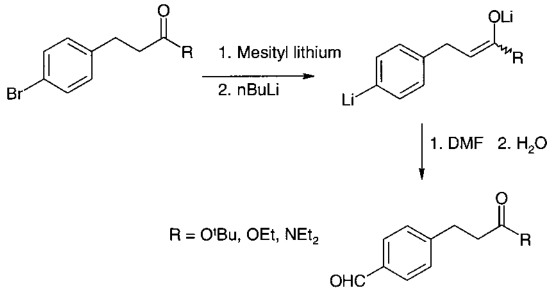
Organic Process Research & Development **2002**, *6*, 338–345

Highlights from the Literature

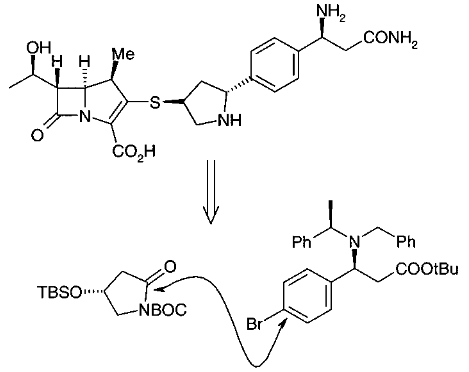
Some Items of Interest to Process R&D Chemists and Engineers

Lithiation Of Aryl Bromides Possessing Carbonyl Groups

A new methodology for the metalation of aryl bromides possessing an active methylene adjacent to a carbonyl group has been described by Yamamoto and co-workers from the Banyu Pharmaceutical Company (*Synlett* **2002**, 561). To avoid self-quenching, selective deprotonation was necessary prior to the halogen−metal exchange reaction. For this purpose the group used mesityllithium prior to subsequent treatment with nBuLi.

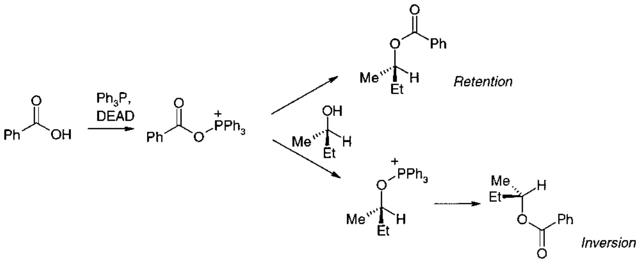


The resultant dianion was quenched with electrophiles in good yield and the group have applied the methodology to the efficient synthesis of a novel carbapenem as shown in the following scheme.



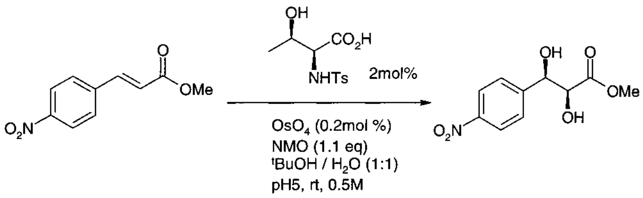
Mitsunobu Reaction

DeShong and co-workers from the University of Maryland have conducted mechanistic studies of the Mitsunobu reaction (*J. Org. Chem.* **2002**, *67*, 1751). This reaction typically gives inversion of configuration in secondary alcohol derivatives. In their paper, a mechanistic explanation for lactonisation of hindered alcohols under the Mitsunobu conditions *with retention* is proposed. This involves the intermediacy of an acyloxyphosphonium salt followed by acyl transfer to the alcohol.



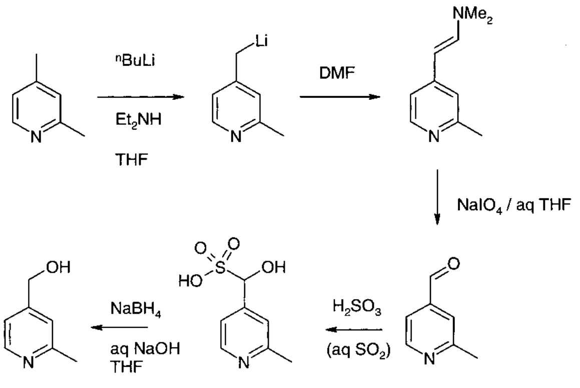
Simple Hydroxyamino Acid Derivatives as Chiral Ligands

Simple hydroxyamino acid derivatives have been reported by Sharpless and co-workers (*Angew. Chem., Int. Ed.* **2002**, *114*, 472) as chiral ligands in osmium-catalysed dihydroxylation and aminohydroxylation of olefins. These are the first examples of asymmetric osmium-catalysed processes proceeding in the second catalytic cycle with resident ligands on the metal centre. Sharpless reports that such processes offer many variables for optimisation (in fact, considerably more than the AD offered when it was at the same stage of development) and present an opportunity for a "quantum jump" in the utility of the osmium-catalysed oxidation processes. This promises to be an exciting area in which to monitor progress!



Regioselective Hydroxylation of 2,4-Lutidine

A practical synthesis of 4-hydroxymethyl-2-methylpyridine has been developed by Ragan and colleagues at Pfizer (Synthesis **2002**, 483). The procedure makes use of Evans' regioselective lithiation of readily available 2,4-lutidine followed by subsequent trapping with dimethylformamide.

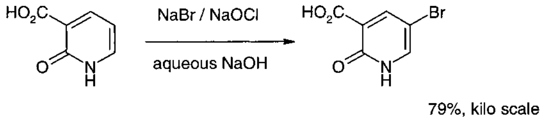


10.1021/op025556g CCC: $22.00

The resultant enamine could be oxidatively cleaved using $NaIO_4$ to generate the aldehyde which was purified as its bisulphite adduct using aqueous sulphur dioxide. Regeneration of the aldehyde followed by reduction furnished the desired alcohol.

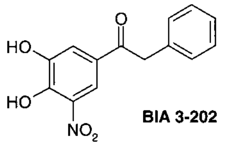
Large-Scale Preparation of 5-Bromo-2-hydroxynicotinic Acid

Bromination of 2-hydroxynicotinic acid has been performed on large scale by Beaulieu and co-workers from Boehringer Ingelheim (*Synthesis* **2002,** 528) using sodium hypobromite generated in situ from sodium bromide and commercial bleach solution. The method safely delivers5-bromo 2-hydroxynicotinic acid (5-bromo-3-carboxy-2(*1H*)-pyridone) without the use of hazardous elemental bromine.



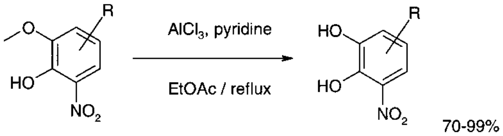
Demethylation of Nitrocatechol Methyl Ethers

BIA 3-202 [1-(3,4-dihydroxy-5-nitrophenyl)-2-phenylethanone] is a potent and highly selective inhibitor of the enzyme catechol-*O*-methyl-transferase which is currently under clinical development for the treatment of Parkinson disease.



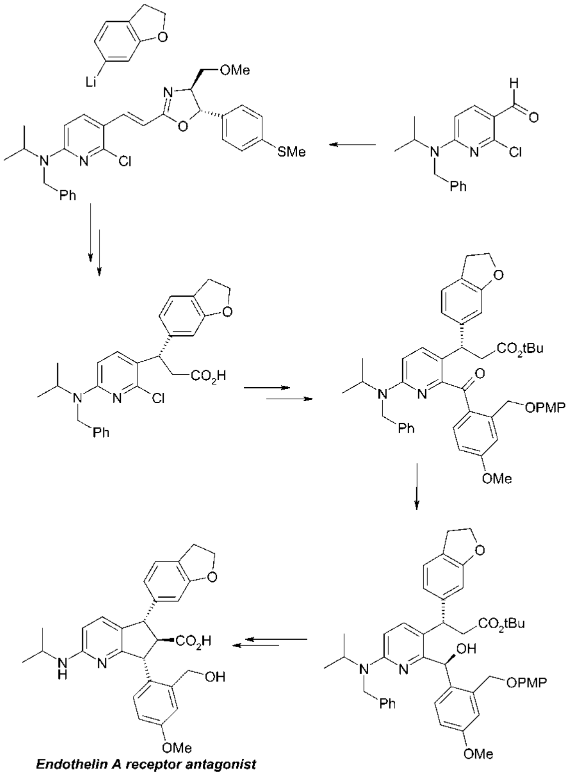
BIA 3-202

These clinical studies have necessitated the production of kilograms of BIA 3-202, and in turn workers at BIAL (*Synth. Commun.* **2002**, *32*, 641) have developed an improved method for the demethylation of nitrocatechol methyl ethers using aluminium chloride and pyridine in ethyl acetate. This method was found to be selective, high yielding, economical, and rapid and may prove useful in the demethylation of other *o*-hydroxyaryl methyl ethers.



Asymmetic Synthesis of a Selective Endothelin A Receptor Antagonist

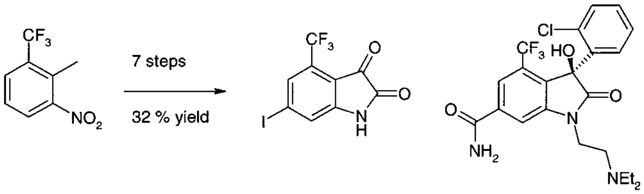
An asymmetric synthesis of a selective endothelin A receptor antagonist has been reported by Kato and co-workers from the Banyu Pharmaceutical Co. (*Tetrahedron* **2002**, *58*, 3409). The starting material (shown in the scheme below) was efficiently prepared by monoamination of inexpensive dichloropyridine followed by a Vilsmeier formylation. Elaboration to the chiral oxazoline followed by asymmetric addition of the aryllithium gave, after hydrolysis, the carboxylic acid shown. Esterification (to the tBu ester) followed by $Pd(OAc)_2$/dppf/CO/NaOAc/toluene/nBuOH-catalysed carbonylation gave an nBu ester intermediate (not shown) which could be readily converted by organometallic addition to the ketone (shown). Diastereoselective reduction of the ketone to the chiral alcohol using LS-Selectride followed by cyclisation and functional group deprotection gave the target compond in 10% overall yield.



Endothelin A receptor antagonist

Concise and Regioselective Synthesis of 6-Iodo-4-trifluoromethylisatin

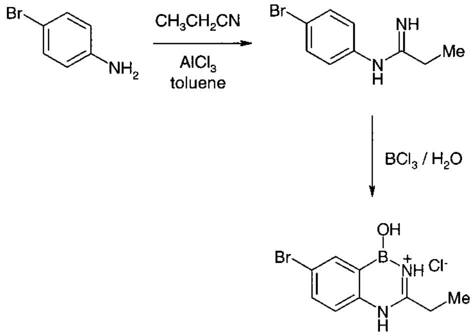
A concise and regioselective synthesis of 6-iodo-4-trifluoromethylisatin, an intermediate in the synthesis of the novel nonpeptidyl growth hormone secretagogue SM-130686 has been reported by Nagata and co-workers from the Sumitomo Pharmaceuticals Research Centre (*Tetrahedron* **2002**, *58*, 3605). The seven-stage synthesis in 32% overall yield starts with 2-methyl-3-nitrobenzotrifluorotoluene. This compound is readily converted to (4-iodo-6-nitro-2-trifluoromethylphenyl)acetic acid via iodination, condensation with dimethyl oxalate, and oxidative decarboxylation. Subsequent esterification followed by reductive cyclisation gave 6-iodo-4-trifluoromethyloxindole. Oxindole 3,3-dibromination followed by hydrolysis gave the desired 6-iodo-4-trifluoromethylisatin. The synthesis was performed on a multigramme scale without the need for chromatographic purifications, and experimental conditions are described in the paper.



SM-130686

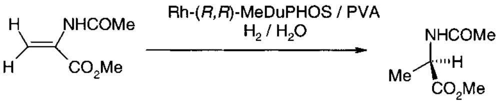
2,4-Diaza-1-borines

A general synthesis of diazaborines incorporating an in situ preparation of amidines from anilines using a nitrile and $AlCl_3$ followed by the addition of BCl_3 and heating (see below) has been reported by Prasad and co-workers from Novartis (*Tetrahedron Lett.* **2002**, *43*, 3255). The diazaborines were isolated as hydrochlorides, and the structure was confirmed by X-ray analysis.



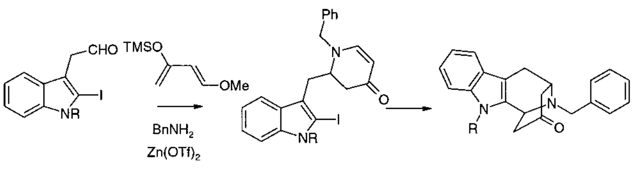
Heterogenisation of Rh-MeDuPHOS by Occlusion in Polyvinyl Alcohol Films

Geresh and colleagues have reported (*Tetrahedron: Asymmetry* **2002**, *13*, 465) a new recyclable chiral heterogeneous catalytic system obtained by the occlusion of Rh-MeDuPHOS in poly(vinyl alcohol) film. An enantiomeric excess of up to 96% was achieved in the asymmetric hydrogenation of methyl 2-acetamidoacrylate in aqueous medium (see below). The group studied leaching of the Rh-MeDuPHOS from the PVA film and found that using a poor solvent for the chiral complex prevents loss. The catalyst system was successfully reused without loss of acivity and enantioselectivity.



Aza Diels−Alder/Intramolecular Heck Cyclisation

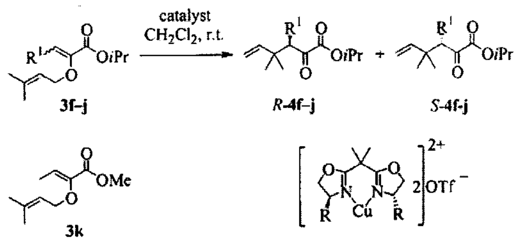
Kuethe and co-workers from Merck report (*Tetrahedron Lett.* **2002**, *43*, 3871) the aza Diels−Alder reactions of 2-iodo-3-indoleacetaldehydes in the presence of zinc triflate to provide 2-(2-iodoindolyl-methyl)-4-pyridones in high yield. Palladium-mediated intramolecular Heck cyclisation gave access to the tetracyclic tetrahydro-β-carboline framework of the ajmaline/sarpagine alkaloids.



Catalysis of the Claisen Rearrangement of Aliphatic Allyl Vinyl Ethers

The thermal Claisen rearrangement of allyl vinyl ethers is generally regarded as a high-performance method for diastereoselective C−C bond formation. M. Hiersemann and L. Abraham (*Eur. J. Org. Chem.* **2002**, 1461) have summerized the attempts to catalyze the Claisen rearrangement of acyclic aliphatic allyl vinyl ethers with chiral and achiral catalysts. The number of known catalysts for the Claisen rearrangement is amazingly limited. The best-suited achiral catalysts found recently are Lewis acids. The best catalysts reported are $Lu(OTf)_3$, $Yb(OTf)_3$, $Sc(OTf)_3$, and $Cu(OTf)_2$, with $Sc(OTf)_3$ being the most active. $Sc(OTf)_3$ although causes a large amount of [1,3]-rearrangement product with the even less prone substrate the R1 = benzyl-derivative (24%). With the more sterically hindered derivative R1 = *i*-Pr the amount of the unwanted [1,3]-rearrangement product is 20% with the even less Lewis acidic $Yb(OTf)_3$. It is suggested that increased Lewis acidity and charge destabilization by substituents in the substrate induces the formation of the unwanted [1,3]-rearrangement product.

For the first time a catalytic enantioselective Claisen rearrangement has been reported utilizing bis(oxazoline)-copper(II) complexes as the chiral catalyst. This new method gives outstanding chemoselectivities in comparison to the achiral catalysts and acceptable enantioselectivities which probably can be further developed.



R = Ph, (*S*,*S*)-**13**: [Cu{(*S*,*S*)-Ph-box}]$(OTf)_2$
R = *t*Bu, (*S*,*S*)-**14**: [Cu{(*S*,*S*)-*t*Bu-box}]$(OTf)_2$

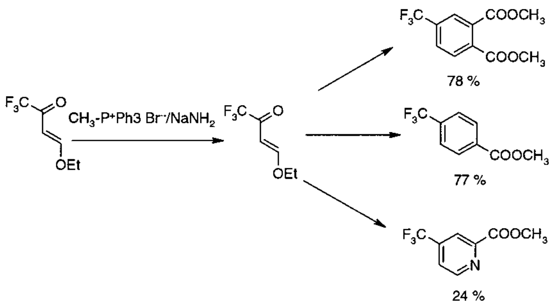
	Substrate	R¹	(*Z*)/(*E*)	Catalyst	*t* [h]	Yield [%]	(*R*)/(*S*)
1	*Z*-**3i**	methyl	96:4	5 mol % (*S*,*S*)-**13**	1	100	91:9
2	*Z*-**3i**	methyl	96:4	5 mol % (*R*,*R*)-**13**	1	100	9:91
4	*Z*-**3i**	methyl	96:4	10 mol % (*S*,*S*)-**14**	24	47	6:94
5	*Z*-**3i**	methyl	96:4	10 mol % (*S*,*S*)-**14**, 4-Å m.s.	24	99	6:94
6	*Z*-**3j**	ethyl	100:0	5 mol % (*S*,*S*)-**13**	2	99	92:8
7	*Z*-**3h**	isopropyl	90:10	5 mol % (*S*,*S*)-**13**	24	98	89:11
8	*Z*-**3g**	isopropenyl	100:0	5 mol % (*S*,*S*)-**13**	1	100	93:7
9	*Z*-**3f**	benzyl	97:3	5 mol % (*S*,*S*)-**13**	1	99	88:12
12	*Z*-**3f**	benzyl	97:3	0.5 mol % (*R*,*R*)-**13**	24	100	12:88

New Diels−Alder Components Opening an Entry To Functionalized (Trifluoromethyl)arenes

The Diels−Alder cycloaddition reaction between 3-trifluoromethyl-1-trimethylsilyloxy-1,3-butadienes and electron-poor dienophiles provides trifluoromethyl-substituted arenes and heterocycles (M. Schlosser et al, *Liebigs Ann.* **1995**, 1587). A major drawback of this method was, however, the lengthy preparation of the substituted butadiene. Now the group of M. Schlosser (*Eur. J. Org. Chem.* **2002**, 1490) has reported a simple synthesis of a dienic equivalent, making the whole method more attractive.

(*E*)-1-Ethoxy-3-trifluoromethyl-1,3-butadiene is easily obtained from the condensation of trifluoroacetic anhydride or -chloride with ethyl vinyl ether followed by a Wittig reaction of the intermediately obtained ketone.

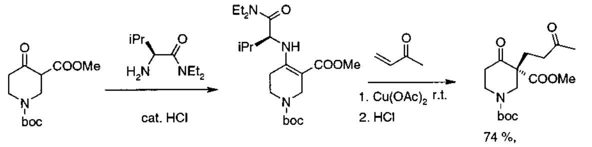
The diene reacts at 100 °C with stoichiometric amounts dimethyl acetylenedicarboxylate and other electron-poor dienophiles to give, after elimination of ethanol, for instance 4-(trifluoromethyl)-phthalate (78%).



Copper-Catalyzed Asymmetric Michael Reactions with α-Amino Acid Amides

J. Christoffers and H. Scharl (*Eur. J. Org. Chem.* **2002**, 1505) have reported a new method for the efficient synthesis of optically pure piperidine derivatives via a copper-catalysed Michael reaction with α-amino acid amides as chiral auxiliaries. The new method has been found to be compatible with carbamate functions in substrate in comparison to the Lewis-based lanthanide-based methods previously reported.

By using L-valine amide as the chiral auxiliary it was possible to obtain the corresponding piperidine derivative with 97% ee.



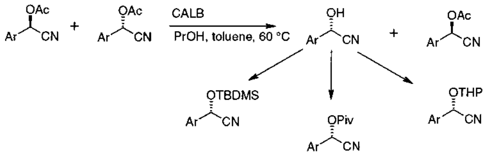
Enantioselective Synthesis of Protected Cyanohydrins

Cyanohydrins are versatile building blocks in organic synthesis. They can readily be converted into a wide range of compounds such as α-hydroxy acids, β-amino alcohols, α-hydroxy ketones, and α-aldehydes. They have been utilized for the synthesis of several pharmaceutical active ingredients, for example, salbutamol and (*S*)-amphetamines.

The group of U. Hanefeld (*Eur. J. Org. Chem.* **2002**, 1516) has reported a new and interesting method for the straightforward preparation of optically active protected cyanohydrins utilizing Lipase B from Candida Antartica (CAL-B) for the kinetic resolution of racemic cyanohydrin acetates under mild conditions.

The protected cyanohydrins were obtained in excellent yield and purity ((*R*): > 91% ee: (*S*): > 97%); if only one of the isomers is needed, recycling of the other isomer is easily done through racemization.

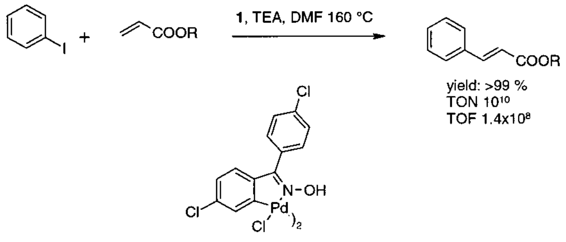
This new method makes use of protected cyanohydrins more interesting for the synthesis of chiral drugs.



Oxime-Derived Palladium Complexes As Very Efficient Catalysts for the Heck Reaction

Oxime-derived, chloro-bridged palladacycles have been found from D. Alonso et al. (*Adv. Synth. Catal.* **2002**, *344*, 172) to be highly efficient complexes for the Heck vinylation of aryl halides. The isolated catalysts are thermally stable, not sensitive to air or moisture and are easily accessible from commodity chemicals.

Extraordinary turnover numbers and rates have been obtained under aerobic conditions for aryl iodides (TON up to 10^{10} and TOF up to 1.4×10^{8} h^{-1}) and deactivated aryl bromides (TON up to 97 000, TOF up to 6063 h^{-1}). Aryl chlorides presented turnover numbers up to 920 showing an important salt effect in the Heck coupling.



1

Sol–Gels Doped with TEMPO As A Recyclable Oxidation Catalyst for Alcohols

C. Bolm et al. (*Adv. Synth. Catal.* **2002**, *344*, 159) have prepared organically modified silicas doped with TEMPO. The catalyst was prepared via the sol–gel method and are highly recyclable catalysts of the oxidation of primary alcohols to aldehydes with sodium hypochlorite as the primary oxidant.

The catalyst is prepared through in-situ reduction of 4-oxo-TEMPO with NABH$_3$CN in the presence of 3-aminopropyltrimethoxysilane. After the reduction the sol–gel is prepared through addition of alkyltrimethoxysilane and NaF which causes an immediate gelation.

The obtained gel has a typical broad pore size (80–300 Å) and surface area for mesoporous sol–gel ormosils.

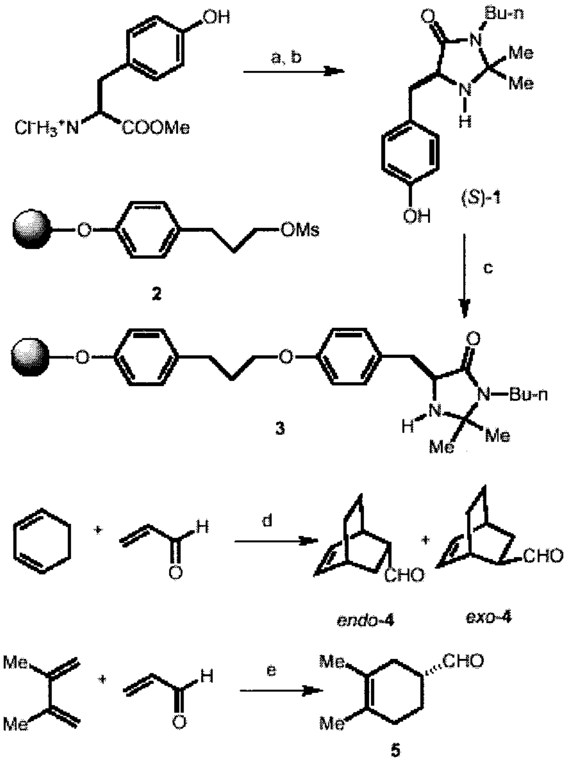
In comparison to unmodified silica-encapsulated TEMPO which lost half of its activity in the first oxidative run the chemically modified fully methylated catalyst was found to be remarkably stable, and the activity of the catalyst showed an increment in the first six runs from 8%. It was also found that no leaching of encapsulated radicals occurred as after filtration of the mixture during the reaction the reaction immediately stopped. In the oxidation no product other than the carbonyl compound was observed. This could be an interesting alternative to other solid-phase-bound TEMPO-based catalysts.

Supported Imidazolidin-4-One: An Efficient Chiral Catalyst for Enantioselective Diels–Alder

Over the past 30 years enantioselective synthesis has become one of the most important frontiers in organic chemistry. Surprisingly, however, relatively few asymmetric transformations have been reported which employ organic molecules as catalyst, despite the widespread availability of enantiopure organic compounds.

The group of D. MacMillan (*J. Am. Chem. Soc.* **2000**, *122*, 4243) has developed a new concept for enantioselective organocatalytic Diels−Alder reactions based upon the use of chiral amine hydrochlorides which react with the dienophilic aldehyde, giving an iminium ion which is sufficiently actived to engage the diene. From the reaction, high yields and enantioselectivities were obtained.

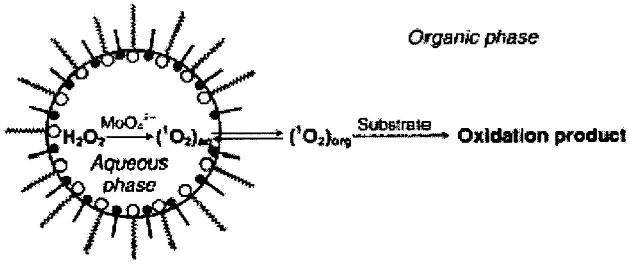
F. Cozzi et al. (*Adv. Synth. Catal.* **2002**, *344*, 149) have now reported a poly(ethylene glycol)-supported variation of the enantioselective organocatalytic Diels−Alder catalyst developed by D. MacMillan. A tyrosine-derived imidazolidin-4-one was immobilised on modified poly(ethylene glycol) and converted in situ into a soluble polymer-supported catalyst. With the catalyst the Diels−Alder cyclization of acrolein with cyclohexadiene and 2,3-dimethyl-1,3-butadiene was studied. Comparable yields and selectivities were obtained with the supported and the nonimmobilized catalyst. This type of chiral organic metal-free catalysts is particularly attractive for immobilization as the catalyst cannot suffer from leaching upon recycling. In the study it was found that the acid employed for the catalyst was important. The best acid found was trifluoroacetic acid. Recycling of the catalyst gave decreasing yields but unchanged high stereoselectivities.



“Dark” Singlet Oxygenation of Hydrophobic Substrates in Enviromentally Friendly Microemulsions

Industrially singlet oxygenation is carried out by classical dye-sensitized photooxidation based on molecular oxygen in special equipment under extreme safety control. The molybdate-catalyzed “dark” singlet oxygenation of hydrophobic compounds with hydrogen peroxide proceeds efficiently with low catalyst loadings (10−3 mol %) in chlorine-free without microemulsions. These microheterogeneous systems are composed of SDS/*n*-butanol/water/organic phase. (V. Nadello et al. *Adv. Synth.Catal.* **2002**, *344*, 184). Very high reactor yields with improved product/SDS ratio can be obtained from these systems. When a liquid substrate has to be peroxidized with chemically generated $^1O_2$, solvent-free microemulsions are the convenient media. When solvents are necessary, the best substitute for the chlorinated solvents is ethyl acetate, allowing a relatively moderate concentration of the substrate in the solvent still being the main substrate for the singlet oxygen.

This new method represents a highly interesting alternative to classical photooxidations which can make large-scale singlet oxygenations much more attractive for the synthesis of pharmaceuticals, agrochemicals, and fine chemicals.



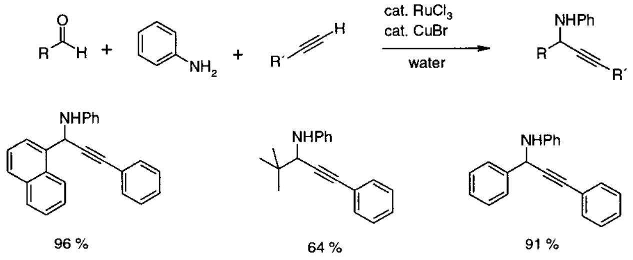
Quasi-Nature Catalysis: C−C−Bond Formation with Late Transition Metals in Air and Water

C.-J. Li (*Acc. Chem. Res.* **2002**, ASAP, May 1, 2002) has described the recent efforts to develop catalytic processes in air and water. It has been shown in several cases that catalysis with late transition metals can not only be carried out in water but can also be carried out in the presence of air or under an atmosphere of air. During the study it was observed that catalytic reactions are less air-sensitive in water than in organic solvents.

The use of ruthenium is mostly related to searching for cleaner C−C bond formation in air via C−H activation. The allylic C−H bond can be activated through ruthenium in water. Through the catalysis of RuCl$_2$(PPh$_3$)$_3$ it is possible to reposition the hydroxylic group with controlled regioselectivity.

Phenylacetylenes have also been effectively added to aldehydes catalyzed by a bimetallic Ru−In catalytic system.

An effective Cu−Ru catalyzed addition of phenylacetylenes to aryl-substituted imines have also been deceloped lately. (see C.-J. Li et al., *Chem. Comm.* **2002**, 268)



Also other catalytic reactions have recently been found to work well under aqueous conditions. For instance the palladium catalyzed coupling of aryl halides with arylhalosilanes. This reaction works well with aryliodides and

$PhMeSiCl_2$ under Pd/C catalysis in aqueous KOH (see C.-J. Li et al. *Tetrahedron Lett.* **2002**, 403).

Although all these reactions are still rather limited in their scope, they could in the future become highly interesting for process research.

Directed Evolution and Biocatalysis

A review describing current progress in the area of directed evolution as applied to Biocatalysis appeared last year from the group of Powell at Maxygen (Powell, K. A. et al. *Angew Chem Int. Ed.*, **2001**, *40*, 3948). The review begins by listing the reasons why biocatalysts, currently used in large-scale industrial processes, have been successful.

- The enzyme existed in a natural isolate with an activity that is close to that required for a commercial process.
- The enzyme could be immobilized with retention of activity, or the activity was such that a single use was still economically viable.
- No cofactors were required for enzyme activity, or whole cells could be used to provide the activity without any significant side reactions.

If some reactions can be run commercially with enzymes, then what limits the broader use of biocatalysis? The limits for the broader use of biocatalysis are seen as,

- The enzyme may not exist in nature or it may be difficult to procure or produce.
- The properties of the enzyme may be unsuitable for chemical synthesis.
- The activity may be insufficient.
- The enzyme may be inhibited by the substrate or the product, it may not work well under suitable operating temperatures or pH values, or it may simply be too labile for effective industrial use.
- The reaction may require an expensive cofactor that cannot be effectively recycled.

With the use of directed evolution, many of these disadvantages can be “designed out”, and since the operation can be quickly carried out robotically, the screening of the new generation of enzymes can also be carried out automatically. Thus, in a short time, promising leads can be identified and activity and stability improved to approach commercial requirements.

The review shows that directed evolution is expanding biocatalytic opportunities for the organic chemist/chemical engineer and suggests that we are on the edge of a new era for industrial biocatalysis.

Alkane Oxidation by Enzymes

Cytochrome P450 monooxygenase enzymes have the ability to insert an oxygen atom into a diverse range of hydrophobic substrates (e.g., fatty acids) and carry out transformations which are difficult or often impossible by chemical means. High regioselectivity and stereoselectivity are also features. The enzymes have a number of disadvantages, however, namely,

- They are only poorly active against nonnatural substrates.
- They cannot tolerate normal processing conditions (e.g., organic solvents)
- They require expensive cofactors (NADPH).

They have been described as a process engineer’s nightmare! By direct evolution, however, enzymes which are more stable and do not require expensive cofactors can be produced.

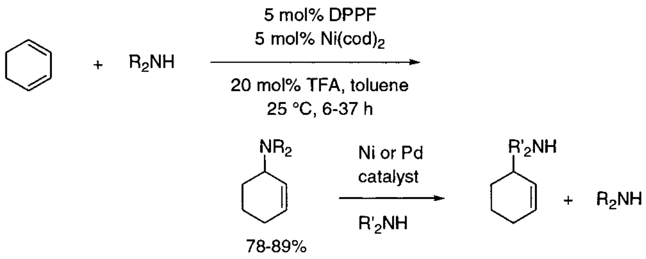
A recent presentation by Frances Arnold at CalTech described the progress her group has made in the oxidation of alkanes using P450-type enzymes (Proceedings, Conference on Industrial Applications of Biotransformations, San Diego 2002, available from Scientific Update).

Encouraging results were obtained in the oxidation of hexane to hexanols using oxygen or hydrogen peroxide with an enzyme obtained from several generations of direct evolution. The evolution was designed not only for activity but also to increase enzymes stability. Preliminary accounts of this work were published last year (Farinas, E. T. et al. *Adv. Synth. Catal*. **2001**, *343*, 601). The ultimate aim is to engineer an enzyme capable of oxidising methane to methanol using oxygen. Already indications are that hydrocarbons as small as propane can be oxidised.

Nickel Catalysed Hydroamination of Dienes. Catalyst Selection Using A Simple Colourimetric Assay

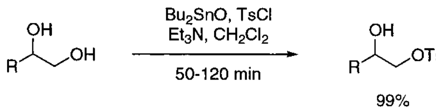
A simple colourimetric assay for consumption of starting amine (using basic nitroferricyanide and acetaldehyde) was used to screen catalysts and ligands in a 96-well plate for the reaction of amines with dienes. This allowed fast identification of the most active catalyst/ligand. (Pawlas, J. et al. *J. Am. Chem. Soc.* **2002**, *124*, 3669).

Surprisingly for nickel catalysts, the thermodynamics favour the reaction of the product (allylic amine) with Ni to form a nickel allyl rather than the reverse. The realisation of these thermodynamics suggested that amines could react with allylic amines in the presence of Ni or Pd catalysts.



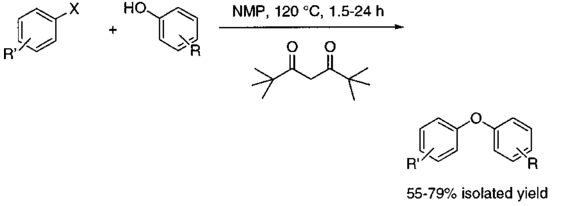
Catalytic Regioselective Sulphonylation of Chelatable Alcohols (for example, Diols)

A study from the group of Martinelli at Lilly (Chemical Process R & D) on the selective sulphonylation of diols and related compounds shows that 2 mol % Bu_2SnO in the presence of triethylamine leads to rapid and selective monotosylation with one equivalent of tosyl chloride. (Martinelli, M. J. et al. *J. Am. Chem. Soc.* **2002**, *124*, 3578). This is a full paper (a preliminary communication appeared in 1999 (*Org. Lett.* **1999,** *1*, 47)) and several other reports—including the use of recoverable fluorous tin oxide—have appeared recently. The development of a resin bound tin oxide will make the procedure more amenable to use on large scale, where even small amounts of tin residues may be problematic.



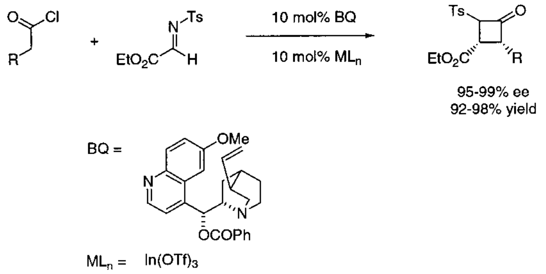
Acceleration of the Ullmann Diaryl Ether Synthesis by Tetramethyl Heptane-3,5-Dione

The Ullmann reaction is traditionally carried out at high temperature in pyridine or quinoline, and yields are low-to-moderate. Buchwald's group have made progress in this area using copper triflate as catalyst, but this may still be expensive for process chemistry; the catalyst is also air-sensitive which could be an issue in scale-up. A number of papers have reported alternative approaches, but a new one from Merck Process R & D (Buck, E. et al. *Org. Lett.* **2002**, *4*, 1623) looks promising for a robust method. Use of tetramethylheptane-3,5-dione in conjunction with CuCl/Cs_2CO_3 allows reactions to be carried out at moderate temperatures and reaction times. A wide variety of substrates can be used.



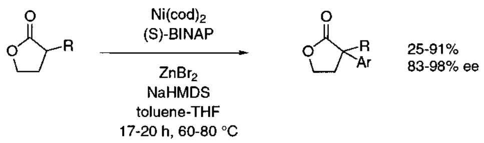
Bifunctional Catalysis in the Synthesis of β-Lactams

A superior catalyst for the cycloaddition of ketenes to imines is shown below. A chiral nucleophile is paired with an achiral Lewis acidic metal salt to yield optically enriched products (France, S. et al. *Org. Lett.* **2002**, *4*, 1603)



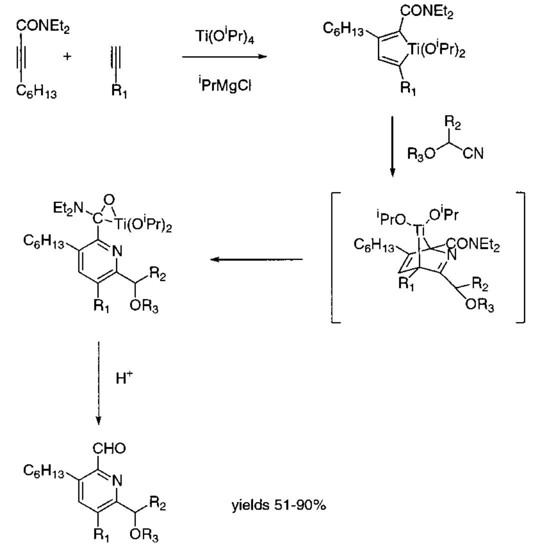
Enantioselective Arylation of α-Substituted Butyrolactones

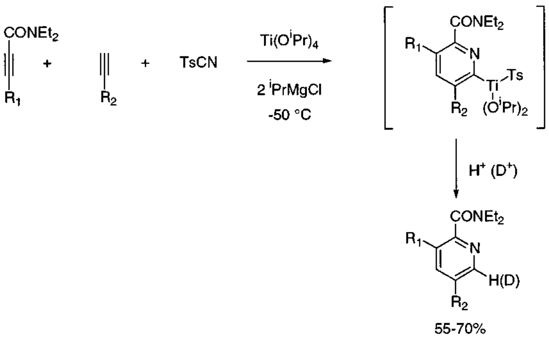
A nickel BINAP catalyst can be used for the arylation of butyrolactones with aryl chlorides and bromides (Spielvogel, D. J. et al. *J. Am. Chem. Soc.* **2002**, *124*, 3500). The reaction is accelerated in the presence of Zn(II), and the stoichiometry is critical, best results being obtained with 15 mol % $ZnBr_2$. With stoichiometric Zn, the reaction is inhibited.



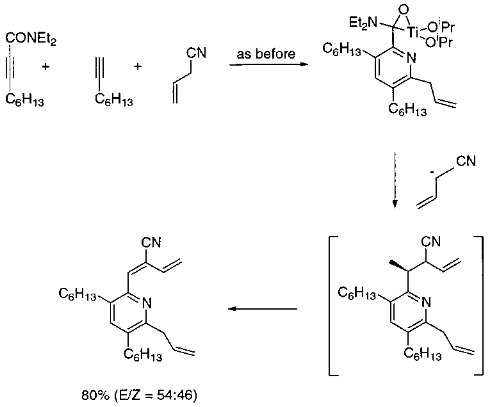
Synthesis of Metalated Pyridines

The assembly of the pyridine ring from two acetylenes and a nitrile has attracted much attention recently because of its synthetic flexibility. Now it has been found (Suzuki, D. et al. *J. Am. Chem. Soc.* **2002**, *124*, 3518) that metalated pyridines can be prepared as shown below in one pot from two acetylenes and tosylcyanide or an alkoxyacetonitrile.





The metalated intermediates can not only be deuterated but also reacted with other species.



Ionic Liquids (IL)

The latest issue of *Green Chemistry* (April, 2002) is a special issue on the subject of Ionic Liquids (IL). This topic is of increasing interest with hundreds of papers appearing each year. However, the issue of purification and the purity of IL is not often addressed. In the foreward to the special issue, Ken Seddon, of Queen's University, Belfast, one of the pioneers in the field, mentions that many published papers are “garbage” because impure IL are being used in the studies. This is an important issue for industrial use. IL are currently expensive, but one would expect the price per kg to drop drastically once tonnage manufacture was in operation. However, the price would depend on the quality required. The problem with IL, if high purity is required, is the method of purification. Since they are nonvolatile, the best purification method would be crystallisation—for very low-melting IL; however, this may be challenging on large scale.

The issue of purity is also mentioned in two of the articles in the special issue. In a paper on the oxidation of alcohols using TPAP (V. Farmer et al. *Green Chem*. **2002**, *4*, 97) the authors indicate that reactions performed on *the same batch* of IL gave consistent results. However different yields of oxidation products were obtained using the same procedure but using *a different batch* of IL. These differences depend on the method used to prepare the IL, and protocols for the synthesis are presented in the paper. Good quality 1-butyl-3-methylimidazolium (bmim)-based IL with the common ions BF_4^-, PF_6^-, $CF_3SO_3^-$, $CF_3CO_2^-$, and $(CF_3SO_2)_2N^-$ are ALWAYS free-flowing, colourless liquids. Impure IL are frequently orange-yellow with variable viscosities—the colour can be removed by multiple recrystallisation. No criteria for purity, however, were provided (i.e. assay method, mp, HPLC etc)—only NMR and MS data were given.

This could be an important issue when the IL are being reused. If all products and by-products cannot be removed by distillation or extraction, is the performance of the IL compromised? If so, can the IL be purified by recrystallisation? If organic solvents are used for this purification, does this destroy the “green” credentials of the IL? If the IL cannot be purified, what is the preferred disposal route—quaternary ammonium salts may not be compatible with organisms in wastewater treatment plants and may need to be incinerated?

In a short review on biocatalysis in IL, Roger Sheldon (University of Delft) (*Green Chem*. **2002**, *4*, 147) also mentions the issue of IL purity, referring to a paper from the group of Kaslauskas (Park, S. et al., *J. Org. Chem*. **2001**, *66*, 8395). In these studies the purification step used in the synthesis of the IL is an important factor to get high conversion rates—use of unpurified IL resulted in 2−5 times slower reaction. The suggested purification methods (addition of silver tetrafluoroborate, removal of silver halide by filtration, followed by chromatography or filtration through silica gel plug, followed by aqueous sodium carbonate wash) will all add costs to the solvent.

Sheldon also notes that little is known about IL degradability and aquatic toxicity—it would seem essential that, before scale-up is carried out on these “green” solvents, a thorough study of these issues should be undertaken.

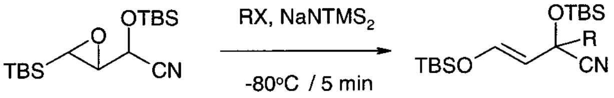
Certain enzymes can be stabilised in IL compared to normal organic solvents and this could be a major advantage for performing biotransformations with highly polar substrates.

Selective Oxidation by Hetergeneous Catalysis

Trevor Laird came across a book with the above title published in 2001 by Kluwer Academic/Plenum (ISBN 0-306-46265-6) in the series Fundamental and Applied Catalysis. The authors of *Selective Oxidation* are G. Centi, F. Cavani, and F. Trifiro. The book surveys recent developments in selective oxidation, with emphasis on bulk and fine chemicals. It is forward looking, with emphasis on future trends, and although written by academic professors, is process-orientated. We hope to review this book in future editions of OPRD.

PUZZLE!

Metalated *O*-silyl cyanohydrins of β-silyl-α,β-epoxyaldehydes have been found to serve (Takeda et al., *Org. Lett.* **2002**, *4*, 1511) as functionalised homoenolate equivalents by a tandem sequence involving a base-promoted ring-opening of the epoxide, Brook rearrangement, and alkylation of the resulting allylic anion. This issue’s puzzle is to work through the mechanism and to then consider the difference in reactivity for each possible diastereomer—Good luck!



Trevor Laird
Editor

Stephen A. Hermitage
GlaxoSmithKline, Gunnels Wood Road, Stevenage,
Hertfordshire, SG1 2NY UK

Ulf Tilstam
Schering AG, Chemical Development, Berlin, Germany

OP025556G