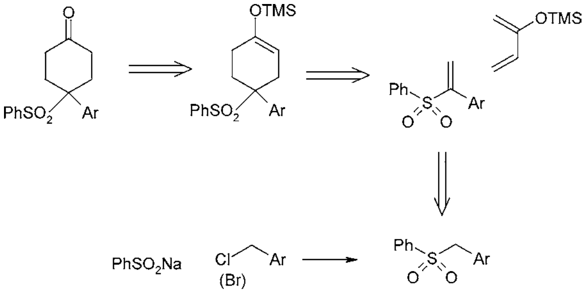
Organic Process Research & Development **2004**, *8*, 544–552

Highlights from the Literature

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

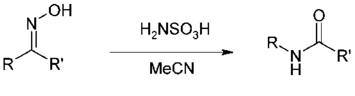
Diels Alder Assembly of 4-Aryl-4-phenylsulfonyl Cyclohexanones

Scott and co-workers have described (*Tetrahedron Lett.* **2004**, 3345) an efficient preparation of 4-aryl-4-phenylsulfonyl cyclohexanones containing a quaternary sulfone-bearing carbon centre. Their synthesis proceeds in 38−78% overall yield by way of three steps, sulfinate alkylation, methylenation, and regioselective Diels−Alder reaction with 2-trimethylsiloxybutadiene. The group describe how conditions for the one-pot conversion of sulfones to vinyl sulfones were developed using *N*,*N*,*N*′*N*′-tetramethylmethylenediamine and acetic anhydride.



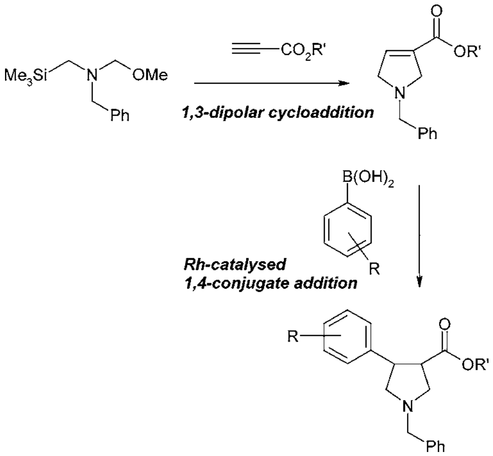
Beckmann Rearrangement Using Sulfamic Acid

Yang and colleagues report (*Tetrahedron Lett.* **2004**, 3369) how sulfamic acid has been used as an efficient catalyst for liquid Beckmann rearrangement of ketoximes in dry acetonitrile. Interestingly, the intrinsic zwitterionic property of sulfamic acid means that it may be removed from the reaction mixture by simply adding diethyl ether followed by filtration. This workup method avoids the need for a basic workup and associated production of waste.



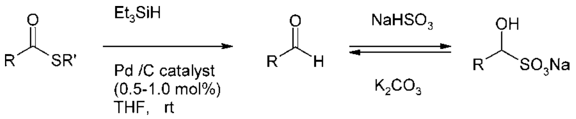
1,3,4-Trisubstituted Pyrrolidines

A number of biologically active compounds possess chiral pyrrolidine architecture. The asymmetric synthesis of 1,3,4-trisubstituted pyrrolidines has been reported by Belyk and co-workers from Merck (*Tetrahedron Lett.* **2004**, 3265) in two steps from readily available starting materials. Their synthesis involves 1,3-dipolar cycloaddition of an azomethine ylide to a propiolate ester followed by a Rh-catalyzed asymmetric 1,4-arylation of the resulting pyrrolidine with an arylboronic acid. Asymmetry was achieved using (*S*)-BINAP, and the enantioselectivity of the 1,4-addition was found to increase with increasing steric bulk of the propiolate ester.



Synthesis of Aldehydes

Complex organic molecules containing the aldehyde functionality are useful building blocks for drug and natural product syntheses. In an effort to develop methods that access this type of molecule under mild conditions, Seki and Kimura have described (*Tetrahedron Lett.* **2004**, 3219) how a highly efficient heterogeneous Pd/C catalyst was found to effect the reduction of thiol esters to their corresponding aldehydes with low catalyst loading (0.5−1.0 mol %). The chemical properties of the Pd/C catalysts together with X-ray fluorescence analysis reveal that the reduction is most likely to proceed on the solid surface of the Pd/C catalyst. In their communication a reaction mechanism through oxidative addition of Pd to the thiol esters is postulated. Practical purification of the aldehyde products may be accomplished using bisulphite adducts.



Enhanced *O*-Dealkylation Conditions

In efforts to prepare the selective estrogen receptor modulator Zewge and colleagues report (*Tetrahedron Lett.* **2004**, 3729) how $SiCl_4$/LiI *O*-dealkylation conditions may be enhanced by the addition of a catalytic amount of BF_3. In their communication a variety of additional substrates are also dealkylated.

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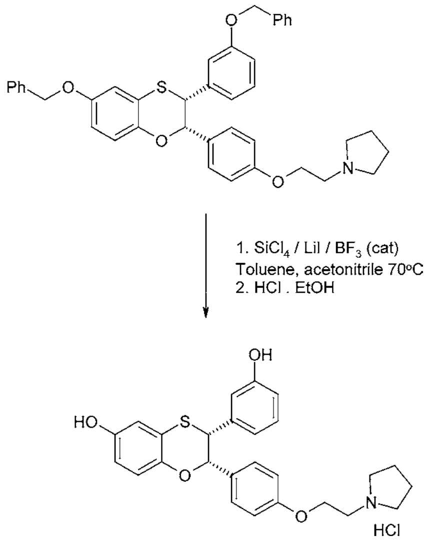
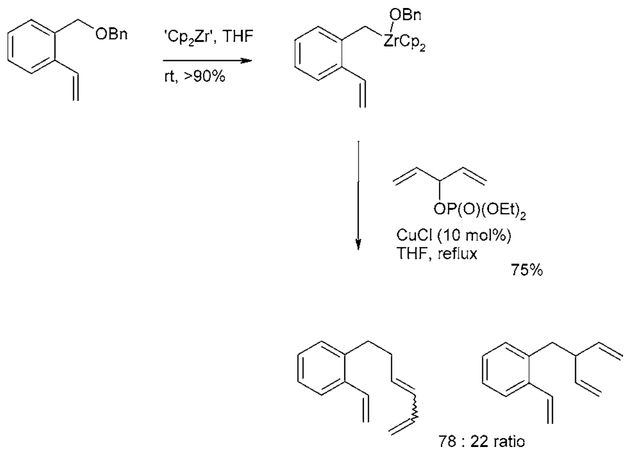
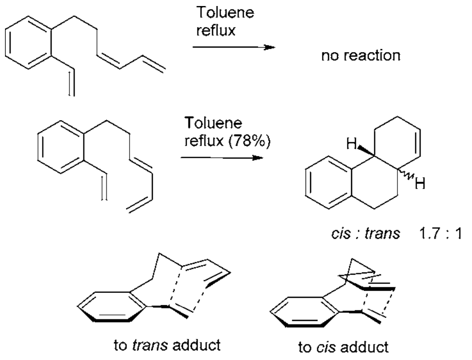


Cu-Catalysed Allylation of an *o*-Vinylbenzylzirconocene Intermediate

The *o*-vinylbenzylzirconocene intermediate may be readily prepared by the reaction of *o*-benzyloxymethylstyrene and "Cp_2Zr" under mild conditions and provides access to a useful synthetic building block for further benzylic funtionalisation. Hanzawa and colleagues describe (*Tetrahedron Lett.* **2004**, 3717) how this intermediate reacts with allylic halides or phosphates in the presence of catalytic amount of CuCl to give allylated products in good yields.

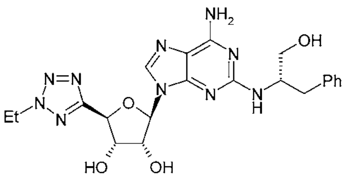




The group go on to describe an interesting elaboration of the product triene in an intramolecular Diels–Alder reaction. At reflux in toluene only the (*E*)-diene was found to react, giving the Diels–Alder adduct as a 1.7:1 mixture of *cis*:*trans* products. The (*Z*)-diene was recovered in quantitative yield.

A2a Agonist

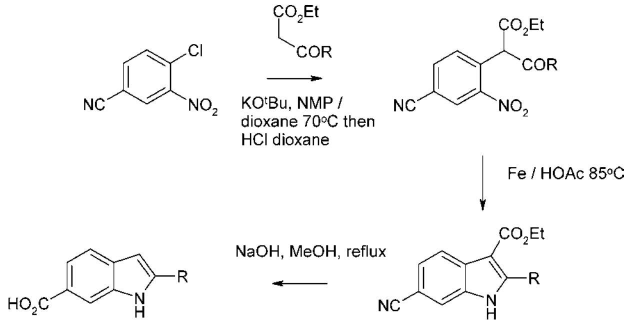
A convergent synthesis of adenosine A2a agonist in the form of its maleate salt is described by Xie and co-workers at GSK (*J. Org. Chem.* **2004**, *69*, 3212). The key step in this approach was the highly selective 9β-glycosylation reaction between 2-haloadenines or an N^2-alkyl-6-chloroguanine and a D-ribose derivative containing a 2-ethyltetrazolyl moiety. Glycosylations of other purine derivatives were also examined, and the methods developed provide efficient access to a variety of adenosine analogues such as 2-alkylaminoadenosines, an attractive class of compounds with antiinflammatory activity.



Adenosine A2a agonist

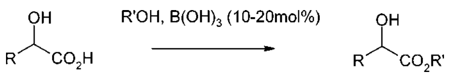
2-Aryl-Indole-6-carboxylic Acids

A practical synthesis of 2-aryl-indole-6-carboxylic acids has been reported by Gallou and colleagues (*Synlett* **2004**, 883). Their synthetic approach has been developed via a sequence consisting of S_NAr reaction, reductive cyclisation, hydrolysis, and decarboxylation. This process is applicable to a variety of "R groups" and is operationally simple.



Boric Acid as Catalyst

Houston and colleagues report (*Org. Lett.* **2004**, 679) how boric acid catalyses the chemoselective esterification of α-hydroxycarboxylic acids without causing significant esterification at other carboxylic acid sites. The procedure is simple, high-yielding, and applicable to the esterification of α-hydroxy carboxylates in the presence of other carboxylic acids, including β-hydroxyacids within the same molecule. For example, malic acid was mono-esterified with methanol



at the α-hydroxycarboxylate in 71% yield. A range of other examples are given.

Electrophilic Br$^+$ from Br−

A mild and versatile procedure for the bromination of olefins and activated arenes by in situ generation of Br$^+$ using (diacetoxyiodo)benzene and lithium bromide has been described by Braddock, Cansell, and Hermitage (*Synlett* **2004**, 461). The method is practically simple and avoids the hazards associated with the use of molecular bromine.

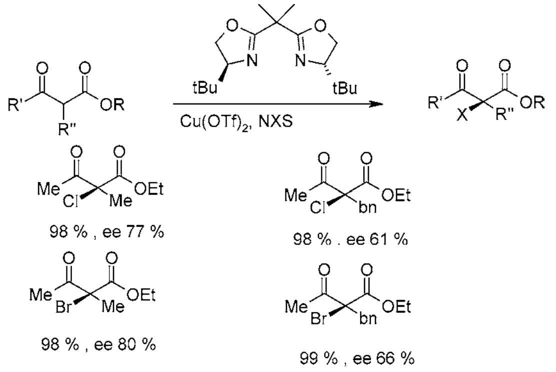
$$\mathrm{PhI(OAc)_2} \xrightarrow{\mathrm{LiBr}} \mathrm{Br^+}\text{ source}$$

Catalytic Ionic Hydrogenations

Traditional catalysts for ketone hydrogenation rely on coordination of the ketone to the metal so that the insertion of the substrate into the M−H bond can occur. In contrast, binding of ketone to the metal is not required for ionic hydrogenations. R. M. Bullock (*Chem.-Eur. J.* **2004**, *10*, 2366) has summarised the development and concept of catalytic ionic hydrogenations. The development of this type of hydrogenation owes much to kinetic and mechanistic studies that demonstrated the breadth of proton- and hydride-transfer capabilities of metal hydrides. When these modes of M−H bond cleavage are coupled to a mechanism that regenerates M−H bonds through reaction with hydrogen, catalytic ionic hydrogenation results. The scope and utility of catalytic ionic hydrogenations is not yet fully defined, but increasing evidence suggests that such mechanisms are becoming more widely recognised. Catalysts based on the inexpensive metals molybdenum and tungsten have been developed, although those are not as active as ruthenium and rhodium catalysts, but ongoing studies are seeking to design catalysts with improved lifetimes and rates.

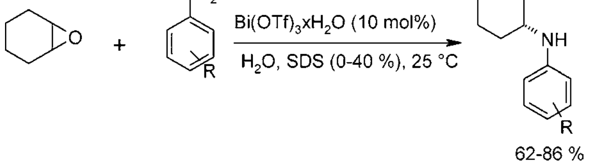
Catalytic Asymmetric Bromination and Chlorination of *β*-Ketoesters

K. Jørgensen et al. (*Chem.-Eur. J.* **2004**, *10*, 2133) have reported a catalytic asymmetric bromination and chlorination of *β*-ketoesters. The reactions proceed for both acyclic and cyclic substrates catalyzed by chiral bisoxazoline−copper(II) complexes giving the corresponding optically active α-bromo- and α-chloro-*β*-ketoesters in high yields and moderate to good enantioselectivities. For the optically active chlorinated products the isolated yields are in the range 88−99% and the enantiomeric excesses up to 77%. Brominated adducts were formed in 70−99% isolated yield and up to 82% ee.



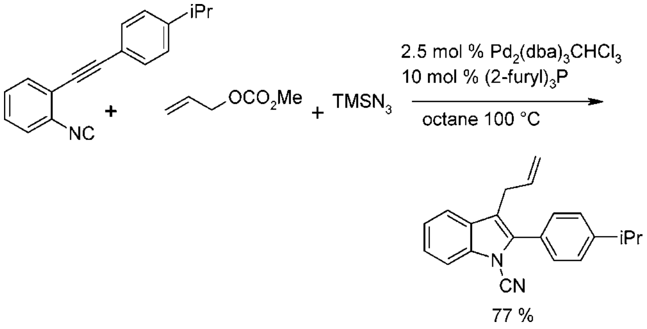
Bismuth(III) Triflate in Organic Synthesis

Bismuth(III) triflate is a new, cheap, and environmentally friendly Lewis acid. C. Le Roux et al. (*Eur. J. Org. Chem.* **2004.** Published online.) have summarised the new findings around the use of this Lewis acid. It appears that Bi(OTf)$_3$ is a new and efficient catalyst for a number of reactions involving various Lewis bases as substrates. The relatively low cost and high catalytic efficiency of Bi(OTf)$_3$ makes it similar to rare earth triflates. The catalytic efficiency in stereoselective synthesis is still to be explored. Although there are few publications compared to those about rare earth triflates, there are indications that the dawn of the use of Bi(OTf)$_3$ in organic synthesis has just begun. There is no doubt that Bi(OTf)$_3$ will emerge as a new and environmentally friendly Lewis acid catalyst.



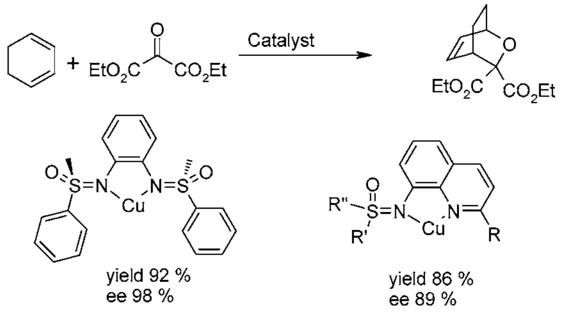
Transition-Metal-Catalysed Reactions in Heterocyclic Synthesis

Y. Yamamoto et al. (*Chem. Rev.* **2004**, *104*, 2127) have written a very comprehensive review on the use of transition metal-catalysed reactions for the synthesis of heterocyclic compounds. Among a variety of new synthetic transformations, transition-metal-catalysed reactions are some of the most attractive methodologies for synthesizing heterocyclic compounds. Through the use of these cross-coupling reactions, heterocyclic compounds having complicated structures can easily be synthesised in a sequential manner.



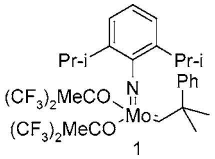
Hetero-Diels−Alder Reactions of Ketones: A Challenge for Chemists

K. A. Jørgensen (*Eur. J. Org. Chem.* **2004**, 2093) has summarised recent developments on hetero-Diels−Alder reaction of ketones, which are more challenging than with aldehydes. The oxygen-containing heterocycles obtained from hetero-Diels−Alder reactions of ketones are important in chemistry. Recent developments have shown that hydrogen-bonding solvents can activate ketones for hetero-Diels−Alder reactions with activated dienes. A chiral Lewis acid catalysis and the reaction of chiral copper(II) complexes are especially useful. For the inverse electron demand hetero-Diels−Alder reactions, chiral copper(II) complexes can catalyze the cycloaddition of α,*β*-unsaturated acyl compounds with electron-rich alkenes in high yield and excellent diastereo- and enantioselectivity.



Synthesis of Oxygen- and Nitrogen-Containing Heterocycles by Ring-Closing Metathesis

A. Deiters et al. (*Chem. Rev.* **2004**, *104*, 2199) have summarised the work that has been done since Grubbs and Fu little more than a decade ago reported that Schrock's molybdenum catalyst **1** could be used to induce efficient cyclisations of functionalised α,*ω*-dienes to give carbocycles and oxygen and nitrogen heterocycles via ring-closing metathesis (RCM). There are an increasing number of applications of RCM to the synthesis of complex and highly functionalised organic molecules of importance in natural product synthesis, chemical biology, and material science. Improved catalysts for specific applications, including enantioselective synthesis, continue to be developed, and it seems likely that even more robust and selective catalysts will be developed.



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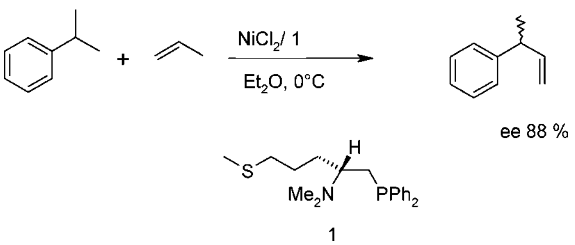
The Development of Bidentate P,N Ligands for Asymmetric Catalysis

The asymmetric transformations to which metal complexes of bidentate P,N ligands have been applied include, among others, palladium-catalyzed allylic substitutions, copper-catalyzed 1,4-additions to enones, and rhodium-catalyzed hydroboration of vinylarenes (Guiry, P. J. et al. *Adv. Synth. Catal.* **2004**, *346*, 497). Excellent enantioselectivities, regioselectivities, and reactivities have been achieved in each of these processes.



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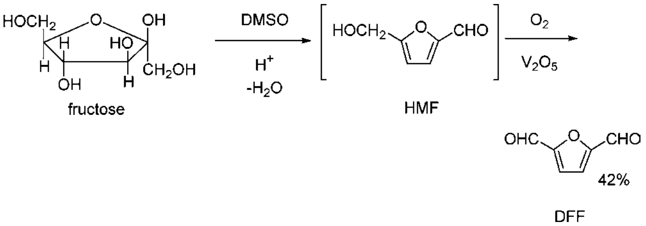
One-Pot Synthesis of 2,5-Diformylfuran from Fructose

A group from DuPont Central R&D at Wilmington have reported a simple procedure for the synthesis of diformylfuran (DFF), used in a wide variety of applications. Prior to this synthesis, DFF was expensive and only available in milligram quantities (30−65 USD per 100 mg).

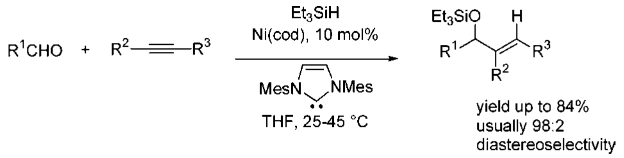
A practical route from fructose is via dehydration then oxidation of the resultant hydroxymethyl furfural (HMF). The dehydration is usually carried out in DMSO, which stabilises the HMF, but it is then difficult to isolate since it is very soluble. This accounts for the limited availability and high cost of HMF (15−44 USD per gram). If the oxidation of HMF could be carried out without HMF isolation, then this would be the best process.

The DuPont workers (Halliday, G. A. et al. *Org. Lett.* **2003**, *5*, 2003) devised a process involving HMF generation by heating fructose in DMSO at 80−135 °C in the presence of an acidic cation-exchange resin, filtering off the resin, adding a vanadium catalyst, and oxidizing HMF to DFG with air. DFF is a low-polarity hydrophobic compound, which can be easily isolated and purified. It is surprisingly stable to oxidation. Unfortunately the oxidation produces unpleasant odours (surprisingly including Me_2S), which need to be scrubbed using hypochlorite.



Nickel-Catalysed Reductive Coupling of Aldehydes and Alkynes

The intramolecular cyclisation of acetylenic aldehydes using nickel catalysts has been reported previously, but a new report focuses on the intermolecular variant, which previously has been of only limited value partly due to competing alkyne trimerisation. A key aspect is the use of "carbene" ligands on nickel, instead of the usual phosphines (Mahandru, G. M. et al. *J. Am. Chem. Soc.* **2004**, *126*, 3698).

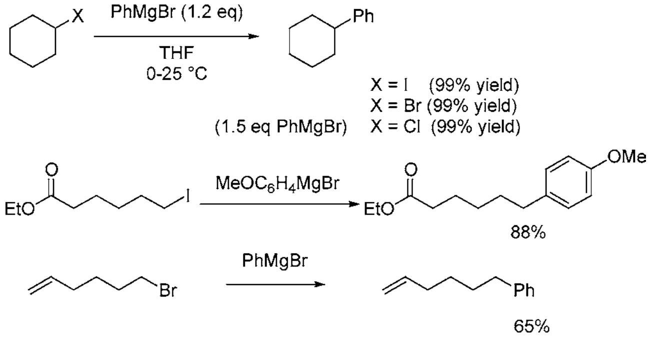


Iron-Catalysed Cross-Coupling of Alkyl Halides with Grignard Reagents

Carbon−carbon bond formation from alkyl halides can be a difficult process, but recent results have shown promise using cobalt and nickel catalysis. (For a recent short review see Cardenas, D. J. *Angew Chem., Int. Ed.* **2003**, *42*, 384). It has now been found that alkyl bromides and iodides (and occasionally chlorides) can react with aryl Grignard reagents to give high yields of coupled products (Nakamura, M. et al. *J. Am. Chem. Soc.* **2004**, *126*, 3686). The reactions proceed using ferric chloride (5 mol %) in THF in the presence of an additive, such as TMEDA (tetramethylethylenediamine). The additive suppresses a tendency to eliminate HX to give an olefin. Slow addition of the Grignard reagent and TMEDA to the alkyl halide and $FeCl_3$ in THF improves the yield.

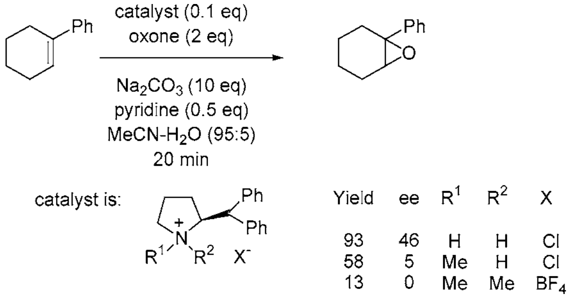
Primary alkyl halides are much less reactive than secondary, and may require a higher temperature, but still give excellent yields. Tertiary halides give a mixture of products. An optically active secondary alkyl halide gives a racemic product, showing that the process is not a simple nucleophilic addition, and may be a radical process.

Functional groups such as alkoxycarbonyl, alkenyl, and alkynyl in the alkyl halide survive intact, but the paper does not mention whether alkyl Grignard reagents were tried—the only data reported is on a variety of aryl Grignard reagents, which all give high yields, the electron-rich aryl Grignards reacting the fastest. The reaction will no doubt be seized on by process chemists worldwide as a cheap and efficient method of carbon−carbon bond formation from readily available raw materials, without the need for precious-metal catalysts or toxic reagents.



Amine-Catalysed Epoxidation of Alkenes

A potentially useful reaction for scale-up is the asymmetric epoxidation of olefins using oxone as reagent in the presence of a chiral amine catalyst (as its salt), recently reported by the group of Aggarwal at the University of Bristol (Adamo, M. F. A. et al. *J. Am. Chem. Soc.* **2003**, *125*, 7596; **2002**, *124*, 11223).



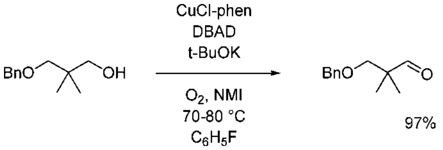
Yield	ee	R^1	R^2	X
93	46	H	H	Cl
58	5	Me	H	Cl
13	0	Me	Me	BF_4

These and other results have been discussed (Armstrong, A. *Angew Chem., Int. Ed.* **2004**, *43*, 1460), and it is suggested that the amine salt interacts with the persulphate anion in different ways with different orientations, which affect the enantioselectivity of the process. Hopefully, this understanding will help in the design of more selective amine salt catalysts and may allow extension of this potentially useful reaction to a wider range of substrates. At present, trisubstituted olefins react well, but terminal olefins other than styrene give poor conversions; stilbene is also unreactive.

Thus, at present this process is inferior to other asymmetric oxidations such as the dioxiranes developed by Shi (Wu, X. Y. et al. *J. Am. Chem. Soc.* **2002**, *124*, 8792; Tian, H. Q. et al. *J. Am. Chem. Soc.* **2002**, *67*, 2435) which have been reported at recent conferences to work well on kilogram scale.

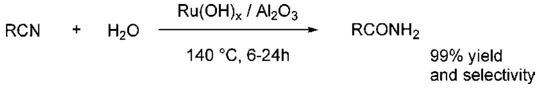
Efficient Copper-Catalysed Aerobic Oxidation of Primary Alcohols to Aldehydes

The group of Markó at Louvain, Belgium has previously reported on a method of oxidizing allylic or benzylic alcohols and secondary aliphatic alcohols to carbonyl derivatives, but the method [CuCl, 1,10-phenanthroline (phen), di-*tert*-butylazodicarboxylate, O_2] failed for primary alcohols (Markó, I. E. et al. *J. Organomet. Chem.* **2001**, *624*, 344). It has now been found that addition of DMAP or *N*-methylimidazole to the system allows the oxidation of primary alcohols to aldehydes. Even highly hindered primary alcohols can be oxidised in good yield (Markó, I. E. et al. *Angew Chem., Int. Ed.* **2004**, *43*, 1588).



Efficient Hydration of Nitriles to Amides in Water

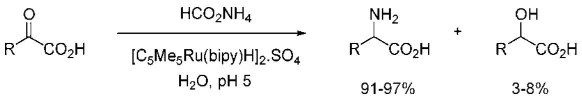
Whilst the hydration of nitriles on industrial scale (e.g., acrylonitrile) is usually carried out using a biotransformation, lab methods invariably use acid or basic hydrolysis; however, this may lead to byproducts, especially if other functional groups are present. It is now reported (Yamaguchi, K. et al. *Angew Chem., Int. Ed.* **2004**, *43*, 1576) that an inexpensive supported ruthenium hydroxide catalyst $Ru(OH)_x/Al_2O_3$ accelerates the hydrolysis of nitriles in water, without any additional acid or base present. Aromatic nitriles hydrolyse faster than aliphatic. The reaction is zero order in water, but first order in catalyst and substrate; however, despite being multiphase, it is not affected by stirring rates in the 500−2000 rpm range. Catalyst separation is by simple filtration, and the catalyst can be recycled.



Reductive Amination of Ketoacids with Ammonia

Although reductive amination is a common synthetic strategy, it is usually carried out with amines rather than ammonia. If a primary amine is required, then a further transformation (such as hydrogenolysis of a benzyl group) is required. The main difficulty with using ammonia as reagent and ketoacids as substrate is the aqueous medium, which needs to be acidic enough to protonate the carbonyl group; however, this causes decomposition of any hydride reducing agents.

A group from Osaka have now found that acid-stable iridium hydride complexes catalyse the reductive amination process (Ogo, S. et al. *J. Am. Chem. Soc.* **2004**, *126*, 3020). Ammonium formate is the reducing agent. The yield is very pH dependent, being maximum at pH 5. At higher pH, e.g. 6.5, more α-hydroxy acid byproduct is formed (up to 19%). TOFs are up to 250.

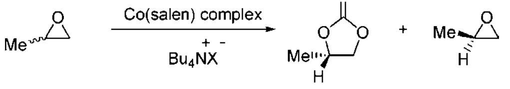


Asymmetric Catalytic Reaction of Epoxides with CO_2: Synthesis of Optically Active Propylene Carbonate

In previous highlights, the reaction of carbon dioxide with epoxides to give propylene carbonate derivatives was mentioned. Now a group from Dalian, China, has reported that the reaction can proceed enantioselectively, in the presence of cobalt salen complexes (Lu, X. B. et al. *J. Am. Chem. Soc.* **2004**, *126*, 3732). The work was stimulated by Jacobsen's mechanistic studies on hydrolytic kinetic resolution of epoxides, where one CO(III) salen molecule acts as Lewis acid catalyst, for epoxides opening and a second as counterion for the nucleophile (Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421; Schaus, S. E. et al. *J. Am. Chem. Soc.* **2002**, *124*, 1307). Thus, the Chinese group used a simple chiral cobalt salen system in the presence of a quaternary ammonium salt.

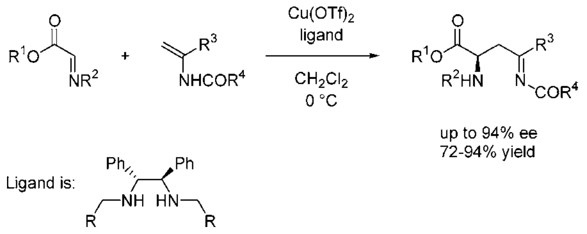
The reaction proceeds without solvent and the unreacted epoxides (for which the ee was not given) and the product could be separated from the catalyst by distillation; the catalyst could be reused.

The choice of anion of the quaternary ammonium salt is important for enantioselectivity, with chloride preferred; however, the rate of reaction is also poorer. It would be interesting to study more widely the effect of counterion and the structure of the phase-transfer catalyst on rate and enantioselectivity (only Bu_4N salts were used, with Cl, Br, and I anions). These preliminary results show promise for the development of a solvent-free atom-efficient synthesis of chiral cyclic carbonates under extremely mild conditions.



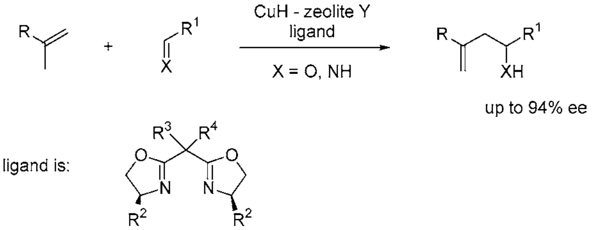
Copper-Catalysed Enantioselective Addition of Enamides to Imines

An ene-type reaction can occur with enamides and imines in the presence of a copper catalyst. Preliminary studies indicate, however, that this is a nucleophilic addition rather than an aza−ene reaction via a cyclic transition state. (Masubara, T. R. et al. *Angew Chem., Int. Ed.* **2004**, *43*, 1679).



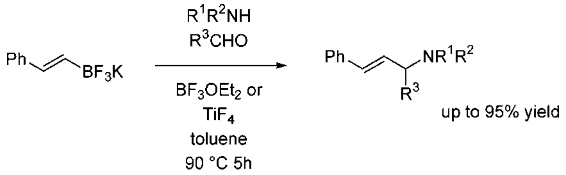
Heterogeneous Enantioselective Ene Reaction

The ene reaction between an olefin and glyoxylic or pyruvic ester (and its imino equivalent) are useful methods for generating α-hydroxy and α-amino acids. When a homogeneous chiral catalyst is used, good enantiomeric excesses are obtained with some substrates, but it is difficult to recycle or reuse the catalyst. A recent report shows that bis-oxazoline-modified CuH zeolite Y catalysts are extremely effective for asymmetric ene reactions and that furthermore the catalysts can be recovered and reused without loss of catalyst performance (Caplan, N. A. et al. *Angew Chem., Int. Ed.* **2004**, *43*, 1685).



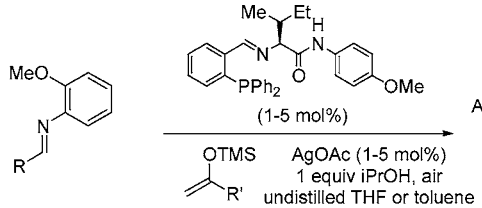
Lewis Acid-Catalysed Mannich-Type Reaction with Potassium Organotrifluoroborates

As an extension of the standard Petasis reaction, which uses boronic acids, it has now been found that aryl, vinyl, and allyl trifluoroborates will react with aldehydes and amines in a three-component reaction to produce substituted amines (Tremblay-Morin, J. P. et al. *Tetrahedron Lett.* **2004**, *415*, 3471).

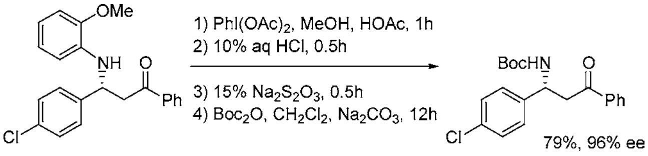


Silver-Catalysed Asymmetric Mannich Reaction

β-Aminocarbonyl compounds are important in the synthesis of biologically active molecules (for a review, see Kobayashi, S. *Chem. Rev.* **1999**, *99*, 1069), and there have been a number of recently disclosed methods for enantioselective addition to an imine, using latent carbonyl functionality. The groups of Snapper and Hoveyda at Boston College now describe a silver-catalysed reaction of silyl enol ethers with aryl, alkyl, alkenyl, and alkynyl imines (Josephsohn, N. S. et al. *J. Am. Chem. Soc.* **2004**, *126*, 3734). The reactions proceed in undistilled solvents, in air, to give moderate to high yields and high enantiomeric excesses of the protected *β*-aminoketones. The "unmasked" *β*-aminoketones are produced in a one-pot oxidation sequence, which can also yield a Boc-protected amine if desired by incorporation of a further $(Boc)_2O$ reagent in the sequence.



R	R'	Temp	Yield (%)	ee (%)
2-napth	Ph	-5	88	98
2-napth	Me	-5	94	92
$NO_2C_6H_4CH$=CH	Ph	-5	98	92
PhC≡C	Ph	4	93	92
PhC≡C	Me	-5	91	88

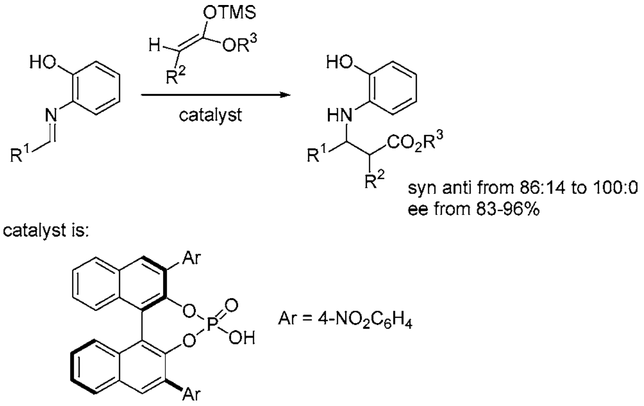


The imine can be preformed by mixing the aldehyde and 2-methoxyaniline in the presence of the silylenol ether and catalysts, and moderate to good yields of the desired protected β-amino-ketone (41−60%) ensue, with high enantiomeric excess (92−94%).

The process looks scaleable, the only disadvantage for the process chemist being the need to remove the methoxyaniline protection group in a three-reaction sequence. The ligand for the process has previously been used by the Snapper−Hoveyda group in related cycloadditions (Josephsohn, N. S. et al. *J. Am. Chem. Soc.* **2003**, *125*, 4018).

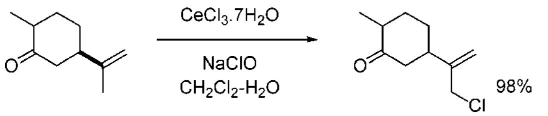
Enantioselective Mannich Reaction Catalysed by a Chiral Brønsted Acid

An alternative to the use of chiral Lewis acids is to use a chiral Brønsted acid such as a phosphoric acid derivative formed from a BINOL-type compound (Akiyama, T. et al. *Angew Chem., Int. Ed.* **2004**, *43*, 1566).



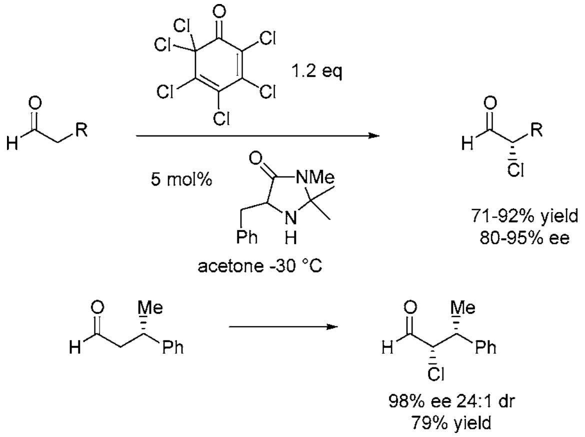
Allylic Chlorination

A simple chlorination method which avoids the use of chlorine itself is to use a combination of cerium trichloride heptahydrate and sodium hypochlorite in a two-phase (dichloromethane−water) system. Best results are with 3 equiv of the reagent, which seems wasteful, but with only 2 equiv many reactions do not go to completion (Moreno-Dorado, F. J. et al. *Tetrahedron Lett.* **2003**, *44*, 6691). The procedure is suitable for acid-sensitive substrates where the previously reported NaOCl−acetic method fails (Van Brunt, M. P. et al. *J. Org. Chem.* **2003**, *68*, 3323).

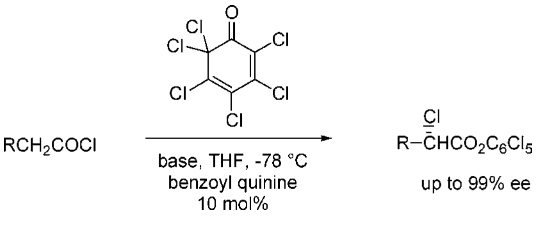


Direct Enantioselective Organocatalytic α-Chlorination of Aldehydes

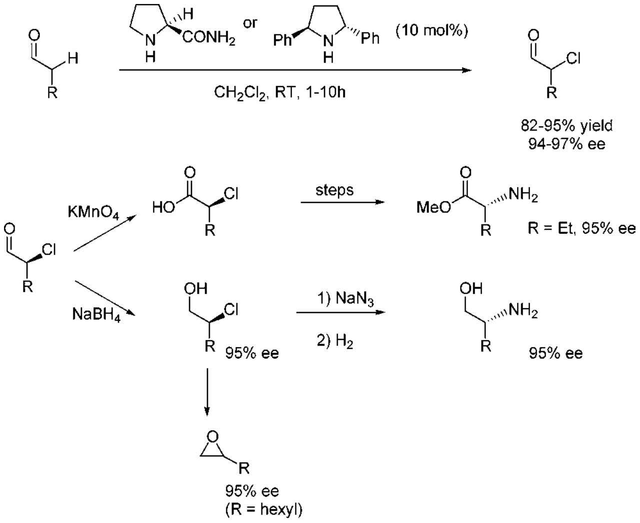
Following on from previous successes in organocatalytic enantioselective processes, the group of MacMillan at CalTech has now reported an efficient α-chlorination of aldehydes (Brochu, M. P. et al. *J. Am. Chem. Soc.* **2004**, *126*, 4108). Initial results with *N*-chlorosuccinimide as the chlorinating agent gave a good conversion but little selectivity; use of the Leckta quinone in the presence of amine catalyst, however, gave excellent results. The reaction can be used on chiral aldehydes to get diastereoselective products.



In the same issue appeared the full paper from the group of Leckta on enantioselective chlorination of acid halides (France, S. et al. *J. Am. Chem. Soc.* **2004**, *126*, 4245). The chlorinating agent is easily made in quantitative yield by treating pentachlorophenol with *tert*-butyl hypochlorite. The reactions with acid chlorides, in the presence of base, proceed via ketenes.



In the following issue of *J. Am. Chem. Soc.* the group of Jorgensen at Aarhus, Denmark, who are also extremely active in organocatalysis, also report on α-chlorination of aldehydes (Halland, N. et al. *J. Am. Chem. Soc.* **2004**, *126*, 4790). In this paper the inexpensive *N*-chlorosuccinimide is used as the reagent. The process gives good yield and ee, but organocatalyst and solvent need to be optimised. Best results were in dichloroethane or dichloromethane, whereas ethanol and THF gave inferior results. Use of DMSO, often a good solvent for organocatalytic reactions, resulted in a racemic product. The best catalysts are shown in the Scheme. The α-chloroaldehydes were converted into a variety of products without loss of stereochemistry.

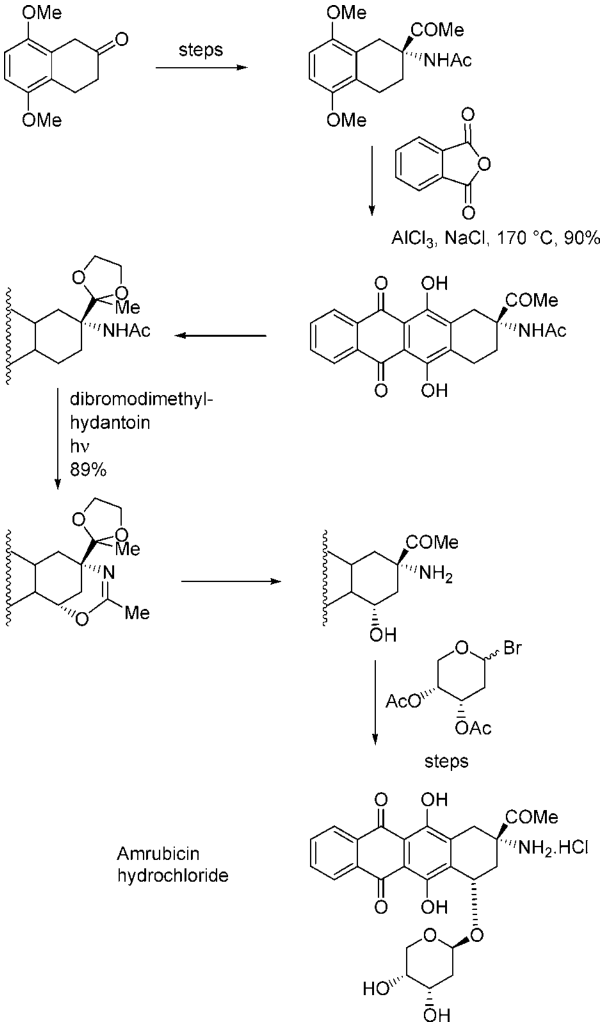


Thematic Issue on Enantioselective Catalysis

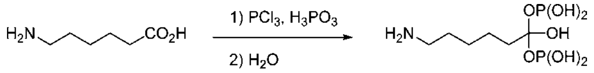
Issue No 8, volume 103 of *Chemical Reviews* was a thematic issue, which should be of interest to those chemists developing enantioselective catalytic processes. Of particular industrial interest may be the reviews on asymmetric Strecker reaction, chiral phase-transfer catalysis, and hydrogenation, but there are another 19 reviews well worth looking at.

Synthetic Approaches to the 2002 New Drugs

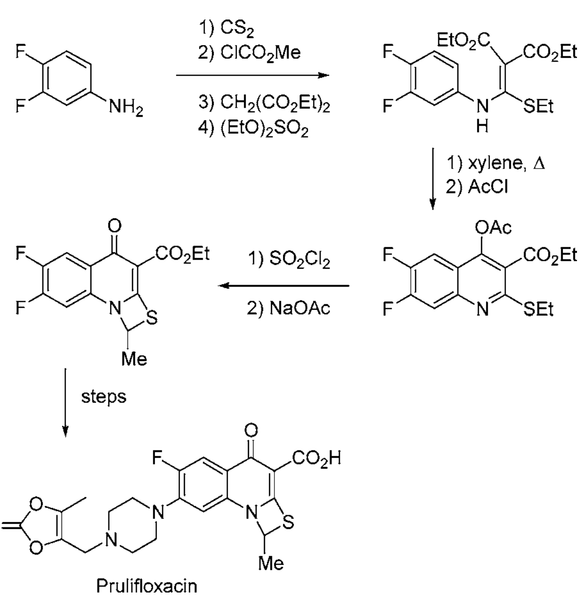
This review analyses the new drugs for which marketing approval was given in 2002 and discusses the synthetic routes used to make them (Li, J. et al. *Mini-Reviews on Medicinal Chemistry* **2004**, *4*, 207). In 2002 33 new chemical entities (including biological drugs) and two diagnostic agents reached the market. The review covers the 28 chemical drugs, based on published and patented syntheses. Looking at some of the syntheses listed and the reagents and solvents used (benzene, silver triflate, etc.), it is clear that the commercial synthesis has not been published. What is clear is that the complexity of the drugs is increasing. For example, the first anthracycline anticancer antibiotic produced by purely synthetic methods, amrubicin hydrochloride (Calsed), was launched by Sumitomo. The key steps are shown in the scheme.



On the other hand, there is a very simple synthesis of the bisphosphonate drug neridronate (Nerixia) marketed by Abiogen Pharma. This is the first treatment ever for osteogenesis imperfecta. The simple synthesis is shown below:

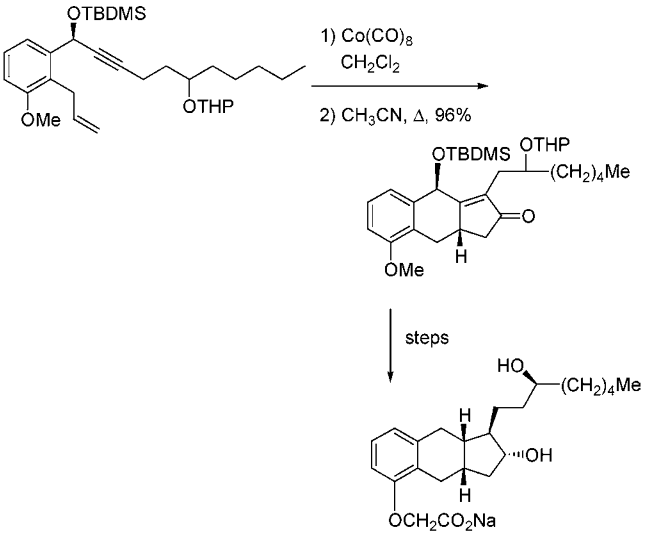


In contrast the fluoroquinolone antibiotic Prulifloxacin from Nippon Shinyaku contains an unusual four-membered



ring which is neatly constructed as shown in the scheme.

The key step in the synthesis of the prostacyclin analogue, treprostinil sodium (Remodulin), developed by United Therapeutics is a Pauson−Khand reaction.



treprostanil sodium

The authors of this lengthy article (from Pfizer R&D, Groton), have done an excellent job in summarizing this information in a highly readable format. It is hoped that they will repeat this on an annual basis.

Salts of Aprotic Polar Solvents

When working with the strong protic acids triflic acid CF_3SO_3H and bis(trifluoromethane-sulphonyl) imide $(CF_3SO_2)_2NH$ in polar solvents, some surprising new salts were found. For example treating DMF in dichloromethane with triflic acid at room temperature gives, after 5 min, a precipitate of the DMF triflate salt. Similar salts could be prepared from acetonitrile and DMSO (but not nitromethane), but not all of these salts were crystalline. With THF, polymerisation of the solvent occurred. In general, the salts were noncorrosive and stable. I wonder if they could be used as ionic liquids? (Favier, I. et al. *Tetrahedron Lett.* **2004**, *45*, 3393).

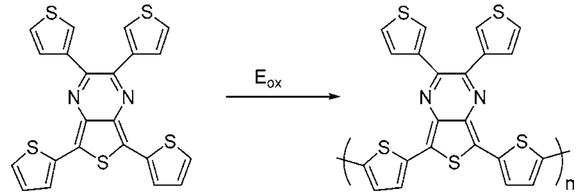
Microwave-Assisted Synthesis: A Critical Technology Overview

An excellent review of the subject has appeared (Nuchter, M. et al. *Green Chem.* **2004**, *6*, 128). The authors focus very much on reaction engineering, but scale-up is also discussed. The authors describe a pilot-plant continuous process for the esterification of linalool with various anhydrides, although yields of around 50% would seem on the low side. Workup includes a reactive distillation step which drives the process through to a more acceptable 85% yield.

Microwaves are also used in the acylation of tocopherols to give the commercial form of vitamin E, tocopheryl acetate. This reaction can be carried out continuously on kilogram scale with a high yield and thus is of great commercial interest.

A Novel Heterocyclic System Useful in Devices

These highlights reflect the interests of the three authors who focus mostly on synthetic methods which are of use in the pharmaceutical industry, where complex molecules are the norm. Another industry in which complex chemistry and purity requirements can be even more demanding is the electronics industry. Current research is examining novel organic structures, either as monomers or as polymers for various device applications. Three primary colours (red, blue, and green) are required for commercial electrochromic applications, and whereas red- and blue-reflecting organics have been obtained, a green-reflecting compound (in the neutral state) has been found difficult to prepare. A recent paper describes the application of a new green-reflecting polythiophene derivative, which may now enable commercial use of these devices (Sonmez, G. et al. *Angew Chem., Int. Ed.* **2004**, *43*, 1498).



dark purple

Hazards of Supported Catalyst Preparation

A letter in the final issue of 2003 of *Chemistry in Britain* (December 2003, p 12) highlights the dangers of preparation of gold catalysts, which are now being used in a number of processes. In two recent papers where the catalyst is prepared by hydrolysis/deposition using $HAuCl_4$ and ammonium carbonate (Fu et al. *Chem. Eng. J.* **2003**, *93*, 41) or ammonia (Xu et al. *Catal. Lett.* **2003**, *85*, 229) it is now suggested that these procedures may risk making fulminating gold, which is explosive and shock sensitive. You have been warned!

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