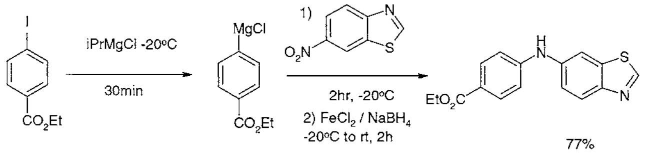
Organic Process Research & Development **2003**, *7*, 2–9

Highlights from the Literature

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

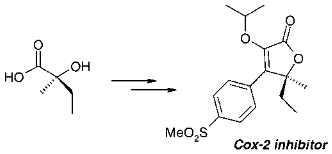
General Preparation of Polyfunctional Diarylamines

The arylation of amines is an important reaction in synthetic organic chemistry since arylamines are commonly found in pharmaceuticals and materials possessing interesting electronic properties. A common approach for their preparation involves palladium cross coupling of amines and aryl halides. A recent publication by Knochel and Sapountzis (*J. Am. Chem. Soc.* **2002**, *124*, 9390) reports a new general preparation of polyfunctional diarylamines by the addition of functionalised arylmagnesium compounds to nitroarenes (see below). The yields are good, and a typical procedure is described.



Practical Enantioselective Synthesis of a COX-2 Specific Inhibitor

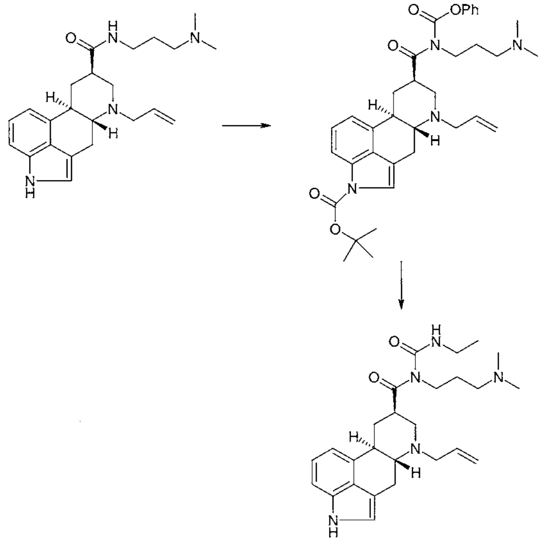
Tan and co-workers describe (*Tetrahedron* **2002**, *58*, 7403) two synthetic strategies towards the COX-2 specific inhibitor (figure) from (*S*)-2-hydroxy-2-methylbutyric acid. These studies have led to the identification of an efficient resolution of (±)-2-hydroxy-2-methylbutyric acid.



Cox-2 inhibitor

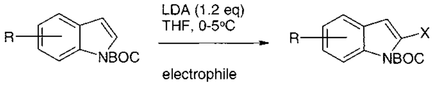
Practical Synthesis of Cabergoline

Cabergoline is an *N*-acylurea derived from 9,10-dihydrolysergic acid, which is a potent prolactin inhibitor. It is marketed by Pharmacia as Dostinex for the treatment of hyperprolactinemia and is currently under active development for the treatment of a variety of CNS disorders. In the existing process, the *N*-acylurea is formed by the reaction of an amide with a large excess of ethyl isocyanate at elevated temperatures. An improved process has been developed by Henegar and co-workers at the Pharmacia Corporation (*J. Org. Chem.* **2002**, *67*, 7147) that eliminates this hazardous reaction. The amide is reacted with phenyl chloroformate and then with ethylamine, which provides a mild and efficient means of forming the unsymmetrical *N*-acylurea.



Non-Cryogenic Method for the Preparation of 2-(Indolyl) Borates, Silanes and Silanols

2-Indolyl borates have been prepared by Vazquez and co-workers at Merck (*J. Org. Chem.* **2002**, 67, 7551) via addition of LDA to a mixture of *N*-Boc-indole and triisopropyl borate at 0−5 °C. Following acidic hydrolysis, the boronic acids were isolated by crystallisation in good-to-excellent yield (73−99%). The method is quite general, tolerating a wide range of functional groups, and also provides access to 2-silyl derivatives (80−91%).



X = $B(OH)_2$, Me_2SiOH, Me_2SiH

Novel Catalytic Kinetic Resolution of Racemic Epoxides To Allylic Alcohols

The kinetic resolution of racemic epoxides via catalytic enantioselective rearrangement to allylic alcohols has been investigated by Andersson at Uppsala University (*Org. Lett.* **2002**, *4*, 3777). The Li salt of (1*S*,3*R*,4*R*)-3-(pyrrolidinyl)-methyl-2-azabicyclo [2.2.1] heptane was used as catalyst in conjunction with LDA for the enantioselective epoxide

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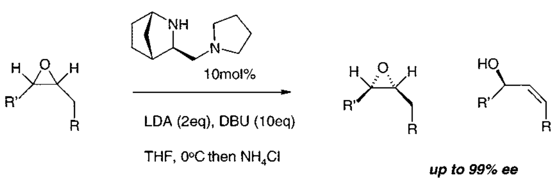
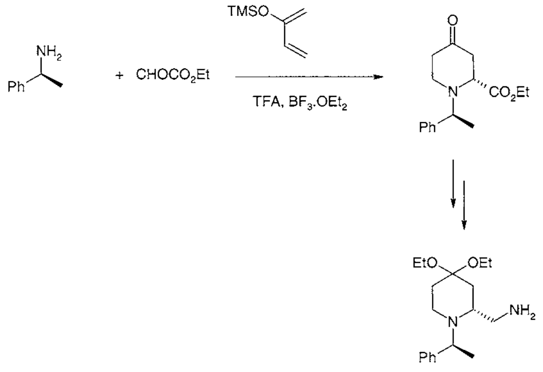
fragmentation and both epoxides and allylic alcohols were obtained in an enantioenriched form after column chromatography.



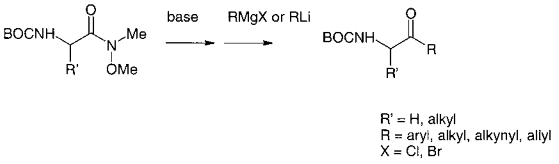
Large Scale Synthesis of 2-Substituted 4-Oxo-piperidine Derivatives

A convenient large-scale chiral synthesis of protected 2-substituted-4-oxo-piperidine derivatives has been described by Lau and co-workers at Novo Nordisk, the Royal Danish School of Pharmacy and the Ontogen corporation (*Tetrahedron* **2002**, *58*, 7339). Hetero Diels–Alder reaction between trifluoroacetic acid–boron trifluoride-activated (1-phenylethylimino)acetic acid ethyl ester and 2-trimethylsilyloxy-1,3-butadiene gave rise to a mixture of two diastereomers of 4-oxo-1-(1-phenyl-ethyl)-piperidine-2-carboxylic acid ethyl ester. Starting from (*S*)-1-phenyl-ethylamine the Diels–Alder adduct can be obtained by crystallisation of the diastereomeric mixture. Reduction of the ester group gave rise to the corresponding hydroxymethyl analogue which was subjected to further functional group transformations to yield the desired protected 2-aminomethyl-4-oxo-piperidine derivative without racemisation.



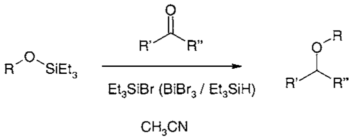
Improved Synthesis of α-BOC-aminoketones

A general procedure to prepare α-BOC-aminoketones in good yields from α-BOC-amino Weinreb amides containing an exchangeable amino proton has been reported by Liu and co-workers from Merck (*Tetrahedron Lett.* **2002**, 8223). By first deprotonating the amino group using 1 equiv of a simple alkyl Grignard base, only a stoichiometric amount, rather than a large excess, of the nucleophile was needed to prepare the ketone.



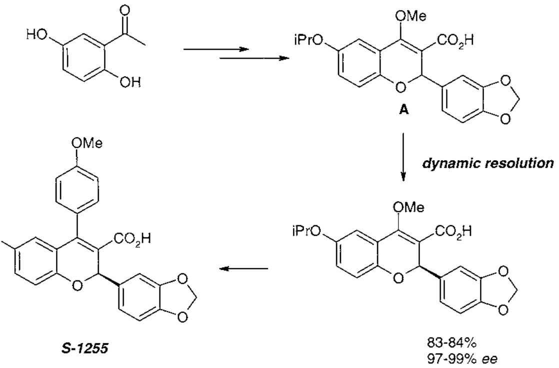
In Situ Generation of Et_3SiBr and Use in Preparation of Dialkyl Ethers

Bajwa and co-workers at Novartis report (*Tetrahedron Lett.* **2002**, *43*, 6709) the $BiBr_3$–Et_3SiH-catalyzed reductive etherifications of silyl ethers with carbonyl compounds. This transformation is catalyzed by the in situ formation of the moisture-sensitive Et_3SiBr and has been verified by independent use of the commercial reagent. Using this method a number of alcohols were transformed under very mild conditions into dialkyl ethers via their silyl intermediates, such as TES, TBDMS, and TIPS.



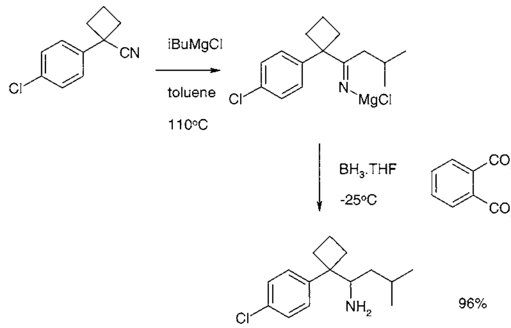
Practical Enantioselective Synthesis of the Endothelin Antagonist S-1255 by Dynamic Resolution

A practical multikilogram-scale synthesis of enantiomerically pure S-1255, a potent and orally active ET_A receptor antagonist, is described by Konoike and colleagues from the Shionogi Research Laboratories (*J. Org. Chem.* **2002**, *67*, 7741). Utilising readily available starting materials and reagents, the entire sequence of reactions starting from 2,5-dihydroxyacetophenone proceeded under mild conditions to give S-1255 in an excellent chemical yield (8 steps, 41% overall yield) and in a high enantiopurity (98% ee). The crucial step of the synthesis is a dynamic resolution of key intermediate **A**. (*R*)-Methoxy acid (*R*)-**A** having 97–99% ee was obtained in 83–84% yield from racemic **A** as a crystalline (1*S*,2*R*)-(+)-norephedrine or (+)-cinchonine salt by the dynamic resolution comprising concurrent crystallisation and in situ racemisation. The synthesis required no chromatographic purification and was amenable to a multikilogram-scale preparation (experimental details reported).



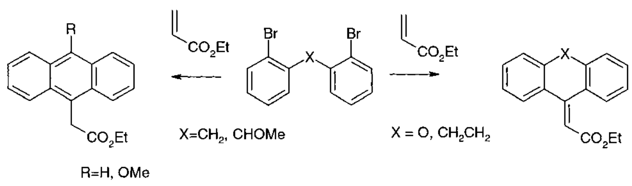
Novel Diacid Accelerated Borane Reducing Agent for Imines

A remarkable effect of diacids in modulating the reactivity of borane has been discovered by Lu, Senanayake, and colleagues at Sepracor (*Tetrahedron Lett.* **2002**, *43*, 8617). This novel mild homogeneous and chemoselective process provides a rapid and excellent access for reduction of a variety of imines with different functionalities (see below).



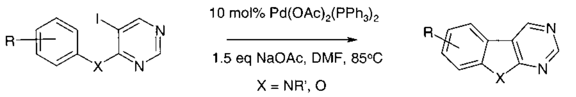
Double Heck Reaction of Bridged *O,O′*-Dibromobiaryls with Ethyl Acrylate

An intermolecular followed by an intramolecular double Heck reaction of bridged *O,O′*-dibromobiaryls with ethyl acrylate is described by Prashad and co-workers from Novartis (*Tetrahedron Lett.* **2002**, *43*, 8559). This double Heck reaction strategy afforded a safe and convenient synthesis of 9-(ethoxycarbonylmethylene)-9*H*-xanthene and a novel route to 9- and 10-substituted anthracene derivatives.



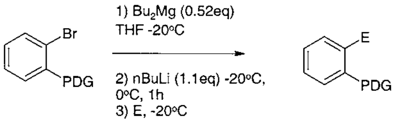
Palladium Catalysed Intramolecular Arylation

Various pyrimido[4,5-*b*]indoles and benzo[4,5]furo[2,3-*d*]pyrimidines have been synthesised by Zhang and colleagues at Johnson and Johnson (*Tetrahedron Lett.* **2002**, *43*, 8235) via a palladium-catalyzed intramolecular arylation of pyrimidine substrates. Thus, 4-aryloxy- or 4-anilino-5-iodopyrimidines were treated with $Pd(OAc)_2(PPh_3)_2$ and base in DMF to give the regioselective cyclised heterocycles in good yields.



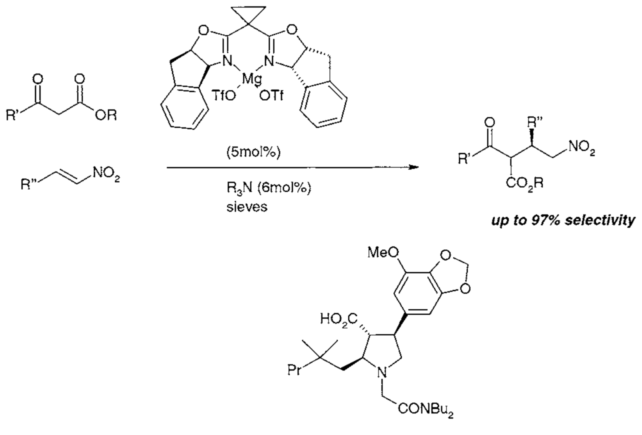
Non-cryogenic Metalation of Aryl Bromides

Bromine−metal exchange of *o*-bromobenzoic acid with Bu_2Mg followed by *n*-BuLi has been successfully reported at noncryogenic temperature (>−20 °C) to give a stabilised metal species which smoothly reacted with several electrophiles by Kato and co-workers at the Banyu Pharmaceutical company (*Tetrahedron Lett.* **2002**, *43*, 7315). This methodology has been expanded to several other bromides bearing proton-donating groups (PDGs) by the group and offers practical advantages for the large scale synthesis of ortho-substituted aryls bearing PDGs.



Catalytic Enantioselective Conjugate Addition of 1,3-Dicarbonyl Compounds To Nitro Alkenes

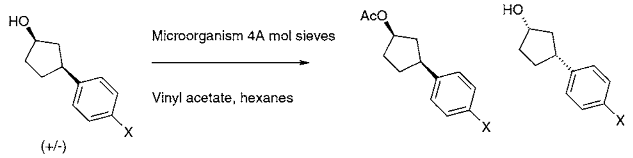
The enantioselective synthesis of endothelin-A antagonist ABT-546 has been accomplished via the discovery and development of a highly selective catalytic asymmetric conjugate addition of ketoesters to nitroolefins by Barnes, Ji, and co-workers at Abbott Laboratories (*J. Am. Chem. Soc.* **2002**, *124*, 13097). Employing just 4 mol % bis(oxazoline)-$Mg(OTf)_2$ complex with an amine cocatalyst, the product nitroketone was obtained with 88% selectivity at the aryl-bearing stereocenter and in good yield on scales ranging to 13 mol. The effects of ligand structure, metal salt, and solvent on the reaction are described by the group, and of particular importance to the reaction is the water content. While water is necessary during the generation of the catalyst, the water must be then removed to maximise stereoselectivity and reactivity.



ABT-546

3-Phenylcyclopentanol Derivatives

An efficient, multigram-scale synthesis of the respective optical isomers of 3-(substituted-phenyl)cyclopentanols was achieved by a lipase-catalyzed transesterification (kinetic resolution) in organic medium by Shimizu and colleagues at Pfizer and Mie University (*Tetrahedron* **2002**, *58*, 8729). The (1*R*,3*S*)-acetate and the (1*S*,3*R*)-alcohol were converted into orally active 5-lipoxygenase inhibitors, respectively, without loss of optical purity.



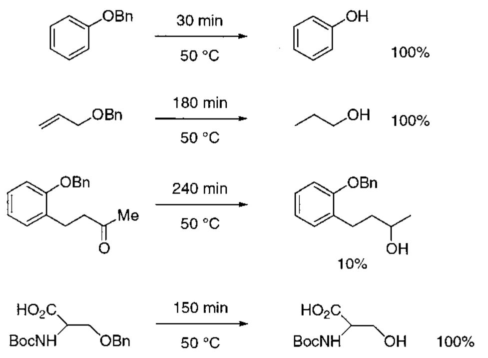
Catalytic Multiphase Hydrogenolysis

A recent review (Joó, F. *Acc. Chem. Res.* **2002**, *35*, 738) points out the advantages of carrying out heterogeneous reactions in aqueous organic biphasic media where the catalyst and product are easily separated. If the substrate or product forms a separate phase, then the need for a solvent may be eliminated. A recent paper reports results on the biphasic hydrogenolysis of benzyl ethers (Perosa, A., et al. *Green Chem.* **2002**, 492).

Using aqueous KOH−isooctane−phase-transfer catalyst mixtures, with Pd/C, Pt/C, or Raney Nickel catalysts, benzyl methyl ether was hydrogenolysed at atmospheric pressure at 50 °C. Under "single"-phase conditions with ethanol as solvent the Pd/C system is efficient, whereas the multiphase system is sluggish. With Pt/C the system is somewhat improved by using multiphase conditions, but conversions are always low.

In contrast the Raney Nickel system is much better under multiphase conditions with quantitative conversion after 150 min in the presence of Aliquot 336. The system was then applied to other benzyl ethers, and the results are shown below.

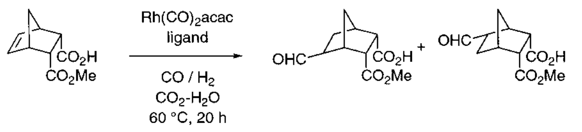
The article does not discuss the potential mixing issues involved in handling a four-phase system involving aqueous, organic, heterogeneous catalyst, and gas. However, the paper indicates that stirring was at 1000 rpm. Scale-up may be problematical, and the system is still much slower than the Pd/C−ethanol methodology. Reduction of double bonds may, of course, compete with debenzylation.



Catalytic Hydroformylation in CO_2/Water Biphasic Media

The Rührchemie/Rhône-Poulenc oxo process is used for making thousands of tonnes of products by hydroformylation of propylene using a water-soluble rhodium catalyst, and has high catalyst turnover numbers. The system is probably triphasic since the gases (CO and H_2) have limited solubility in the organic substrate/product layer or in the aqueous/catalyst layer. The use of supercritical CO_2 in which gases have increased solubility may make this process truly biphasic.

A recent report from the group of Leitner at Mülheim/Aachen (McCarthy, M., et al. *Green Chem*. **2002**, *4*, 501) uses CO_2 as the stationary catalyst phase and water as the continuous phase for hydroformylation of polar substrates (which are not active in the Rührchemie methodology). Turnover numbers of up to 3560 were achieved, and rhodium leaching to the aqueous phase was 0.3 ppm.



catalyst is: $P(\text{-}C_6H_4CH_2CH_2C_6F_{13})_3$

Hydrogenation Technology for Fine Chemical and Pharmaceutical Applications

A recent review of this topic has appeared from chemists and engineers working at Air Products (Machado, R. M., et al. *Curr. Opin. Drug Discovery Dev.* **2001**, *4*, 745). The article begins with a discussion of mixing and process equipment. The traditional approach of using a stirred-tank reactor with hydrogen being fed to a sparge tube below a flat-blade Rushton turbine can cause problems when the impeller becomes flooded with gas and power transmission to the liquid is lost. Effectiveness in mixing is also lost and may erode selectivity. New asymmetric concave blades in disc turbine design can dramatically improve the efficiency of gas distribution, without loss of power transfer (Vasconcelos, J. M. T., et al. *Ind. Eng. Chem. Res.* **2000**, *39*, 203; (Chemineer). U.S. Patent 5,478,535, 1995.

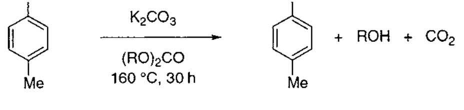
The companies Ekato and Biazzi have coupled novel mixing and heat transfer technology into a stirred-tank reactor to meet the requirements of process productivity with easy-to-clean equipment suitable for GMP production. These reactors are an alternative to the well-established loop reactors developed by Buss.

The review also covers on-line monitoring using mid-IR, near-IR, and FTIR methods and these methods have been used by several companies to track short-lived intermediates (e.g., Leblond, C., et al. *Top. Catal.* **1998**, *5*, 148).

Other topics covered include high-throughput experimentation, process intensification, microreactors, supercritical hydrogenation, heterogenisation of homogeneous catalysts and modified heterogeneous catalysts (including bimetallic catalysis and new supports). There are many of references to other review articles that may have been missed, particularly from the catalysis literature.

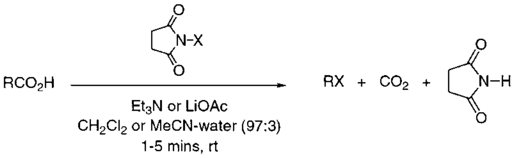
Clean Alkylation

A clean and environmentally friendly method for the alkylation of phenols involves the reaction of the phenol with a dialkyl carbonate in the absence of solvent, using potassium carbonate as base (Ouk, S., et al. *Green Chemistry* **2002**, *4*, 431). It was shown that potassium carbonate was much more effective than other carbonates and that potassium hydroxide gave only 47% yield compared to 90% with potassium carbonate. The reaction is carried out in a semi-continuous manner, suitable for scale-up. The alcohol byproduct is distilled out as it is formed.



Catalytic Hunsdiecker Reactions of Unsaturated Acids

Although the Hunsdiecker reaction for converting a CO_2H group to halogen is well-known, it is normally difficult to apply to the preparation of bromo-olefins. There have been many recent reports on how to get around these difficulties, but one that may have scale-up potential is the use of triethylamine or lithium acetate as catalyst in either dichloromethane or aqueous acetonitrile, and NBS as brominating agent. (Das, J. P., et al. *J. Org. Chem.* **2002**, *67*, 7801). The reaction is first-order with respect to the catalyst, implying that the reaction goes via the carboxylate anion. Reactions in wet acetonitrile are 5−10 times faster than in acetonitrile itself, depending on the catalyst.

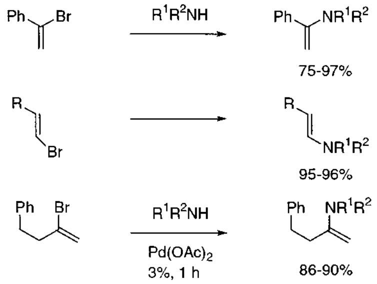


X	R	yield
Cl	ArCH=CH	60-89
Br	ArCH=CH	70-90
I	ArCH=CH	70-75
Br	-CH=CH	86
I	-CH=CH	60
Br	ArC≡C	85-92
I	ArC≡C	90-97

Enamine Formation by Palladium-Catalysed Amination of Alkenyl Bromides

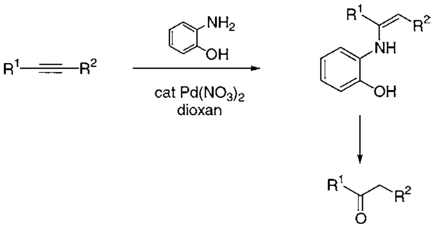
Enamines are usually prepared from carbonyl compounds, but selectivity and functional group tolerance can be poor. Hydroamination of alkynes can also be used. The recent development of the Hartwig and Buchwald systems for aromatic amination has now been extended to bromoolefins (Barluenga, J., et al. *Chem. Commun.* **2002**, 2362) and gives high yields and selectivity.

Best yields in a model system (α-bromo-styrene and morpholine) were obtained with $Pd_2(dba)_3$ (1 mol %) and BINAP, and this has been used to explore the scope of the process and the selectivity. In the latter example in the above scheme, extended reaction time caused isomerisation of the terminal enamine to the more substituted internal enamine.



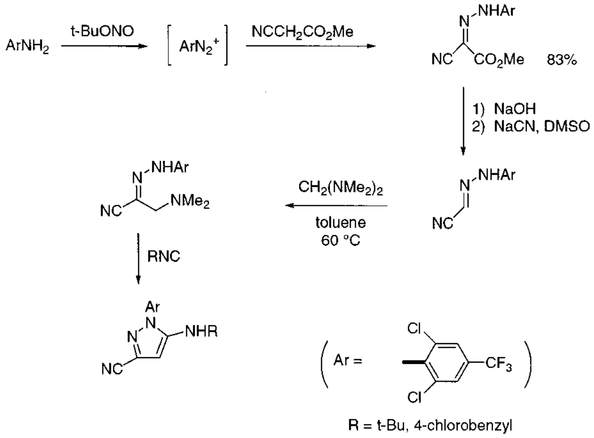
Palladium-Catalysed Hydroamination: Effect of Additives

Hydroamination of alkenes and olefins is an attractive atom-economical process but is usually restricted (with one or two exceptions) to terminal alkynes—for reviews, see: Muller, T. E., et al. *Chem. Rev.* **1998**, *98*, 675 and Nabis, M., et al. *Angew. Chem., Int. Ed.* **2001**, *40*, 3983. A recent communication from the group of Yamamoto at Tohoku (Shimada, T., et al. *J. Am. Chem. Soc.* **2002**, *124*, 12670) has shown that certain amines work better than others. Thus *o*-aminophenol gave 96% yield, whereas the meta and para derivatives gave 48 and 30%, respectively, and other substituted anilines provided yields in the 11−18% range. It is suggested that a chelation effect is responsible for the improved results. However, simple amino alcohols such as ethanolamine do not work. Dioxan is the best solvent with DMF, DMSO, butanol, toluene, and octane being less effective. (The acetylene is unfortunately used in excess, and yields in this paper are based on the less expensive aminophenol.)



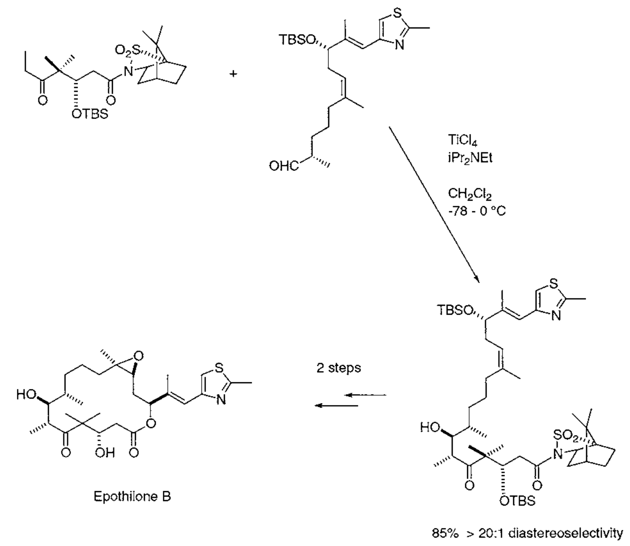
Synthesis of Substituted Pyrazoles Used as Herbicides Using Cycloaddition of Mannich Products From Hydrazones

Subsituted pyrazoles are herbicides of high insecticide activity, and new methods of making analogues have been devised. The method involves coupling diazonium compounds with methyl cyanoacetate in a mixture of TFA and trifluoroethanol (3:2), a most unusual solvent choice. The reason is that a large excess of acid is required, but the reaction must not solidify. The resultant cyano hydrazone is decarboxylated using tributylphosphine or cyanide in DMSO and subjected to a Mannich reaction. The resultant product on cycloaddition to isocyanides gives pyrazoles in good yield (Ancel, J. E., et al. *Tetrahedron Lett.* **2002**, *43*, 8319).



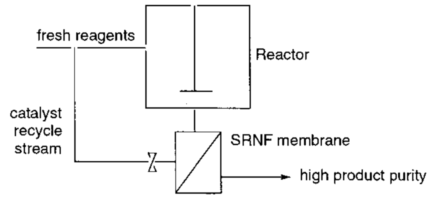
Diasteroselective Titanium Enolate Reaction for Potential Large-Scale Epothilone Synthesis

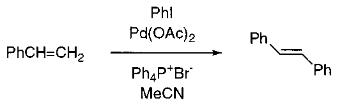
A group of workers at Novartis have developed a highly diastereoselective addition of a titanium enolate to give an efficient convergent entry to epothilones. The process is robust and has been followed by FTIR. Selective deprotonation alpha to the ketone occurs with titanium reagents, and aldol reaction occurs with >20:1 selectivity. The resultant product can be converted to epothilone B (Koch, G., et al. *Org. Lett.* **2002**, *4*, 3811).



Nanofiltration Membranes for Catalyst Recycle

The recycle of homogeneous catalysts (e.g., from Heck reactions) from worked-up reaction mixtures has previously been shown to be effective using solvent-resistant nanofiltration membranes (SRNF). However, the technique is sensitive to catalyst stability, and declining catalyst activity with repeated use can be a problem. A new report (Nair, D., et al. *Green Chem.* **2002**, *4*, 319) shows that certain catalysts are more stable to recycling and that moderate turnover numbers of >1000 can be obtained. The study led to increased reactor productivity, high reaction rates, and waste minimisation.





Waste Elimination in Condensation Reactions of Industrial Importance

Industrial condensation reactions, such as aldol reactions are usually catalysed, often homogeneously, by strong caustic bases. Recent work from the company Synetix, now part of Johnson Matthey, has demonstrated the practical application of heterogenised base catalysts (Kelly, G. J., et al. *Green Chem.* **2002**, *4*, 392). These catalysts have enhanced selectivity and eliminate the generation of organic-contaminated waste caustic streams. Despite these advantages a recent review (Tanabe, K., et al. *Appl. Catal. A* **1999**, *181*, 399) identified only 10 out of 127 processes which used a solid base. The reasons users do not switch from liquid to solids may be the following:

the capital already invested in the process

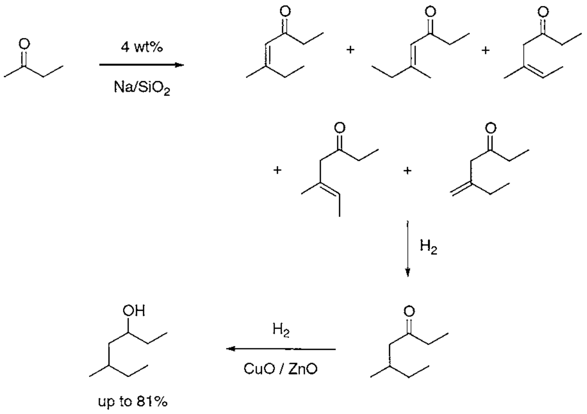
lack of confidence in the new bases

the low cost of caustic bases

lack of awareness of the overall cost advantages when issues such as selectivity, and waste elimination are taken into account

Often when aldehyde−ketone condensations take place, a catalytic reduction step follows, and there may be advantages to using a single catalyst such as palladium-doped sodium on silica, although these catalysts may be more prone to deactivation.

The paper shows that methyl ethyl ketone can self-condense in the gas phase at 325−400° to give a mixture of "dimers" from which the 5-methyl-4-hepten-3-ones are the major products. On hydrogenation (either in a combined reaction or in a separate process) good yields of reduced products are obtained.



Preparation of Polymer-Supported Ligands and Metal Complexes for Use in Catalysis

N. E. Leadbeaker and M. Marco (*Chem. Rev.* **2002**, *102*, 3217) have summarised the development of polymer-supported ligands and metal complexes for use in catalysis. Although a huge amount of data have been collected, there are still several key areas that need to be developed to be able to prepare supported metal complexes more reliably and to better understand their activity.

Developing new methods for preparation and functionalisation of solid support and their analytical characterisation is one important field as well as achieving a better understanding of the interaction of the solid support with the metal complexes, understanding that different reactivities and selectivities can be found. For comparison see "High Turnovers Achieved with an Immobilized Ir-Diphosphine Catalyst in an Imine Hydrogenation" below.

It is very important to characterise the heterogeneous catalysts in detail. There have appeared a number of reports where the immobilised complexes are not fully characterised. This is of particular concern when the activities of these are compared with those of the "homogeneous analogues". It is also important to ascertain that if an immobilised catalyst is recycled many times that it remains the same over all cycles. The problem with metal leakage from the complexes during reactions is also not completely solved.

Asymmetric Organocatalytic Diels–Alder Reactions on Solid Support

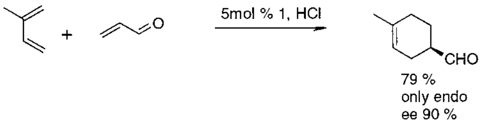
Organocatalytic methods hold considerable promise among novel catalytic asymmetric processes owing to their potential advantages over metal-catalyzed processes:

1. No expensive metals are required.
2. There is no risk for metal leakage.
3. The catalysts are often easier to modify and study.

In addition organocatalysts are often simple, easily accessible, stable organic molecules (amino acids, sugar derivatives, peptides, or peptidomimetics). A. M. P. Koskinen et al. (*Adv. Synth. Catal.* **2002**, *344*, 941) have reported on the synthesis and evaluation of different organocatalysts for enantioselective Diels–Alder reactions. The solid-supported catalysts were obtained through immobilisation of fmoc-protected phenylalanine on polystyrene or silica functionalised with a primary amine side chain. After deprotection and cyclisation to the imidazolidinone with acetone the catalysts were ready for use.

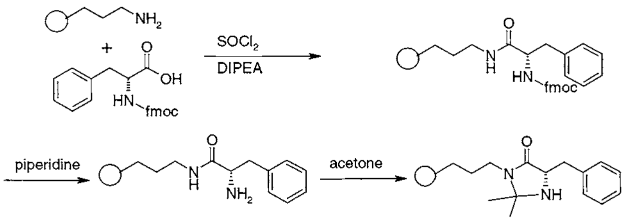
Both catalysts were found to be highly enantioselective in Diels–Alder reactions with various dienes in a mixture of acetonitrile and aqueous HCl. However, the silica-supported catalyst was found to be superior in all cases in comparison to the polystyrene-supported one. Under the same reaction conditions the silica-supported catalyst **1** gave higher endo/exo selectivity and yield with the equivalent high ee. The solid-supported catalysts were found to be easily separated through filtration and could immediately be reused. In the second run it was not necessary to add any extra acid to activate the catalyst.

This kind of strong interference from the polymer backbone in the reaction has also been reported for metal-containing solid-supported catalysts and is an important issue in heterogeneous catalysis. Through changes in the polymer backbone it is easy to modify the activity of the catalyst.



A Practical Synthesis of α,*β*-Unsaturated Imides, Useful for Conjugate Addition Reactions

S. N. Goodman and E. N. Jacobsen (*Adv. Synth. Catal.* **2002**, *344*, 953) have reported a new and efficient synthesis of α,*β*-unsaturated imides from the crystalline phosphonate imide easily obtained from α-chlorobenzylacetamide and triethyl phosphite. The phosphonate imide could easily be condensed with different aldehydes using DBU as base. The condensation with aldehydes was found to tolerate different functional groups (even alcohols), and the condensation could also be performed in water without loss in yield.



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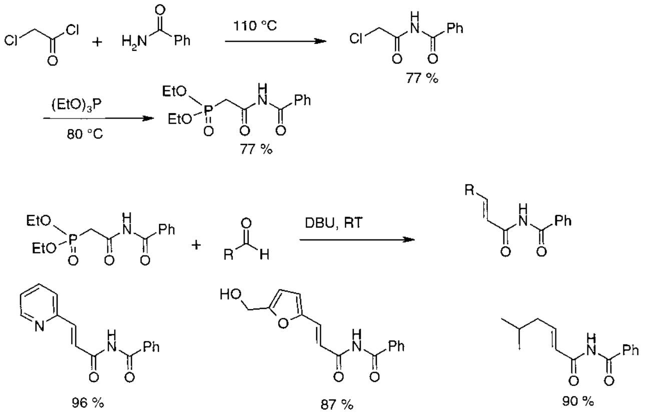
The Chemistry of C_2 Symmetric Bis-sulphoxides: A New Approach To Asymmetric Chemistry

C_2 symmetric bis-sulphoxides have seen a renaissance in the last 10 years due to new developments in asymmetric oxidations. B. Delouvrié et al. (*Eur. J. Org. Chem.* **2002**, 3507) have summarised recent achievements in the use of C_2 symmetric bis-sulphoxides as tools for asymmetric synthesis. Several of these bis-sulphoxides are easily available, even in enantiopure form, and their uses in organic synthesis span from anionic condensations to cycloadditions.

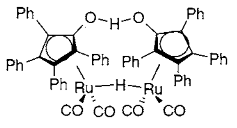
They have also been used for more specific applications such as desymmetrisation useful for synthesis of natural products and coordination to metals for catalysis.



Efficient Lipase-Catalyzed Dynamic Kinetic Resolution of *β*-Hydroxy Nitriles

During the past decade dynamic kinetic resolution (DKR) has become an active and important area of research in organic synthesis. DKR is a powerful tool to prepare enantiomerically enriched compounds in high yields that overcomes the 50% barrier in traditional kinetic resolutions. O. Pàmics and J.-E. Bäckvall (*Adv. Synth. Catal.* **2002**, *344*, 947) have reported on the DKR of *β*-hydroxy nitriles using *Candida antartica* lipase B (CALB, Novazym 435) as a transesterification catalyst and *p*-chlorophenylacetate as acyl donor. For the racemisation the free alcohol is oxidised to the corresponding ketone, which is reduced back to the alcohol using the ruthenium catalyst (**1**). The corresponding enantiopure acetates were obtained in yields 72–98% with ee's normally between 87 and 97%; however, only with methoxy-substituted aryl substrates were the ee's low at 36–44%. The main impurity from the sequence is the corresponding ketone. The amount of ketone can be suppressed through the addition of 0.5 equiv of 2,4-dimethyl-3-pentanol.

The nonbenzylic *β*-acetoxy nitriles were easily hydrolyzed with LiOH in methanol without deteration of the ee. The benzylic derivatives afforded under these conditions mainly



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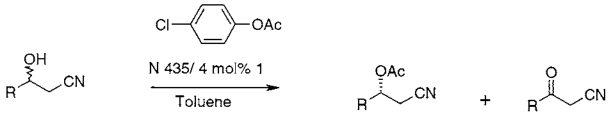


the elimination product. Using another lipase (PS-C, N-435, AK) it was possible to hydrolyze the acetates without accompanying elimination, but during the hydrolysis the ee dropped from 97 to 86%. The β-hydroxy nitriles were easily converted to the corresponding β-hydroxy carboxylic acids and β-amino alcohols in excellent yields.

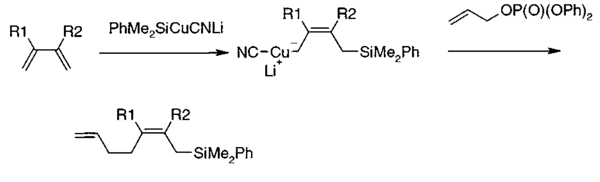
High Turnovers Achieved with an Immobilized Ir-Diphosphine Catalyst in an Imine Hydrogenation

H.-U. Blaser et al. (*Adv. Synth. Catal.* **2002**, *344*, 974) have now reported on the results from the immobilisation of the successful Ir-xyliphos catalyst used for the production of metalachlor (see Highlights from the Literature. *Org. Process Res. Dev.* **2002**, *6*, 742−748). The catalyst was immobilised on polystyrene and silica. Also a soluble dimeric xyliphos ligand and an extractable derivative thereof were synthesised and tested in the imine hydrogenation. From this study it was found that wide-pore silica was the best solid support for this catalyst, whereas polystyrene was found unsuitable. The silica-bound and the extractable catalysts were found suitable for industrial-scale applications (TON > 100 000, TOF up to 20 000 h^{-1}). The lower activity of the solid-supported catalyst in comparison to the homogeneous catalyst (TON of 2 000 000 and TOF values around 600 000 h^{-1}) is tentatively explained by the higher local catalyst loading on the surface, leading to increased irreversible formation of an inactive dimer of the catalyst.

Regioselective 1,4-Silylcupration of 1,3-Dienes

Y. Lipius and J.-E. Bäckvall (*Eur. J. Org. Chem.* **2002**, 3527) have described a new efficient 1,4-silylcupration of terminal dienes followed by electrophilic trapping with various electrophiles. The method provides an easy access to substituted 1,5-diene systems containing a silyl group, which is a useful intermediate in organic synthesis.

Allylic phosphates give exclusively the 1,4-addition product, whereas other electrophiles such as water or acetyl chloride give a mixture of 1,2- and 1,4-addition products. Depending on the nature of the electrophile exclusively 1,2-addition can also be obtained. Especially carbon dioxide is highly selective for 1,2-addition, giving β-silyl-substituted unsaturated carboxylic acids. The best silylcopper reagent for this transformation is $PhMe_2SiCuCNLi$ as all of the silylspecies in the regent is utilised in the reaction.



A Practical Recycle of Ligand-Free Pd Catalyst for Heck Coupling Reactions

Ligand-free palladium has been found by A. H. M. de Vries et al. (*Adv. Synth. Catal.* **2002**, *344*, 996) to be almost quantitatively recovered from Heck reaction mixtures through filtration after deposit on a carrier such as silica or Celite. The deposited catalyst can be reactivated to its original activity by addition of a small amount of iodine or bromine prior to the next reaction cycle. The catalyst shows excellent yields and selectivities even for aryl bromides. The reoxidised catalyst showed also in a third run the same high yield and selectivity as in the first one. The intention to use other oxidants such as sodium periodate failed, giving no active catalyst.

A Practical NMR-Based High-Throughput Assay for Screening of Enantioselective Catalysts

Recently the use of combinatorial methods has been applied to the screening of enantioselective catalyst libraries. One of the prerequisites for practical implementation is the availability of high-throughput screening systems for determining enantioselectivity. Various methods based on UV/vis spectroscopy, mass spectroscopy, capillary array electrophoresis, just to mention a few, have been developed over the past few years. None of these systems is generally applicable. In addition precision also varies from system to system, ±10% of the true value being common. Now M. T. Reetz et al. (*Adv. Synth. Catal.* **2002**, *344*, 1008) have developed a new high-throughput screening system based on NMR spectroscopy, allowing for at least 1400 ee determinations per day with an exceptional high degree of accuracy (±2% or ±5%, depending on the method used). The easiest way is to add an NMR shift reagent to the enantiomeric mixture and screen the diastereomeric mixtures with short measurement times in a flow-through cell. Using this technique about one sample a minute can be measured with an accuracy of about ±5%. A more accurate method is to prepare a ^{13}C-labeled derivative of one of the enantiomers, mix it with the nonlabeled isomer to a racemic mixture, and do the screening using the NMR technique. This method is especially good for selective hydrolysis of, for instance, acetates where the labeling is in the acetyl group.

Since NMR instrumentation is available in essentially all laboratories, this technique could become standard. The only additional equipment needed is an appropriate flow-through cell coupled to an auto-sampler.

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