Synthesis

Editorial

Dieter Enders, editor of SYNTHESIS since 1985

When in 1971 the University of Giessen offered me a position as full professor of organic chemistry (succession of *F. Kröhnke* on *Liebig*'s chair) a delegation of three ambitious chemistry students from Giessen visited me in Karlsruhe to enquire whether, in case I accepted the offer, they could carry out the experimental diploma work (*cf.* master thesis) in my group. One of the three candidates was actually Dieter Enders, who subsequently finished the Diploma and PhD theses in record time (by 1972 and by 1974, respectively). The topic of his work was *umpolung* of amine/imine reactivity, mainly through lithiated nitrosamines.[1] Dieter then joined *E. J. Corey*'s group for postdoctoral research (1974–1975), in which he studied the generation of lithiated *tert*-butylimines and dimethylhydrazones (enolate equivalents) and their reactions with various electrophiles.[2] In the period 1972–1975, Dieter received a highly competitive stipend of the *Studienstiftung des Deutschen Volkes*.

Back from Harvard Dieter started independent research for a *Habilitation*. In 1979 he became a Privatdozent (corresponding to an assistant professor) in Giessen, and already one year later he moved to the University of Bonn as associate professor; from 1975 through 1984 he was recipient of prestigious fellowships of the *Fonds der Chemischen Industrie* and the *Deutsche Forschungsgemeinschaft* (DFG). In 1985 he accepted the offer of the Rheinisch-Westfälische Technische Hochschule (RWTH) in Aachen, where he held the chair of organic chemistry until his retirement in 2014. He now continues doing research financed by an advanced grant from the European Research Council (ERC).

As major part of the habilitation, Dieter developed the SAMP/RAMP chiral-auxiliary system for syntheses of enantiopure compounds, which turned out to be a gold mine and to become his trade mark all the way into the 21st century.[3] Over the years, applications of this method for overall enantioselective transformations involved not only a myriad of classical reactions of main-group organic chemistry [for instance α-carbonyl alkylation and introduction of heteroatoms (Si, N, P, O, S, halogens), aldol addition, benzoin condensation, *Mannich* reaction, *Michael* and *aza-Michael* additions, allylations, and allylic rearrangements, *Diels–Alder* and 1,3-dipolar cycloadditions etc.], but also led to the discovery of new types of reactivities, such as a non-organometallic *umpolung* of formaldehyde. In the three- volume *Compendium of Chiral Auxiliary Applications* edited by *G. Roos* (Academic Press: New York, **2002**), covering the period up to the year 2000, there are pages and pages of examples published by the Enders group, and the SAMP formula is shown on the cover of the volumes, which also contain applications of the *Pioneer Auxiliary* SMP.[4] Chiral triazolinylidene carbene catalysts, which are actually *organo-*

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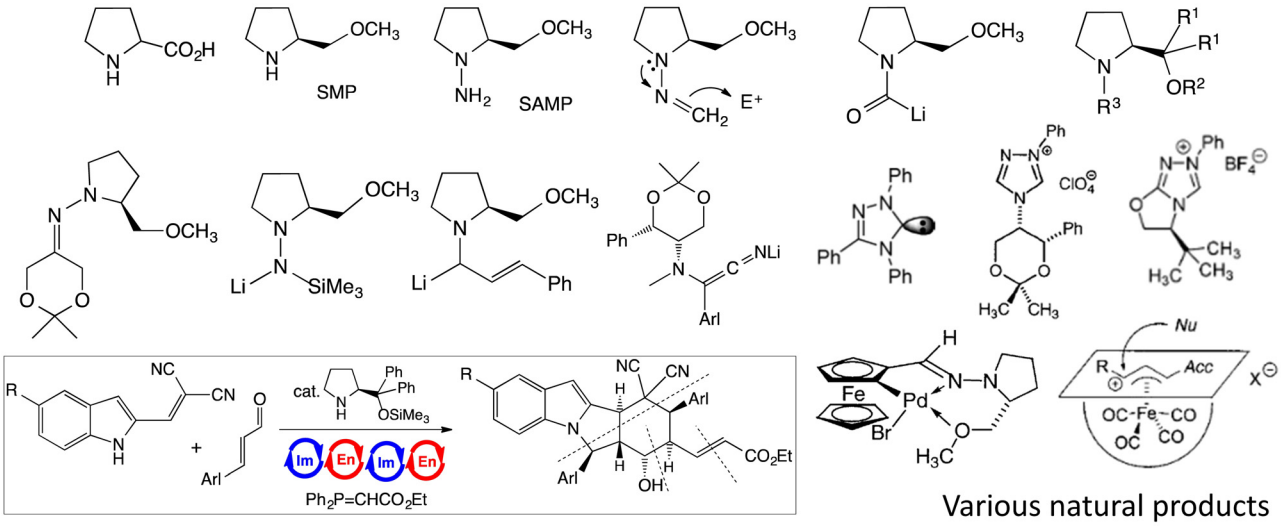
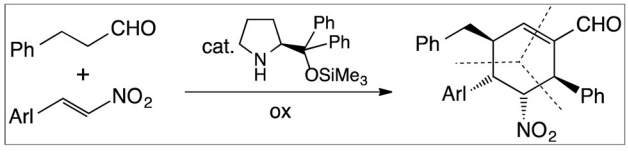


Alkaloids

Ladybugs (*Coleoptera: Coccinellidae*)
Mexican Bean Beetle

Pheromones

Small Forest Ant
Drosophila mulleri
Banded Cucumber Beetle
Cigarette Beetle
Pitch Pine Looper
Banana Weevil Cosmopolites sordidus
Palm Weevils
Rice and Corn Beetle
New Zealand Ascidian Pseudodistoma novaezelandiae
Eucalypt Longicorn, Phoracantha synonyma



fragrants
lignanes
carbohydrates

Various natural products

(*R,R*)-Statin
(+)-Aspicilin
L-threo- and D-erythro-Sphingosine
(–)-Malingolide
(*R,S*)-Dehydroiridodiol
(–)-Neonepetalactone
(+)-Conagenin
(–)-(*R*)- and (+)-(*S*)-[6]-Gingerol
(4*R*,6*S*,7*S*)-Serricornin
(–)-Callystatin A
(*S*)-(+)-Argentilactone
(–)-Callystatin A
(–)-Lintetralin
Attenol A and B
(+)-Altholactone

catalysts, became another field to which Dieter turned[5] in the 1990s to carry out enantioselective benzoin condensations, *Stetter* reactions, and other processes.

Besides the contributions to main group chemistry there are also a number of enantioselective transformations in the list of Dieter's achievements, which make use of transition and lanthanide elements (Cr, Fe, Zr, Ru, Rh, Pd, Ag, Ce, Yb, Au). Most remarkable are various iron derivatives, for instance chiral tetracarbonyl iron allyl complexes, applied for allylic substitutions with self-regeneration of stereocenters.[6]

At the turn of the century, a 30-year period of chiral auxiliaries ended and was replaced by a boom called enantioselective *organocatalysis*, lasting until today. The re-discovery of organocatalysis[7] started with proline (*cf. Yamada*, *Wiechert*, and *Hajos* in 1969, 1971, and 1974) and one of the reactions studied first in 2001 was the *Michael* addition of ketones to nitrostyrene (*List*, *Barbas*, *Enders*[8]), a type of reaction dear to the Enders group.[9]

While other organocatalysts, such as chiral carbenes, squaramides, and Brønsted acids, were also used by Dieter in previous and subsequent investigations, the most prominent catalysts employed in his recent publications are proline-derived pyrrolidines, especially those of the *Hayashi–Jørgensen*-type (*S*)- or (*R*)-2-[$ArI_2(R_3SiO)C$]-pyrrolidines.[10] It turned out that whole sequences of reactions could be achieved by the same or two different chiral organocatalysts, which would, for instance, activate an enal moiety by iminium-ion formation and an aldehyde group by enamine formation in the same reaction mixture, forming enantiopure products with up to six, sometimes all adjacent stereogenic centers in densely functionalized products; "collaborations" of organocatalysts and organometallic catalysts for performing reaction sequences are also possible. Dieter's group has specialized in one-pot sequence transformations:[11] in the list of his last 170 publications (numbers 410–580) since 2005 there are no less than 60 papers containing the term "tandem", "domino",[12] "triple domino", "branched domino", "cascade", "triple- or quadruple-cascade", "one-pot", "multi-component" and/or "sequence" in

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the title. In a way, Dieter has become the master of domino reactions within the community of chemists specializing in organocatalysis;[11,13] last year he actually invited the international community of colleagues in the field for the first DOMINOCAT Symposium in Aachen.[14]

Understandably from my own background, I have, so far, discussed Dieter's accomplishments in synthetic methodology most comprehensively. It would, however, not be fair to omit mentioning that the Enders group has published numerous applications of their methods for the syntheses of natural products and of compounds with biologically activity . When browsing through Dieter's list of publications it becomes evident that ca. 15% contain the name of a natural product, with a preference for insect pheromones and defence alkaloids as well as fragrances, in the title. There are also cytotoxic and antifungal compounds, protease and glycosidase inhibitors, amino- and carba-sugars, and a *de novo* carbohydrate synthesis, to mention only a few. In the corresponding papers, the enantio- and diastereoselective synthesis of the compounds is described, which often includes determination of structure or correction thereof (absolute and relative configuration!). Possible practical applications on an industrial scale of some of the products (*cf.* a >250 kg/a spiroketal bark-beetle aggregation pheromone) are evidenced by a number of patents filed under Dieter's name.

As service to the community of organic chemists, Dieter Enders has not only meticulously documented the results of his research group in experimental sections of his publications, but he has also written comprehensive review articles and book chapters about various areas he had been engaged in, and he "spread the news" in hundreds of invited lectures given in universities, in companies, and at meetings all over the world.

The influence and impact of Dieter Enders in organic chemistry of Germany is evident from his leading role in establishing and maintaining a collaborative research center (DFG-Sonderforschungsbereich, SFB), entitled "Asymmetric Syntheses with Chemical and Biological Methods", and massively supported for a maximum term of twelve years; SFBs are "long-term university research centers in which scientists and researchers work together within a cross-disciplinary research program" (here RWTH Aachen, HHU Düsseldorf, Research Center Jülich). Dieter Enders was also instrumental in a similar DFG project (Transferbereich), fund-

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ing collaborative efforts of universities and companies, entitled "Stereoselective Synthesis of Active Agents".

For his research achievements Dieter Enders received many awards, including the Leibniz-Preis (DFG), the Yamada Award (Japan), the Emil-Fischer-Medaille (GDCh), an Arthur C. Cope Scholar Award (ACS), the Robert Robinson Award (RSC) and the Ryoji Noyori Prize (SSOCJ, Japan), and he is member of the National Academy of Sciences (Leopoldina, Germany) and of the Akademie der Wissenschaften (Göttingen). He is or was member of many advisory bodies, of the Senates of RWTH and DFG, and of seven journals. Most importantly, he has been an editor for SYNTHESIS since 1985, was its editor-in-chief for 16 years, and is still the editor for reviews, leaving his mark on the journal. In appreciation of this contribution, the present bisected special issue of SYNTHESIS is dedicated to Dieter Enders, whose international status in the community of organic chemists cannot be demonstrated better than by looking at the names of prestigious authors, and the titles and content of almost 50 papers dedicated to him. Thus, the diploma student from Giessen has become a worldwide prominent synthetic organic chemist!

Dieter's success is not only due to his talent as chemist, but also to his quality as a research supervisor, teacher, and lecturer, attracting the best students into his group. His personality and the way of his leadership ("Doktorvater") led to a strong, emotional relation with his students and collaborators, which I could feel during his retirement ("Entpflichtung") function in Aachen (2014) where former associates were present, many of them holding professorial positions all over the world.

Last not least to mention is Dieter's personal life. He was born in 1946 and raised in Butzbach (Wetteraukreis in the State of Hessen, half-way between Frankfurt and Giessen), a small town widely known for its high security prison. After primary and secondary school (Abitur 1965, Weidig-Gymnasium in Butzbach) he registered as a chemistry student at the Justus Liebig University of Giessen in April 1965. In the fall of the same year, Dieter was called to do compulsory military service for almost two years, reaching the rank of Lieutenant. He then continued his chemical studies at the University of Giessen, from which he obtained the degree of Diplomchemiker in May 1972.

Dieter is married to Mechthild, called Meggie by him and their close friends; she is the strong woman behind the successful man; they have three children.

Dieter Seebach
ETH Zürich
November 2016

(1) D. Seebach, D. Enders *Angew. Chem.* **1975**, *87*, 1–18; *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 15–32. *Umpolung of Amine Reactivity. Nucleophilic α-(Secondary Amino)-Alkylation via Metalated Nitrosamines.*

(2) E. J. Corey, D. Enders *Chem. Ber.* **1978**, *111*, 1337–1361. *Generation and Synthetic Use of Metallated Dimethylhydrazones – Regio- and Stereoselective Alkylation of Carbonyl Compounds.*

(3) A. Job, C. F. Janek, W. Bettray, R. Peters, D. Enders *Tetrahedron* **2002**, *58*, 2253–2329. *The SAMP-/RAMP-Hydrazone Methodology in Asymmetric Synthesis.*

(4) D. Enders, M. Klatt *Synthesis* **1996**, 1403–1418. *Asymmetric Synthesis with (S)-2-Methoxymethylpyrrolidine (SMP) – a Pioneer Auxiliary.*

(5) D. Enders, O. Niemeier, A. Henseler *Chem. Rev.* **2007**, *107*, 5606–5655. *Organocatalysis by N-Heterocyclic Carbenes.*

(6) D. Enders, B. Jandeleit, S. von Berg, G. Raabe, J. Runsink *Organometallics* **2001**, *20*, 4312–4332. *Iron-Mediated Allylic Substitution Reactions with Chirality Transfer. Stereochemistry of Formation of Diastereo- and Enantiomerically Enriched Olefinic and Allylic Tetracarbonyl Iron Complexes.*

(7) (a) W. Langenbeck, In *Die Organischen Katalysatoren und ihre Beziehung zu den Fermenten*; Springer: Berlin, **1935**. (b) See also A. Berkessel, H. Groeger, *Asymmetric Organocatalysis*; Wiley-VCH: Weinheim, **2005**, and (c) the Special Issue of *Chem. Rev.* **2007**, *107*, 5413–5883.

(8) D. Enders, A. Seki *Synlett* **2002**, 26–28 and references cited therein. *Proline-Catalyzed Enantioselective Michael Additions of Ketones to Nitrostyrene.*

(9) O. M. Berner, L. Tedeschi, D. Enders *Eur. J. Org. Chem.* **2002**, 1877–1894. *Asymmetric Michael Additions to Nitroalkenes.*

(10) Intriguingly, Dieter Enders is coauthor of a 1978 Organic Syntheses Procedure for the preparation of *rac*-[2-(Ph_2(HO)C)-pyrrolidine]: D. Enders, R. Pieter, B. Renger, D. Seebach *Org. Synth.* **1978**, *58*, 113–121. *Nucleophilic α-Secondary Aminoalkylation: 2-(Diphenylhydroxymethyl)pyrrolidine.*

(11) (a) D. Enders, M. R. M. Hüttl, C. Grondal, G. Raabe *Nature* **2006**, *441*, 861–863. *Control of Four Stereocentres in a Triple Cascade Organocatalytic Reaction.* (b) D. Enders, C. Grondal, M. R. M. Hüttl *Angew. Chem.* **2007**, *119*, 1590–1601; *Angew. Chem. Int. Ed. Engl.* **2007**, *46*, 1570–1581. *Asymmetric Organocatalytic Domino Reactions.* (c) D. Enders, A. A. Narine *J. Org Chem.* **2008**, *73*, 7857–7870. *Lessons from Nature: Biomimetic Organocatalytic Carbon–Carbon Bond Formations.*

(12) For examples of non-organocatalytic and non-enantioselective domino reactions, see: (a) L. F. Tietze *Chem. Rev.* **1996**, *96*, 115–136. (b) D. Seebach *Angew. Chem.* **1990**, *102*, 1362–1409; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1320–1367 (Table 4). *Organic Synthesis – Where now?*

(13) C. Grondal, M. Jeanty, D. Enders *Nature Chem.* **2010**, *2*, 167–178. *Organocatalytic Cascade Reactions as a New Tool in Total Synthesis.*

(14) T. Broja, P. J. W. Fuchs, K. Zeitler *Nature Chem.* **2015**, *7*, 950–951. *Domino reactions: More than just a game.*

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