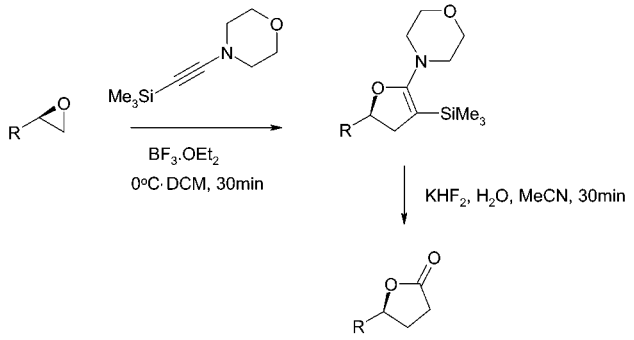
Organic Process Research & Development **2002**, *6*, 207−215

Highlights from the Literature

Some Items of Interest to Process R&D Chemists and Engineers

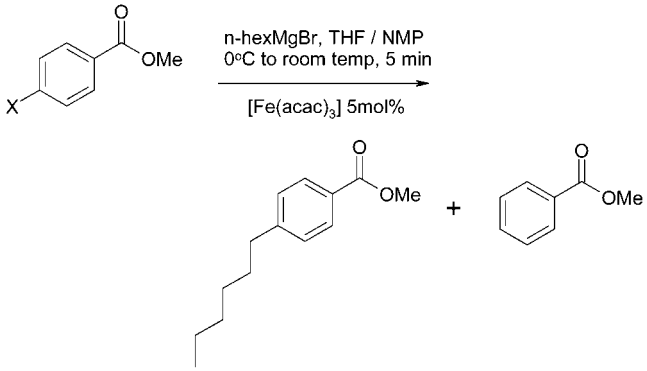
Conversion Of Terminal Epoxides into γ-Butanolides

Jacobsen and Movassaghi have reported a direct method for the conversion of terminal epoxides into γ-butanolides (*J. Am. Chem. Soc.* **2002**, *124*, 2456). In their method chiral epoxides react with 1-morpholino-2-trimethylsilyl acetylene and boron trifluoride diethyl etherate to give the corresponding keteneaminals. Subsequent hydrolysis and protodesilylation gave the γ-butanolides without loss of chirality through the series of synthetic manipulations. The net transformation is equivalent to the addition of an acetate enolate opening of an epoxide and is compatible with a wide variety of functional groups.



Iron-Catalysed Cross Coupling

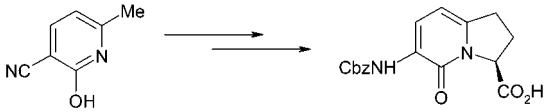
Classic cross coupling processes such as the Kumada−Corriu, Negishi, Stille, or Suzuki reactions are of utmost importance in modern day synthetic organic chemistry. These transformations are usually catalysed by palladium or nickel complexes, with aryl iodides and bromides amongst the best substrates. A recent publication by Furstner and Leitner (*Angew. Chem., Int. Ed.* **2002**, *41*, 609) describes the iron-catalysed cross coupling reactions



of alkyl Grignard reagents with aryl chlorides, tosylates, and triflates. Their method is distinguished by a number of advantages, (1) expensive noble metals are replaced by cheap, stable, commercially available, and toxicologically benign iron salts, (2) aryl chlorides, tosylates, and triflates provide better results over the corresponding bromides or iodides, (3) the reaction can be performed under "ligand-free" conditions, and (4) the reaction times are usually very short. The authors describe a proposed formal catalytic cycle for the iron-catalysed reaction in the paper.

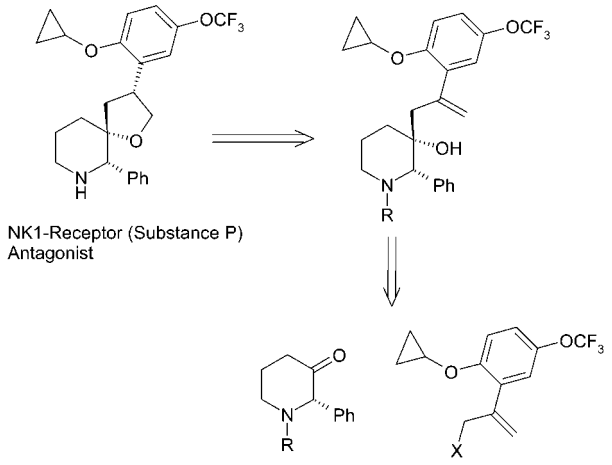
Synthesis Paper

Dragovich and co-workers from Pfizer describe (*J. Org. Chem.* **2002**, *67*, 741) their 11-step preparation of an optically active bicyclic 2-pyridone dipeptide mimetic from the commercially available 2-hydroxy-6-methylnicotinonitrile in 3.3% overall yield and 60% ee.



Synthesis Paper

Maligres and co-workers from Merck disclose their synthesis of a nonpeptidal (−)-spirobicyclic NK-1 antagonist (*J. Org. Chem.* **2002**, *67*, 1093). The retrosynthesis is shown in the following scheme and reveals an allylic halide bearing a cyclopropoxy-substituted aryl group and a 2-phenyl-3-piperidone. The stereochemistry in the spirobicyclic system bearing the three chiral centres is initially set via a diastereoselective zinc-mediated coupling of the allylic bromide to the BOC-protected piperidone (R═BOC). The remaining benzylic asymmetric centre is set by a diastereoselective hydroboration followed by cyclisation to the spirocyclic system.



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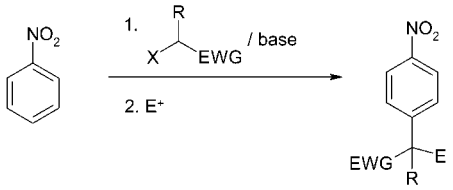
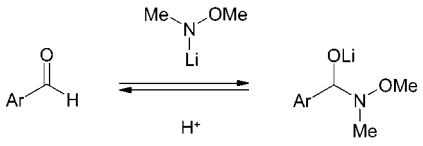
Three-Component Coupling Process Based on Vicarious Nucleophilic Substitution (VNS_{AR})−Alkylation Reactions

Lawrence and co-workers have recently reported that vicarious nucleophilic substitution reactions may be quenched with a series of alkyl halides to construct α-quaternary centres (*J. Org. Chem.* **2002**, *67*, 457). This one-pot VNS−alkylation reaction (shown in the scheme below) offers a convenient route to a range of α-substituted nitrobenzyl phosphine oxides, sulphones and esters. In addition since extra functionality is introduced in the "quench" part of the reaction this procedure may offer alternative approaches to substrates containing functionality that would have been previously incompatible with the initial VNS reaction. The group have used this methodology to develop a route to indoprofen in four steps and 24% overall yield from nitrobenzene using readily available inexpensive starting materials.



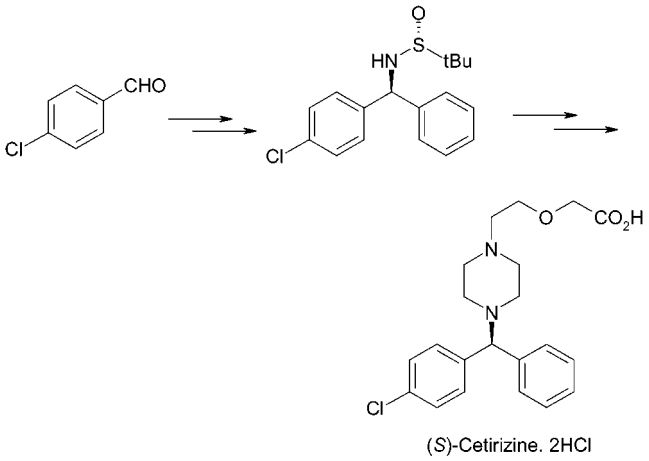
N,*O*-Dimethylhydroxylamide As an Efficient in Situ Protecting Agent

Roschangar and co-workers from GSK describe (*Tetrahedron* **2002**, *58*, 1657) how lithium *N*,*O*-dimethylhydroxylamide may be used as a highly efficient and weakly ortho directing in situ protecting agent for aryl aldehydes at temperatures convenient for large-scale processing as depicted in the following scheme. They point out that the low boiling point of *N*,*O*-dimethylhydroxylamine allows for the facile removal of the reagent from the reaction mixture by low-temperature vacuum distillation thus alleviating the thermal hazards associated with its handling.



Asymmetric Synthesis

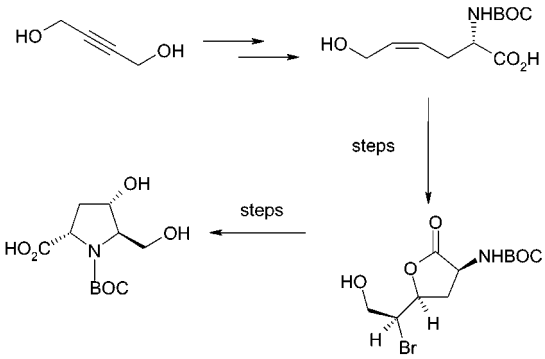
Cetirizine dihydrochloride is a nonsedating histamine H1-receptor antagonist used for the treatment of allergies. Preliminary results indicate that the levorotatory enantiomer of cetirizine displays a better pharmacological profile than the racemic mixture and is currently marketed as Xyzal in Europe. Senanayake and co-workers have described the asymmetric synthesis (*Tetrahedron Lett.* **2002**, *43*, 923) of the (*S*)-enantiomer via a diastereoselective Davis−Ellman type addition to *N*-*tert*-butanesulfinyl aldimines (derived from *p*-chlorobenzaldehyde). The paper goes on to describe the elaboration of the sulfinamide product to the desired drug substance.



(*S*)-Cetirizine. 2HCl

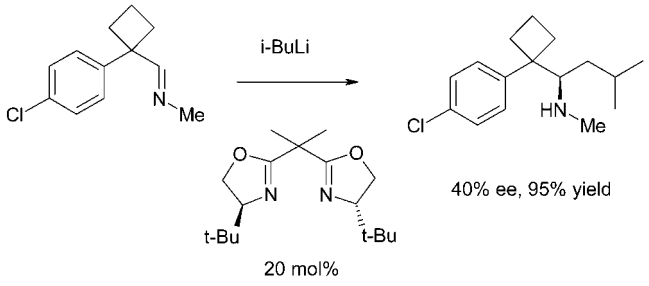
Stereoselective Synthesis

Holt and co-workers have described a concise and scaleable route to both isomers of *Z*-2-*tert*-butoxycarbonyl-amino-6-hydroxyhex-4-enoic acid (*Tetrahedron Lett.* **2002**, *43*, 1545) from butyne-1,4-diol utilising L- and D-acylase enzymes to supply (*S*)- and (*R*)-amino acids in a one pot reaction. These amino acids were readily converted to both isomers of Bulgecinine using a key electrophilic bromolactonisation reaction. Bulgecins are glycopeptide bacterial metabolites isolated from cultures of *Pseudomonas acidophila* and of *P. mesoacidophila*. They have no antibacterial activity themselves, but when used in conjunction with β-lactam antibiotics, they enhance the antibiotic effect.



Asymmetric Synthesis of (*R*)-Desmethylsibutramine

A catalytic enantioselective addition of *i*-BuLi to the aldimine (see below) derived from methylamine and 1-(4-chlorophenyl)cyclobutanecarboxylaldehyde was used as the key step in the asymmetric synthesis of (*R*)-desmethyl-sibutramine by Senanayake and co-workers (*Tetrahedron Lett.* **2002**, *43*, 2331). This compound is a single enantiomer version of a pharmacologically active metabolite of sibutramine, a new class of compound for the treatment of obesity.

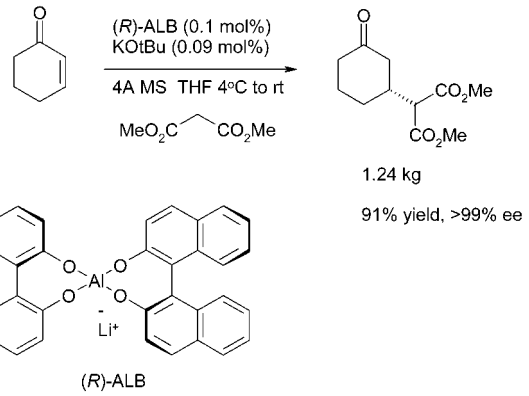


20 mol%

40% ee, 95% yield

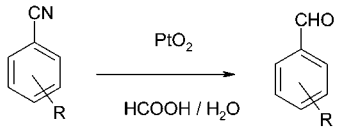
Chiral Catalytic Michael Reaction

A highly practical and efficient procedure for the large scale synthesis of enantiomerically pure (*R*)-3-[bis(methoxycarbonyl)methyl]cyclohexanone using an (*R*)-AlLi-bis(binaphthoxide) ((*R*)-ALB) complex catalysed asymmetric Michael reaction has been developed by Shibasaki and co-workers (*Tetrahedron* **2002**, *58*, 2585). The reaction could be successfully accelerated under highly concentrated conditions without lowering the chemical yield or the high enantiomeric excess and has been performed on >1-kg scale.



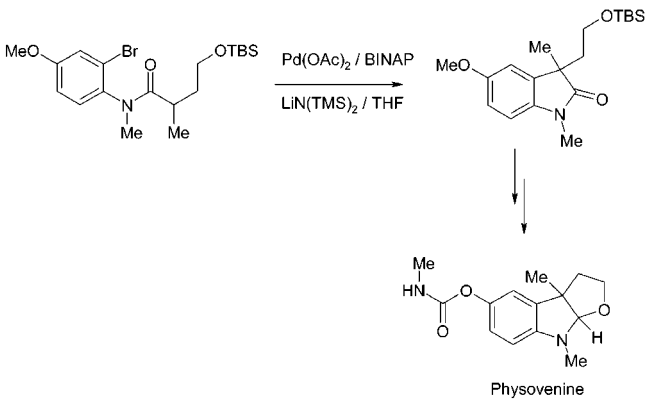
Nitriles to Aldehydes

A variety of aromatic nitriles have been reduced to the corresponding aldehydes using platinum (IV) oxide in aqueous formic acid with yields ranging from 76 to 94% (*Tetrahedron Lett.* **2002**, *43*, 1395). This mild method developed by Xi and co-workers at MedImmune Inc offers a convenient method that may find application in synthesis of more elaborate molecules.



Formal Total Synthesis of Physovenine

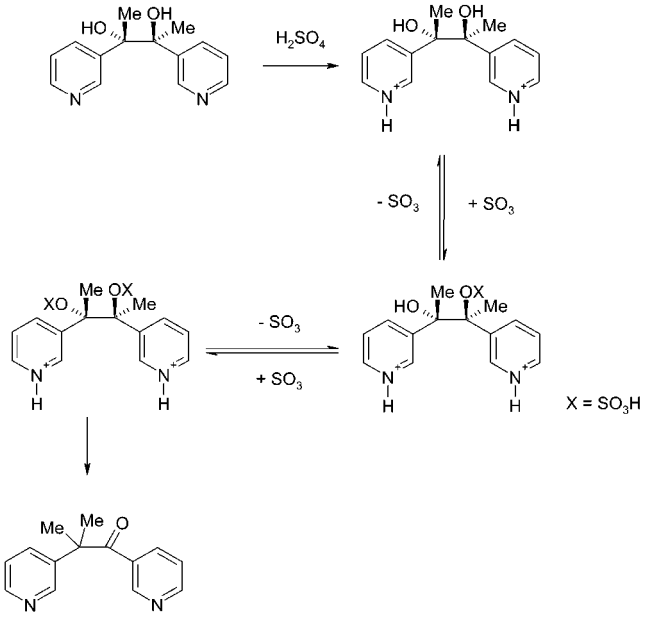
An expedient formal total synthesis of physovenine has been reported by Zhang from the Lilly research laboratories (*Tetrahedron Lett.* **2002**, *43*, 1363). The key step (depicted below)



involves an oxindole synthesis via palladium-catalysed intramolecular arylation of an *o*-bromoanilide. The group report an ee of 11% using (*R*)-BINAP, and the reaction appears to be both ligand- and solvent-dependent offering opportunities for future developmental tuning of the reaction conditions.

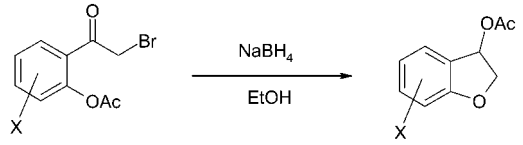
Mechanistic Organic Chemistry

The mechanism of the pinacol−pinacolone rearrangement of 2,3-di-(3-pyridyl)-2,3-butanediol in sulphuric acid has been studied by Prasad and co-workers from Novartis (*Tetrahedron Lett.* **2002**, *43*, 2161). It was found that the *meso* and racemic forms give mono and bis-SO_3 addition products which rearrange to the ketone and two other major by-products. The formation of SO_3 addition products and a marked increase in the reaction rates with greater amount of SO_3 suggest an alternative mechanism involving sulphonyloxy leaving groups. This paper highlights the importance of understanding the fundamental organic chemistry that is occurring inside a round-bottom flask to be able to make sensible changes to the reaction conditions to make an improvement to yield and quality of the product.



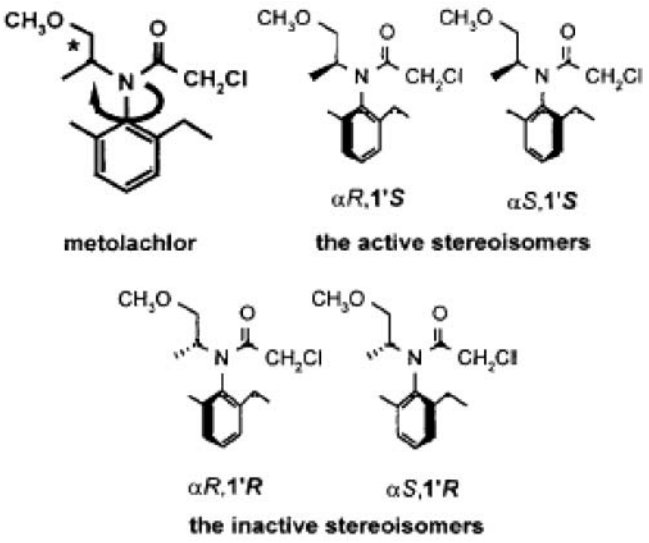
Synthesis of 2,3-Dihydrobenzofuran Involving a Facile Acyl Migration

Reduction of aryl α-bromoketones in the presence of *o*-acetoxy functionality leads to the 2,3-dihydrobenzofuran derivatives involving a process of facile acyl migration as depicted in the following scheme (*Tetrahedron Lett.* **2002**, *43*, 1923). Li and co-workers at Bristol Myers Squibb have demonstrated this to be a general method for the synthesis of this type of compound on a variety of substrates involving acetophenones with both electron-withdrawing and -donating substituents.



The Chiral Switch of (*S*)-Metolachlor: A Personal Account of an Industrial Odyssey in Asymmetric Catalysis

H.-U. Blaser (*Adv. Synth. Catal.* **2002**, *344*, 17) has written a fascinating chronicle over the various development phases of the Ir-catalyzed enantioselective hydrogenation for the manufacture of 1′-(*S*)-metolachlor the active ingredient in Dual Magnum one of the most important grass herbicides for use in maize. The final process is now the largest application of asymmetric catalysis, and the Ir-xyliphos catalyst achieves tons of 2,000,000 and tof values around 600000 h-1. The project started in 1982 as a consequence of the huge manufacture (>20,000 t/y) of Dual containing all four stereoisomers where only the two 1′-S-metolachlor were active.



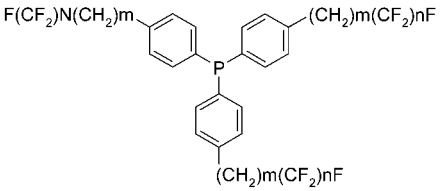
Due to low price and large volume it was from the beginning clear that only a catalytic route would be feasible. This project caught the catalysis group at Ciba−Geigy quite unprepared, having experience only in heterogeneous hydrogenations. The paper recounts the various breakthroughs and set-backs and how the final catalytic system slowly evolved. The project ended in 1996 as the first large-scale batch was produced in the plant. This chronicle describes in detail how important it is to realize that entering a field like homogeneous catalysis brings a process research group to the utmost front of research and that it will take time to gather know-how prior to process development. Another important lesson to be learned from this paper is that catalyst activity is very important issue and that one cannot simply concentrate on enantioselectivity and that substrate specificity seems to be especially high for enantioselective catalysis, especially for catalyst activity.

Nucleation Control in Solution-Mediated Phase Transformation

The group of R. J. Davey (*J. Phys. Chem. B* **2002**, *106*, 1954) has published a work on the effect of different kinds of stirring and the amount of structurally related impurities on the transformation of the metastable form into the stable polymorph. The paper describes the kinetics of the solution-mediated phase transformation between forms I and II of dihydroxybenzoic acid. Surprisingly, secondary nucleation is found to dominate the kinetic processes. The scale of the crystallization experiment and the technique of stirring was extremely important for the transformation time. Agitation with a magnetic stirring bar produced significantly more secondary nuclei decreasing the time for transformation as compared to stirring with a propeller agitator. The addition of 2 mol % of benzaldehyde prolonged the transformation time with more then 10 times due to lack of hydrogen bonding for the chain prolongation in the more stable form. These observations have a significant impact on process and product control during the development phase from work in the lab to production scale in the pharmaceutical industry.

A Green Hydrogen Peroxide Synthesis

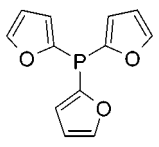
Hydrogen peroxide is widely accepted as a green oxidant, as it is easy to handle and relatively nontoxic and it breaks down readily in the environment to benign by-products. However, the anthraquinone process by which most of the world's hydrogen peroxide is produced requires significant energy and generates considerable waste, lowering the sustainability of the process. The group of E. J. Beckman (*Acc. Chem. Res.* **2002**) has developed a new and more economic method for the production of hydrogen peroxide from oxygen and hydrogen in $scCO_2$ using the CO_2-soluble Pd(2+) or Pd(0) catalyst. Previous work has shown that the use of perfluorinated phosphine ligands creates organometallic catalysts with significantly higher solubility in $scCO_2$ than the hydrogen carbon analogues (Noyori, R. et al. Homogeneous Catalysis in Supercritical Fluids. *Chem. Rev.* **1999**, *99*, 475).



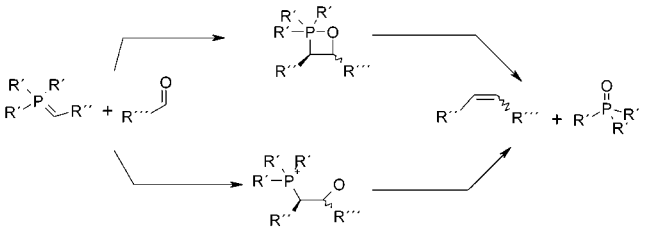
Using CO_2 as solvent circumvents many of the problems combined with the manufacture of hydrogen peroxide as CO_2 is a nonoxidizable and nonflammable organic solvent. The group also investigated the use of the produced hydrogen peroxide in CO_2/H_2O for the epoxidation of alkenes via percarbonate-catalyzed epoxidation as a useful system.

A Wittig Reaction with Improved (*Z*)-Selectivity

S. Berger et al. (*Eur. J. Org. Chem.* **2002**, 1143) has shown that Wittig reactions with ylides bearing one two or three 2-furyl-groups directly bound to the phosphorus atom have a greatly improved (*Z*)-alkene selectivity of up to 98:2 obtained with the trifuranylphosphine.

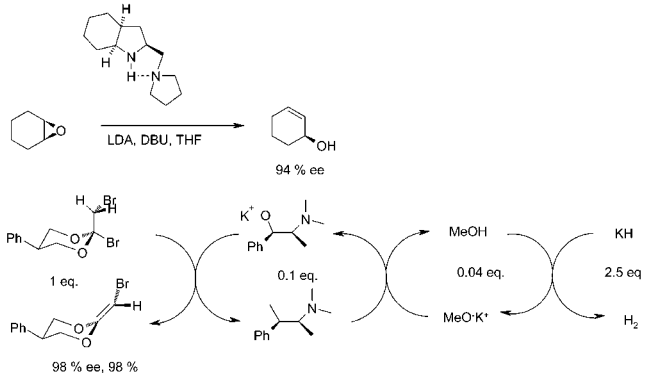


The required phosphonium salts bearing 2-furyl groups are easily accessible from common chemicals. The best results were obtained when NaHMDS was used as base. The intermediate oxaphosphetanes were also found to have a higher stability than related ones from triphenyl phosphines.



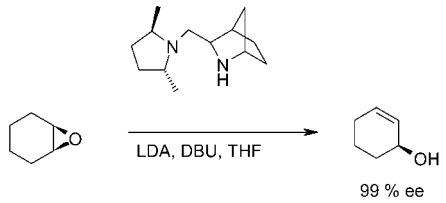
Recent Developments in Substoichiometric Chiral Deprotonation

J. Eames (*Eur. J. Org. Chem.* **2002**, 393) has compiled the latest results reported on substoichiometrically mediated chiral deprotonation. In this microreview the effect that reaction parameters (such as solvent, temperature, and additive) has on the stereoselectivity is also discussed. Until now it has been shown that the use of substoichiometric amounts of chiral bases is an efficient route for the synthesis of optically active allylic alcohols, silyl enol ethers, and vinyl bromides. There is currently only a limited number of applications due primarily to the infancy of the strategy and lack of mechanistic information about the role of different additives. In the transformation of an epoxide to an optically active allylic alcohol a large excess of DBU has been found to be of major advantage. In the dehydrobromination it was found that to obtain the high enantioselectivity a catalytic amount of methanol was necessary.



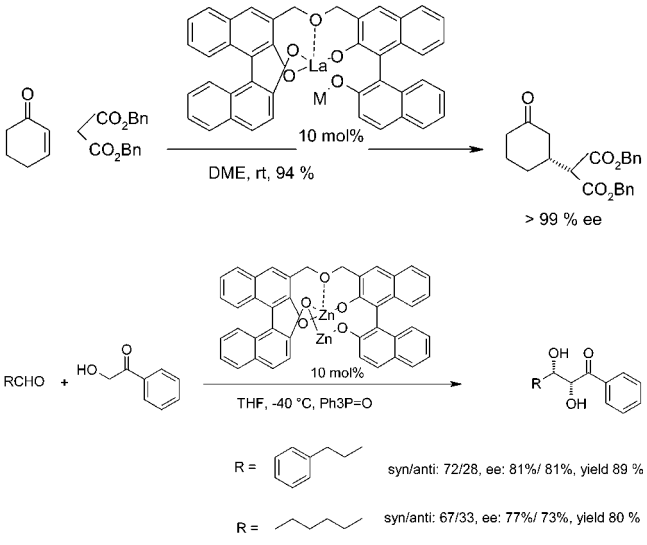
New Catalysts for Base-Promoted Isomerization of Epoxides to Allylic Alcohols

On the topic of substoichiometric chiral base-induced isomerization of epoxides to optically active allylic alcohols, the group of P. G. Andersson (*J. Org. Chem.* **2002**, *67*, 1567) has reported their most recent results with a new chiral base. The new catalyst exhibits exceptionally high enantioselectivity and reactivity; several substrates were rearranged with enantioselectivities of 98−99% ee.



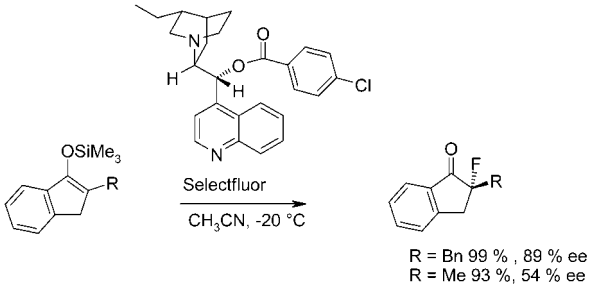
Practical Asymmetric Multifunctional Catalysis

Linked-BINOL was first designed to increase the stability of the Ga−Li−BINOL complex against ligand exchange with 4-methoxyphenol. An oxygen-containing linked BINOL, a semi-crown ether, was found to be an effective monomeric Ga−Li-complex with higher stability. This Ga−Li-linked BINOL complex promoted the epoxide opening reaction in up to 96% ee. From the ligand an air-stable storable La-linked BINOL complex has been developed which promotes the Michael reaction with >99% ee. Also a dinuclear Zn−Zn-linked BINOL complex has also been developed of the group of M. Shibasaki (*Adv. Synth. Catal.* **2002**, *344*, 3) which promotes the enantio- and diastereoselective direct aldol reaction in up to 99% ee when the electron-rich 2-methoxy-2′-hydroxyacetophenone was used as substrate. The use of aryl ketones is a potentially advantageous over alkyl ketones because the aromatic ring functions as a placeholder for further conversions via regioselective rearrangements. Electron-rich methoxy-substituted acetophenones facilitate conversions such as Baeyer−Villiger oxidation.



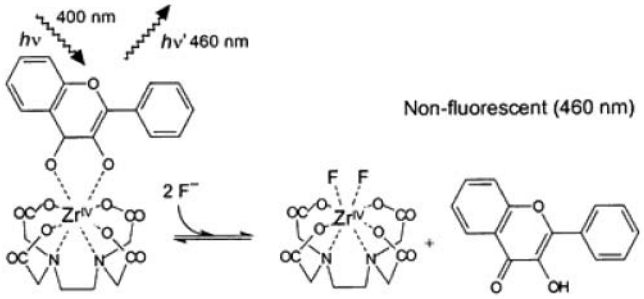
Electrophilic Fluorodesilylation

V. Gouverneur and B. Greedy (*Chem. Eur. J.* **2002**, *8*, 766) describe the concept of electrophilic fluorodesilylation for the mild introduction of fluorine atoms in the late stage in a synthesis. Although still not mechanistically clear these fluorodesilylation processes have opened the door for exciting further development of this new type of introduction of fluorine atoms. The further development in asymmetric electrophilic fluorodesilylation methodology could potentially provide a mild access to compounds difficult to obtain by other means.



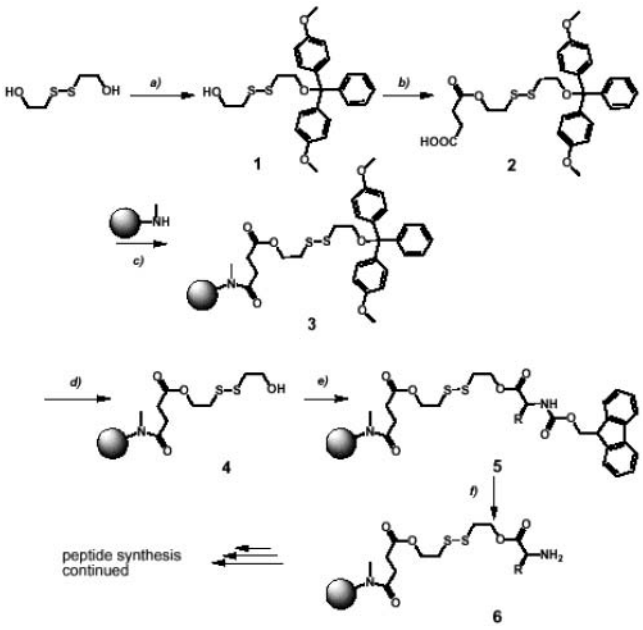
Fluorometric Detection of Fluoride Ion by Ligand-Exchange Reaction

An aqueous solution composed of $[Zr(H_2O)_2edta]\cdot 2H_2O$ and 3-hydroxyflavone (flavonol) exhibits an intense blue fluorescence (λ_{max}= 460 nm) upon excitation at 400 nm and the signal intensity decreases with the addition of fluoride ion. This observation has been interpreted by the ligand exchange of flavonol coordinated to Zr(IV) with fluoride ion. On the basis of this phenomenon, Y. Takahashi et al. (*J. Chem. Soc., Perkin Trans. I* **2002**, 759) have fabricated a simple fluorescent detection system of fluoride ion available in aqueous media. The present signaling system provides a simple, rapid, and selective detection method of fluoride ion, which covers the concentration range from 1×10^{-3} to 3×10^{-6} M without any significant interference from common anions.



A Useful Disulfide Linker for Single-Bead Analysis of Peptide Libraries

W.-D. Woggon et al. (*Helv. Chim. Acta* **2002**, *85*, 495) have developed a disulfide-linker for conventional peptide synthesis, attached to a PEGA-resin. The loading used was 0.17 mmol/g. Reductive hydrolysis cleaves the linker within 2 min, liberating the synthesized peptide for rapid direct sequencing by tandem mass spectrometry. The linker eliminates itself under the reaction conditions making the direct sequencing possible. The method has been tested for 10 peptides in a single-bead fashion. It was found that the linker survives ordinary peptide-coupling conditions. It was found that it was enough material from a single bead to clearly identify the synthesized peptide through tandem mass spectrometry. This makes the linker useful for the analysis of "split & mix libraries" of short peptides.



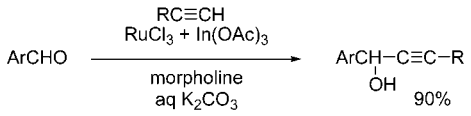
Recent Advances in Solventless Organic Reactions

A review of recent advances in organic reactions, carried out in the absence of solvent has appeared (Cave, G. W. V. et al. *Chem. Commun.* **2001**, 2159). Removing organic solvents from chemical synthesis is seen as important by the Green Chemistry movement in the drive towards benign chemical technologies. The article does point out the main disadvantage of solventless reactions, which is the formation of hotspots and the possibility of runaway reactions. Another disadvantage is the difficulty of handling solid material or highly viscous mixtures. The authors' answer to this is the use of advanced reactor design and better engineering.

Certain reactions, for example the condensation of aromatic aldehydes with methyl ketones lend themselves to this procedure and have, in fact been carried out on plant scale in this way in some companies since the 1970s. It will be interesting to see whether this area is taken up by the fine chemicals industry, where the advantages of high space−time-yield and environmentally friendliness may need to be balanced out with the disadvantages (potential heat- and mass-transfer problems on larger scale). For high specification products there will always need to be solvents used in work-up and purification steps, such as recrystallisations.

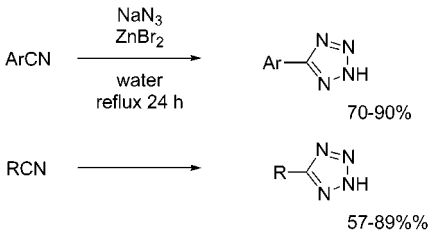
Metal-Catalysed Reactions in Water.

A perspective article from one of the leaders in the field of organic reactions in water has appeared (Li, C.-J. *Green Chemistry* **2002**, *4*, 1). These perspective articles are quite short but highlight the important issues—in this case the focus is on C−C bond forming reactions in water. In a later paper from the same group (Wei, C. et al. *Green Chemistry* **2002**, *4*, 39), the reaction of aldehydes with acetylenes is explored.



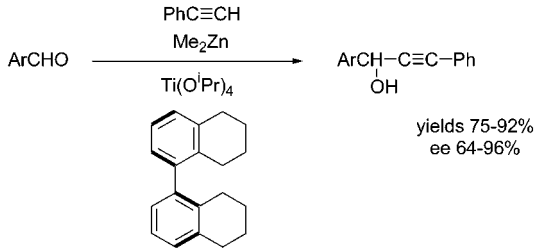
Preparation of Tetrazoles from Nitriles in Water

The addition of sodium azide to nitriles proceeds readily in water using zinc salts as catalysts (Demko, Z. P. et al. *J. Org. Chem.* **2001**, *66*, 7945). The reaction is applicable to a wide variety of nitriles, both activated and unactivated. The procedure is carried out at pH 7−8, minimising the release of hydrazoic aid. By using only a slight excess of sodium azide, release of hydrazoic acid during the acidic work-up can be avoided. The reaction has been run on 100 g scale.



Titanium-Catalysed Enantioselective Alkynylation of Aldehydes

There seems to be a great deal of interest in the reaction of acetylenes with carbonyl compounds in the last year. Following on from the work of Carreira (*J. Am. Chem. Soc.* **2001**, *123*, 9687; **2000**, *122*, 1806) a group from Hong Kong has recently found that a titanium catalyst, derived from titanium tetraisopropoxide and the ligand octahydrobinaphthol, gives good enantioselectivity in the reaction of aromatic aldehydes with phenylacetylene (Lu, G. et al. *Chem. Commun*. **2002**, 172). Some aliphatic aldehydes reacted with ees in the 74−82% range.

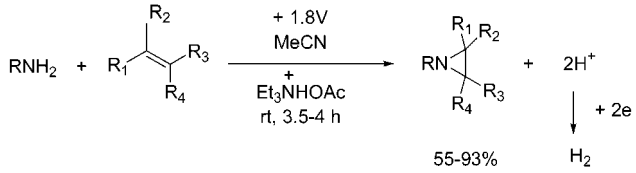


Silica-Supported TEMPO Catalysts

The Anelli procedure for oxidation of alcohols to aldehydes involves TEMPO in conjunction with hypochlorite as oxidising agent (Anelli, P. L. et al. *J. Org. Chem*. **1987**, *52*, 2559; *Org. Synth.* **1990**, *69*, 212). It is a method which has been successfully scaled up when mild reaction conditions and high selectivity are required. Now, the application of silica-supported TEMPO allows for catalyst recycling (Fey, T. et al. *J. Org. Chem*. **2001**, *66*, 8154). The oxidation of a variety of alcohols worked well, and in some cases recycling of the catalyst over 10 cycles was possible without appreciable loss of activity.

Practical Aziridination of Olefins Using Electrochemical Oxidation

Although there are efficient methods for olefin aziridination, these often involve stoichiometric oxidising agents such as lead tetraacetate. A new approach uses clean electrochemical oxidation and is successful with a wide variety of olefin substrates. Although it was originally thought that catalytic amounts of lead would be required, it was found that a simple combination of platinum electrodes, triethylamine, and acetic acid leads to formal nitrene transfer to olefins. (Siu, T. et al. *J. Am. Chem. Soc.* **2002**, *124*, 530).



Nitroalkanes: Can They Be Obtained Directly from Alcohols and Sodium Nitrite?

A paper in 2000 (Barvah, A. et al. *Syn. Lett*. **2000**, 1064) reported the reaction of alcohols with sodium nitrite in the presence of acetic and hydrochloric acids—conditions very similar to those routinely applied for the synthesis of nitrites.

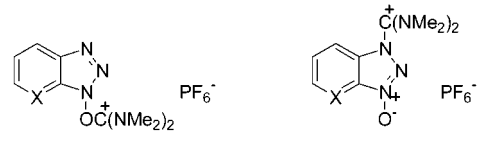
Unfortunately, this procedure has been repeated several times (Makosza, M. et al. *Syn. Lett*. **2001**, 1121) and the products are always the nitrites, with no trace of the nitro compound. Thus, it looks as if the earlier report was erroneous. Maybe the workers from the original report may respond with a confirmation of their original results, or a retraction!

Snapshots of a Working Catalyst

A review describing the possibilities and limitations of "in situ" spectroscopy in the field of heterogeneous catalysis has appeared (Weckhuysen, B. M. *Chem. Commun*. **2002**, 97). Monitoring the events taking place in the reactor can help with understanding reaction mechanisms, which must aid process improvement. IR, Raman, X-ray absorption, NMR, UV−visible, Mössbauer, and electron paramagnetic resonance spectra are all evaluated.

Peptide-Coupling Agents

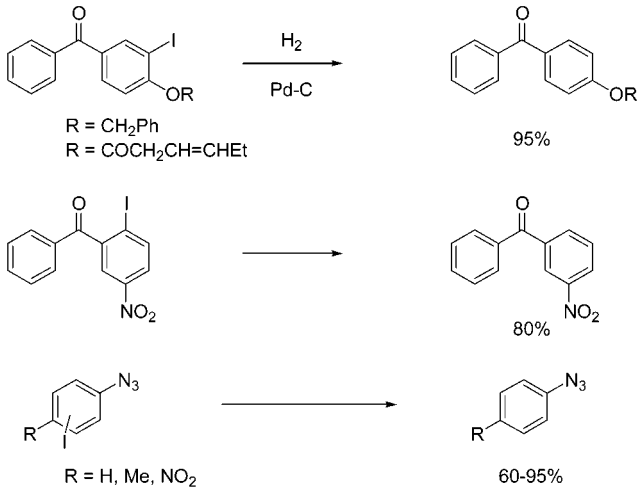
The most popular peptide-coupling agents are reagents based on phosphonium (BOP, PyBOP) and guanidinum salts (HBTU, HATU). The latter salts were originally assigned the structures **1a** and **1b** shown below but these were subsequently revised to **2a** and **2b**. By changing the reaction conditions in the synthesis, compounds of structure **1a** and **1b** have now been prepared, and they are, in fact, better peptide-coupling agents than **2a** and **2b**. It is suggested that these compounds are designated the abbreviations O-HBTU and O-HATU respectively (Carpino, L. et al. *Angew. Chem., Int. Ed.* **2002**, *41*, 442).



Chemoselective Hydrogenolysis of Iodoarenes

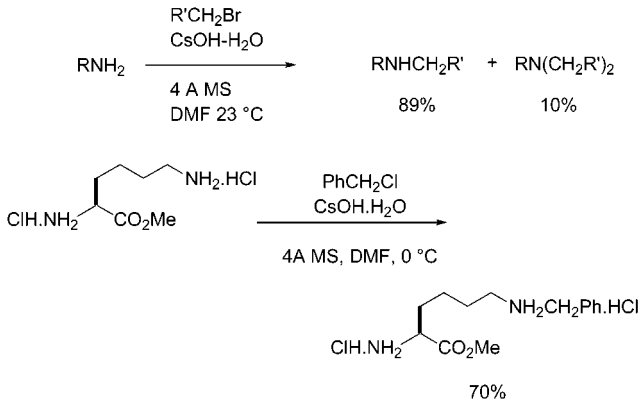
Catalytic hydrodehalogenation using Pd/C and hydrogen works best to remove iodine, with bromine and chlorine

behaving more sluggishly. This allows iodine to be selectively removed from aromatic rings even when nitro, azide, benzyl, carbonyl, and double bonds are present (Faucher, N. et al. *J. Org. Chem.* **2002**, *67*, 932).



Direct N-Alkylation of Amines

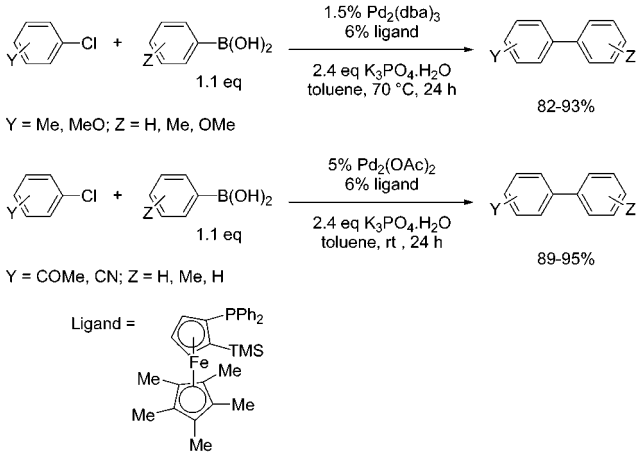
A procedure was recently described which gives selective monoalkylation of amines under mild conditions (Salvatore, R. N. et al. *Org. Lett.* **1999**, *1*, 1893). This method suppresses overalkylation and has been useful in complex syntheses (Wipf, P. et al. *J. Org. Chem.* **2001**, *66*, 3133). The full paper on this alkylation process has now appeared (Salvatore, R. N. et al. *J. Org. Chem.* **2002**, *67*, 674), and the scope of the process has been examined. Thus cesium hydroxide is the only base where dialkylation is at 10% or below—LiOH, NaOH, KOH, and RbOH all give poor selectivity. DMF is a better solvent than NMP, DMAc, or DMSO. Addition of molecular sieves or use of dry CsOH gives best yields. The reaction is useful for the alkylation of simple amines, amino acids, and diamines. The less hygroscopic cesium carbonate can also work well for some substrates, but for others, the hygroscopic hydroxide gives better selectivity.



Mild Method for Suzuki Coupling of Aryl Chlorides in the Presence of a Triarylphosphine

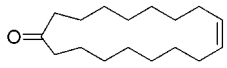
The low reactivity of aryl chlorides in palladium-catalysed coupling reactions has been ascribed to their reluctance to oxidatively add to palladium; thus electron-donating ligands are successful—alkylphosphines working where aryl phosphines fail. A recent report from the group of Fu at MIT (Liu, S.-Y. et al. *Chem. Commun.* **2001**, 2408) describes the use of a ferrocenyl triarylphosphine in Suzuki reactions of activated aryl chlorides *at room temperature*, and unactivated aryl chlorides at 70 °C.

The structure of the ligand is crucial—the ligand without Me groups on the ferrocene gives lower yields (37%), and if the TMS group is omitted, yields are very poor (8%).



Application of Olefin Metathesis in Oleochemistry

Metathesis of natural oils and fats allows the conversion of readily available and renewable feedstocks to be converted into novel chemical products. A recent review (Moi, J. C. *Green Chemistry* **2002**, *4*, 5) summarises progress in this field. An example is the synthesis of civetone from methyl oleate.



civetone

Combinatorial Methods for the Discovery and Optimisation of Homogeneous Catalysts

A review has appeared (Dahmen, S. et al. *Synthesis* **2001**, 1431) on the use of combinatorial methods to discover new catalysts, taking advantage of serendipity. It is argued that the more traditional design and screening approaches are based on mechanistic bias, and lead to catalyst structures which were expected. The ability to make and screen large numbers of metals and ligands using automated techniques, however, allows for *unreasonable* metal/ligand combinations—this serendipity has already lead to the discovery of new catalysts.

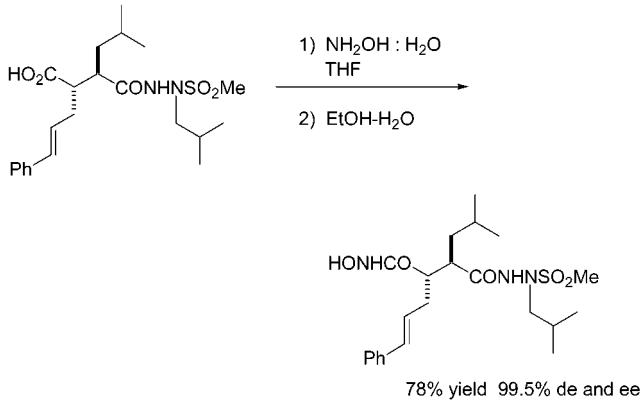
The review covers both solution- and solid-phase methods, and also covers analytical methods for FAST determination of product yield and purity. It is particularly valuable in asymmetric catalysis to have quick analysis of ee, but HPLC or GC methods are often too slow. The combination of HPLC, to separate the product from by-products, with CD and UV absorption (to measure enantiopurity) has given ee determinations in 1.5 min (Mikami, K. et al. *Chem. Eur. J.* **2001**, *7*, 730). An alternative method is to use capillary electrophoresis, which allows the determination of over 7000 ee measurements per day—a commercially available capillary

electrophoreses is available from Amersham Pharmacia (see Reetz, M. T. et al. *Angew Chem., Int. Ed.* **2000**, *39*, 3891).

The article points out the dangers in conventional catalyst screening methods, where one parameter is held constant as another is varied. Since critical parameters for catalysis are often mutually dependent, this methodology is unlikely to lead to optimum catalysts. Combinatorial catalysis, however, allows for two-dimensional screens, which should pick up any interdependency of variables, and is therefore more likely to lead to improved catalysis.

The Importance of Solvent Effects

In the reaction of a complex molecule containing a carboxylic acid, the final step was the conversion of the carboxylic acid to the hydroxamic acid with hydroxylamine hydrate. In dichloromethane a 1:1 mixture of O and N acylation took place, whereas in THF, a 6:94 ratio was obtained, which on crystallisation from aqueous ethanol yields the pure drug substance RO 32-7315, a TNF-X-converting enzyme inhibitor. (Hilpert, H. *Tetrahedron* **2001**, *57*, 7675).

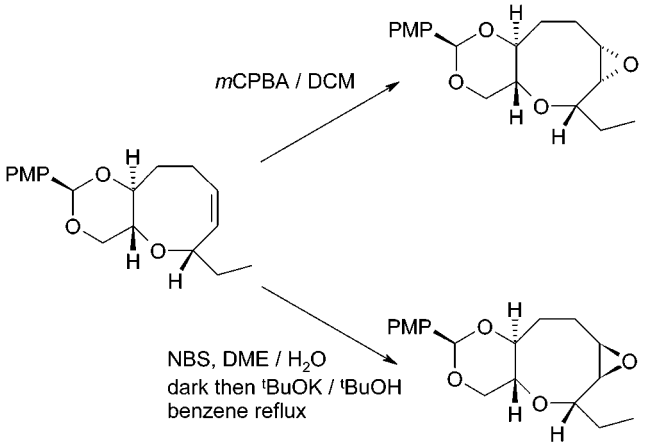


New Design for Cryorganic Reactors for Control of Exothermic Batch Processes

An article in the February edition of *The Chemical Engineer* (*Chem. Engineer* **2002**, February, 40) describes an improved reactor for carrying out low-temperature reactions and for working with very exothermic processes. Liquid nitrogen is used as the coolant, but in contrast to conventional reactors for low-temperature work where boiling of the liquid nitrogen causes unpredictable and uncontrollable transient flow regimes in the coolant (with subsequent change in heat transfer coefficient), a novel baffle design allows for efficient controlled heat removal, with low liquid nitrogen usage, faster cooling rates (10 °C per min in a 8000-L reactor), better temperature gradients, and thus improved space−time yield. It is suggested that this will allow direct, reliable, and reproducible scale-up from 1 L to 12,000 L. Small-scale units are also available. Equipment is available from Kelvin Cryosystems in U.S.A., Manrochem in UK.

Puzzle

This issue's puzzle is a mechanistic one. Both enantiomers of the epoxide derived from the alkene shown in the following scheme can be prepared using a different set of reagents; however, the π-facial selectivity is the same. Can you explain why both epoxides can be formed?



The answer is in a paper by Clark (*Tetrahedron Lett.* **1998**, *39*, 8321) concerning the synthesis of medium-sized allylic ethers by ring-closing metathesis. Good Luck!

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