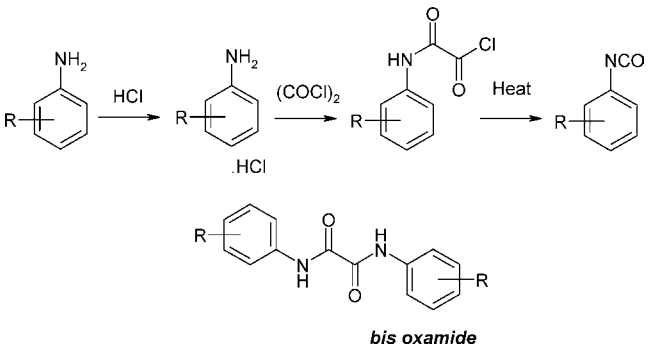
Organic Process Research & Development **2004**, *8,* 690–696

Highlights from the Literature

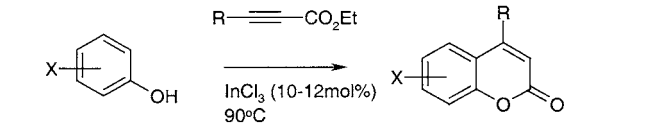
Some Items of Interest to Process R&D Chemists and Engineers

Generation of Phenyl Isocyanates



A convenient method for the generation of phenyl isocyanates from anilines has been reported by Oh and colleagues at GlaxoSmithKline (*Tetrahedron Lett.* **2004**, *45*, 4769.) Acylation of a variety of substituted aniline hydrochlorides with oxalyl chloride gave the intermediate oxamic chlorides, which smoothly undergo thermal decomposition to the corresponding isocyanates. The group have discovered that bisoxamide formation may be suppressed by use of the aniline hydrochloride salts.

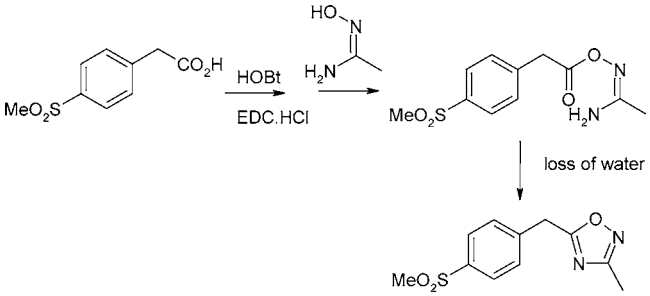
Coumarin Ring Skeleton



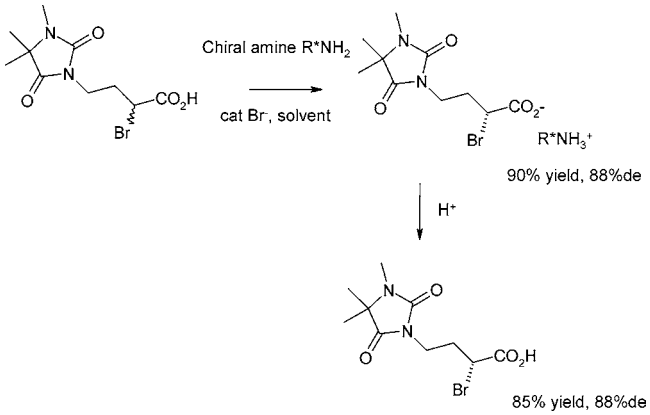
Ring oxygenated coumarins have been prepared in a single-step by condensation of appropriately substituted phenols with acetylenic esters using catalytic amounts of indium chloride in the absence of solvent by Kalyanam and co-workers (*Synth. Commun.* **2004**, 1909). Although the yields are moderate, the simplicity of this method to provide the coumarin ring skeleton is worthy of note as the structural motif is found in a number of fragrance, pharmaceutical and agrochemical compounds.

1,2,4-Oxadiazoles

Substituted 1,2,4-oxadiazoles are important pharmacophores found in drug candidates, often used to replace ester or amide motifs. In a recent report (*Synth. Commun.* **2004**, 1863) Pipik and colleagues report a one-pot synthesis of 1,2,4-oxadiazoles from carboxylic acids and amidoximes. Activation of the carboxylic acid using hydroxybenzotriazole (HOBt) and EDC/HCl followed by reaction with an amidoxime gave the oxime ester which could be dehydrated to give the oxadiazole ring in situ. They report the method to be scalable (30 kg) and applicable to a variety of substrates.



Crystallisation-Induced Dynamic Resolution (CIDR)



Kiau and colleagues from Bristol Myers Squibb report (*J. Org. Chem.* **2004**, 69, 4256) a novel route to enantiomerically enriched chiral α-substituted carboxylic acids. They use the concept of crystallisation-induced dynamic resolution (CIDR) to resolve a racemic α-substituted carboxylic acid by formation of a diastereomeric salt with a homochiral amine in the presence of a reagent capable of effecting racemisation at the α-centre. Since the diastereomeric salts exhibit different solubility it is possible, using this technique, to facilitate conversion to the desired homochiral diastereomeric salt.

In the example shown in the scheme, the racemic α-bromo acid is converted with (1*R*,2*S*)-2-amino-1,2-diphenylethanol in the presence of a catalytic amount of tetrabutylammonium bromide into its *R*-enantiomer in 90% yield with 88% ee.

The group have used parallel experimentation to enable rapid screening for suitable dynamic resolution conditions and the use of kinetic studies to help define the influence of temperature, tetrabutylammonium bromide concentration, molarity, and solvent polarity on the resolution rate, product yield, and enantiomeric excess.

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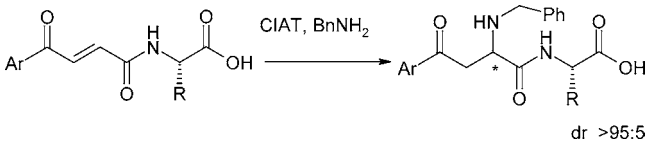
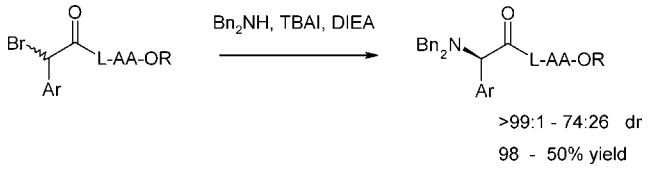
The application of crystallisation-induced asymmetric transformations (CIAT) by simply crystallizing one of two equilibrating isomers is a powerful and efficient methodology. Berkeš and co-workers (*Tetrahedron Lett.* **2004**, *45*, 4755) report how adducts from the reversible conjugate addition of benzylamine to enantiopure amides of aroylacrylic acid possess high enantiomeric and diastereomeric purity. This should find application to the synthesis of metalloproteinase inhibitors building blocks.

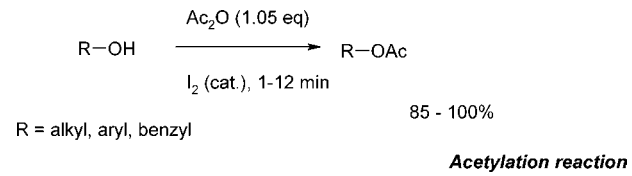


Dynamic Kinetic Resolution



In this arena of dynamic processes, Park and colleagues have demonstrated (*Tetrahedron* **2004**, 6311) that dynamic resolution of α-bromo amides can be applied towards the preparation of enantioenriched dipeptide analogues. The team have used dibenzylamine, TBAI, and a base to provide a series of dipeptide analogues in 50−98% yields with diastereomeric ratios from 74:26 to >99:1. They report how mechanistic investigations suggest that the α-bromo acetamides are configurationally labile under the reaction condition and the primary pathway of the asymmetric induction is a dynamic kinetic resolution.

Acetylation Conditions



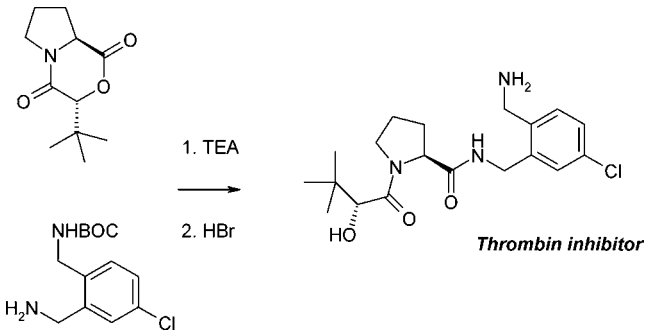
Acetylation reaction

Catalytic quantities of iodine have been found by Phukan (*Tetrahedron Lett.* **2004**, *45*, 4785) to promote quantitative acetylation of alcohols in a very short time with an equimolar amount of acetic anhydride under solvent-free conditions at room temperature. The rate of acetylation is reported to be comparable to reactions catalysed by TMSOTf.

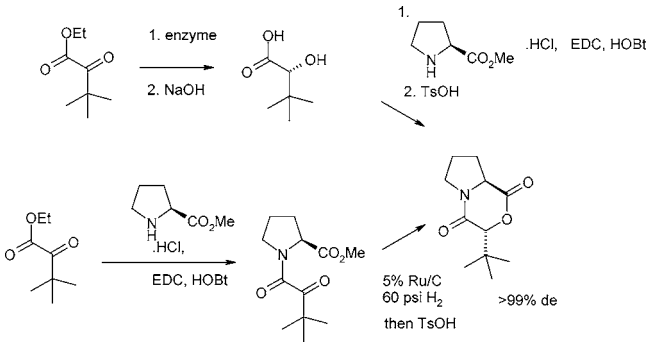
Thrombin Inhibitor Synthesis

The synthesis of a potent thrombin inhibitor has been disclosed by workers from Merck (*J. Org. Chem.* **2004**, *69*, 3620) and accomplished by a mild lactone aminolysis between an orthogonally protected bis-benzylic amine and a diastereomerically pure lactone (scheme).

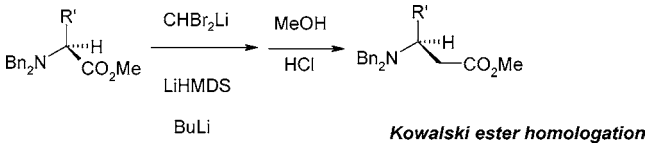
The lactone was synthesised in two ways by the team. First by the condensation of L-proline methyl ester with an enantiomerically pure hydroxy acid, which in turn was



synthesised by a highly stereoselective (>500:1 er) and productive (100000:1, S/C) enzymatic reduction of an α-ketoester. In addition, a second route to the enantiomerically pure lactone was accomplished by a substrate-controlled diastereoselective ketoamide reduction.



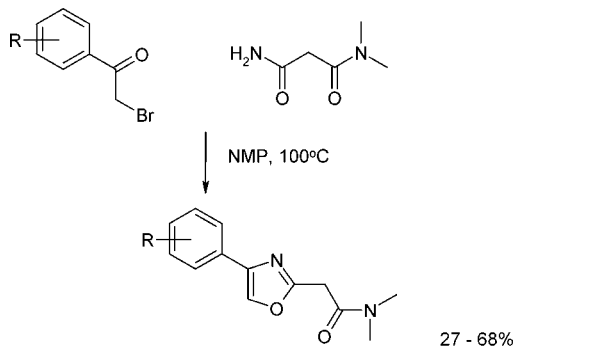
Kowalski Ester Homologation



Kowalski ester homologation

Gallagher and co-workers from the University of Bristol, UK, report (*J. Org.Chem.* **2004**, *69*, 4849) how they have applied the Kowalski ester homologation protocol to a range of α-amino esters to provide *β*-amino esters with excellent levels of enantio- and diastereocontrol. A key feature of their chemistry is the nature of the N-protecting group that is employed, and the method provides a complementary alternative to the Arndt−Eistert procedure.

Oxazole Synthesis

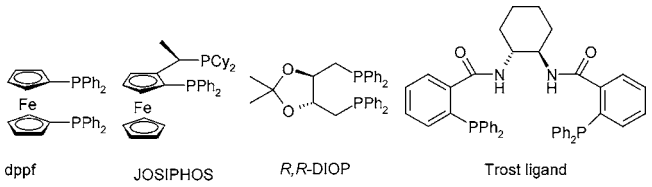


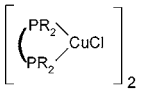
Oxazole synthesis

A practical and readily scaleable synthesis of *N*,*N*-dimethylpropanediamide (scheme) has been described (*Syn-*

lett **2004**, 1334) by Ragan et al from Pfizer. The utility of this compound in the preparation of several 2,4-disubstituted oxazoles from α-bromoketones is reported both on laboratory and pilot-plant scales.

Scavenging and Reclamation of Phosphine Ligands

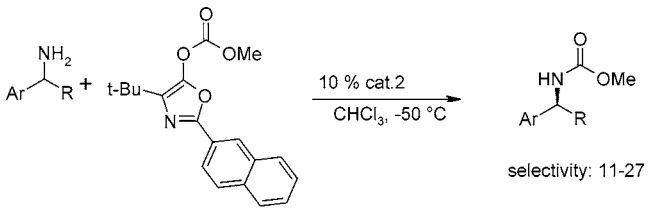


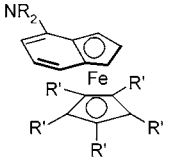


A number of group 10 transition metal catalysed reactions rely on the concomitant use of phosphine ligands. Lipshutz and colleagues report (*Org. Lett.* **2004**, *69*, 2305) a simple method for the rapid removal of these unwanted (but often valuable) phosphines from crude reaction mixtures after workup. Inexpensive CuCl is used to precipitate the phosphines as their CuCl−phosphine complexes which can be removed by simple filtration. In their communication a method to liberate the phosphine from the CuCl complex is also described.

Asymmetric Catalysis with "Planar-Chiral" Derivatives of 4-(Dimethylamino)pyridine

G. C. Fu (*Acc. Chem. Res*. **2004**, *37*, published online May 5, 2004, http://dx.doi.org/10.1021/ar030051b) has summarised the work that his group has done on chiral Lewis base (nucleophilic) catalysis based upon "planar-chiral" derivatives of 4-(dimethylamino)pyridine, a highly versatile nucleophilic catalyst that are effective in a diverse array of processes, including the Staudinger synthesis of β-lactams, the acylation of silyl ketene acetals, and the kinetic resolution of amines.

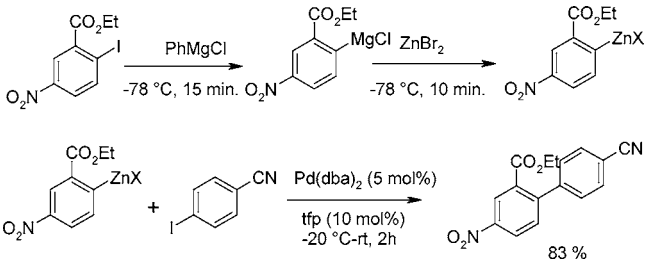




NR_2 = dimethylamino R'= Me 1
pyrrolidino Ph 2
dimethylamino Ph 3
pyrrolidino Me 4

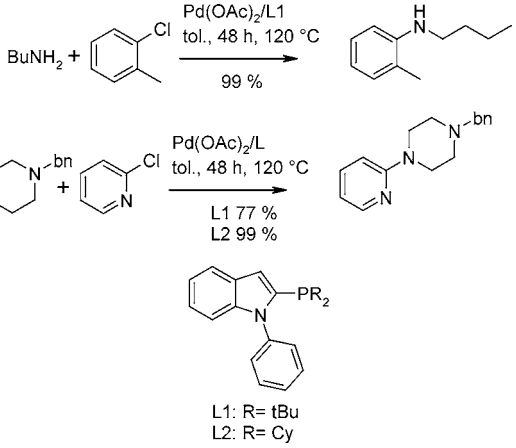
Synthesis of Nitro-Substituted Polyfunctional Biphenyls

P. Knochel et al. (*Adv. Synth. Catal.* **2004**, *346*, 709) have reported a synthesis of nitro-substituted polyfunctional biphenyls by Negishi cross-coupling of *o*-nitroarylzinc reagents. The iodine−magnesium exchange reaction allows the preparation of polyfunctional arylmagnesium species bearing a nitro group in the ortho position. After transmetalation to the corresponding arylzinc compound, these undergo a palladium-catalysed Negishi cross-coupling with various aryl iodides giving polyfunctionalised biphenyls in moderate to good yields.



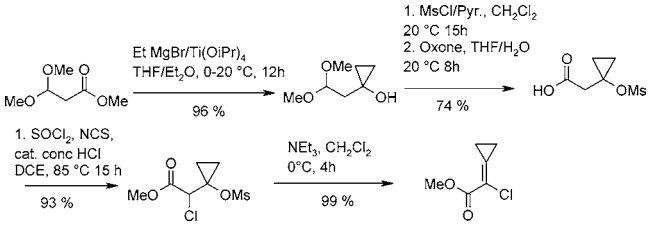
New Ligands for a General Palladium-Catalysed Amination of Aryl Chlorides

M. Beller et al. (*Chem. Eur. J.* **2004**, *10*, 2983) have synthesised a new series of monodentate N-substituted heteroarylphosphines, which have been found to be useful ligands for the palladium-catalysed amination of aryl and heteroaryl chlorides. Coupling of both activated and deactivated chloroarenes proceeds with the best catalytic systems under mild conditions (rt to 60 °C) giving products in excellent yields.



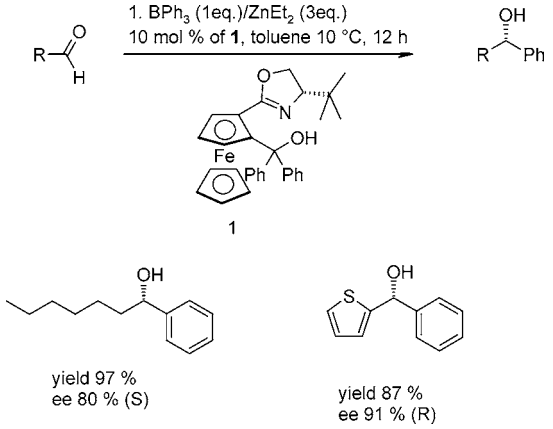
Advanced Synthesis of Cyclopropylideneacetates: Versatile Building Blocks

A. de Meijere et al. *(Adv. Synth. Catal*. **2004**, *346*, 760) have reported a new efficient synthesis towards methyl 2-chloro-2-cyclopropylideneacetate as well as the 2-bromo analogue each in six simple steps with overall yields of 68 and 51% which make these valuable multifunctional building blocks conveniently available.



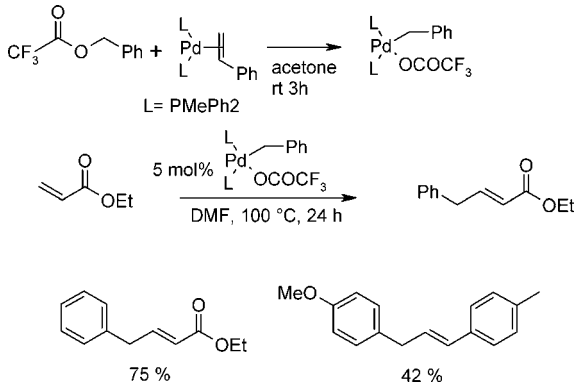
Highly Enantioselective Synthesis of Secondary Alcohols Using Triphenyl Borane

C. Bolm et al. *(Adv. Synth. Catal*. **2004**, *346*, 867) have reported an asymmetric phenyl transfer reaction with triphenylborane as aryl source and a ferrocene-based catalyst that gives secondary alcohols in high yields and enantioselectivities. The method allows the synthesis of a broad range of secondary alcohols, not only biaryl but also secondary alcohols, from aliphatic aldehydes.



Heck-Type Benzylation of Olefins with Benzyl Trifluoroacetates

I. Shimizu et al. (*Chem. Lett*. **2004**, *33*, 348) have reported a new synthetic method for 1-aryl-2-alkenes from 1-olefins by benzylation, treating with benzyl trifluoroacetates using palladium catalyst. The benzyl carboxylates oxidatively add to Pd(0) complexes to give a benzyl(trifluoroacetato)-palladium (II) complex which reacts with 1-olefins to give the products in moderate to good yields.

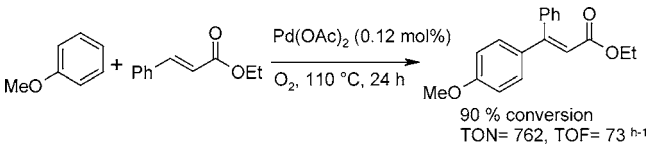


Palladium-Catalysed Aerobic Dehydrogenation

Catalytic aerobic dehydrogenation of organic substrates is going through a renaissance (B. M. Stoltz, *Chem. Lett.* **2004**, *33*, 362). Recent advances in this area have led to the discovery of palladium-catalysed alcohol dehydrogenations and oxidative hetero- and carbocyclisations. The development of asymmetric catalytic dehydrogenations is the latest advance in a long line of catalytic asymmetric oxidation reactions.

Room-Temperature Aerobic Copper-Catalysed Selective Oxidation of Primary Alcohols to Aldehydes

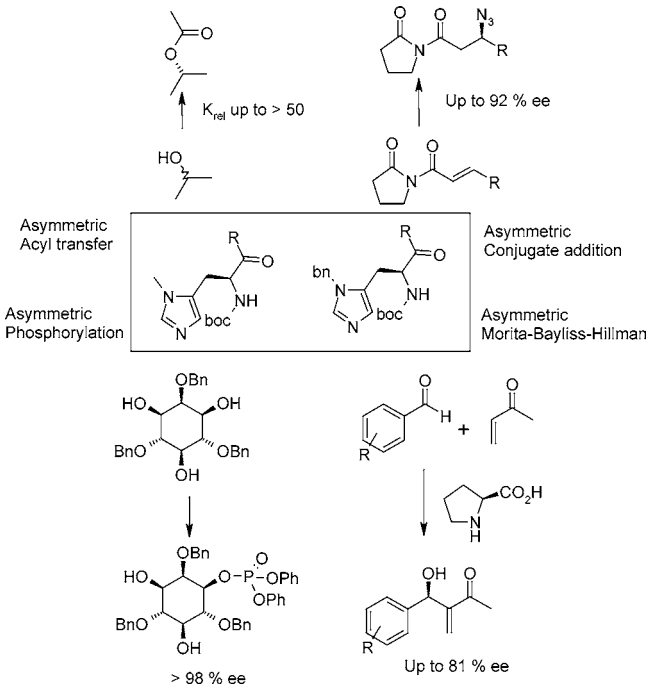
R. A. Sheldon et al. (*Adv. Synth. Catal*. **2004**, *346*, 805) have reported a novel aerobic oxidation of primary alcohols



to aldehydes with good conversions and selectivities. Secondary alcohols give no conversion under the reaction conditions. The reaction is carried out under air at room temperature and is catalysed using a copper(II)−amine complex with TEMPO and base as cocatalysts. The best results were obtained with $CuBr_2$ and 4,4′-dimethyl-2,2′-bipyridine as ligand.

In Search of Peptide-Based Catalysts for Asymmetric Organic Synthesis

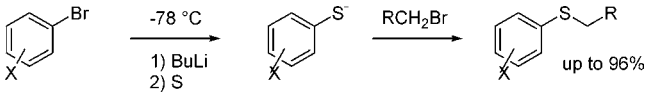
S. J. Miller (*Acc. Chem. Res*. **2004**, *37*, published online March 9, 2004, http://dx.doi.org/10.1021/ar030061c) has summarised the work that has been done on the search for short peptide sequences that function as asymmetric catalysts for a variety of reactions.The specific development of catalysts for enantioselective acylation, phosphorylation, conjugate addition, and Morita−Bayliss−Hillman reactions is described. The interplay of physical organic hypotheses and screening has led to catalysts for a number of disparate bond constructions.



Synthesis of Aryl Sulphides from Sulphur

A recent publication claims to have discovered a method of making sulphides from aryllithiums, sulphur, and an alkyl halide (Han, J. et al. *J. Org. Chem.* **2004**, *69*, 3236). However, the method has been used in industry for many years in heterocyclic chemistry (e.g. for the synthesis of 2-mercaptothiophene and its alkylated derivatives) and was reported in *Organic Process Research & Development*. The new paper does give some insight into the scope of the reaction, and yields are excellent. The authors have also

carefully studied the reaction conditions, and this nonsmelly process will be very useful for development chemists. The one-pot procedure makes it a fast process for generating sulphides and compares favorably with classical procedures and with the GlaxoSmithKline one-pot method via reduction of sulphonyl chlorides in the presence of activated alcohols (Martin, M. T. et al. *Tetrahedron Lett.* **2002**, *43*, 2145).



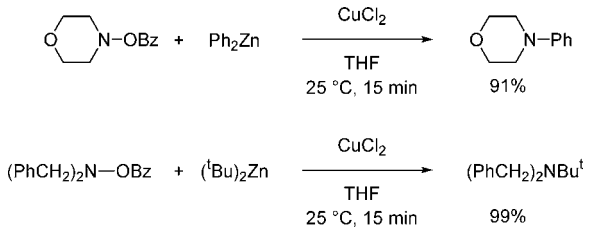
Asymmetric Catalysis in the Pharmaceutical Industry

A four-page essay from Pfizer chemists Joel Hawkins and Tim Watson makes fascinating reading (Hawkins, J. M. *Angew Chem., Int. Ed.* **2004**, *43*, 3224). They discuss the various ways of making enantiomerically pure APIs pointing out the advantages and pitfalls of each method. Economics and intellectual property issues are highlighted, with the importance of a company's freedom to operate a process both internally and externally with multiple outsource partners being a key issue. This is something that discoverers and marketers of new asymmetric catalysts do not always consider.

Process robustness of a catalytic step is also discussed from a critical viewpoint and may be at odds with catalyst loading. It is suggested that processes which operate at low catalyst loadings in the lab may also work in the plant but only under ideal conditions. If there are minor changes (e.g. to the amount of residual solvent in a substrate, to cycle time, to quality of solvent particularly if recycled), then catalytic activity or enantioselectivity may be jeopardised. Examples are provided from recent literature.

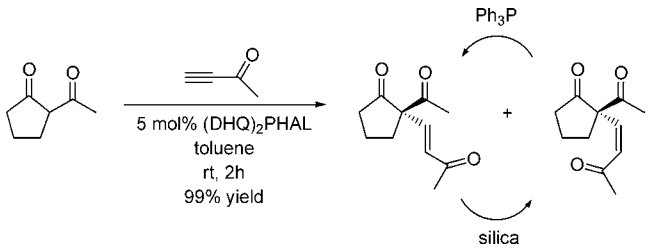
Synthesis of Tertiary Amines

A new method of making tertiary amines relies on the copper-catalysed electrophilic amination of organozinc reagents. Initially, amine derivatives R_2N-X were reacted with organometallics such as Grignard reagents, but poor results were obtained when X = Cl. When organozincs ArZnX were used and X = OBz, high yields of *tert*-amines were obtained (Berman, A. M. *J. Am. Chem. Soc.* **2004**, *126*, 5680). The method is appropriate for amines not accessible by other means.

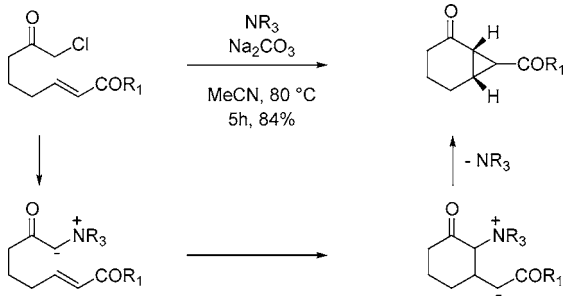


More Organocatalytic Reactions

The group of Jorgensen at Aarhus (Denmark) has reported that cinchona alkaloid derivatives catalysed the addition of β-diketones to alkynones at room temperature (Bella, M. et al. *J. Am. Chem. Soc.* **2004**, *126*, 5672). A mixture of E and Z isomeric products is obtained, but treatment with a catalytic amount of Bu_3P or iodine isomerises the mixture to the more stable E isomer. In contrast, use of silica gel gives the Z isomer. Moderate to high enantiomeric excesses are obtained.



The group of Gaunt at Cambridge, UK, has also used cinchona alkaloids in a novel enantioselective cyclopropanation reaction. The intramolecular cyclopropanation relies on formation of an ammonium ylide as shown below, with subsequent regeneration of the amine during cyclopropane formation.



This cyclopropanation avoids the use of diazo precursors and gives products in very high diastereomeric excess (>95%). Use of cinchona alkaloids as the catalyst (20 mol %) gives products in 64% ee, the ee being enhanced by addition of salts such as sodium bromide or iodide (ee increased to 95%). This powerful and simple method introduces three new stereocentres and two new C−C bonds simultaneously, whilst forming two new rings. No doubt the scope of this methodology will be expanded in recent months (Bremeyer, N. et al. *Angew Chem., Int. Ed.* **2004**, *43*, 2681).

Palladium-Catalysed Cyanation of Aryl Halides

The group of Beller at Rostock has devised a way to use the less poisonous potassium hexacyanoferrate (II) as a cyanating agent and to use all six cyanide groups. The key is to use a palladium acetate catalyst and a ligand such as dppf in NMP solvent. In the cyanation of bromobenzene as little as 0.01 mol % of catalyst is required giving a TON of 9700. A wide range of aromatic and heterocyclic halides can be displaced, including ortho substituted derivatives (Schareina, T. et al. *Chem. Commun.* **2004**, 1388).

Polymorph Control of Cocrystallisation

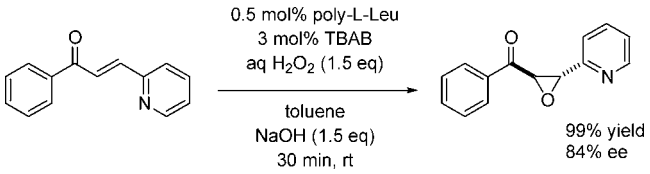
The technique of cocrystallisation continues to gain significance since, for a drug, it can be an effective means of controlling a drug's physical properties (Remenar, J. F. et al. *J. Am. Chem. Soc.* **2003**, *125*, 8456). If polymorphic cocrystals are formed, a means to control the production of a specific form can be a problem. A recent paper from the Pfizer Institute at Cambridge, UK, on a model system (caffeine−glutaric acid) suggests that control of polymor-

phism is possible. Evaporation of a mixture of the two components in chloroform produces both rods and blocks of the cocrystals (both 1:1 adducts). If the two solids are ground together in a mill, with the addition of a small amount of a solvent (solvent drop grinding), then the polymorphic form of the crystal can be controlled. In the absence of a solvent or with a nonpolar solvent, form I cocrystals are produced, whereas when a more polar solvent (dichloromethane, acetonitrile, or water) is used, form II predominates (Trask, A. V. et al. *Chem. Commun.* **2004**, 890).

Julia–Colonna Epoxidation

The asymmetric epoxidation of α-*β*-unsaturated ketones using hydrogen peroxide and a polyamide (e.g., poly-L-leucine) catalyst is known as the Julia–Colonna epoxidation. It often gives excellent enantioselectivity but has limited scope, and scale-up can be a problem. The polymeric catalyst is virtually insoluble in the aqueous–organic two-phase medium and can swell, making stirring of the three-phase mixture difficult. It has now been found by scientists at Bayer that addition of a phase-transfer catalyst not only accelerates the reaction but also allows a reduction in the amount of peroxide and base used.

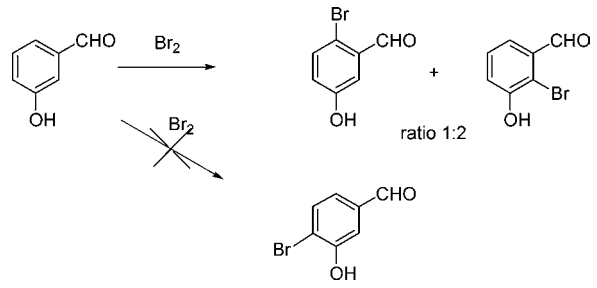
Another potential scale-up issue is that the polymeric catalyst needs preactivation, but the phase-transfer catalytic protocol causes a sharp reduction in the induction period (Geller, T. et al. *Tetrahedron Lett.* **2004**, *45*, 5065 and 5069).



The following publication from the group of Roberts at Liverpool in collaboration with a UK company, StylaCats, reports on a slightly different modification of the Julia–Colonna procedure for the asymmetric epoxidation of α-α-unsaturated sulphones (Lopez-Pedrora, J.-M. et al. *Tetrahedron Lett.* **2004**, *45*, 5073).

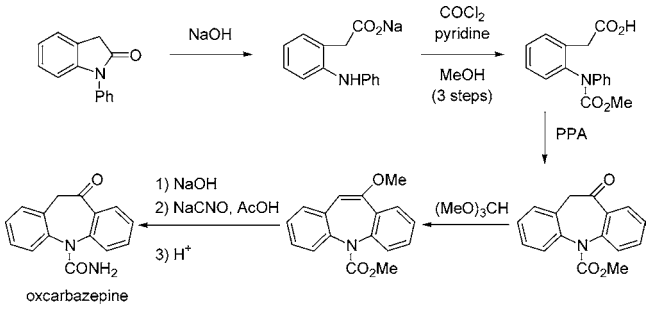
Beware of Incorrect Literature

A recent paper shows conclusively that bromination of 3-hydroxybenzaldehyde gives only the two products of bromination ortho to the aldehyde and not 4-bromo-3-hydroxybenzaldehyde as reported in the older literature (Van Otterlo, W. A. L. et al. *Tetrahedron Lett.* **2004**, *45*, 5091).



New Synthesis of Oxcarbazepine

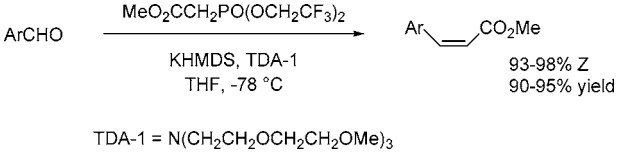
Oxcarbazepine, the active ingredient of the Novartis drug Trileptal is used in the treatment of epilepsy. Now, an improved synthetic route, suitable for low-cost manufacture, has been developed (Kaufmann, D. et al. *Tetrahedron Lett.* **2004**, *45*, 5275). The synthesis uses the readily available *N*-phenylindalone as starting material followed by ring opening, N-functionalisation, and ring-closure. Conversion of the ester to the carbonate cannot be achieved directly, and synthesis of the final product was via an indirect method involving isocyanic acid treatment.



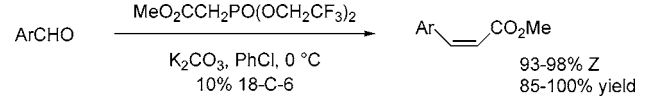
Z-Selective Synthesis of α-*β*-Unsaturated Esters Using the Horner–Wadsworth–Emmons (HWE) Olefination

The Wittig reaction (for a review, see Maryanoff, B. et al. *Chem. Rev.* **1989**, *89*, 863) is an excellent method for making unsaturated compounds, and the HWE variant is excellent for E olefins. The latter has the advantage on scale that the byproduct is water-soluble, whereas for the normal Wittig reaction, the removal of Ph_3PO is notoriously troublesome (BASF and others have solved this problem and routinely operate on large scale, using a continuous process).

Other groups have varied the phosphonate reagent to enable the HWE reaction to give Z unsaturated esters. The Still reagent, however, needs a large excess of expensive 18-crown-6 and KHMDS as base at low temperature. It has now been found that the crown ether can be replaced by the cheaper TDA-1 (available from Rhodia in bulk), and the high Z selectivity is retained. The alternative reagent developed by Ando, $EtO_2CCH_2PO(OPh)_2$, cannot be used with TDA-1.



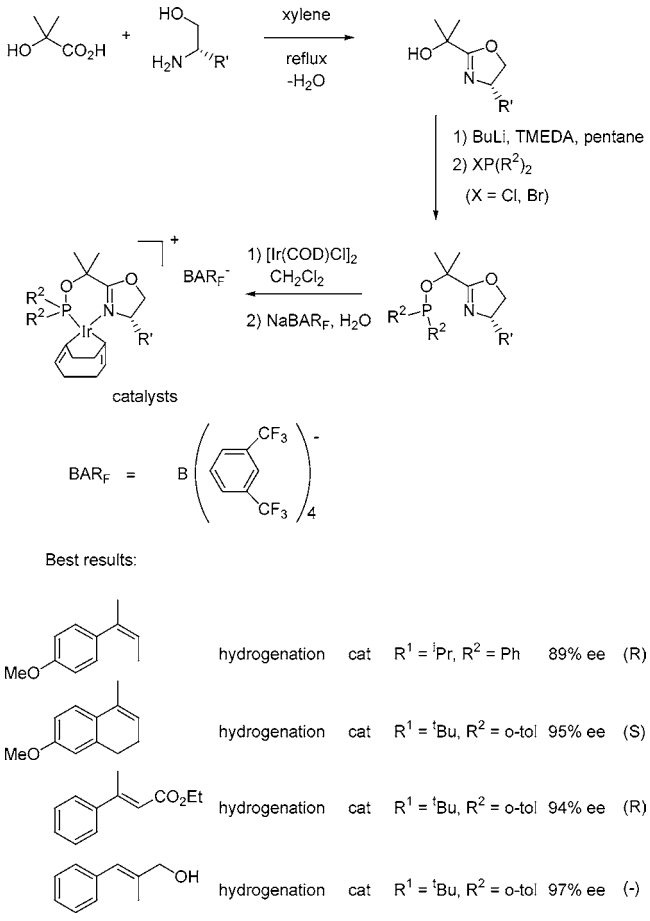
It has now been found that potassium carbonate in chlorobenzene can be used as base, but the methodology requires 10 mol % of 18-crown-6 at 0 °C (Touchard, F. P. *Tetrahedron Lett.* **2004**, *45*, 5519)



Simple Ligands for Iridium-Catalysed Asymmetric Hydrogenation

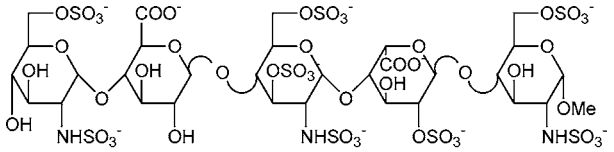
Iridium complexes with chiral P,N-ligands are often complimentary to the well-known rhodium and ruthenium

counterparts. They do not require a coordinating group next to the C≡C bond for efficient, highly enantioselective hydrogenation of olefins, whereas Rh and Ru complexes do (Pfalz, A. et al. *Adv. Synth. Catal.* **2003**, *345*, 33; Helmchen, G. et al. *Acc. Chem. Res.* **2000**, *33*, 336). The latest publication from the group of Pfalz (Smidt, S. et al. *Org. Lett.* **2004**, *6*, 2023) describes a series of very simple ligands for iridium, suitably named SimplePhox, and some of these are available for purchase from Strem. The ligands are oxazolines and phosphinites and can be synthesised in only two steps from simple carboxylic acids, amino alcohols, and halophosphines. After complexation with iridium (COD)Cl and formation of a cationic salt with the amusingly named BARF anion, the catalysts were highly effective in hydrogenations of trisubstituted olefins, giving high yields. The enantiomeric excess varied with ligand structure and could therefore be tuned to give best results.

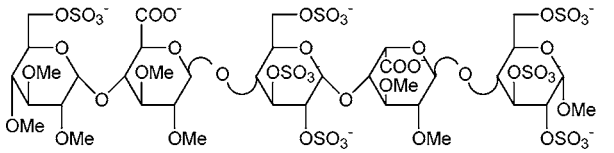


Drug Complexity

There is a feeling amongst process chemists that drugs coming into development are more complex structurally than in previous decades. Some very complex drugs, such as polysaccharides, have recently come onto the market—the antithrombotic drug Arixtra (Fondaparinux), marketed by Organon and Sanofi-Synthelabo, is a pentasaccharide (I). The multikilogram synthesis of this drug was a severe challenge for the process chemist and engineer (I believe the commercial synthesis is over 40 steps). The newer analogue, idraparinux, now in late-phase clinical trials, is not only easier to synthesise but also has the advantage of a long half-life in patients and needs to be administered only once a week. (Petiton, M. et al. *Angew. Chem., Int. Ed.* **2004**, *24*, 3118). The lack of nitrogen groups in the molecule simplifies the synthesis.



Fondaparinux



Idraparinux

For the future it appears that a 16-mer (SanOrg 213781) is a candidate for development, being of superior antithrombin activity to heparin. This promises to be an even more challenging scale-up problem for the Organon/Sanofi development chemists and engineers.

Fine Chemicals Manufacture

Recently, I (T.L.) came across a book, *Fine Chemicals Manufacture: Technology and Engineering*, by A. Cybulski, J. A. Moulijn, M. M. Sharma, and R. A. Sheldon (Elsevier: Amsterdam, 2001, ISBN 0-444-32202-x) which we did not get the opportunity to review in *Organic Process Research & Development*. After an introduction, the chapters on Fine Chemicals and Their Synthesis: A Chemical Point of View, Catalysis in Fine Chemicals, Selectivity Engineering, Process Development, Separation Methods, and Production Plants complete the volume. Unfortunately and surprisingly, there is no index. Over 200 pages are devoted to the chapter on Process Development, which is a chemical engineer's view rather than a chemist's. This means that there is an emphasis on scale-up, mixing, kinetics, and modeling, rather than on optimization (DOE is not mentioned) and analysis. The chapter would be enhanced (for chemists) by more case studies. Nevertheless, this is a useful review of these topics. The chapter on Production Plants is interesting and includes topics such as "production planning" and "scheduling", not normally covered in books.

The book contains hundreds of references, often to the chemical engineering literature, and these may not have been picked up by chemists.

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