Organic Process Research & Development **2002**, *6*, 580–590

Highlights from the Literature

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

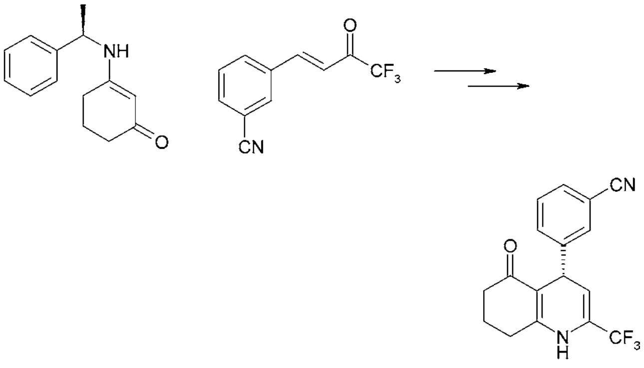
Mild Iodination

Aryl iodides have assumed increasing importance in organic synthesis over the past number of years as versatile substrates for cross coupling reactions. A variety of aromatic compounds substituted with methoxy or methyl groups have been regioselectively iodinated with *N*-iodosuccinimide and catalytic trifluoroacetic acid with excellent yields under mild conditions and *short reaction times* by Colobert and co-workers (*Tetrahedron Lett.* **2002**, *43*, 5047). The group propose that the active iodinating agent is the "in situ" formed iodine trifluoroacetate.

$$\mathrm{Ar{-}H} \xrightarrow[\mathrm{CF_3CO_2H\ (0.3eq)}]{\mathrm{NIS\ (1.1eq)}} \mathrm{Ar{-}I}$$

Asymmetric Michael Addition

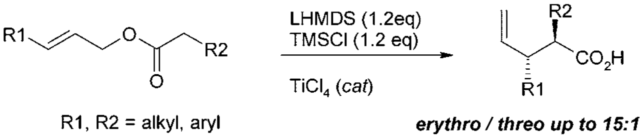
A concise, convergent asymmetric synthesis of the 4-substituted-1,4-dihydropyridine ZD0947 (see following scheme) has been achieved via a novel asymmetic Michael addition of an optically pure vinylogous amide to an α,*β*-unsaturated ketone by workers at Syngenta and Astra Zeneca (*Tetrahedron Lett.* **2002**, *43*, 4931). The overall process is three steps from readily available starting materials and provides an economical manufacturing route to ZD0947 which was required as a candidate for the treatment of urinary incontinence.



ZD0947

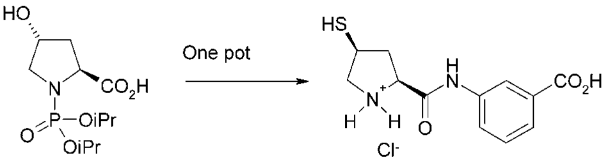
Highly Diastereoselective Lewis Acid-Promoted Claisen–Ireland Rearrangement

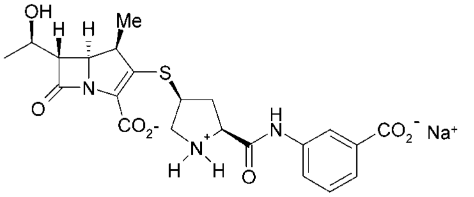
Koch and co-workers have published an interesting communication regarding highly diastereoselective Lewis acid-promoted Claisen–Ireland rearrangements. In their paper (*Tetrahedron Lett.* **2002**, *43*, 4837) they describe how in the presence of catalytic amounts of Lewis acids, silyl ketene acetals of *trans* allylic esters undergo a highly diastereoselective Claisen–Ireland rearrangement to the corresponding disubstituted $\gamma-\delta$ unsaturated *ethyro* carboxylic acids. Diastereoselectivities of up to 15:1 were achieved by the group when $TiCl_4$ was used as catalyst. In comparison, the uncatalysed process proceeded slowly and with significantly lower selectivity. A wide range of aryl- and alkyl-substituents were tolerated.



Ertapenem

Ertapenem is a new parenteral broad spectrum carbapenem antibiotic with a unique efficacy profile in the late stages of development at Merck. The compound is stable against renal dehydropeptidase-I and resistant to most *β*-lactamases. An efficient synthesis of the 2-aminocarbonylpyrrolidin-4-ylthio-containing side chain of ertapenem has been described by Brands and colleagues at Merck (*J. Org. Chem.* **2002**, *67*, 4771). The starting material *N*-(*O,O*-diisopropyl phosphoryl)-*trans*-4-hydroxy-L-proline (shown in the following scheme) is converted to (2*S*)-*cis*-3-[[(4-mercapto-2-pyrrolidinyl)carbonyl]amino]benzoic acid monohydrochloride in a series of six reactions. The development of each of these reactions and the isolation of the product is described in their paper.





Ertapenem

Protection of Hydroxamic Acids

Couturier and co-workers from Pfizer have recently reported (*J. Org. Chem.* **2002**, *67*, 4833) their general, high-yielding procedure to protect hydroxamic acids as 5,5-dimethyl-1,4,2-dioxazoles where both the NH and OH are derivatised in a nonprotic form. The dioxazoles are stable to a wide variety of reaction conditions and readily revert back to the hydroxamic acid by treatment with Nafion-H in 2-propanol. Their method is applicable to primary, secondary, tertiary, and aromatic hydroxamic acids, and the dioxazole

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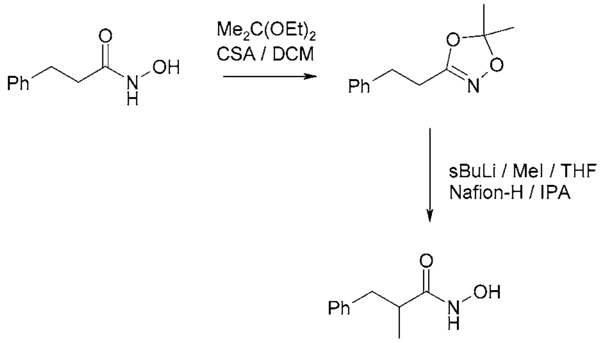
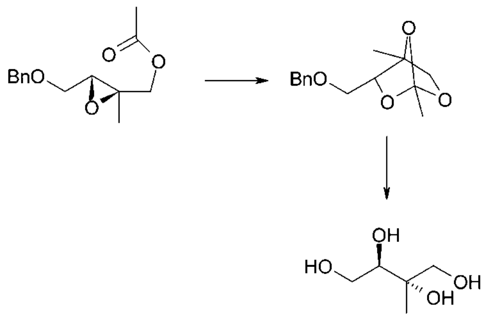
provides a handle that allows α-functionalisation (see following scheme).



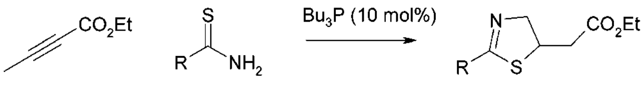
Biomimetic Synthesis

Giner and co-workers from the State University of New York report (*J. Org. Chem.* **2002**, *67*, 4856) how the biomimetic epoxy ester−ortho ester rearrangement can be applied to a new synthesis of 2-methyl-D-erythritol, a branched five-carbon sugar of importance to the deoxyxylulose pathway of isoprenoid biosynthesis. Labeling studies with O-18 indicated that this reaction proceeds exclusively via a 5-exo cyclisation.



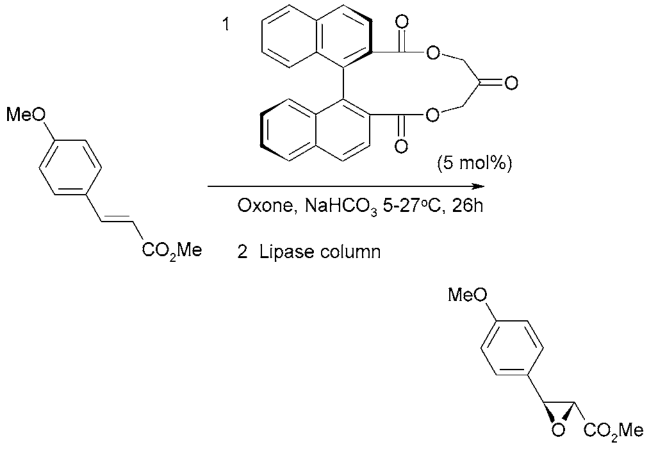
A New Synthesis of Thiazolines

The annulation of thioamides with 2-alkynoates and 2,3-dienoates under the catalysis of tri-*n*-butylphosphine for the preparation of thiazolines has been described by workers at GSK (*J. Org. Chem.* **2002**, *67*, 4595). This ring structure is present in a variety of biologically active molecules, and this synthesis provides a new entry, particularly to molecules possessing 2-aryl substituents.



Diltiazem Intermediate

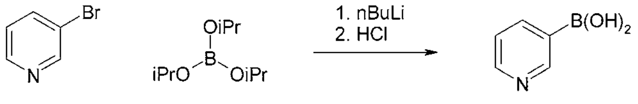
A practical synthesis of methyl (2*R*,3*S*)-3-(4-methoxyphenyl)glycidate (see scheme), a key intermediate for diltiazem, has been developed by Seki and co-workers at Tanabe Seiyaku Co. Ltd. In their synthesis (*J. Org. Chem.* **2002**, *67*, 4599) treatment of methyl (*E*)-4 methoxy cinnamate with a chiral dioxirane, generated in situ from the chiral ketone and oxone provided the epoxide in 77% ee and 89% yield. The crude mixture of epoxides could be efficiently separated by use of novel and simple lipase column to furnish the optically active epoxide.



74%, >99% ee

Borate Esters

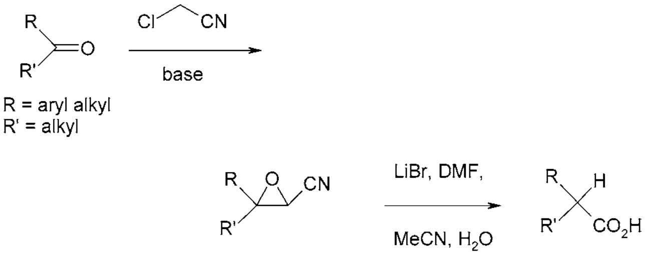
3-Pyridylboronic acid has been prepared in high yield and bulk quantity by scientists at Merck (*J. Org. Chem.* **2002**, *67*, 5394) from 3-bromopyridine via a protocol of lithium−halogen exchange and "in situ quench". In their method butyllithium is added to a ***mixture*** of 3-bromopyridine and triisopropyl borate. The 3-lithiopyridine intermediate generated reacts rapidly with the borate in the reaction mixture, thereby minimising the chance for side reactions. In a separate publication (*Tetrahedron Lett.* **2002**, *43*, 4285) the group describe the preparation of other 3-substituted pyridines via the addition of other electrophiles to 3-lithiopyridine.



Boronic acid

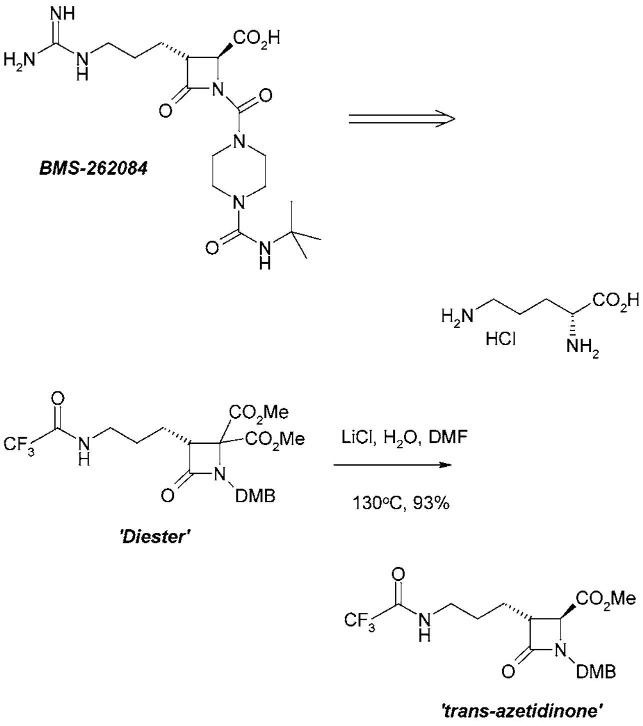
Rearrangement of Epoxynitriles

A convenient two-step homologation of both aliphatic and aromatic ketones to the corresponding carboxylic acid derivatives has been developed by Badham and colleagues at GSK (*J. Org. Chem.* **2002**, *67*, 5440). As outlined in the following scheme, the ketones were converted to their epoxynitriles using the Darzens reaction. In the second step, a Lewis acid-mediated rearrangement of these epoxynitriles with lithium bromide was achieved to give homologated secondary carboxylic acids in good yields. Water was found to be essential for the rearrangement reaction.



Stereoselective Synthesis

BMS-262084 is a subnanomolar inhibitor of tryptase and suppresses induced inflammation in animal lungs. A highly stereoselective synthesis of this compound has been reported (*J. Org. Chem.* **2002**, *67*, 3595) by Qian and co-workers at Bristol Myers Squibb in 10 steps from D-ornithine in 30% overall yield. Key to this synthesis was the discovery and development of a highly diastereoselective demethoxycarbonylation of the diester (illustrated in the following scheme) to the *trans*-azetidinone.



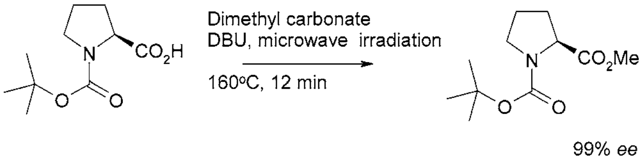
DMB = 2,4-dimethoxybenzyl

^{1}H NMR Coupling Constants

Hoye and Zhao have published an addendum (*J. Org. Chem.* **2002**, *67*, 4014) to their "Practical Guide to First-Order Multiplet Analysis in ^{1}H NMR Spectroscopy" (*J. Org. Chem.* **1994**, *59*, 4096). In this publication a systematic procedure to decipher first-order ^{1}H NMR multiplets is described.

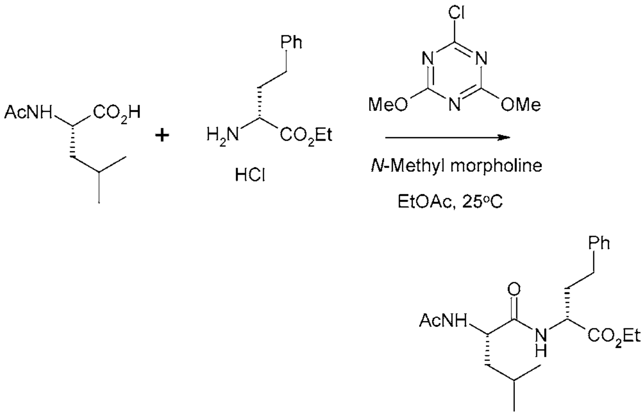
Large-Scale Microwave-Accelerated Esterification

Esterification of carboxylic acids with dimethyl carbonate can be accelerated using DBU as the catalyst (chemical acceleration) and microwave irradiation as energy (physical acceleration) as reported by Shieh and colleagues from Novartis (*Tetrahedron Lett.* **2002**, *43*, 5607). Combining these two strategies has enabled the group to esterify a variety a carboxylic acids in a matter of minutes compared with hours under thermal conditions alone. In addition the group have combined this technology with a continuous flow reactor capable of processing multigramme quantities of substrate.



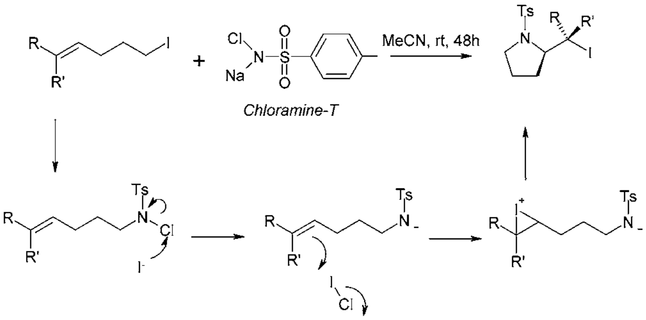
Peptide Bond Formation

Garrett and co-workers have described a one-pot, one-step procedure (*Tetrahedron Lett.* **2002**, *43*, 4161) for the coupling of carboxylic acids and amines using 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) as coupling agent. Chiral amino acids with unhindered *N*-substituents can be effectively coupled without loss of stereochemical integrity. Additionally, when the product is a nonwater soluble solid, the reaction may be run in acetonitrile and many of the products isolated by simply adding water and recovering the precipitate.



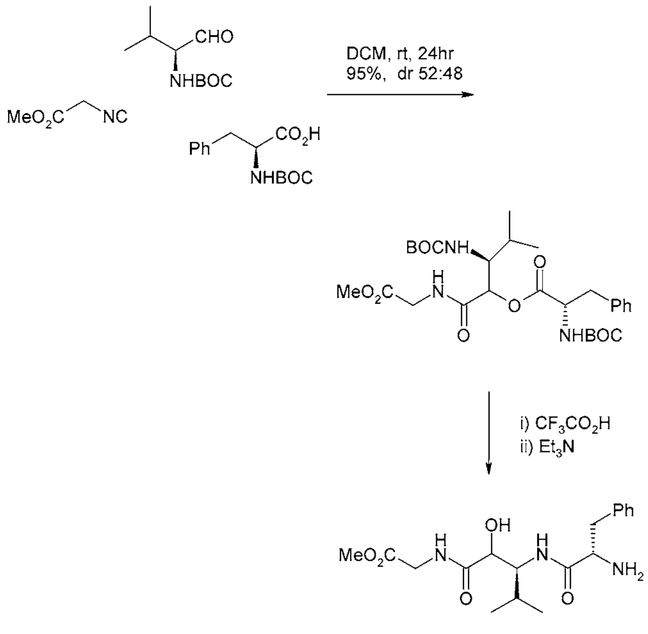
Iodine Atom-Transfer Cyclisation

Komatsu and co-workers from Osaka University have reported (*Org. Lett.* **2002**, *4*, 2097) that pyrrolidines and bicyclic pyrrolidine derivatives can be prepared from γ-iodo olefins using commercially available chloramine-T as a nitrogen source. The cyclisation proceeds with high stereoselectivity via a cyclic iodonium intermediate. The iodo group of the substrate has multiple roles during the reaction, namely (i) leaving group for substitution with chloramine-T, (ii) Lewis acid for abstraction of Cl, (iii) activator of the olefin, (iv) stereocontrolling cyclic cation and (v) functional group of the final product (see scheme).



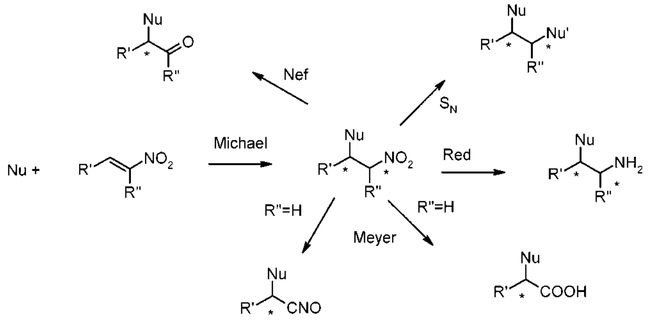
Modified Passerini Reaction

Banfi, Guanti, and co-workers have described short syntheses of protease inhibitors via a modified Passerini condensation of *N*-BOC-α-aminoaldehydes (*Tetrahedron Lett.* **2002**, *43*, 4067). In their communication these complex peptidomimetic structures are built quickly and efficiently in good yield.



Asymmetric Michael Additions To Nitroalkenes

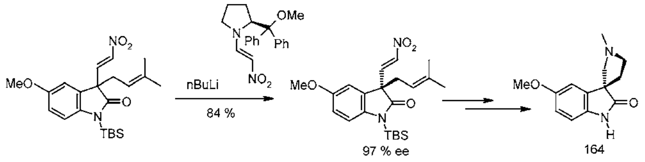
The use of highly reactive nitroalkenes as Michael acceptors opens the way to synthetically very useful C−C and C−X bond-forming reactions and subsequent transformations. To make the use of nitroalkenes even more attractive, a number of new efficient synthetic methods have been developed in recent years. D. Enders et al. (*Eur. J. Org. Chem.* **2002**, 1877) have summarised the application of nitroalkenes as Michael acceptors in asymmetric conjugate additions. Among the Michael acceptors, the nitro group is the most electron-withdrawing and also the most versatile as it can serve as masked functionality, which can be further transformed after the addition. The Nef reaction, the nucleophilic displacement, the reduction to an amino group, the Meyer reaction, and the conversion to nitriles or nitrile oxide are just a few examples.



The most versatile preparation of nitroalkenes involves the Henry condensation reaction of an aldehyde or ketone with a nitroalkane followed by dehydration (for further information, see: Barrett, A. G. M. and Grabowski, G. G. *Chem. Rev.* **1986**, *86*, 751). To handle the safety risks with nitroalkanes on large scale the Henry condensation reaction is a good candidate for continuous processes in micro- or minireactors.

The review is divided into four major parts: substrate-controlled diastereoselective Michael addition, auxiliary-controlled conjugate addition, asymmetric Michael additions employing enantiopure additives or catalysts, and applications to the synthesis of natural and biologically active products. The high degree of stereo control that can be achieved in conjugate additions to nitroalkenes has been thoroughly shown by substrate-, auxiliary-, and additive-controlled reactions as well catalytic versions.

In the section for synthesis of natural and biologically active products, only some representative examples have been summarised as, for instance, the synthesis of (−)-horsfiline (**164**).

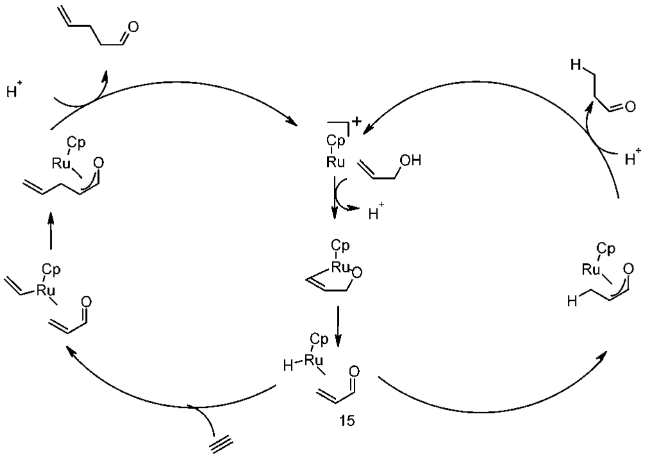


On Inventing Reactions For Atom Efficiency

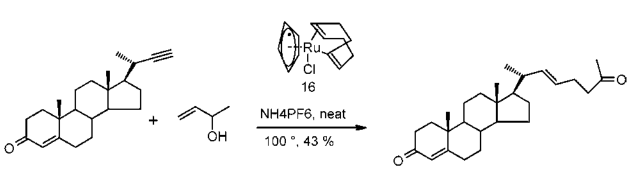
B. Trost has highlighted the work of his group in the development of atom-economical reactions utilizing one ruthenium complex (*Acc. Chem. Res.* **2002**, ASAP, March 8.).

There are many issues that must be addressed to make organic synthesis more environmentally benign by design. One fundamental consideration is the stoichiometry of the process. The fact that we have barely begun to probe the possibilities offered by catalysis emphasises that extraordinary opportunities exist to improve the toolbox of methodologies that are more atom-economical. The work from the group of Barry Trost is a good example of this. Using one type of a ruthenium complex, over 20 new reactions have evolved. Considering how many ruthenium catalysts can be imagined, the number of reactions yet to be discovered must be staggering. A semirational process provides valuable guidance since the proposed hypothesis leading to the discovery does not always turn out to be the actual mechanism.

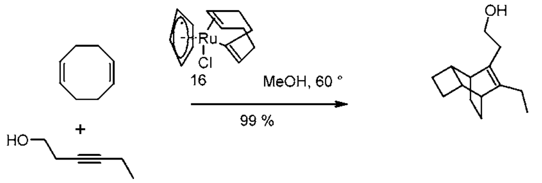
The following scheme illustrates this example involving the mechanistic rationale for the isomerisation of allyl alcohols and its implication for related processes.



The proposal in the scheme invokes a ruthenium hydride intermediate **15**. Such a species might be diverted by a hydrometalation of an alkyne to follow cycle B. This was indeed found using a more coordinatively unsaturated complex **16**, a simple addition results in the formation of γ,δ-unsaturated ketones.



Through studying complex **16** a minor byproduct was observed that proved to be an adduct of COD and the alkyne. From this it was possible to develop a general [2 + 2 + 2] cycloaddition.



Water is Beautiful

The latest issue of *Advanced Synthesis and Catalysis* is dedicated to organic reactions in water. Water is a beautiful solvent in many aspects; it is cheap, safe, and clean. Among the various solvents used in organic reactions water is without doubt the most inexpensive. Its lack of inflammable, explosive, mutagenic, and carcinogenic properties make the use of water favorable in the industry as well as laboratories. Control of reaction temperature is easy in water due to the very high heat capacity of water.

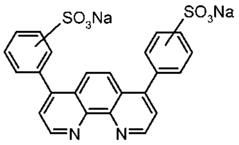
Enzymes organise very efficient reactions in the presence of water as solvent in living cells. Enzymatic reactions, which proceed in high yields with high selectivity and mild conditions, are goals for organic chemists in the industry or academia.

Catalytic Conversions In Water: Mechanistic Investigations On The Palladium-Catalysed Aerobic Oxidation Of Alcohols

Water-soluble complexes of palladium(II) with phenanthroline-derivatives are stable, recyclable catalysts for the selective aerobic oxidation of a wide range of alcohols to aldehydes, ketones, and carboxylic acids in a biphasic liquid−liquid system.

Traditionally, oxidations of alcohols are performed with stoichiometric amounts of inorganic oxidants. The oxidants are not only relatively expensive, they also generate copious amounts of heavy-metal waste.

There is a definite need for catalytic oxidations employing oxygen or hydrogen peroxide as the stoichiometric oxidant. These oxidants are atom-efficient, producing water as sole byproduct. The group of R. A. Sheldon has previously reported on the aerobic oxidation of alcohols with a water-soluble palladium complex of bathophenanthroline disulphonate (*Science* **2000**, *287*, 1636). Now they report on a mechanistic investigation utilizing this catalyst in aqueous media (*Adv. Synth. Catal.* **2002**, *344*, 355).



The catalyst proved to be highly active in water and could be recycled several times without significant loss of activity or selectivity.

The catalyst was found to be most active for small (=water-soluble) alcohols. Activated alcohols such as benzylic or allylic alcohols reacted relatively slowly.

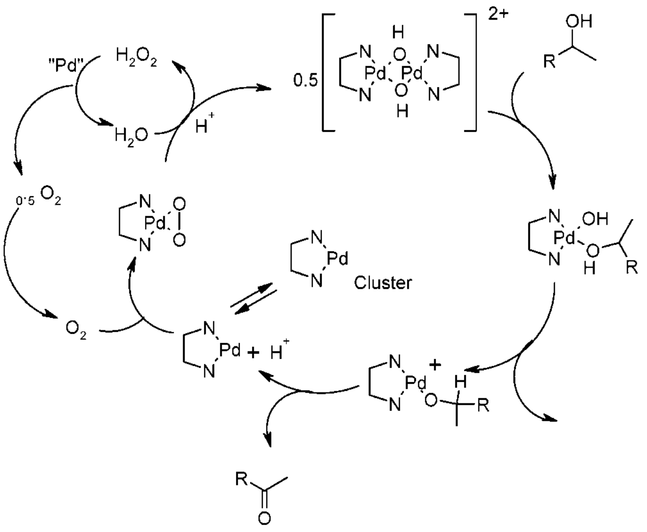
Primary aliphatic alcohols initially formed aldehydes, but under reaction conditions they were oxidised further to carboxylic acids. This could be prevented through the addition of the radical scavanger TEMPO.

For the reaction the best ratio palladium/ligand was found to be 1/1.

Many alcohol oxidations are performed under strongly alkaline conditions because the reaction involves abstraction of a proton from an alcohol coordinated to the metal center.

During this investigation a high pH was found to be unnecessary for a smooth transformation. Some sodium acetate was found to be beneficial to prevent the formation of palladium black.

From the investigation a plausible catalytic cycle for palladium−phenanthroline-catalysed oxidation of alcohols in water can be described. The starting dimeric complex is in equilibrium with 2 equiv of palladium monomer which reacts via alkoxide/β-hydride elimination.



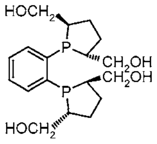
Asymmetric Organometallic-Catalysed Reactions In Aqueous Media

Although water-soluble organometallic catalysts have been known since the 1960s, it is only recently that this methodology has been extended to the synthesis of chiral compounds starting from achiral substrates. D. Sinou (*Adv.*

Synth. Catal. **2002**, *344*, 221) has summarised the recent results from asymmetric transformations in the presence of water in a homogeneous way as well as in a two-phase system.

Considerable interest has developed recently in asymmetric organometallic catalysis in water. The first goal was the recycling of the toxic and often costly catalyst via the use of a two-phase water—organic solvent system. A newer goal is to use a safe, nontoxic, and cheap solvent to realize a green chemical process. However, this approach needs special techniques to solubilise the catalyst and the products in the aqueous phase; catalysts have to be stable under the conditions and particularly against hydrolysis. Asymmetric hydrogenation of prochiral substrates has been one of the most studied reactions, but these approaches have also been successfully applied to carbonylation, oxidation, alkylation, 1,4-addition, cyclopropanation, Diels—Alder reaction, and aldol condensations. In oxidations and carbonylations only low enantioselectivities have been reached in water, very high enantioselectivities have been reached in palladium-catalysed alkylations in the presence of surfactants and in Diels—Alder reactions and aldol reactions in the presence of Lewis acids. In the last two reactions even higher activities are observed in water than in organic solvents.

The rhodium complex from ligand **30** reduced 2-acetamidoacrylic acid and its methyl ester with a high rate and enantioselectivity of up to 99.6 and 93.6% respectively.



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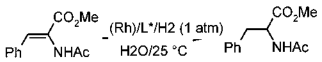
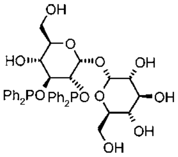
Sometimes the use of surfactants is beneficial for the reactions. Uemura et al. noticed a huge increase in enantioselectivities in the reduction of methyl α-acetamidocinnamates in the presence of SDS using water-soluble ligands.



L*	SDS	ee %
28	yes	90
	no	55
29	yes	>99
	no	88



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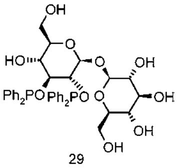

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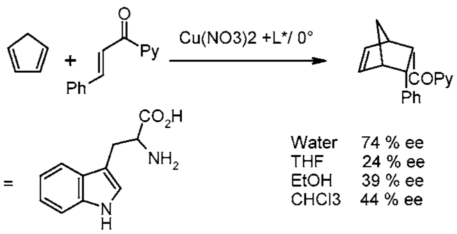
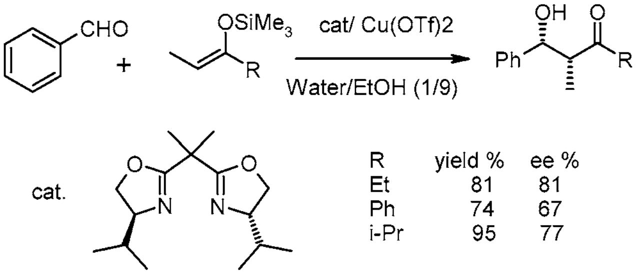
Engberts et al. have shown the beneficial effect of water on the activity and selectivity in the D—A reaction between cyclopentadiene and unsaturated ketones in the presence of copper complexes of chiral amino acids. The yields obtained exceeding 90% and enantioselectivities of up to 74%.



Water	74 % ee
THF	24 % ee
EtOH	39 % ee
CHCl3	44 % ee

Kobayashi and co-workers carried out catalysed asymmetric aldol condensations in aqueous media. Very high chemical yields as well as diastereo- and enantioselectivities (up to 85%) were obtained.



R	yield %	ee %
Et	81	81
Ph	74	67
i-Pr	95	77

New Highly Efficient Workup For Sulphonated Diphosphines

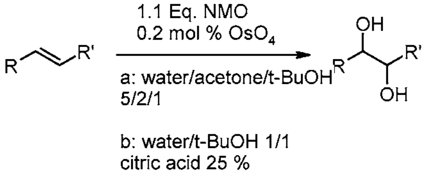
W. P. Mul et al. (*Adv. Synth. Catal.* **2002**, *344*, 293) have developed a new more efficient workup for the sulfonylation reaction of various diphosphines for the synthesis of water-soluble diphosphine ligands.

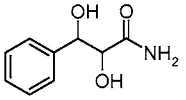
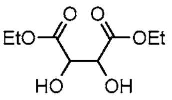
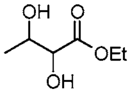
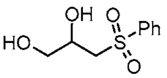
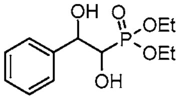
Despite the fact that high-performance catalysts are available, TPPTS is still the only water-soluble ligand that is industrially applied. The main reason is that application of a homogeneous catalyst at industrial scale requires the applied ligand system to be synthetically readily available. Most synthetic protocols involve the use of fuming sulfuric acid; the laborious workup methods applied until now involving neutralisation of the sulfuric acid followed by tedious purification of the synthesised ligand have put a strain on the industrial use of sulfonated ligands. The group of W. P Mul found that a simple dilution of the reaction mixture after the sulfonation with water causes the precipitation of the different ligands from the acidic water. A simple filtration and washing gives the wanted ligand in pure form.

Osmium-Catalysed Dihydroxylation Of Olefins In Acidic Media

Addition of osmium tetroxide to olefins is one of the more selective and reliable methods for two simple reasons: osmium tetroxide reacts with virtually all olefins, and it reacts slowly, if at all, with other common organic functional groups.

The group from B. Sharpless has developed a new variation of their dihydroxylation with osmium tetroxide which has some advantages in comparison to the old method (*Adv. Synth. Catal.* **2002**, *344*, 421). The new method run under aqueous acidic conditions expands the range of substrates that can be efficiently dihydroxylated. Citric acid appears to be the best acid for keeping the pH in the desired range. The obtained diols are exceptionally pure. The reaction can be performed at elevated temperatures without loss or decomposition of catalyst or oxidant and without overoxidation of the obtained diol.



Product	yield a: standard cond.	B. new cond.
	50	96
	<10	76
	45	67
	<40	78
	30	77

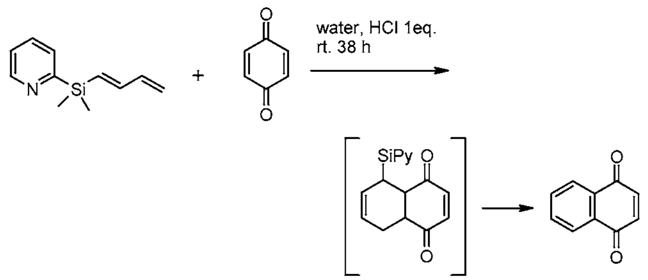
2-Pyridyldimethylsilyl Group A Removable Hydrophilic Group In Aqueous Organic Reactions. Formation Of Molecular Aggregates And Dramatic Rate Enhancement In D−A Reactions

The Diels−Alder reaction is currently one of the more active areas of research where the use of water give rise to exceptional rate enhancement and appreciable high stereoselectivity. In 1980 Breslow made the first observation of dramatic rate acceleration of the Diels−Alder reaction in water probably due to poor solubility of the reaction components in water which causes an increase of hydrophobic interactions.

An alternative approach is the use of an aqueous soluble diene, dienophile, or both, which has been reported by Grieco using dienes with hydrophilic groups such as sodium salts of carboxylic or phosphoric acids, and ammonium salts. These dienes undergo the D−A reaction in water at enhanced rates and stereoselectivities.

J. Yoshida et al. (*Adv. Synth. Catal.* **2002**, *344*, 441) have now reported on a novel methodology for aqueous organic reactions utilizing a 2-pyridyldimethylsilyl (2-PyMe$_2$Si) group as a removable hydrophilic group. It was found that 1,3-dienes bearing the PyMe$_2$Si group form molecular aggregates in water when 1.0 equiv of HCl was added.

The Diels−Alder reaction of these dienes took place at room temperature in water. The corresponding reaction in organic solvent was found to be much slower. The removal of the PyMe$_2$Si group could easily be accomplished by desilylation, oxidation, and electrophilic substitution.



In the future we will probably see a variety of different water-soluble protecting groups designed for various kinds of reactions in the same way as we have over the past decade seen a vast number of different groups used for the solid-phase organic synthesis. Correctly designed, these groups could probably be used as water-solubilizing protecting groups through entire synthesis sequences.

Dehydrative Esterification Of Carboxylic Acids In Water Catalysed By A Polymeric Sulfonic Acid

Organic reactions in water have been subject of much recent research. Although various efficient synthetic reactions in aqueous media have been developed thus far, there are still problems to be solved. One of the most difficult problems is that large amounts of water as a solvent have detrimental effects on reactions in which water molecules must be removed during the reaction. An example is acid-catalysed direct esterification of carboxylic acids with alcohols. Usually the obtained water molecules have to be removed (azeotropically or using a dehydrating agent) to shift the reaction to the ester. K. Manabe and S. Kobayashi (*Adv. Synth. Catal.* **2002**, *344*, 270) have now developed a new concept for the dehydrative esterification of carboxylic acids with alcohols in water with an efficient hydrophobic polystyrene-supported sulfonic acid as recyclable catalyst.

In these reactions, esters were obtained in high yields without using any dehydrating agent or apparatus. The presence of long alkyl chains on the polymeric support of the sulfonic acid significantly affected the catalytic activity.

The reaction has been shown to work very well with hydrophobic long-chain carboxylic acids and alcohols. But it still has to be shown if the concept also holds for carboxylic acids and alcohols with a higher water solubility. In this case lipophilic protecting groups would be helpful when the substrate is too water-soluble.

Recent Developments In The Chemistry Of Polyvalent Iodine Compounds

V. Z. Zhdakin and P. J. Stang (*Chem. Rev.* **2002**, *102*, 2523) have summarised the chemistry of polyvalent iodine compounds over the last 5 years. The organic chemistry of these compounds has experienced an unprecedented, explosive development. Just in the last 5 years a wide variety of new reagents have been introduced, and polyvalent iodine chemistry is employed increasingly in organic synthesis. This surging interest in iodine compounds is mainly due to the useful oxidizing properties of polyvalent organic iodine (III) and (V) compounds, combined with their benign environmental character and commercial availability. There has been a surge of activity in different areas including the synthetic application of the Dess–Martin periodinane and similar oxidizing agents based on iodine (V), catalytic oxidations with iodosylbenzene and catalytic imidations with iodonium imides, azidations with azidoiodinanes, the chemistry of benziodoxoles and benziodazoles. It can be anticipated that this trend will continue in the following years. The use of polymer-supported polyvalent iodine reagents and the transition-metal-catalysed coupling reactions of iodonium salts will probably increase the extensive interest in the chemistry of iodine compounds.

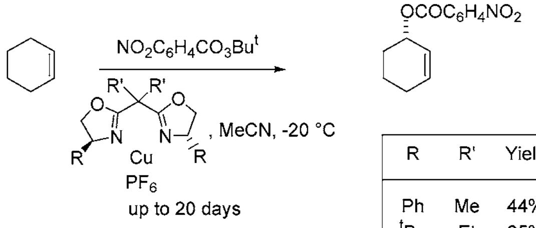
Nitrous Oxide as an Oxidizing Agent

Nitrous oxide is an inert gas with very little interesting chemistry. However, it contains 36% oxygen, and the byproduct of any oxidation would be nitrogen; thus, chemists have recently examined ways of utilizing N_2O for oxidations, with limited success being achieved with hydrocarbon oxidation using heterogeneous catalysts such as zeolites. Now a group from Israel (Ben-Daniel, R. et al. *J. Am. Chem. Soc.* **2002**, *124*, 8788) has shown that epoxidation of olefins can be carried out by manganese-substituted polyoxometalate catalysts. Reactions were highly selective, but slow, requiring 150° in fluorobenzene as solvent.

The reaction has been shown to involve Mn(II) which implies the N_2O initially acts as a reducing agent to generate the active catalyst. A disproportionation mechanism involving conversion of Mn(III) to Mn(II) and Mn(V) does not fit the ESR spectral evidence.

Allylic Oxidation of Olefins

Allylic oxidation of olefins using copper catalysts with bis-oxazoline ligands has been shown to give high enantioselectivity, although reactions are slow and the selectivity is very sensitive to the structure of the ligand (Andrus, M. B. et al. *J. Am. Chem. Soc.* **2002**, *124*, 8806).

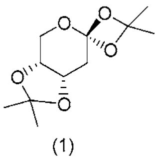


R	R'	Yield	ee
Ph	Me	44%	96%
^{t}Bu	Et	25%	16%
^{t}Bu	Me	61%	84%

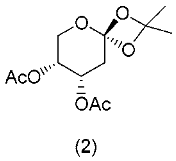
With cyclopentene, an ee of 99% was achieved with oxazoline (R = Ph, R′ = Et), whereas with cycloheptene, best ee was with R = ^{i}Pr or tBu, R′ = Me. For this to be practically useful, much better catalyst turnover needs to be achieved, but these results are very promising.

Epoxidation of α,β-Unsaturated Ketones Using Dioxiranes

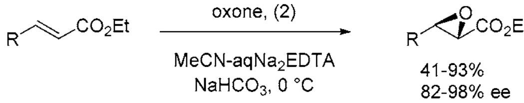
Although chiral dioxiranes such as (**1**) have been shown to be effective for asymmetric epoxidation of olefins, they are ineffective for the epoxidation of α,β-unsaturated ketones because of competing Baeyer–Villager oxidation of the catalyst. Now, the group of Shi in Colorado (Wu, X. Y. et al. *J. Am. Chem. Soc.* **2002**, *124*, 8792) has found that catalyst (**2**) is effective for α,β unsaturated esters in good yield and excellent enantioselectivity. Cis isomers gave poorer ee's.



(1)

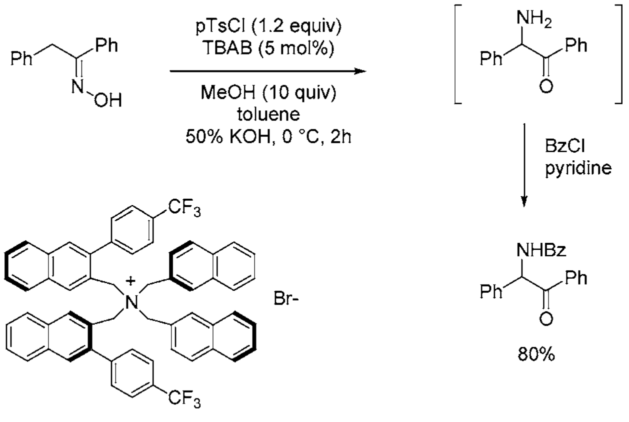


(2)

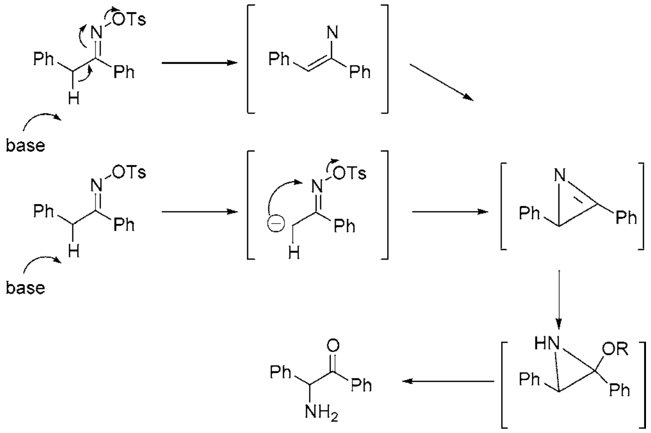


Enantioselective Neber Rearrangement

The Neber rearrangement, discovered in 1926, is an effective way of converting a ketone via its oxime sulphonate into an α-aminoketone. Researchers in Japan (Ooi, T. et al. *J. Am. Chem. Soc.* **2002**, *124*, 7640) have now found that the reaction will occur under phase-transfer catalysis, which allows the oxime to be tosylated in situ.

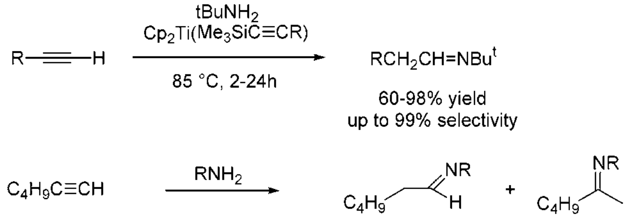


Using chiral phase-transfer catalysts, moderate ee's (30–20%) can be achieved with yields in the range 60–95%. Best results were achieved with the catalyst (A) and mesitylene rather than toluene a solvent. It is important that the oxime is in the Z configuration for good ee. The (*E*)-oxime gives only racemate but in reasonable yield. It is suggested that in this case the pathway is via a nitrene, rather than the concerted pathway proposed to account for asymmetric induction. For the (*E*)-isomer a syn displacment would be unfavorable, and the nitrene mechanism is preferred.



Hydroamination of Terminal Alkynes

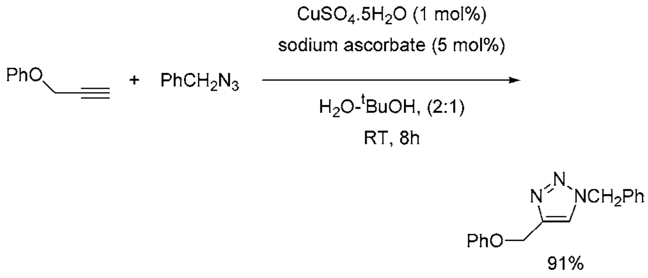
We have previously highlighted the intermolecular hydroamination of internal alkynes, reported by the groups of Bergmann (*J. Am. Chem. Soc.* **2001**, *12*, 2923) and Doye (*Angew. Chem., Int. Ed.* **2001**, *40*, 2305). Now the group of Beller at Rostock, Germany has reported the hydroamination of terminal olefins to give imines in an anti-Markovnikov fashion. (Tillack. A. et al. *Angew. Chem., Int. Ed.* **2002**, *41*, 2541). High selectivity is obtained in the addition of *tert*-butylamine to a wide variety of acetylenes and bis-acetylenes, but when the amine is changed, the selectivity drops.



	anti-M	M
R = tBu	99	1
R = secBu	3	1
R = Ph	1	3

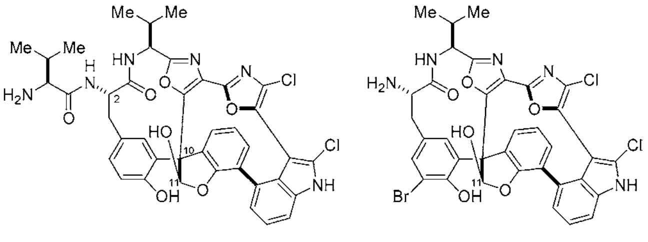
Selective Triazole Formation

The dipolar cycloaddition of azides to acetylenes normally gives a 1:1 mixture of products which limits its synthetic utility. The group of Sharpless at Scripps has now found that copper (I) catalysis radically improves the selectivity for the 1,4-disubstituted triazole and allows a simple method of synthesis in high yield. The copper (I) catalyst is easily generated from copper (II) and sodium ascorbate (Rostovtsev, V. V. et al. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596).



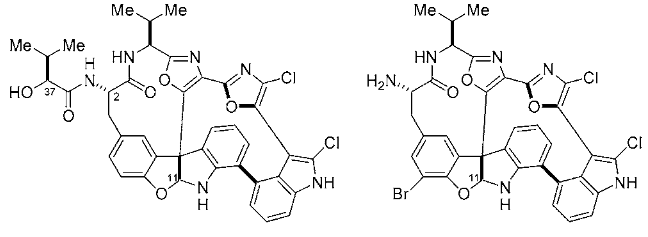
X-ray Crystallography Does Not Always Give the Correct Structure

When we determine the structure of a complex natural product we assume that X-ray crystallography combined with NMR spectroscopy will always give the absolute structure. It comes as a surprise, therefore, to find that the X-ray crystallographic analysis of a simple derivative of the natural product diazonamide B, determined in 1991, has turned out to be incorrect. Total synthesis of the material yielded a different structure, and the original structure has now been reassigned with the NH_2 and OH reversed. This is discussed in a highlight article (Ritter, T. et al. *Angew. Chem., Int. Ed.* **2002**, *41*, 2489).



nominal diazonamide A
1991 assignment

nominal diazonamide B
1991 assignment



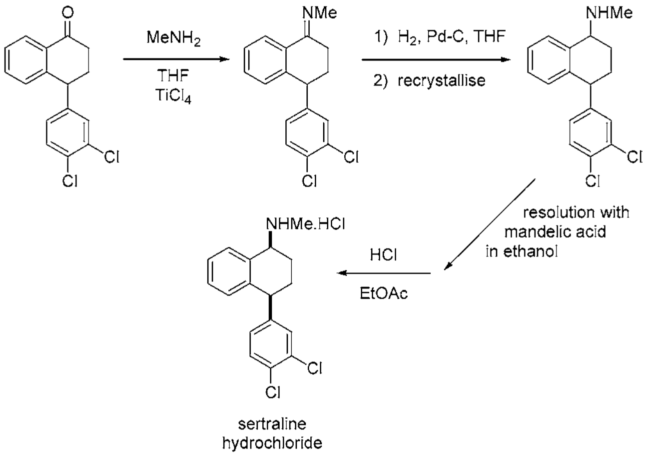
(-)-diazonamide A
2001 assignment

diazonamide B
2001 assignment

Pfizer Chemists Win Green Chemistry Award

For their work on process improvements to the sertraline hydrochloride (Zoloft) process, Pfizer chemists Geraldine Taber, Juan Colberg, and David Pfisterer have received a Green Chemistry Award. The original process is shown below. In the new process the first three steps are telescoped, and no intermediates are isolated. The solvent is changed to ethanol, and $TiCl_4$ is not now required since the imine precipitates out, driving the reaction to completion. Switching from Pd−C which gives a cis−trans ratio of 6:1 to $Pd-CaCo_3$ (18:1 ratio) improves the process. With other improvements and recycling, the overall yield has nearly doubled to 37%, and raw materials (and the costs) have been significantly reduced (*Chem. Eng. News* **2002**, *80*, 29).

From an environmental viewpoint the solvent usage is reduced from 240 000 to 24 000 L per tonne of sertraline, and 440 tonnes of TiO_2 waste is eliminated along with 150 tonnes of 35% HCl waste, 100 tonnes of NaOH waste, and methylamine hydrochloride salt waste.



New Procedures from *Organic Syntheses*

The latest edition of *Organic Syntheses* (**2002**, *79*) contains, as always, a wide range of interesting synthetic procedures. This issue contains improved preparations for relatively simple molecules such as 3-(4-bromobenzoyl)-propanoic acid, 2-amino-3 fluorobenzoic acid, and even caprolactam. As always the reactions are suitable for scale-up, but the workups are often lengthy and environmentally unfriendly and need extensive modification for kilogramme-scale operation. It was particularly disappointing to see one preparation (p 251) using carbon tetrachloride as solvent, without any mention of its toxicity or how the material could be safely disposed of.

It was also good to see preparations of ionic liquids such as 1-butyl-3-methylimidazolium salts, although no criterion for purity was given. As mentioned in last month's Highlights, purity is an important criterion for success when using ionic liquids as solvents.

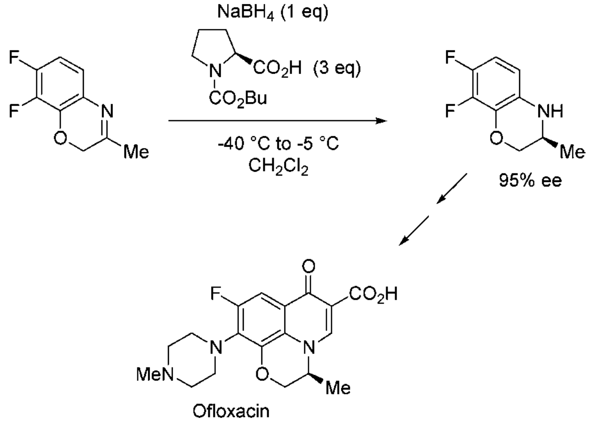
Rapid Determination of Enantiomeric Excess

Although automated, parallel reaction optimisation is now used widely in process R & D, a major limitation to high throughput work can be the analysis. This is particularly true of methodologies requiring enantiomeric excess determination. A recent review (Finn, M. G. *Chirality* **2002**, *14*, 534) covers emerging methods for the rapid determination of enantiomeric excess.

Boron-Based Reducing Agents for Asymmetric Synthesis: A Review

A review on boron-based reducing agents for asymmetric reduction of funtionalised ketones and detimines has recently appeared (Cho, B. T. *Aldrichimica Acta* **2002**, *35*, 3). For the imines, best results are obtained with cyclic compounds where the geometry is fixed. For example a synthesis of nonracemic oflaxacin has been achieved using the method shown below.

This issue of *Aldrichimica Acta* is dedicated to Professor H. C. Brown on his 90th birthday and also contains a review from one of Brown's co-workers (Ramachandran, P. V. *Aldrichimica Acta* **2002**, *35*, 23) on pinane-based allyl boranes. A monograph, *Organoboranes for Synthesis,* by Ramachandran and Brown (Oxford University Press, 2001) was published recently.



3-Iodoxybenzoic Acid: Handle With Care

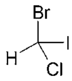
We recently highlighted the increasing use of compounds containing iodine−oxygen bonds in organic synthesis, particularly oxidations. A recent issue of *Chemical and Engineering News* (*Chem. Eng. News* **2002**, *80*, 4) contained a letter from scientists at Bristol Myers Squibb in Wilmington, who had had an explosion in the lab when making a 200-g batch of 3-iodoxybenzoic acid. After filtration of the product, washing, and air-drying, the compound exploded when being spooned into a storage bottle, destroying the funnel and other glass items in the vicinity. The chemist received only minor injuries as a result of wearing proper protective items. The shock sensitivity of this compound had not previously been reported. Whether the explosion was due to the compound itself or was caused by impurities is unclear. However, the message is clear—all iodoxy compounds should be handled with care, and if scale-up is planned, extensive safety testing is required.

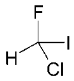
Explosion At Pfizer Plant

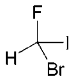
An explosion at Pfizer's Groton research complex on June 25th, due to a borane−THF container in a warehouse, put five people in hospital and severely damaged the building. It is suspected that the container became over-pressurised before the explosion, and five other containers were subsequently found to be under higher than expected pressure (*Chem. Eng. News* **2002**, *80*, 7). It would be wise to inspect all similar containers for signs of over-pressurisation. No doubt the suppliers have contacted all users already and suggested remedial action. We hope to report further details on this incident once the accident investigation has been published.

PUZZLE

Chiral halomethanes are the smallest chiral molecules and have the general formula CWXYZ where W, X, Y, and Z can be H, F, Cl, Br, I. All such molecules lack any symmetry (that is they belong to the C_1 point group). Experimental determination of the maximum optical rotation and absolute configuration of these halo methanes are of great interest in the context of modern theories of optical activity. As a real challenge in this issue of OPRD, how would you prepare the following halogenated derivatives of methane? If you need any help, see *Tetrahedron* **2002**, 5923!







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