 70); recent modification s. H. Becker, K.B. Sharpless, Angew. Chem. Intern. Ed. *35*, 448–51 (1996); elaboration to asym. aminohydroxylation s. ibid. 451–4.
[58] Synth. Meth. *46*, 106s*46–9*.
[59] Review s. Synth. Meth. *47*, 113s*50* (p. 461).
[60] Review s. Synth. Meth. *49*, 162s*50* (p. 462); non-oxidative use of Ti-silicate in Mukaiyama aldol condensation s. R. Kumar et al., Chem. Commun. *1996*, 129–30.

is quite new, as reflected in a recent amination of enoxysilanes using a nitridomanganese(V) complex[61]. But let us conclude this section with the reagent of the moment: methylrhenium trioxide. In combination with H_2O_2 it rivals dimethyldioxirane in mildness and chemoselectivity[62], and in non-oxidative capacity it effectively catalyzes a number of key transformations[63].

Asymmetric synthesis is a fundamental element of modern synthetic organic chemistry, particularly in areas such as drug design[64], total synthesis of natural products, and, more recently, in stereoregular α-olefin polymerization[65]. It is complexed by fundamental elements within itself and not a little complicated by the jargon of the day – deracemization, desymmetrization [asymmetrization], dynamic kinetic resolution, enantiodifferentiation, asymmetric automultiplication, absolute asymmetric synthesis, and more – each (save the last two) being subordinate to the constraints imposed by internal or external chirality. It all conspires to make an overview difficult, and a systematic analysis almost impossible. High in priority, and immediacy, however, is the first aspect, deracemization, by which a single enantiomer may be obtained in *quantitative* yield by reaction of a racemic substrate. Kinetic resolution offers, at best, 50% of each enantiomer by virtue of selective conversion of the faster reacting antipode; however, by inducing the [unwanted] slower reacting antipode to epimerize as reaction proceeds could raise the chemical yield of the desired enantiomer substantially. Hence the emergence of dynamic kinetic resolution[66]. Such epimerization may arise by the agency of a prochiral enolate, as in the enzymatic asym. hydrolysis of α-(arylthio)thiolic acid esters[67], or through a dissociation-recombinant mechanism, as in the resolution of 1,1-hydroxythioethers via enzymatic asym. O-acylation[68]. An alternative 2-step device is at hand for the deracemization of a sec. alcohol: classical enzymatic kinetic resolution by O-acetylation affords 50% of the desired (R)-acetate, and the slower-reacting (S)-alcohol is converted to the same enantiomer by subsequent Mitsunobu inversion with acetic acid[69]. The same Mitsunobu displacement is applied in the multistep conversion of a racemic *syn*-1,3-diol to a single enantiomer of the corre-

[61] E.M. Carreira et al., J. Am. Chem. Soc. *118*, 915–6 (1996).
[62] Recent applications s. R.W. Murray et al., Tetrahedron Letters *37*, 805–8 (1996); Z. Zhu, J.H. Espenson, J. Org. Chem. *60*, 7728–32 (1995); improved procedures with H_2O_2-urea cf. W. Adam, C.M. Mitchell, Angew. Chem. Intern. Ed. *35*, 533–5 (1996).
[63] $MeReO_3$ as dehydrating agent s. Z. Zhu, J.H. Espenson, J. Org. Chem. *61*, 324–8 (1996); cyclopropanation s. ibid. *60*, 7091 (1995).
[64] Review of preparation of chiral drugs s. S.C. Stinson, Chem. Eng. News *73*, No. 41, 44–74 (1996); reviews of asym. synthesis s. Synth. Meth. *47*, 646s*50* (p. 462).
[65] Recent developments s. J.E. Bercaw et al., J. Am. Chem. Soc. *118*, 1045–53 (1996); T.J. Marks et al., ibid. *117*, 12114–29 (1995).
[66] Review s. Synth. Meth. *50*, 54s*50* (p. 463).
[67] D.S. Tan et al., J. Am. Chem. Soc. *117*, 9093–4 (1995).
[68] S. Brand et al., Tetrahedron Letters *36*, 8493–6 (1995).
[69] L.T. Kanerva et al., Tetrahedron:Asym. *6*, 1779–86 (1995).

sponding *anti*-1,3-diol, the essential step involving selective cleavage of the equatorial carbon-oxygen bond of intermediate *l*-menthone cyclic acetals[70]. Another developing aspect of asym. synthesis is 'desymmetrization', wherein a symmetrical molecule is converted to an optically active product by the agency of a chiral auxiliary. Enzymatic hydrolysis (of *meso*-diesters) and O-acylation (of *meso*-diols) has been adapted exhaustively in this area[71], but chemical means are also available. Chiral 1,3-dioxolane-4,5-dimethanols (TADDOLS) – arguably the ligands of the moment – have thus been adapted for desymmetrization of anhydrides by titanium(IV)-catalyzed alcoholysis[72], while enantiodifferentiation of aldehyde groups in a *meso*-dialdehyde is possible by asym. aldol condensation via boron enolates[73]. Unfavourable 1,2-addition of stabilized nucleophiles to α,β-ethyleneoxo compounds can also be achieved by Pd-catalyzed desymmetrization of the corresponding α,β-ethyleneacylals in the presence of chiral 1,2-bis[*o*-(diphenylphosphino)benzoylamino]cyclohexanes[74], the same ligands having been 'rigidified' to enhance asymmetric Pd-catalyzed 1,2-addition of an N-nucleophile to a vinyloxirane[75]. The stereoelectronic effect of remote substitution on face-selectivity has also been recognised, as in asym. reduction of p,p′-disubstituted benzophenones with Corey's 1,3,2-oxazaborolidines[76], while the beneficial effects of dipole alignment in the transition state are apparent in asymmetric aldol condensation with chiral bicyclic N-acylsultams[77]. In a similar vein, asym. catalysis with chiral 1,1′-bi-2-naphthol complexes can be enhanced by incorporation of two different metals (heterobimetallic catalysis), as in the novel asym. Michael addition-aldol condensation with a lithium aluminium 1,1′-bi-2-naphthoxide[78]. However, expensive (R)- or (S)-BINOL can be avoided altogether by using inexpensive *racemic* BINOL in the presence of a readily accessible chiral 'dopand', e.g. diisopropyl D-tartrate, which effectively 'poisons' one of the enantiomers[79]. An even cheaper option might be to invest in catalytic asym. automultiplication, wherein asymmetric induction can be achieved *without* an added chiral reagent if the product itself functions as a chiral ligand[80]. Alternatives to traditional chiral auxiliaries are legion. Thus, chiral phosphinoaryl-Δ^2-oxazolines

[70] T. Harada et al., J. Am. Chem. Soc. *117*, 12346–7 (1995).
[71] Review s. E. Schoffers et al., Tetrahedron *52*, 3769–826 (1996).
[72] D. Seebach et al., Angew. Chem. Intern. Ed. *34*, 2395–6 (1995); by asym. aminolysis s. T. Albers et al., Synthesis *1996*, 393–8.
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[74] B.M. Trost et al., J. Am. Chem. Soc. *117*, 7247–8 (1995).
[75] B.M. Trost, R.C. Bunt, Angew. Chem. Intern. Ed. *35*, 99–102 (1996).
[76] E.J. Corey et al., Tetrahedron Letters *36*, 9153–6 (1995); transmission of chirality through conjugation, s.a. T. Sato et al., Angew. Chem. Intern. Ed. *34*, 2254–6 (1995).
[77] R.K. Boeckman, Jr., B.T. Connell, J. Am. Chem. Soc. *117*, 12368–9 (1995).
[78] H. Wallmann et al., Angew. Chem. Intern. Ed. *35*, 104–6 (1996).
[79] J.W. Faller et al., J. Am. Chem. Soc. *118*, 1217–8 (1996).
[80] K. Soai et al., J. Am. Chem. Soc. *118*, 471–2 (1996).

have proven superior to the Noyori BINAP reagent in both asym. transfer hydrogenation of *dialkyl* ketones[81], and in asym. Heck reactions[82]; in addition, chiral aminoselenides may replace aminoalcohols in asymmetric 1,2-addition of dialkylzincs[83], while C_2-symmetric *tetradentate* Schiff bases are recommended in, for example, cobalt(II)-catalyzed asym. reduction of aryl ketones with $NaBH_4$[84].

Biocatalyzed organic syntheses are clearly here to stay[85], although, in fairness, generality has only been achieved with a handful of reaction types: yeast-catalyzed asym. reduction of ketones, enzymatic hydrolysis, O-acylation, glycosidation[86], peptide synthesis, aldol condensation, and a few others. We still await a Diels-Alder-ase[87], and until such time as carbon-carbon bond formation becomes generally amenable to bio-intervention, it might, as Trost argues, serve the community better by lending more ear and space to the emerging abiological routes[88]. Notwithstanding, certain developments are at hand: crystalline cross-linked enzyme preparations exhibit higher enantioselectivity compared with crude, commercial preparations and are more stable than the corresponding purified enzyme[89]; ultrasonication has an accelerating influence[90], and in yeast-catalyzed asym. reduction the *acetone powdered* preparation of *Geotrichum candidum* is considerably more efficient than the resting cells[91]. The same organism features in the novel deracemization of sec. alcohols by intervention of both an oxidase and a reductase[92], while another yeast species, *Yarrowia lipolytica*, is remarkable in that it reduces ketones to *anti*-Prelog (R)-alcohols (contrasting with baker's yeast)[93]. A particular reference might also be given to enzymatic deprotection[94], chymotrypsin-catalyzed peptide synthesis with choline esters[94], and to a new laccase preparation for oxidation of methylarenes and benzyl alcohols[95].

A major limitation in adapting biocatalysis more routinely is that enzyme activity is normally restricted to a narrow range of solvents and temperature.

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[83] T. Wirth, Tetrahedron Letters *36*, 7849–52 (1995); review s. Synth. Meth. *42*, 616s*50* (p. 460).
[84] T. Mukaiyama et al., Angew. Chem. Intern. Ed. *34*, 2145–7 (1995).
[85] Recent reviews in biocatalysis s. Synth. Meth. *28*, 13s*50* (p. 459).
[86] Review of chemoenzymatic carbohydrate synthesis s. H.J.M. Gijsen et al., Chem. Rev. *96*, 443–74 (1996); s.a. Synth. Meth. *49*, 195s*50* (p. 462).
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[91] K. Nakamura et al., Tetrahedron Letters *37*, 1629–32 (1996).
[92] K. Nakamura et al., Tetrahedron Letters *36*, 6263–6 (1995).
[93] A. Medici, Tetrahedron *52*, 3547–52 (1996).
[94] H.-D. Jakubke et al., Angew. Chem. Intern. Ed. *35*, 106–9 (1996); H. Waldmann et al., ibid. *34*, 2259–62 (1995).
[95] C.-L. Chen et al., J. Org. Chem. *60*, 4320–1 (1995); Synth. Commun. *26*, 315–20 (1996).