Organic Synthesis
State of the Art 2003–2005
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Preface

Starting in January of 2003, I have been publishing a weekly Organic Highlights column (http://www.organic-chemistry.org/). Each column covers a topic, pulling together the most significant developments in that area of organic synthesis over the previous six months. All of the columns published in 2004 and 2005 are included in this book.

So, why this book, if the columns are already available free on the Web? First, there are a lot of them, 103 in this book. It is convenient having them all in one place. Too, there is an index of senior authors, and a subject/transformation index. Most important, this collection of columns, taken together, is an effective overview of the most important developments in organic synthesis over the two-year period. The dates have been left on the columns in this volume, so they will be easy to locate on the Web. The web columns include electronic links to the articles cited.

There are journals that publish abstracts and/or highlights. The columns here differ from those efforts in that these columns take the most important developments in an area, e.g. the Diels-Alder reaction, over a six-month period, and put them all together, with an accompanying analysis of the significance of each contribution.

The first column of each month is devoted to a total synthesis. So many outstanding total syntheses appear each year, no attempt was made to be comprehensive. Rather, each synthesis chosen was selected because it contributed in some important way to the developing concepts of synthesis strategy and design. It is important to note that even if a total synthesis was not featured as such, all new reaction chemistry in that synthesis was included at the appropriate place in these Highlights.

I recommend this book to the beginning student, as an overview of the state of the art of organic synthesis. I recommend this book to the accomplished practitioner, as a handy reference volume covering current developments in the field.

These Highlights are primarily drawn from the Journal of the American Chemical Society, Journal of Organic Chemistry, Angewandte Chemie, Organic Letters, Tetrahedron Letters, and Chemical Communications. If you come across a paper in some other journal that you think is worthy of inclusion, please send it to me!

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Transition Metal Mediated Reactions in Organic Synthesis

January 12, 2004

This week’s Highlights focuses on three transition metal-catalyzed reactions. Jin-Quan Yu of Cambridge University reports (Organic Lett. 2003, 5, 4665-4668) that Pd nanoparticles catalyze the hydrogenolysis of benzylic epoxides. The reaction proceeds with inversion of absolute configuration (1 → 2).

Laurel Schafer of the University of British Columbia reports (Organic Lett. 2003, 5, 4733-4736) that terminal alkynes undergo smooth hydroamination with a Ti catalyst. The intermediate imine 4 can be hydrolyzed to the aldehyde 5 or reduced directly to the amine 6. The alkyne to aldehyde conversion has previously been carried out by hydroboration/oxidation (J. Org. Chem. 1996, 61, 3224), hydrosilylation/oxidation (Tetrahedron Lett. 1984, 25, 321), or Ru catalysis (J. Am. Chem. Soc. 2001, 123, 11917). There was no previous general procedure for the anti-Markownikov conversion of a terminal alkyne to the amine.

The construction of enantiomerically-pure carbocycles is a general problem in organic synthesis. Dirk Trauner (UC Berkeley) reports (Organic Lett. 2003, 5, 4113-4115) an elegant intramolecular Heck cyclization. The alcohol 7 is readily prepared in enantiomerically-pure form. Conditions can be varied so that either 8 or 9 is the dominant product from the cyclization.
Biocatalytic Asymmetric Hydrogen Transfer

January 19, 2004

Bioreductions and biooxidations, although they can be highly selective, have often been limited by the requirement for expensive reducing or oxidizing biological cofactors. Wolfgang Kroutil of the University of Graz reports (J. Org. Chem. 2003, 68, 402-406. DOI) that aqueous suspensions of the whole lyophilized cells of *Rhodococcus ruber* DSM 44541 show alcohol dehydrogenase activity even in the presence of high concentrations of isopropanol or acetone. The organic co-solvent then serves as the "co-factor", driving reduction or oxidation. At the end of the reaction, the mixture is centrifuged, and the organic solvent is dried and concentrated. This promises to be an easily scalable preparative method.

The usual selectivities are observed, with aryl alkyl ketones and alkyl methyl ketones being reduced with high enantioselectivity (1 -> 2 and 3 -> 4). That 5 is reduced to 6 with high ee, with the reducing enzymes differentiating between an ethyl and an n-pentyl group, is even more impressive.

![Chemical Structures](image)

The 2-tetralone 7 (R = R' = H) is reduced to the alcohol 8 with respectable enantioselectivity. An intriguing question is, what would happen with R or R' = alkyl? Would one enantiomer reduce more rapidly than the other, perhaps with high diastereoselectivity? Could the other enantiomer (especially R = alkyl) epimerize under the reaction conditions?

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The selective reduction of 5 suggests that 9 and/or 12 might reduce with high enantioselectivity. This would open an inexpensive route to enantiomerically-pure epoxides, important intermediates for organic synthesis.
The saga of efficient enantioselective catalysis by the amino acid proline continues. Nearly simultaneously, Dave MacMillan of Caltech and Yujiro Hayashi of the Tokyo University of Science reported (J. Am. Chem. Soc. 125: 10808, 2003; Tetrahedron Lett. 44: 8293, 2003) that exposure of an aldehyde 1 or ketone 4 to nitrosobenzene and catalytic proline gives the oxamination products 2 and 5 in excellent yield and ee. Reduction of 2 is reported to give the terminal diol 3 in 98% ee. The N-O bond can also be reduced with CuSO₄. The importance of prompt publication is underlined by these two publications – the MacMillan paper was submitted in July, and the Hayashi paper in August.

Many methods have been developed for asymmetric allylation. One of the best is the procedure reported by Masahisa Nakada of Waseda University (J. Am. Chem. Soc. 125: 1140, 2003). This uses the inexpensive allyl or methallyl chlorides directly. The reduction of the chloride with Mn metal is catalyzed by CrCl₃. When the addition is carried out in the presence of 10 mol % of the enantiomerically-pure ligand 7, the product is formed in high yield and ee.
One of the severest challenges of asymmetric synthesis is the direct enantioselective construction of quaternary stereogenic centers. Brian Pagenkopf of the University of Texas has reported (Chem. Communications 2003: 2592) that alkynyl aluminum reagents will open a trisubstituted epoxide such as 10 at the more substituted center, with inversion of absolute configuration. As the epoxide 10 is available in high ee from 9 by the method of Yian Shi of Colorado State (J. Am. Chem. Soc. 119: 11224, 1997), this opens a direct route to quaternary cyclic stereogenic centers.
Enantioselective Synthesis of Borrelidin
February 2, 2004

There are two criteria for judging any total synthesis: the importance of the molecule that has been prepared, and the creativity evidenced in the synthetic route. When the natural product has only two rings, as with borrelidin 1, the standards are even higher. The enantioselective total synthesis of borrelidin by Jim Morken of the University of North Carolina (J. Am. Chem. Soc. 125: 1458, 2003) more than exceeds those standards.

Borrelidin 1 has attracted attention because it inhibits angiogenesis, and so potentially blocks tumor growth, with an IC₅₀ of 0.8 nM. Retrosynthetic analysis of 1 led the investigators to the prospective intermediates 2 and 3. To assemble these two fragments, they iteratively deployed the elegant enantio- and diastereoselective intermolecular reductive ester aldol condensation that they had recently developed. This transformation is exemplified by the homologation of 4 to 6 catalyzed by the enantiomerically-pure Ir complex 5.

The final stages of the synthesis illustrate both the power and the current limitations of transition-metal mediated C-C bond formation. Coupling of 2 and 3 led to the ene-yne 7. Pd-mediated hydrostannylation of the alkyne proceeded with high geometric control, but tended to...
give the undesired regioisomer. The authors found that with the acetate, the ratio could be improved to 1 : 1. Iodination followed by Stille coupling then gave the dienyl nitrile 9.
Enantioselective Ring Construction

February 9, 2004

New methods are being developed for the enantioselective construction of both heterocyclic and carbocyclic rings. Justin DuBois of Stanford reports (J. Am. Chem. Soc. 125: 2029, 2003) that his intramolecular Rh-mediated nitrene C-H insertion cyclizes 1 to 2 with high diastereoselectivity. The N,O-acetal opens smoothly with the alkynyl zinc, again with high diastereocontrol. The tosylate is stable to the alkyne addition conditions, but after reduction of the alkyne to the alkene the tosylate is readily displaced, to give 4. After osmylation, the sulfamate undergoes smooth Sn2 displacement with cyanide ion, leading, after reduction, to the indolizidine 6.

Sundarababu Baskaran of IIT-Madras offers (Organic Lett. 5: 583, 2003) an alternative route to indolizidines. Exposure of the epoxide 7 to Lewis acid followed by reduction leads to 11 as a single diastereomer. The authors hypothesize that this rearrangement is proceeding via intermediates 8 - 10. Tosylation of 11 followed by homologation leads to the Dendrobatid alkaloid 12.
Intramolecular carbon-carbon formation to convert inexpensive, enantiomerically-pure carbohydrates directly to highly functionalized, enantiomerically-pure carbocycles has long been a goal of organic synthesis. Ramón J. Estévez of the University of Santiago in Spain reports (Organic Lett. 5:1423, 2003) that TBAF smoothly converts the triflate derived from 13 into 14, without competing β-elimination.
The efficient construction of substituted heterocycles is central to medicinal chemistry. Yoshinori Kondo of Tohoku University reports (J. Am. Chem. Soc. 125: 8082, 2003) that the novel base 2 will, in the presence of ZnI₂ and an aldehyde, deprotonate heterocycles, to give the hydroxyalkylated products 3 and 5. Benzene rings also participate – 6 is converted to 7.

Free radical cyclizations have often been carried out with tin reagents, which are toxic, and an environmental hazard. As an alternative, phosphorus reagents have been developed, but these suffer from the shortcoming that they are aqueous, and so it is difficult to get them into contact with the organic substrate. John A. Murphy of the University of Strathclyde in Glasgow reports (Organic Lett. 5: 2971, 2003) that diethyl phosphine oxide (DEPO), which is soluble in organic solvents as well as in water, serves efficiently as a hydride source and radical mediator, smoothly cyclizing 8 to the indolone 9. The oxidized phosphonic acid byproduct is easily separated by aqueous extraction.
The Wittig reaction efficiently olefinates aldehydes and ketones, but not esters or amides. Several early-transition-metal approaches have been taken to this problem. Recently, Takeshi Takeda of the Tokyo University of Agriculture and Technology reported (Tetrahedron Lett. 44: 5571, 2003) that the titanocene reagent can effect the condensation of an amide $10$ with a thioacetal $11$ to give the enamine $12$. On hydrolysis, $12$ is converted into the ketone $13$. When the reaction is intramolecular, reduction proceeds all the way, to give the pyrrolidine $15$. 

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\begin{array}{c}
\text{Ph}\text{\`C}\text{\`N}\text{\`Ph} + \text{PhS}\text{\`C}\text{\`SPh} \xrightarrow{\text{Cp}_2\text{Ti}[\text{P(OEt)}_3]} \text{Ph}\text{\`C}\text{\`N}\text{\`Ph} \xrightarrow{\text{Ph}} \text{Ph}\text{\`C}\text{\`O} \\
10 & 11 & 12 & 13
\end{array}
\]

\[
\begin{array}{c}
\text{PhS}\text{\`C}\text{\`N}\text{\`Ph} \xrightarrow{\text{Cp}_2\text{Ti}[\text{P(OEt)}_3]} \text{Ph}\text{\`C}\text{\`N}\text{\`Ph} \xrightarrow{\text{Ph}} \text{Ph}\text{\`C}\text{\`O} \\
14 & 15
\end{array}
\]