Part I

Asymmetric Synthesis – The Essentials.
Edited by Mathias Christmann and Stefan Bräse

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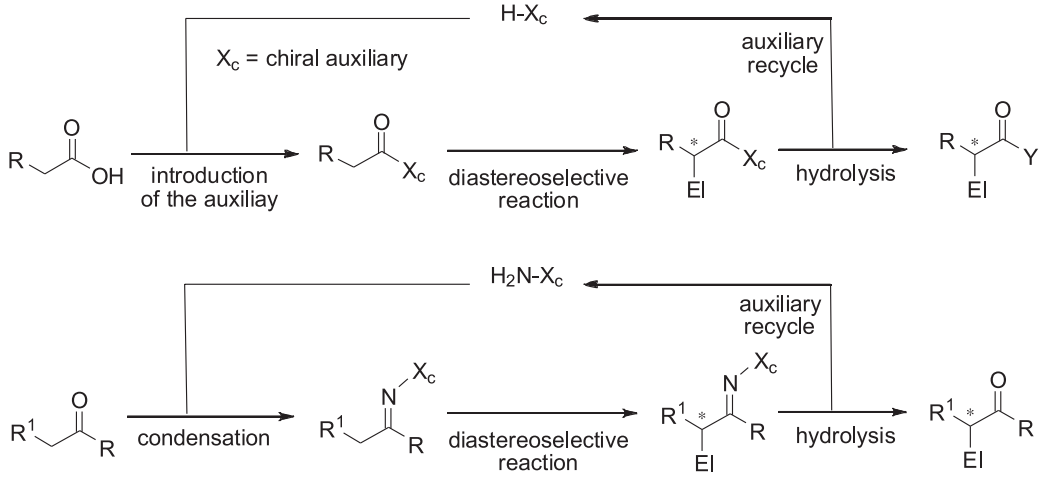
Chiral Auxiliaries in Asymmetric Synthesis

David A. Evans, Harvard University, USA, Günter Helmchen, Organisch-Chemisches Institut der Universität Heidelberg, Germany, and Magnus Rüping, Johann Wolfgang Goethe-University Frankfurt, Germany

Background

The use of chiral auxiliaries in the synthesis of enantiomerically pure compounds has found wide application for a variety of reactions over the last three decades. Despite the extensive developments in this area by many academic and industrial research groups, new auxiliary controlled reactions continue to evolve frequently [1]. First objectives in this area have been to develop chiral enolate-derived reactions, wherein the chiral auxiliary (X_c) is both readily available and easily recovered after the desired bond construction has been achieved (Scheme 1).



Scheme 1 Diastereoselective synthesis with chiral auxiliaries.

Generally, the major issues which have to be addressed in the development of diastereoselective transformations using chiral auxiliaries are threefold in nature. Subsequent to a facile introduction, the chiral auxiliary X_c must provide a strong predisposition for a highly selective enolization process; it must provide a strong

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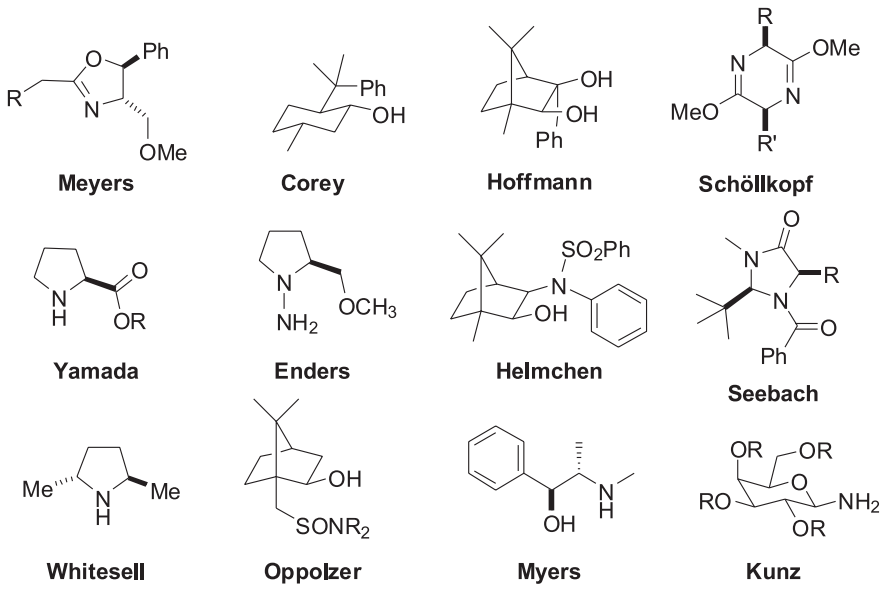


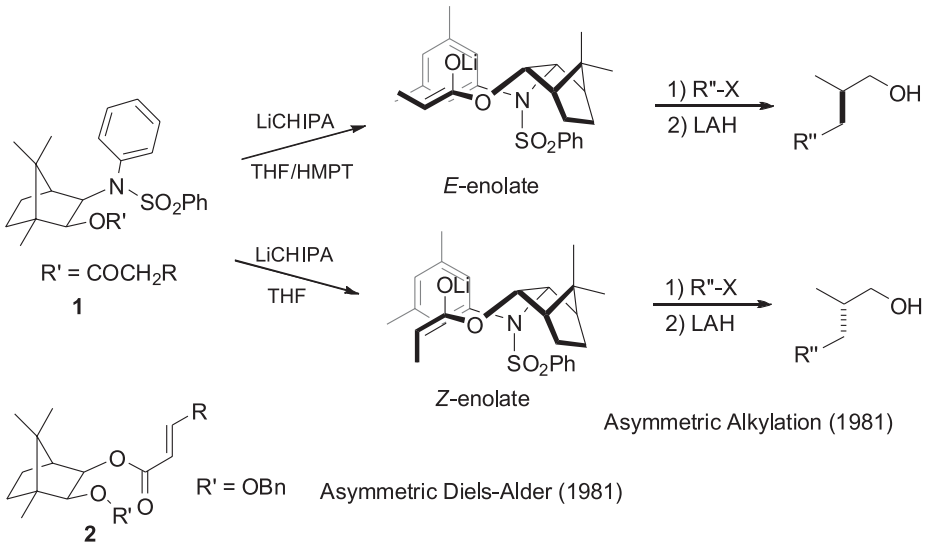
Figure 1 Selected chiral auxiliaries which have been successfully applied in asymmetric synthesis.

bias for enolate diastereoface selection in the new bond construction; and its non-destructive and mild cleavage must occur without racemization of the desired products. Today an arsenal of chiral auxiliaries is available meeting the above criteria in full or in part. Of the numerous chiral auxiliaries that have been developed over the past years some of the effectively applied auxiliaries are shown in Fig. 1. The majority of chiral auxiliaries are derived from inexpensive, chiral natural sources and most of the diastereoselective reactions reported proceed with high levels of diastereoselection. The most widely employed auxiliary controlled reactions are the asymmetric alkylations, aldol and Diels-Alder reactions.

Results

From the numerous auxiliary controlled reactions reported, a notable early example of an effective diastereoselective alkylation and Diels-Alder reaction has been developed by the Helmchen group, using the concave camphor-derived chiral auxiliaries **1** and **2** (Scheme 2) [2]. In this asymmetric alkylation procedure, a selective deprotonation leads to the corresponding *E*- or *Z*- ester enolate, which upon reaction with an alkyl halide and subsequent reduction results in enantiopure pure alcohols, valuable chiral building blocks and synthons for the synthesis of natural products. Remarkably, both diastereomers can be selectively obtained starting from the same chiral camphor derivative by simply changing the solvent.

One of the most utilized type of auxiliaries is the class of chiral oxazolidinones **1**, initially developed in the Evans group [3]. These chiral imides have been applied to a wide range of asymmetric transformations and the methodology devel-



Scheme 2 Asymmetric alkylations and Diels-Alder reaction using Helmchen's camphor-derived auxiliaries.

oped has been most successful in the stereoselective construction of numerous chiral building blocks, as well as natural products, antibiotics and medicinally important compounds. Subsequent to the initial reports regarding oxazolidininone **1**, many structural variants (Fig. 2) have been developed which display different cleavage reactivity or complimentary diastereoselectivity compared to **1**.

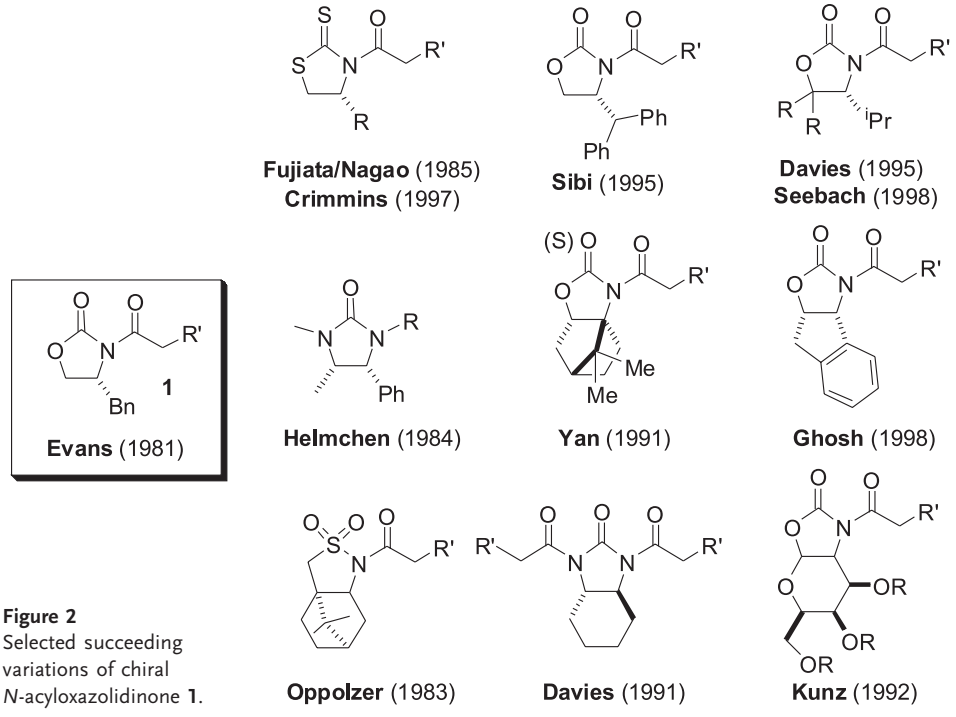
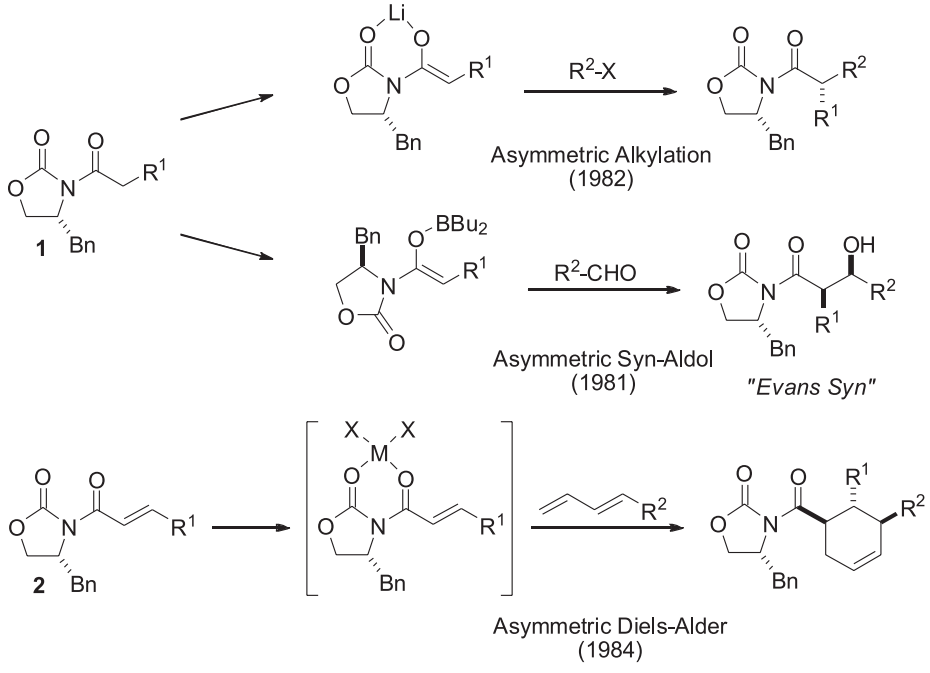


Figure 2
Selected succeeding variations of chiral *N*-acyloxazolidinone **1**.

Oxazolidinones of type **1**, which were initially developed for an efficient asymmetric C–C bond construction in the synthesis of several polyketide-derived natural products, have proved to be a gold standard and have continually been employed by the Evans group and numerous other groups over the last 20 years.

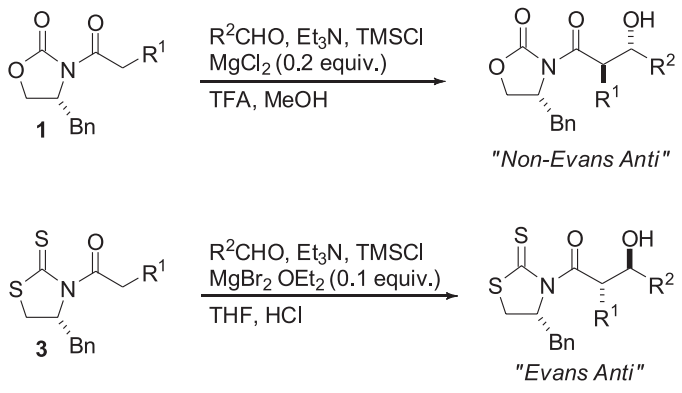
The first asymmetric reactions involving these chiral enolate synthons were the aldol and alkylation reactions. In these reactions selective enolization to form the *Z*-enolates ($Z{:}E > 100$) were achieved using either lithium and sodium amide bases or dibutylboryl trifluorosulfonate. Subsequent alkylation or aldol reaction of the corresponding metal enolates resulted in the products with highest levels of asymmetric induction (Scheme 3). Based on these seminal observations many other reactions employing chiral oxazolidinones have been reported over the years and the application will continue to be of great importance in the future [4].



Scheme 3 Initial asymmetric alkylation, aldol and Diels-Alder reactions.

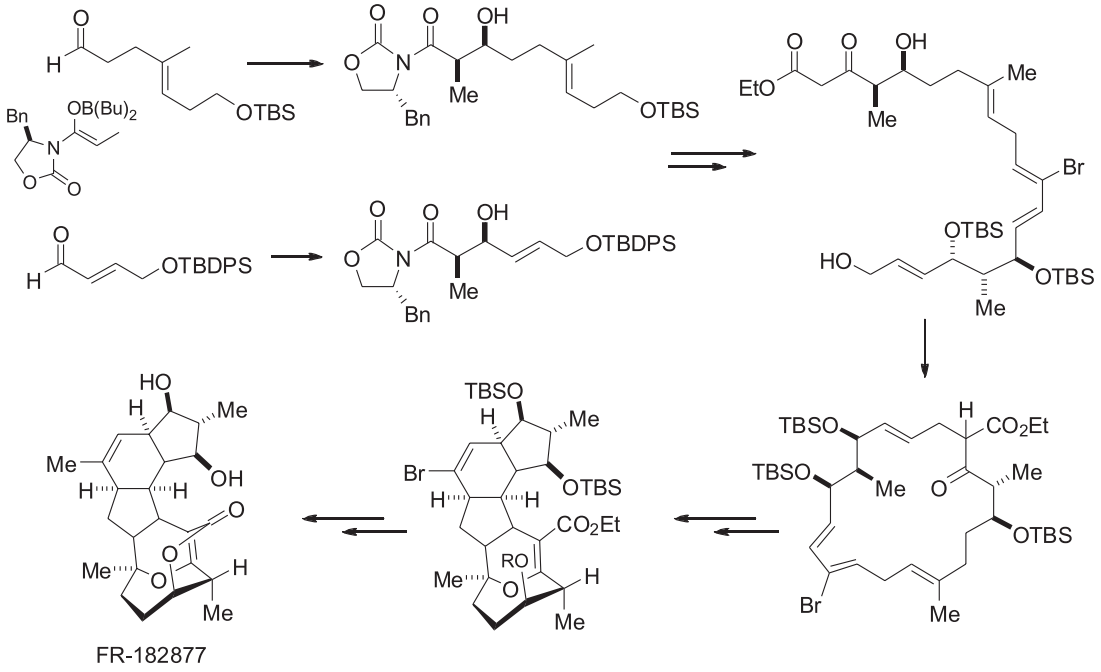
The original reports on the asymmetric aldol reactions mediated by boron or titanium resulted in the *syn* aldol product with very high diastereoselectivity. More recent studies by the Evans group have demonstrated an extension of the aldol process, which employs the same oxazolidinone **1** or the thiazolidine thione **2**, in the presence of catalytic amounts of magnesium salts, forming the *anti* aldol products, which were previously more difficult to access (Scheme 4) [5].

The significant cost effectiveness and facile scale-up of these magnesium halide catalyzed anti aldol reactions render them valuable methods for the preparation of various chiral building blocks and biologically important compounds, especially as all four diastereoisomers can be prepared from a single isomer of the auxiliary.



Scheme 4 Catalytic diastereoselective anti-aldol reactions.

The application of aldol reactions in natural product synthesis has recently been highlighted in the synthesis of FR-182877 by Evans, where all stereochemical relationships in the target structure were obtained from chiral oxazolidinone auxiliary controlled aldol reactions. Similar to the syntheses of himachalene [6] and phomoidride B [7], the asymmetric aldol reaction was the fundamental step for the construction of the key fragments of FR-182877, which were then united via a Suzuki coupling, followed by macrolactonization and oxidation. A subsequent Diels-Alder-Hetero-Diels-Alder reaction cascade culminated in the synthesis of hexacyclic FR-182877 (Scheme 5) [8].



Scheme 5 Synthesis of FR-182877 using the auxiliary controlled aldol reactions and a Diels-Alder reaction cascade.

Summary

Asymmetric reactions employing chiral auxiliaries have experienced a remarkable progress over the past decades. Recent results from our groups, as well as many others, demonstrate that auxiliary-controlled reactions are still essential tools in the construction of complex molecular targets. The ready availability of the starting materials, the facile and versatile cleavage, as well as the applicability and reliability in a variety of stereoselective transformations, allows chiral auxiliaries to endure today as excellent synthetic intermediates in asymmetric synthesis.

CV of David A. Evans

David A. Evans was born in Washington D.C. in 1941. He received his A.B. degree from Oberlin College in 1963. He obtained his Ph.D. at the California Institute of Technology in 1967, where he worked under the direction of Professor Robert E. Ireland. In that year he joined the faculty at the University of California, Los Angeles. In 1973 he was promoted to the rank of Full Professor and shortly thereafter returned to Caltech where he remained until 1983. He then joined the Faculty at Harvard University and in 1990 he was appointed as the Abbott and James Lawrence Professor of Chemistry.

CV of Günter Helmchen

Günter Helmchen (b. 1940) is a Full Professor at the University of Heidelberg and director of the Institute of Organic Chemistry. He pursued undergraduate studies at the TH Hannover (Dipl.-Chem. 1965). His graduate work, completed in 1971, was carried out under the guidance of Professor V. Prelog at the ETH Zürich in the area of stereochemistry. He then joined the group of H. Muxfeldt for postdoctoral studies in the area of natural product synthesis and carried out a Habilitationsarbeit at the Technical University of Stuttgart (1975–1980). In 1980 he was appointed Professor C3 at the University of Würzburg. In 1985 he moved to his present position. His interest in catalysis dates back to ca. 1990. His scientific work has been recognized by a variety of scientific prizes and research awards, international lectureships and the invitation to join the advisory boards of scientific journals.

CV of Magnus Rüping

Magnus Rüping was born in Telgte, Germany, in 1972. He studied at the Technical University of Berlin, Trinity College Dublin and ETH Zürich. He obtained his Ph.D. in 2002 from ETH under the guidance of Professor Dieter Seebach. After carrying out postdoctoral work with Professor David A. Evans at Harvard University, he joined the Johann Wolfgang Goethe-University Frankfurt as Degussa Endowed Professor of Chemistry in fall 2004.

Selected References

1. (a) *Houben-Weyl, Methods in Organic Chemistry, Stereoselective Synthesis*, G. Helmchen, R.W. Hoffmann, J. Mulzer, E. Schaumann (Eds.), Thieme-Verlag, Stuttgart, **1995**; (b) *Compendium of Chiral Auxiliary Applications*, G. Roos (Ed.), Academic Press, New York, **2002**.

2. (a) R. Schmierer, G. Grotemeier, G. Helmchen, A. Selim, *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 207–208. Functional Groups at Concave Sites: Asymmetric Alkylation of Esters with Very High Stereoselectivity and Reversal of Configuration by Change of Solvent; (b) G. Helmchen, R. Schmierer, *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 205–207, Functional Groups at Concave Sites: Asymmetric Diels-Alder Synthesis with Almost Complete (Lewis-Acid Catalyzed) or High (Uncatalyzed) Stereoselectivity.

3. D. A. Evans. *Aldrichim. Acta* **1982**, *15*, 23–32, Studies in Asymmetric Synthesis. The Development of Practical Chiral Enolate Synthons.

4. D. J. Ager, I. Prakash, D. R. Schaad, *Aldrichim. Acta* **1997**, *30*, 3–12, Chiral Oxazolidinones in Asymmetric Synthesis.

5. (a) D. A. Evans, J. S. Tedrow, J. T. Shaw, C. W. Downey, *J. Am. Chem. Soc.* **2002**, *124*, 392–393, Diasteroselective Magnesium Halide Catalyzed Anti-Aldol Reactions of Chiral N-Acyloxazolidinones; (b) D. A. Evans, C. W. Downey, J. T. Shaw, J. S. Tedrow, *Organic Lett.* **2002**, *4*, 1127–1130, *Magnesium Halide-Catalyzed Anti-Aldol Reaction of Chiral N-Acylthiazolidinethiones.*

6. D. A. Evans, D. H. B. Ripin, J. S. Johnson, E. A. Shaughnessy, *Angew. Chem. Int. Engl.* **1997**, *36*, 2119–2121, *A New Strategy for Extending N-Acyl Imides as Chiral Auxiliaries for Aldol and Diels-Alder Reactions: Application to an Enantioselective Synthesis of α-Himachalene.*

7. N. Waizumi, T. Itoh, T. Fukuyama *J. Am. Chem. Soc.* **2000**, *122*, 7825–7826, Total Synthesis of (–)-CP-263,114 (Phomoidride B).

8. D. A. Evans, J. T. Starr *Angew. Chem. Int. Ed.* **2002**, *41*, 1787–1790, A Cascade Cycloaddition Strategy Leading to the Total Synthesis of (–)-FR182877.