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Theilheimer's Synthetic Methods of Organic Chemistry

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Preface

The present *Theilheimer* volume, the fourth in the Tenth Series, contains abstracts and supplementary data from papers published in the field of synthetic organic chemistry in the latter half of 1993 and the first half of 1994. The *Trends* section (p. XI) contains references to data published from the second half of 1994 to March 1995.

As always, emphasis is placed on new functional group conversions, the synthesis of key ring systems and ring transformations in general, and such data as may be of value in routine synthetic chemistry.

The abstracts and supplementary data are arranged according to the Systematic Classification (Survey see p. XXIV) so that reactions of the same type appear together. This is designed to encourage browsing, while the Subject Index serves as the principle tool for retrieving specific information. Subject Index nomenclature – notably that relating to complex functions – may be accessed through the specially developed cross-reference network or via the Formula Index of Complex Functional Groups (s. Volume *48*, p. 471). The formulae of the new functional groups which appear in this volume are published as an update (p. 467).

The Supplementary References Index (p. 468) directs the reader to updated information on previously abstracted methods. This data may be a one-line reference or an edited sub-section, such as updated information on special reaction types and methodology, e.g. asym. enzymatic hydrolysis (p. 5), solid-phase peptide synthesis (p. 136), and enantiomer separations (p. 393). Reviews are also retrievable as supplementary references via the Subject and Supplementary References Index. For convenience and scanning purposes, these reviews are tabulated together (p. 398).

This volume also includes a number of key methods published in the patent literature, e.g. Synth. Meth. *49*, 56. The corresponding *Chem. Abstr.* numbers will appear in the next *Theilheimer* volume as supplementary references.

I would like to express my gratitude to Dr. Theilheimer for his encouragement in the preparation of these yearbooks, and to my colleagues at Derwent Information Ltd., London, whose *Journal of Synthetic Methods* provides the data for inclusion in these volumes.

April 1995 *A.F. Finch*, Editor

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.

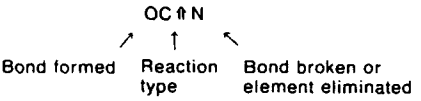
A brief review, *Trends in Synthetic Organic Chemistry*, stresses highlights of general interest and calls attention to developments too recent to be included in the body of the text.

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 468) 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. XXIV), 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.

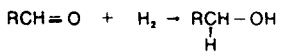


The first part of the symbol refers to the chemical bond formed during the reaction, expressed as a combination of the symbols for the two elements bonded together, e.g. HN, NC, CC. The order of the elements is as follows:

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

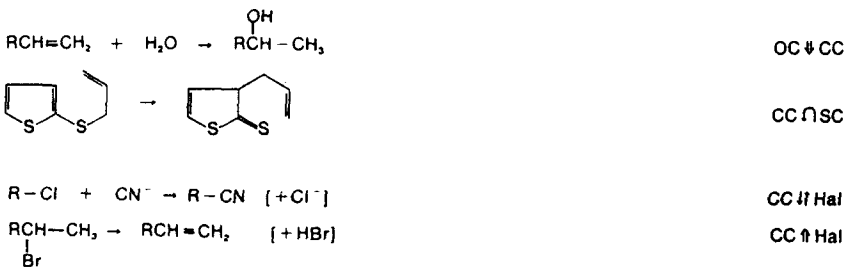
Thus, for the formation of a hydrogen-nitrogen bond, the notation is HN, not NH.

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.



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.

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.

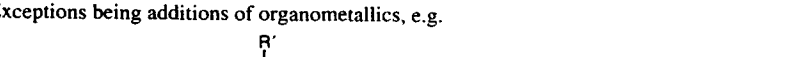
Deoxygenations, quaternizations, stable radical formations, and certain rare reaction types are included as the last few methods in the yearbook. The reaction symbols for these incorporates the special symbols El (electron pair), Het (heteropolar bond), Rad (radical), Res (resolutions), and Oth (other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

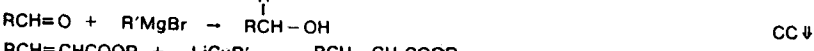
The following rules simplify the use of the reaction symbols:

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.





[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 1995

The fullerene saga of the late eighties will be recalled in years to come as something rather special in the annals of science, not only from the purely chemical perspective, but also as a testimony to multidisciplinary collaboration and a constant reminder that in any sphere of science one is likely to find inspiration across a variety of adjacent borders. In the area of synthetic design, there has always been a sizeable overlay with pharmacology and medicine, as reflected in the taxol story last year (Trends 1994, Volume *48*). But more recently the driving force has come more from our understanding of the complexities of natural process. From biochemistry, we are constantly tapping the chemo- and stereo-selectivity of enzymes[1], in part with a view to securing molecules in a high state of optical purity. Our understanding of metalloenzymes has also spurred the design of simpler model systems in the pursuit of new catalysts, such as transition metal porphyrin and Schiff base complexes which mimic the oxygen-transfer of cytochrome C 450[2]. From immunology, we have adapted the concept of antibody generation for the preparation of highly site-specific 'abzymes': a process which has an interesting parallel in the combinatorial analog synthesis of large, random peptide and small-molecule libraries[3]. But it is, arguably, the most fundamental of all natural processes – the light harvesting mechanism of energy transfer in plants and microorganisms – which has stimulated the most dramatic developments in chemistry, with the promise of reducing many of today's macroscale processes to molecular ones. Here, one heralds the design of 'molecular wires': structurally modifiable molecular entities and supramolecular assemblies with the property of absorbing light energy, and directing it by electron or charge transfer to specific locations in the same molecular framework[4]. We are, indeed, not far from replacing classical electronic circuitry by 'molecular circuitry' with all the customary refinements offered by switches and shunts, and (one might envisage) resistances[5]. Not unrelated, are photorefractive organic polymers which, by the same mechanism of electron

[1] Reviews of enzyme catalysis s. Synth. Meth. *28*, 13s*49* (p. 399).

[2] Recent application in aqueous media with a water-soluble Mn(III)-porphyrin complex s. T.-C. Zheng, D.E. Richardson, Tetrahedron Letters *36*, 833–6, 837–40 (1995); developments in catalyzed epoxidation s. this volume (p. 61).

[3] Procedure for binary coding and screening of compound libraries s. P. Eckes, Angew. Chem. Intern. Ed. *33*, 1573–5 (1994); recent application of Fmoc-amino-acid fluorides to multiple peptide synthesis s. H. Wenschuh et al., Tetrahedron Letters *36*, 1247–50 (1995).

[4] Recent examples of multi-porphyrin light harvesting arrays s. J.S. Lindsey et al., J. Am. Chem. Soc. *116*, 9759–60, 10578–92 (1994).

[5] Overview of self-assembly processes as potential molecular machines s. E.C. Constable, D. Smith, Chem. Brit. *31*, 33–7 (1995).

transfer along a molecular framework, have the potential of storing, in image form, encyclopaedic volumes of data at the molecular level[6]. The impact of such on materials science cannot even be estimated.

While the modelling of 'molecular wires' has been largely restricted to linear systems, there will doubtless be future diversification with branched molecules for channelling energy along different pathways. Here, there is an obvious outlet for *dendrimers* and cascade molecules, research into which is currently in exponential growth and offering a variety of potential applications: in redox chemistry, liquid crystal research, coordination chemistry, drug design, and medical engineering[7]. A particular feature is their ready functionalization and elaboration for specific requirements. Dendridic surfactants, for example, can be manipulated for their solubilizing characteristics[8], dendridic fulvenes, ferrocenes[9], and polysilanes[10] for their potential superconducting properties, and chiral peptidyl dendrimers[11] for highly specific guest-host interactions. The surface characteristics of dendridic polysilane spheres offer in addition the possibility of appending transition metals for use as heterogeneous catalysts. Not only are they readily modifiable and easily recovered after reaction, there is the added bonus of stability, in contrast with conventionally supported or homogeneous catalysts where leaching of the metal is often a problem[12].

Leaching and loss of sensitive and/or expensive homogeneous transition metal catalysts on work-up can also be prevented by suitable placement of the catalyst in a heterogeneous environment. Thus, in Noyori-type asym. hydrogenation (cf. Synth. Meth. *42*, 45), a water-soluble ruthenium 2,2′-bis-(triarylphosphino)-1,1′-naphthyl(chloro)ruthenium complex has been supported on a thin film of hydrophilic ethylene glycol on a controlled-pore glass surface, thereby exposing the catalyst over a large surface area to the substrate dissolved in a hydrophobic organic phase[13]. The same principle (with product separation in mind) has also been applied in an aqueous organic 2-phase system, reaction being accelerated by promoter ligands (e.g. PPh_3) in the organic phase which tempt the water-soluble transition metal catalyst to the interface where the substrate (in the organic phase) is transformed[14].

[6] Overview s. R. Dagani, Chem. Eng. News *73*, No. 8, 28–32 (1995).
[7] Overviews s. F. Vögtle et al., Angew. Chem. Intern. Ed. *33*, 2413–20 (1994); R.F. Service, Science *267*, 458–9 (1995).
[8] T.M. Chapman et al., J. Am. Chem. Soc. *116*, 11195–6 (1994).
[9] A.J. Bard, Nature *374*, 13 (1995).
[10] J.B. Lambert et al., Angew. Chem. Intern. Ed. *34*, 98–9 (1995).
[11] Note the principle of generating three peptide chains from a common nitrogen atom, W. Steglich et al., Tetrahedron Letters *36*, 857–60 (1995).
[12] G. van Koten et al., Nature *372*, 659 (1994).
[13] K.T. Wan, M.E. Davis, Nature *370*, 449–50 (1994).
[14] R.V. Chaudhari et al., Nature *373*, 501–3 (1995).

While considering developments in transition metal catalysis, it is perhaps worth elaborating on what might be generalized as 'dual catalysis'. There are many strands: coupling of two steps with the same catalyst, exemplified by such tandem processes as hydroboration-cross-coupling[15]; sequential coupling with different catalysts[16], and in tandem processes with the same catalyst in different oxidation states[17]. Another facet is the cooperative effect of two metal centres in binuclear catalysis[18], and another, inspired by hydrolytic metalloenzyme activity, illustrates the potential of achieving enormous rate enhancement (10^{13}-fold!) by the concerted action of two of the same transition metal ions in a suitably coordinated environment[19]. The synergistic effect of combining catalysts is a further manifestation, exemplified by the hydrogenation of carboxylic acids with a Group 8–10 late transition metal combined with a Group 6 or 7 early transition metal carbonyl[20]. More startling, however, is the bifunctional catalytic activity of transition metal-substituted polyoxometallates, which can facilitate quite independent processes simultaneously in a catalytic cycle. Here, metal-substituted polyoxomolybdates promote, in one operation, the oxygenation of hydrocarbons to hydroperoxides and their subsequent utilization, *in situ*, as oxygen transfer agents in catalyzed epoxidation[21]. The dynamic action of polyoxometallates is also matched, in spectacular fashion, by their own dynamic assembly, *in situ*, from non-catalytic fragments. A new breed of so-called 'smart' catalysts has thus been realized, the ultimate goal being to fashion an 'immortal' species which can perform its catalytic role and have, at the same time, an inbuilt self-replicating mind should adventitious degradation happen to take place during reaction[22].

Turning to more specific aspects of transition metal catalysis, procedures initiated by oxidative addition of Pd(0) to the carbon-halogen bond, such as Heck arylation, have been extended by trapping the intermediate organopalladium(II) species before the familiar β-hydrogen elimination has a chance to terminate reaction. An appended unsaturation thus facilitates ring closure via intramolecular carbopalladation, which may then be developed in cascade fashion to build highly condensed systems prior to elimination of the catalysts[23]. In the presence of carbon monoxide, there is the added possibility of introducing a carbonyl function via inter- or intra-molecular acylpallada-

[15] Example s. Synth. Meth. *49*, 836.
[16] Example s. Synth. Meth. *49*, 831.
[17] Example s. Synth. Meth. *49*, 922.
[18] Example s. Synth. Meth. *49*, 125.
[19] A. Tsubouchi, T.C. Bruice, J. Am. Chem. Soc. *116*, 11614–5 (1994); overview of such model hydrolytic systems s. M.W. Göbel, Angew. Chem. Intern. Ed. *33*, 1141–3 (1994).
[20] T. Fuchikami et al., Tetrahedron Letters *36*, 1059–62 (1995).
[21] R. Neumann, M. Dahan, J. Chem. Soc. Chem. Commun. *1995*, 171–2.
[22] C.L. Hill, X. Zhang, Nature *373*, 324–6 (1995).
[23] Example s. Synth. Meth. *49*, 829.

tion[24], termination being effected by a variety of nucleophiles, again, inter- or intra-molecularly[25]. Substrates with a *saturated* carbon-halogen bond participate in the same conversion, although here the intermediate organo-palladium(II) species is generated via radical ring closure induced by single electron transfer[26]. By direct analogy, oxidative addition of Pd(0) to the silicon-chlorine bond preceeds intramolecular silylpalladation of the acetylene function[27], while intermolecular carbopalladation of allenes with CH-acidic compds. is considered to arise via oxidation addition to the carbon-hydrogen bond[28]. With reference to palladium π-allyl chemistry, asymmetric C-allylation is a recurring theme, where the nature of the external chiral auxiliary[29] and the counterion[30] can dramatically influence the enantioselectivity. Kinetic deracemization of allyl esters can be effected by applying the same methodology[31], while Bäckvall's intramolecular 1,4-addition via π-allyl species (Synth. Meth. *46*, 445) has been extended in a new carbocyclization by using allylsilanes as the appended nucleophile[32]. Displacement of substituents at the 2-position of π-allyl systems, however, is not so easy – unless, that is, one resorts to Pt-catalysis, by which an intramolecular displacement of oxygen by nitrogen is made possible by the favourable formation of platinacyclobutanes[33]. As for nickel catalysis, applications are many and varied, and, to some extent, offer inexpensive alternatives to established methods, such as Pd-catalyzed transfer hydrogenation[34] and Ru-catalyzed asym. hydrogenation[35]. Suzuki-type cross-coupling of boronic acids can also be achieved under Ni-catalysis[36], as also intramolecular carbometalation via oxidative addition of nickel(0)[37]. Processes initiated by oxidative addition of Ni(0) to the silicon-hydrogen bond are exemplified by a new regio- and stereo-specific ring closure to produce cyclic 2-vinylalcohols[38], while intermolecular carbonickelation-cross-coupling of alkynes can be carried out via oxidative addition of Ni(0) to the silicon-chlorine bond[39]. Water-soluble Ni-

[24] Example s. E. Negishi et al., J. Am. Chem. Soc. *116*, 7923–4 (1994).
[25] Recent example of fused lactam closure s. E. Negishi et al., Tetrahedron Letters *36*, 1771–4 (1995).
[26] N. Miyaura et al., J. Chem. Soc. Chem. Commun. *1995*, 295–6.
[27] M. Suginome et al., Tetrahedron Letters *35*, 8635–8 (1994).
[28] Y. Yamamoto et al., J. Am. Chem. Soc. *116*, 6019–20 (1994).
[29] Developments s. Synth. Meth. *41*, 737s*49* (p. 309); note, however, the reversal of regioselectivity by using chiral tungsten complexes, G.C. Lloyd-Jones, A. Pfaltz, Angew. Chem. Intern. Ed. *34*, 462–4 (1995).
[30] s. Synth. Meth. *49*, 782.
[31] B.M. Trost, M.G. Organ, J. Am. Chem. Soc. *116*, 10320–1 (1994).
[32] A.M. Castano, J.E. Bäckvall, J. Am. Chem. Soc. *117*, 560–1 (1995).
[33] S. Murai et al., J. Am. Chem. Soc. *116*, 4125–6 (1994).
[34] S. Iyer, J.P. Varghese, J. Chem. Soc. Chem. Commun. *1995*, 465–6.
[35] s. Synth. Meth. *49*, 56.
[36] V. Percec et al., J. Org. Chem. *60*, 1060–5 (1995).
[37] A. Delgado et al., J. Am. Chem. Soc. *116*, 12133–4 (1994).
[38] M. Mori et al., J. Am. Chem. Soc. *116*, 9771–2 (1994).
[39] S. Ikeda, Y. Sato, J. Am. Chem. Soc. *116*, 5975–6 (1994).

and Pd-catalysts are also welcome as the trend to replacing organic solvents by more acceptable aqueous media gathers momentum[40]. Under rhodium catalysis, there is an interesting *o*-alkylation with olefins[41] which parallels the Ru-catalyzed version of Murai (Synth. Meth. *49*, 679), as well as the first synthetically viable selective activation of the carbon-carbon[42] and carbon-fluorine bond[43] under homogeneous conditions. The same metal participates in oxidative addition to the silicon-hydrogen bond in a novel silylative carbonylation of diynes as an alternative [with functionalization!] to the Pauson-Khand methodology[44]. A ruthenium version of the Trost metathesis of 1,6-dienes (Synth. Meth. *43*, 651) has also been extended to 1,7-enynes by an altogether unrelated mechanism[45].

Among the newly available Lewis acid catalysts, perhaps ytterbium triflate takes pride of place for it's versatility in achiral and chiral mode, coupled with its insensitivity to water[46]. Hard on its heels comes $Sc(OTf)_3$ and, more recently, $Hf(OTf)_4$[47]. The oxygenophilicity of aluminium has been tapped in diverse contexts. In Diels-Alder synthesis (Subject Index: **'Diene synthesis'**) with enones, for example, the familiar *endo*-approach of the diene is blocked by encapsulation of the carbonyl group with a hindered Al-aroxide[48]; and, by the same mechanism, with the same reagent, the formyl group of enals can be blocked so that Michael-type addition can take place without the complication of 1,2-addition[49]; in asym. Claisen rearrangement of allyl vinyl ethers, it is an sp^3 oxygen which is 'pocketed' (by a chiral Al-aroxide) in such a way that face selectivity of the ensuing [3.3]-sigmatropic shift is maximized[50]. Among novel transition metal-centred Lewis acids, chromium, molybdenum and tungsten metal-imide complexes have recently surfaced[51], while a chiral rhenium Lewis acid facilitates asym. 1,4-addition

[40] Recent examples include: dehalogenation in aq. media with $NaBH_4$ and a water-soluble Ni-complex, M. Stiles, J. Org. Chem. *59*, 5381–5 (1994); Stille-coupling in aq. media with a water-soluble Pd-complex, N.A. Bumagin et al., Tetrahedron Letters *36*, 125–8 (1995); Suzuki-coupling with fragile (Z)-enoates s. J.P. Genêt et al., ibid. 1443–6.

[41] Y.-G. Lim et al., J. Chem. Soc. Chem. Commun. *1994*, 2267–8.

[42] M. Murakami et al., Nature *370*, 540–1 (1994).

[43] M. Aizenberg, D. Milstein, Science *265*, 359–61 (1994).

[44] I. Ojima et al., J. Org. Chem. *59*, 7594–5 (1994).

[45] S. Murai et al., J. Am. Chem. Soc. *116*, 6049–50 (1994).

[46] Review of water-tolerant lanthanide(III) triflates s. Synth. Meth. *48*, 201s*49* (p. 402); more recent applications include: regiospecific ring opening of epoxides, P. Crotti et al., Tetrahedron Letters *35*, 6537–40 (1994); of oxetanes, ibid. 7089–92; of cyclic sulfites, W.J. Sanders, L.L. Kiessling, ibid. 7335–8 (1994); of aziridines, M. Meguro et al., ibid. 7395–8; Sakurai-type reaction with allylstannanes, N. Greeves et al., ibid. 4639–40; and high-pressure Michael addition, G. Jenner, ibid. *36*, 233–6 (1995).

[47] Friedel-Crafts acylation with $Sc(OTf)_3$ s. S. Kobayashi et al., Synlett *1994*, 545–6; with $Hf(OTf)_4$ cf. Tetrahedron Letters *36*, 409–12 (1995).

[48] H. Yamamoto et al., J. Am. Chem. Soc. *116*, 12115–6 (1994).

[49] H. Yamamoto et al., J. Am. Chem. Soc. *116*, 4131–2 (1994).

[50] H. Yamamoto et al., J. Am. Chem. Soc. *117*, 1165–6 (1995).

[51] W.-H. Leung et al., Tetrahedron Letters *36*, 107–8 (1995).

of organocuprates[52]. Niobium pentachloride is also noteworthy for directing the Sakurai reaction towards cyclopropanation (with two equivalents of allylsilane)[53]. In the context of asymmetric Lewis acid catalysis, there is a novel concept of Brønsted acid-assistance by which face selectivity can be dramatically enhanced. This is exemplified by asym. protonation of enoxysilanes[54], asym. diene[55] and heterodiene[56] synthesis, and the first efficient asym. synthesis of β-aminocarboxylic acid esters from an achiral imine[56].

With the increasing demands from medicine, biochemistry, and materials science for compounds in a high state of optical purity, it is not surprising that asymmetric synthesis continues to play an ever-increasing role in everyday organic chemistry. There are certain key elements, among which: asym. induction by external chiral auxiliaries (natural or otherwise); by internal (substrate-incorporated) chiral residues (natural or otherwise); kinetic resolution, asymmetrization; and associated aspects[57], such as methods of determining absolute configuration and enantiomeric purity. Among chiral reagents (enzymes aside), axially asymmetric 1,1′-bi-2-naphthyls continue to play a central role, either as coordinating ligands in transition metal catalysis [through phosphine-substitution][58] or in Lewis acid catalysis, where solvent and temperature have also been shown to have a critical effect on enantioselectivity[59]. As a development of this theme, the pioneering asym. hydrogenation of ketones with Ru-BINAP [Synth. Meth. *42*, 45] has now been upgraded by using iridium instead[60], while asym. hydrogenation of olefins is less expensive with the nickel-BINAP equivalent[35]. Furthermore, hydrogenated BINAP catalysts may be superior[61], as also chiral bi(phenanthryl) analogs[62]. However, the most significant advance has been made with the design of chiral ethylene-1,2-bis(η^5-4,5,6,7-tetrahydro-1-indenyl)titanocene-1,1′-binaphthyl-2,2′-diolates, which have proved invaluable for asym. hydrogenation of *unfunctionalized* trisubst. olefins and imines[63] and of ketones[64].

[52] Y. Wang, J.A. Gladysz, J. Org. Chem. *60*, 903–9 (1995).
[53] K. Suzuki et al., Tetrahedron Letters *36*, 899–902 (1995).
[54] H. Yamamoto et al., J. Am. Chem. Soc. *116*, 11179–80 (1994).
[55] S. Kobayashi et al., J. Org. Chem. *59*, 3758–9 (1994).
[56] K. Ishihara et al., J. Am. Chem. Soc. *116*, 10520–4 (1994).
[57] s. **Res** section (p. 393).
[58] Recent examples include asym. 1,4-hydrosilylation, Y. Hatanaka et al., Tetrahedron Letters *35*, 7981–2 (1994); and asym. [2+2+2]-cycloaddition, Y. Sato et al., J. Org. Chem. *59*, 6133–5 (1994).
[59] D. Krishnamurthy, G.E. Keck, J. Am. Chem. Soc. *117*, 2363–4 (1995); with tridentate chiral ligands s. E.M. Carreira et al., ibid. *116*, 8837–8 (1994); effect of achiral additives on reversal of enantioselectivity s. S. Kobayashi, H. Ishitani, ibid. 4083–4; asym. [2+2]-cycloaddition s. S. Miyano et al., J. Chem. Soc. Perkin Trans. I *1994*, 1549–50.
[60] H. Takaya et al., J. Am. Chem. Soc. *115*, 3318–9 (1993).
[61] H. Takaya et al., J. Chem. Soc. Perkin Trans. I *1994*, 2309–32.
[62] T. Hiyashi et al., Tetrahedron Letters *35*, 4813–6 (1994).
[63] s. Synth. Meth. *49*, 54; of enamines s. N.E. Lee, S.L. Buchwald, J. Am. Chem. Soc. *116*, 5985–6 (1994); with kinetic resolution s. ibid. 9373–4.
[64] S.L. Buchwald et al., J. Am. Chem. Soc. *116*, 11667–70 (1994).

Asym. induction with chiral diamines[65], 2-aminoalcohols[66] and bis(Δ^2-oxazolines)[67] is an ongoing theme, and more recently, chiral 1,2-bis(sulfonylamines)[68] have been exploited to good effect. Chiral tetramines[69] in catalytic amount induce asymmetry in α-benzylation and accelerate reaction at the same time, while amphoteric 1,3,2-dioxaborolane-4,5-dicarboxamides[70] facilitate cyclopropanation of *cis*- or *trans*-allyl alcohols by virtue of *dual* chelation to both oxygen (of the substrate) and an auxiliary metal (zinc). In routine asymmetric Pd- or Ru-catalyzed conversions, however, the introduction of ferrocenyldiphosphines[71] and ruthenocenyldiphosphines[72] as chiral ligands presents a major breakthrough in terms of enhancement of enantioselectivity. With regard to asym. induction by internal chiral auxiliaries, there are further outlets for Evans-type 2-oxazolidones[73], Oppolzer-type sultams[74], Meyers-type Δ^2-oxazolines[75], and menthol-based substrates[76]. Induction with chiral bicyclic lactams (in asym. aldol condensation)[77] and with bicyclic thiolactams (in asym. thio-Claisen rearrangement)[78] are variations on the theme, while the pseudoephedrine[79] residue is more advantageous than ephedrine in terms of product separation. Perhaps the most notable highlight, however, is a recent asym. C-α-alkylation of α-aminoesters in the

[65] Recent examples include asym. induction with bis(aziridines), D. Tanner et al., Tetrahedron Letters *35*, 4631–4 (1994); asym. *o*-α-alkylation with sparteine, P. Beak et al., J. Am. Chem. Soc. *116*, 9755–6 (1994); and reversal of enantioselectivity with chiral 1,2-amines, S. Kobayashi, M. Horibe, ibid. 9805–6.

[66] Note, for example, catalytic asym. protonation with (–)-isopropylephedrine s. C. Fehr, J. Galindo, Angew. Chem. Intern. Ed. *33*, 1888–9 (1994); asym. β-lactam condensation s. F. Cozzi et al., Tetrahedron Letters *36*, 613–6 (1995).

[67] Recent application to asym. addition of RLi to aldimines s. S.E. Denmark et al., J. Am. Chem. Soc. *116*, 8797–8 (1994); asym. Pd-catalyzed hetero- and carbo-annulation of allenes s. R.C. Larock, J.M. Zenner, *60*, 482–3 (1995).

[68] Recent examples include: asym. synthesis of sec. alcohols, P. Knochel et al., Tetrahedron Letters *35*, 4539–40 (1994); asym. [2+2]-cycloaddition, s. Miyano et al., J. Chem. Soc. Chem. Commun. *1994*, 2281–2.

[69] K. Koga et al., J. Am. Chem. Soc. *116*, 8829–30 (1994).

[70] A.B. Charette, H. Juteau, J. Am. Chem. Soc. *116*, 2651–2 (1994).

[71] A. Togni et al., J. Am. Chem. Soc. *116*, 4062–6 (1994).

[72] s. Synth. Meth. *49*, 555.

[73] With rigid 3-acyl-2-oxazolidones s. C. Palomo et al., J. Chem. Soc. Chem. Commun. *1994*, 1861–2; use in resolution of carboxylic acids s. G. Li et al., J. Chem. Soc. Perkin Trans. I *1994*, 3057–9; asym. addition to N-tosylimines s. P.B. Wyatt et al., Tetrahedron *50*, 12755–72 (1994).

[74] Asym. Michael addition s. L.N. Pridgen et al., J. Org. Chem. *59*, 7188–9 (1994); asym. radical substitution s. E. Baciocchi et al., Synlett *1994*, 821–2.

[75] Note asym. Michael addition of amines to the benzene ring, M. Shimano, A.I. Meyers, J. Am. Chem. Soc. *116*, 6437–8 (1994). Review of Δ^2-oxazolines s. Synth. Meth. *47*, 711s*49* (p. 402).

[76] Note asym. reductive N-methylation, J.D.F. de Sousa et al., J. Am. Chem. Soc. *116*, 9745–6 (1994).

[77] R.K. Boeckman, Jr. et al., Tetrahedron Letters *35*, 8521–4 (1994).

[78] P.N. Devine, A.I. Meyers, J. Am. Chem. Soc. *116*, 2633–4 (1994).

[79] A.G. Myers et al., J. Am. Chem. Soc. *116*, 9361–2 (1994); note also consideration of added salt effects on enantioselectivity, K. Rück, Angew. Chem. Intern. Ed. *34*, 433–5 (1995).

absence of an external chiral source (the chirality of the substrate effectively remaining intact on enolization)[80]. The key aspect of kinetic resolution can, perhaps, best be surveyed under the Subject Index entry **'Stereoisomers'** and the **Res** section (p. 393), although a special mention might be made of the dynamic element by which a racemic substrate can be converted to one enantiomer *almost exclusively* if there is a mechanism for converting the lesser reactive enantiomer to the more reactive one[81]. Asymmetrization is normally associated with conversions of *meso*-substrates, but the successful asym. diene syntheses with a symmetrical maleimide is evidence that such asymmetrization can also be achieved with a C_{2v}-symmetric olefin (thought not, alas, with maleic anhydride!)[82]. Kinetic resolution can also accompany diene synthesis[83]. For devotees of asym. dihydroxylation, there is now an in-depth review[84]; and, finally, for all, there is the prospect of preparing homochiral products with *partially resolved* [inexpensive!] ligands, underscoring non-linear effects in asymmetric catalysis[85].

The unique site- and stereo-selectivity of enzymes accounts for the ongoing development of laboratory-scale enzymatic or microbiological techniques, of which the most notable in the last few years gave been associated with asym. microbiological hydrogenation of ketones (p. 42), lipase-catalyzed hydrolyses (p. 4–5), transesterification (p. 90), and, more recently, microbiological oxidation of alcohols (Synth. Meth. *49*, 995). Many such processes proceed with kinetic resolution, and have been adapted for the preparation of compounds in a high state of optical purity. However, destabilization of enzyme preparations is sometimes a problem, which, for lipases, can now be overcome by their entrapment, heterogeneously, in tailor-made hydrophobic sol-gels[86]. The same is true for reducing microbes which may be entrapped within a water-adsorbent polymer so that reaction can be undertaken (with high enantioselectivity) in *organic* media (hexane)[87]; heptane, however, provides an alternative to aqueous media for microbiological oxidation with *Bacillus stereothermophilus* for an easier work-up[88], while glycosidation is considerably cheaper with recombinant whole cells than with an enzyme preparation[89]. For adjusting (engineering) enzyme specificities, it has been demonstrated that by changing three amino-acids of the standard

[80] K. Fuji et al., J. Am. Chem. Soc. *116*, 10809–10 (1994).
[81] Examples of dynamic kinetic resolution s. K. Nunami et al., Tetrahedron Letters *35*, 8639–42 (1994); N.J. Turner et al., ibid. *36*, 1113–6 (1995).
[82] E.J. Corey et al., J. Am. Chem. Soc. *116*, 12089–90 (1994).
[83] E. Winterfeldt et al., Angew. Chem. Intern. Ed. *34*, 448–50 (1995).
[84] s. Synth. Meth. *48*, 142*s49* (p. 402); update s. **OC ↓ CC** (p. 64).
[85] H.B. Kagan et al., J. Am. Chem. Soc. *116*, 9430–9 (1994).
[86] M.T. Reetz et al., Angew. Chem. Intern. Ed. *34*, 301–3 (1995).
[87] K. Nakamura et al., Tetrahedron Letters *36*, 265–6 (1995).
[88] A. Medici et al., Tetrahedron Letters *36*, 441–2 (1995).
[89] C.-H. Wong et al., Angew. Chem. Intern. Ed. *33*, 1241–2 (1994).

lipase PS the enantioselectivity of the hydrolase can be reversed[90], whereas replacement of just one amino-acid may be sufficient to provide an optimum enzyme for hydrocarbon oxidation[91]. The recently engineered subtiligase (a subtilisin mutant with adjustable sequence specificities) is, perhaps, even more notable as reflected in its role during RNase A synthesis[92] and in cyclization of linear peptide esters[93]. Abzymes (antibody catalysts) perhaps represent the ultimate in tailor-made catalysts, but practical applications have not materialized in view of the specialized experimentology and deficiencies in yield. Here, Lerner's enantioselective hydrolysis of enolethers (not achievable by chemical means!) on the *multigram* scale with conventional laboratory apparatus will hopefully assuage the detractors[94]. There is also an indication, at least in respect of tailoring antibodies to DNA, that antibodies can be generated by semi-synthetic means *in vitro*[95]. Recent highlights in this field include abzyme-catalyzed cationic ring closures[96], deprotection[97], and the feasibility of rate enhancement under general base catalysis[98].

The upsurge in radical-based methodologies has been matched by a variety of novel procedures for generating radicals. Alkyl radicals – readily obtainable from halides by the classical tin hydride route – are now accessible more cleanly by photolysis of bromides in the presence of Et_3N[99], or from hydrocarbons via photo-induced single electron transfer[100]. They can also be generated in aq. media by using water-soluble organotin(IV) dicarboxylates in the presence of $NaBH_4$ and a water-soluble initiator[101]. Photolytic methods have also been adapted for the generation of β-ketoalkyl[102] and carbalkoxyl [ROC(O)O•] radicals[103], whereas anionic 1-oxidoalkylidenepentacarbonylchromium complexes serve as novel precursors of acyl radicals[104]. With reference to nitrogen-centred radicals, due mention should be made of ring closures of azidoiodides via cyclic aminyl radicals[105], which follows an earlier methodology via N-stannylaminyl radicals[106]. Sulfonyl radicals, however, feature in oxidative procedures based on single electron

[90] Y. Hirose et al., Tetrahedron Letters *36*, 1063–6 (1995).
[91] J. Chem. Soc. Chem. Commun. *1994*, 2761–2.
[92] Overview of such peptide ligases s. H.-D. Jakubke, Angew. Chem. Intern. Ed. *34*, 175–7 (1995).
[93] D.Y. Jackson et al., J. Am. Chem. Soc. *117*, 819–20 (1995).
[94] R.A. Lerner et al., Angew. Chem. Intern. Ed. *33*, 475–7 (1994).
[95] S.M. Barbas et al., J. Am. Chem. Soc. *116*, 2161–2 (1994).
[96] R.A. Lerner et al., Science *264*, 1289–93 (1994).
[97] K.D. Janda et al., J. Am. Chem. Soc. *117*, 2123–7 (1995).
[98] S.N. Thorn et al., Nature *273*, 228–30 (1995).
[99] J. Cossey et al., Tetrahedron Letters *35*, 8161–2 (1994).
[100] M. Mella et al., J. Chem. Soc. Chem. Commun. *1995*, 41–2.
[101] R. Rai, D.B. Collum, Tetrahedron Letters *35*, 6221–4 (1994).
[102] G. Pandey et al., Tetrahedron Letters *35*, 7837–40 (1994).
[103] M. Newcomb, D. Dhanabalasingam, Tetrahedron Letters *35*, 5193–6 (1994).
[104] H. Sakurai, K. Narasaka, Chem. Letters *1994*, 2017–20.
[105] S. Kim et al., J. Am. Chem. Soc. *116*, 5521–2 (1994).
[106] S. Kim et al., J. Am. Chem. Soc. *115*, 3328–9 (1993).