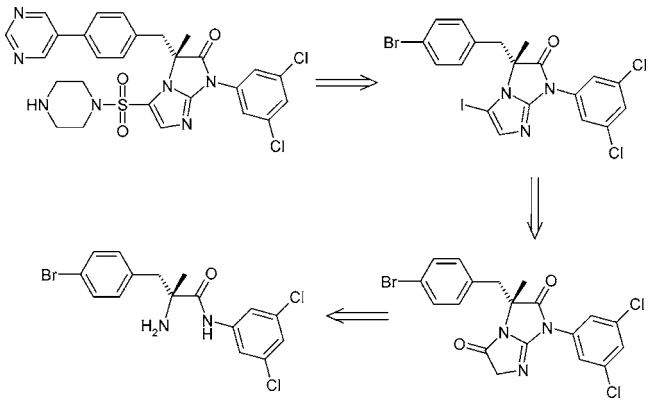
Organic Process Research & Development **2003**, *7*, 776–783

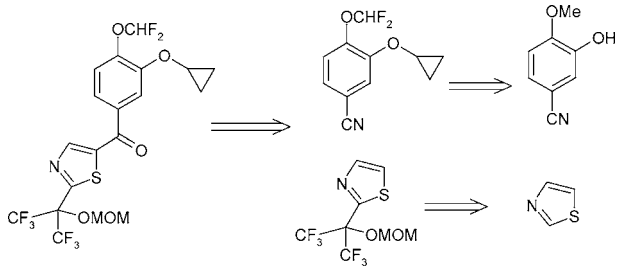
Highlights from the Literature

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

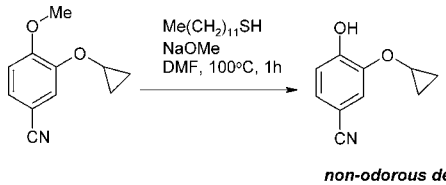
Second Generation LFA-1 Inhibitors. Frutos and Johnson from Boehringer Ingelheim report (*Tetrahedron Lett.* **2003**, *44*, 6509) their synthetic efforts towards a new class of LFA-1 (lymphocyte function-related antigen) inhibitors. The highlights of their approach are shown (below) in the retrosynthetic sense and include transformation of the amino amide into the iodide, an advanced intermediate in the sequence towards 1H-imidazo[1,2-α]imidazol-2-ones.



Thiazole Ketone Synthesis. Frey and co-workers from Merck describe (*Tetrahedron* **2003**, *59*, 6363) how the highly functionalised thiazole ketone was prepared via addition of a thiazole anion to an aromatic nitrile in good overall yield after hydrolysis.

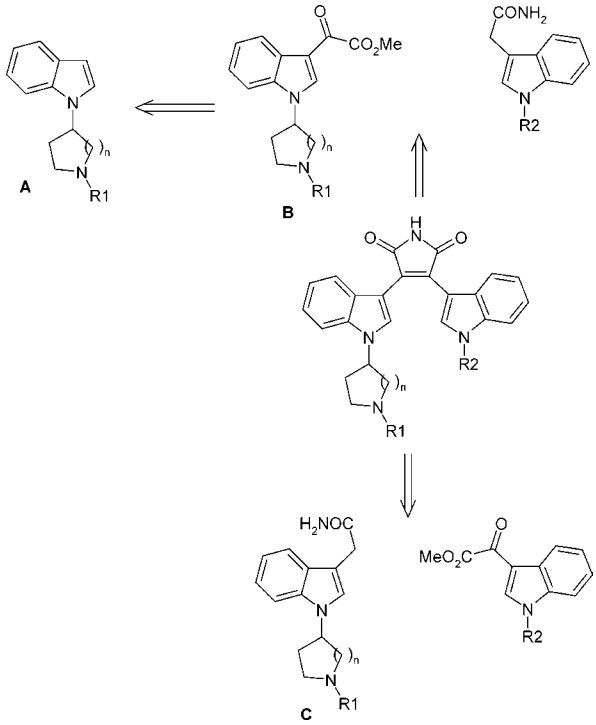


The group go on to explore the generality of the approach providing access to a variety of thiazole ketones. In addition the group describe a nonodorous demethylation reaction substituting traditional sodium ethanethiolate for the dodecane equivalent (see the following scheme)



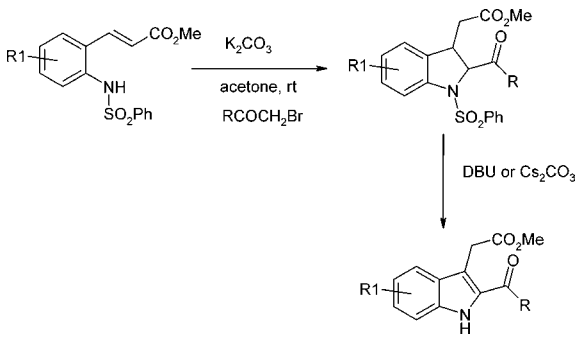
non-odorous deprotection

Approaches to *N*-(Azacycloalkyl)bisindolylmaleimides. *N*-(Azacycloalkyl)bisindolylmaleimides (see below)



have been identified to be selective inhibitors of PKC. Faul and colleagues from Lilly report (*Tetrahedron* **2003**, *59*, 7215) their synthetic approaches employed to prepare this class of compounds that resulted in development of efficient methods for preparation of *N*-(azacycloalkyl) indole **A**, indole-3-acetamide **C**, and indole-3-glyoxylate ester **B** derivatives.

2-Acylindole-3-acetic Acids. On the theme of indoles, Stevens and colleagues from Pfizer at the Nagoya laboratories describe (*Tetrahedron Letters*, **2003**, *44*, 7269) an efficient and expedient synthetic route to 2-acylindole-3-acetic acids. Their approach is outlined in the scheme



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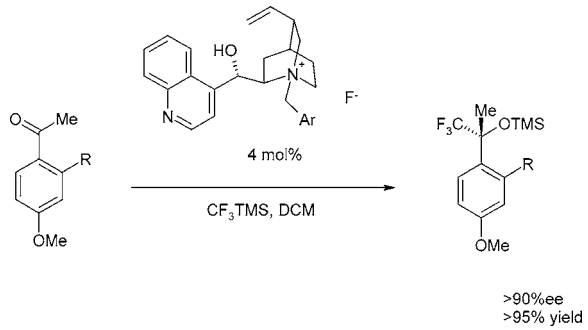
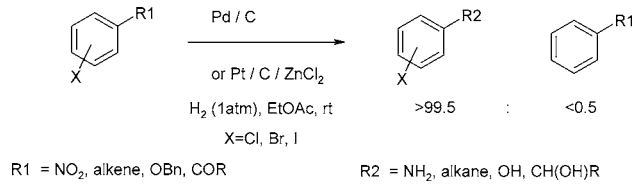
and utilises a one-pot room-temperature indole ring construction via the in situ generation of indoline intermediate.

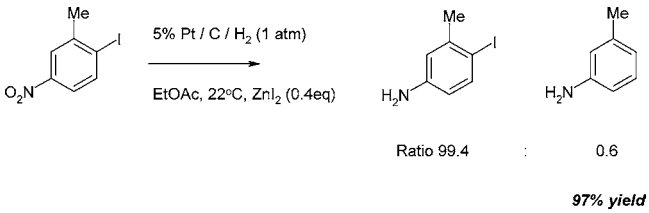
Enantioselective Addition of a Trifluoromethyl Anion to Aryl Ketone. The identification and development of a catalyst for the enantioselective nucleophilic addition of a trifluoromethyl anion to a ketone is described by Caron and co-workers from Pfizer (*Synthesis* **2003**, 1693). The easily prepared cinchonine-derived catalyst was used in amounts as low as 4 mol % to afford enantiomeric excess as high as 92%.



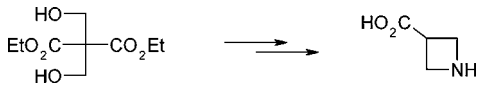
ZnX_2-Modulated Pd/C and Pt/C Catalysts. Novel ZnX_2-modulated Pd/C and Pt/C catalysts have been developed by Wu and colleagues at the Schering Plough research institute (*Synthesis* **2003**, 1657) to chemoselectively hydrogenate halogen-substituted nitroarenes, alkenes, benzyl ethers, and aromatic ketones.



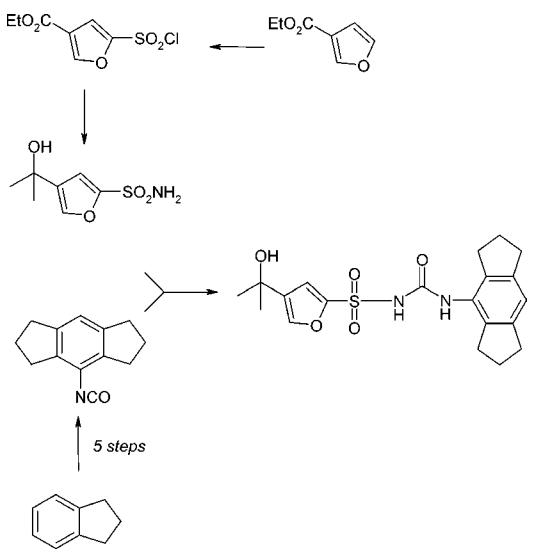
Of notable interest is that the group report one of the first examples of a highly chemoselective hydrogenation of iodonitroarenes to the amine (following scheme) using ZnI_2 to modulate the catalyst reactivity.



Azetidine-3-carboxylic Acid. Azetidine-3-carboxylic acid is a β-amino acid used for the preparation of a variety of pharmaceutically active compounds. A practical and convenient synthesis of azetidine-3-carboxylic acid from commercially available diethylbis(hydroxymethyl)malonate is reported by Miller et al from Merck (*Synth. Commun.* **2003**, 3347). Azetidine ring-formation was achieved in high yield by cyclization of bistriflate of the diol and benzylamine. Decarboxylation under carefully pH-controlled conditions gave the mono acid azetidine that was hydrogenated to give the target amino acid.

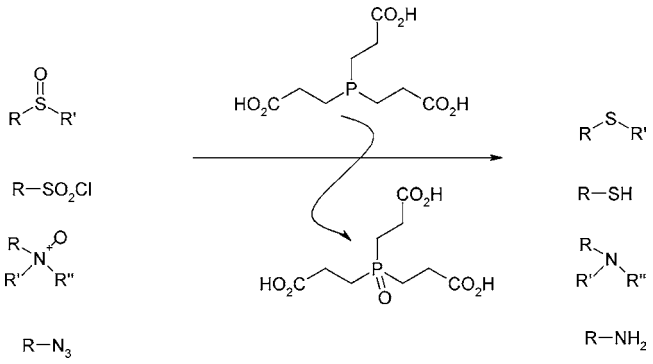


Synthesis of Antiinflammatory Agent. A novel synthesis of the antiinflammatory agent 1-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)-3-[4-(1-hydroxy-1-methyl-ethyl)-furan-2-sulfonyl] urea has been reported by Urban and colleagues from Pfizer (*Synth. Commun.* **2003**, 2029). The key sulfonamide was prepared starting from ethyl 3-furoate via a one-pot sulfonylation with chlorosulfonic acid in methylene chloride followed by pyridinium salt formation and reaction with phosphorus pentachloride to provide ethyl 2-(chlorosulfonyl)-4-furoate. This sulfonyl chloride was treated with ammonium bicarbonate to form sulfonamide, followed by treatment with excess methylmagnesium chloride to provide 4-(1-hydroxy-1-methyl-ethyl)-furan-2-sulfonamide. 4-Isocyanato-1,2,3,5,6,7-hexahydro-*s*-indacene was prepared from indan in five steps. The desired sulfonyl urea was formed via coupling of the sodium salt of the sulphonamide and the isocyanate (formed by addition of the aniline to di-*tert*-butyl dicarbonate and DMAP at room temperature). This chemistry has been utilised by the group on >100-kg scale.

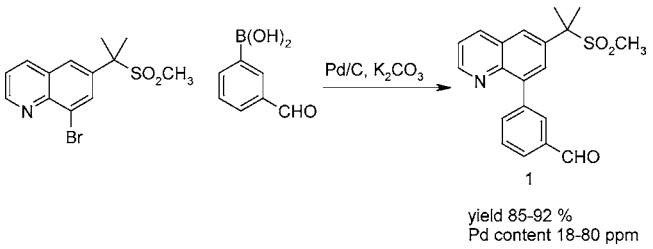


Phosphine Reductions. Tris(2-carboxyethyl)phosphine (TCEP) has been shown by Farcher and Grand-Maitre (*Synth. Commun.* **2003**, 3503) to efficiently reduce sulfoxides, sulfonyl chlorides, *N*-oxides, and azides with significant practical value in excellent yields. TCEP is particularly attractive compared to other trialkylphosphines because it is an air-stable and odorless solid. Also, this phosphine and its corresponding oxide are water soluble, thus facilitating a

clean isolation of the desired end-product using simple aqueous/organic extraction procedures.

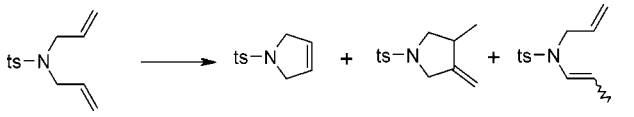


Suzuki−Miyuara Coupling with Quasi-heterogeneous Palladium. Merck process group has published a detailed study of the Pd/C-catalyzed Suzuki-Miyaura reaction for the synthesis of **1**, which was obtained in excellent yield with low levels of residual palladium after simple filtration and precipitation (Conlon, D. A. et al., *Adv. Synth. Catal*. **2003**, *345*, 931). The low level of residual palladium is an important criterion for pharmaceuticals and the use of a heterogeneous catalyst is motivated by the ease of separation. It was found that palladium was dissolved from the solid support during the oxidative addition step. The soluble palladium concentration increases during the reaction reaching a maximum at ca. 90% conversion before falling to <4 ppm after completion of the reaction. The time to reach such a low level of dissolved palladium was found to be dependent on the base, the amount and type of carbon support, and the time elapsed between reaction completion and product isolation.

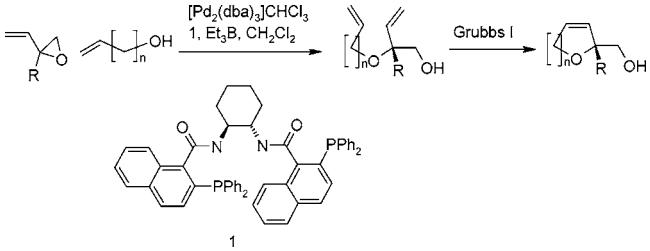


A Practical High-Throughput Screening System for Enantioselectivity by FTIR Spectroscopy. Reetz, M. T. et al. (*Chem. Eur. J*. **2003**, *9*, 3882) have for the first time applied FTIR spectroscopy to the measurement of enantiomeric purity. The underlying concept is based on the use of pseudoenantiomers that are ^{13}C-labeled at appropriate positions. Upon applying Lambert−Beer's law in the determination of the concentrations of both enantiomers, the enantiomeric excess values are accessible with an accuracy of ±5%. The application of commercially available high-throughput FTIR system allows a throughput of up to 10 000 samples per day. This method could be of interest in the area of combinatorial asymmetric catalysis.

Synthesis and Utilization of Protic Imidazolium Salts in Homogeneous Catalysis. M. Picquet et al. (*Adv. Synth. Catal*. **2003**, *345*, 959) have synthesized and studied protic 1-alkylimidazolium salts as ionic liquid solvents for the dimerization of methyl acrylate and ring-closing metathesis (RCM) of *N*,*N*-diallyltosyl amide with cationic ruthenium allenylidene complexes. Protonation of 1-alkylimidazoles provides halogen-free salts which act as ionic liquids and proton reservoir in proton- and metal-assisted catalytic processes and lead to significant improvements in activity and selectivity. In the RCM of *N*,*N*-diallyltosyl amide with cationic ruthenium allenylidene complexes it was found that, when 1-butylimidazoliumtriflate (HBIM-OTf) was used as solvent for the reaction, the reaction was completed within 15 min at 34 °C with 100% selectivity for the 2,5-dihydropyrrole. This reaction has previously been performed in toluene at 80 °C with a reaction time of 1 h or in ionic liquids where the reaction is sluggish and nonselective. The reaction product was easily extracted from HBIM-OTf with ether. The obtained yield was 97%.



Asymmetric Synthesis of Oxygen Heterocycles via Pd-Catalyzed Dynamic Kinetic Transformations. Trost, B. M. et al. *Chem. Eur. J*. **2003**, *9*, 4442) have developed an asymmetric allylic alkylation (AAA) of racemic butadiene and isoprene monoepoxide with unsaturated alcohols in the presence of a chiral palladium catalyst and a boron cocatalyst to give 3-alkoxy-4-hydroxy-1-butene and 3-alkoxy-4-hydroxy-3-methyl-1-butene, respectively, with excellent regio- and enantioselectivity in a dynamic kinetic asymmetric transformation whereby both enantiomers of the starting epoxide provides the same enantiomeric product, which is an ideal substrate for the Ru-catalyzed ring-closing metathesis. In this way five-, six-, and seven-membered oxygen heterocycles are readily available enantiomerically pure in a simple two-step process. The process has been used for the synthesis of unnatural and unusual nucleosides, which are not readily accessible by other means.



Development of Modular Dipeptide-Analogue Ligands for Ruthenium-Catalyzed Enantioselective Transfer Hydrogenation of Ketones. A library of novel dipeptide analogue ligands based on the combination of *tert*-butoxycarbonyl (*N*-Boc)-protected α-amino acids and chiral vicinal amino alcohols have been prepared by Adolfsson et al. (*Chem. Eur. J*. **2003**, *9*, 403). These highly modular ligands

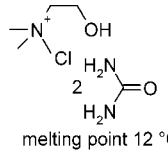
were combined with $[RuCl_2(p\text{-cymene})]_2$, and the resulting metal complexes were screened as catalysts for the enantioselective reduction of acetophenone under phase-transfer hydrogenation conditions using 2-propanol as hydrogen donor. Several of the catalysts gave very good enantioselectivity of 1-phenylethanol (up to 98%). Although most of the ligands contain two stereo centers, it was found that the absolute configuration of the product was determined by the configuration amino acid part. The combination of *N*-Boc-L-alanine and (*R*)-phenyl glycinol (**Boc-L-Ab**) and its enantiomer N−Boc-D-alanine and (S)-phenylglycinol (**Boc-D-Aa**) were found to be the best ligands for the hydrogenation process giving very high yield (99%) and enantioselectivity (94%). Also the transfer hydrogenation of other alkyl aryl ketones were studied, giving moderate to good yields and high to excellent enantioselectivities.

Baeyer−Villiger Monooxygenases, an Emerging Family of Flavin-Dependent Biocatalysts. Baeyer−Villiger monooxygenases (BVMOs) are flavoenzymes that catalyze a remarkably wide variety of oxidative reactions such as regio- and enantioselective Baeyer−Villiger oxidations and sulfoxidations. Several of these conversions are difficult to achieve using chemical approaches. Due to their selectivity and catalytic efficiency, BVMOs are highly valuable biocatalysts for the synthesis of a broad range of fine chemicals. For a long time, only one member of this class of biocatalysts had been cloned and overexpressed which has limited their application for synthetic processes. Recently,though, a number of new genes that encode BVMOs have been sequenced and overexpressed. Kamerbeek, N. M. et al. (*Adv. Synth. Catal.* **2003**, *345*, 667) have summarized the biocatalytic properties of these new BVMOs.

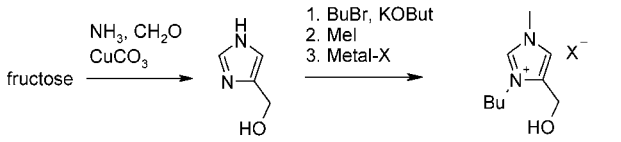
Combinatorial Design of Copper-Based Mixed Nanoclusters Useful For The Suzuki Cross-Coupling. Rothenberg, G. et al. (*Adv. Synth. Catal.*, **2003**, *345*, 979) have found that nanoclusters of copper or copper/ palladium mixtures are good catalysts for the Suzuki cross-coupling. The catalysts are applicable to a wide range of iodo- and bromoarenes and give moderate yields with chloroaryl substrates.Cluster activity and stability was found to be strongly dependent on the preparation method and the reaction conditions used for the cross-coupling It was found that tetraoctylammonium ions on the surface of the nanoclusters gave a stabilizing effect on the clusters. The bimetallic Cu/Pd cluster was found to be active for a wide range of substrates.

Supported Rhodium Nanoparticles in Catalysis: The Role of Stabilizers on Catalytic Activity. Rhodium nanoparticles supported on γ-Al_2O_3, derived from arene solvated Rh atoms stabilized by trioctylamine (TOA), are valuable catalysts in hydrogenation and silylformylation reactions (Vitulli, G. et al. *J. Organomet. Chem.* **2003**, *681*, 37). They are more active than the analogous commercial catalyst, as well as sample similarly prepared in the absence of TOA. HRTEM measurements, IR studies on absorbed CO species, and X-ray absorption fine structure analysis all showed the role of TOA in controlling the particle growth in the preparative process and in stabilizing the resulting Rh particles against erosion by CO or oxidation. It was found that although the particles have a medium size of 1.1 nm the IR spectrum after CO admission only contained bands from Rh(0) species. In the cases where no TOA was used in the preparation of the nanoparticles or commercial catalyst the IR spectrum showed mainly Rh(I) bands from Rh(I) carbonyl species.

Room-Temperature Ionic Liquids from Biorenewable Sources. Handy, S. T. (*Chem. Eur. J.* **2003**, *9*, 2938) has summarized the work done on biorenewable room-temperature ionic liquids (RTILs) over the last 5 years. RTILs have attracted a great deal of attention as environmentally benign solvents for organic synthesis. The imidazole-derived RTILs are used as substitute for "inert" conventional solvents, but there is an opportunity to get chiral or functionalized (protic or Lewis basic) RTILs as catalytic solvents for instance acylation reactions. In many cases, these new solvents are based on the modification of natural products. These new interesting materials are only the beginning of what could be an exciting new area of designed solvents.

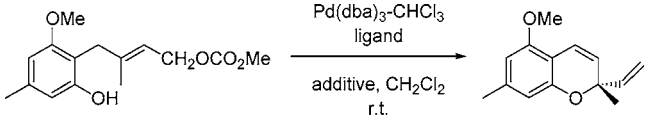


melting point 12 °C

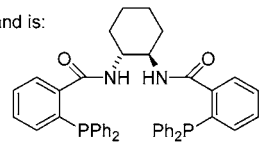


overall yield 64 %

Unusual Additive Effects on the Enantiomeric Excess of Products from Asymmetric Alkylations. Although good yields could be obtained in the cyclisation of 2-substituted phenols to chromans, the enantiomeric excesses were low when a variety of chiral ligands were used. However, a dramatic increase in ee was observed when 1 equiv of acetic acid was added (Trost, B. M. et al. *J. Am. Chem. Soc.* **2003**, *125*, 9276). The absolute configuration of the product was also reversed. Benzoic acid gave similar results, whereas for phosphoric acid this was similar to the result when no additive was present. The reaction has been applied to a wide range of substrates.



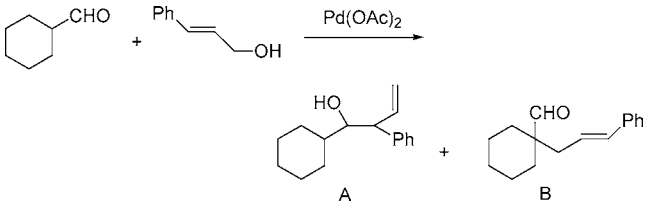
ligand is:



	Yield	ee
no additive	95%	-14
Et_3N	96	-22
AcOH	94	+84
$PhCO_2H$	98	+75
H_3PO_4	99	-5
$Bu_4N^+OAc^-$	99	+66
$Bu_4N^+Cl^-$	40	+63

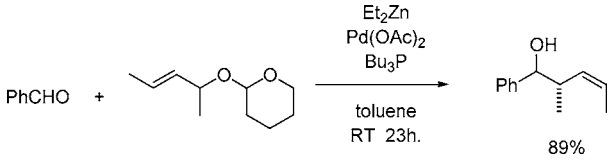
Palladium-Catalysed Nucleophilic Alkylation of Aldehydes with Allylic Alcohols and Ethers. Nucleophilic

alkylation of an aromatic aldehyde has been achieved using allylic alcohols in the presence of Et_3B and a palladium catalyst. Whilst this reaction does not work for aliphatic aldehydes, it has now been shown that replacement of Et_3B by Et_2Zn can now effect selective alkylation (Kimura, M. et al. *Angew. Chem., Int. Ed.* **2003**, *42*, 3392).

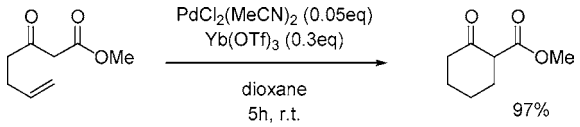


RM	phosphane	solvent	time	A (%)	B (%)
Et_3B	PPh_3	THF	4	39	30
Et_3Zn	PPh_3	THF	30	18	0
Et_3Zn	PBu_3	Tol	30	79	0

Under similar conditions, aromatic aldehydes can be alkylated exclusively to give the *Z* product using tetrahydropyranyl ethers.

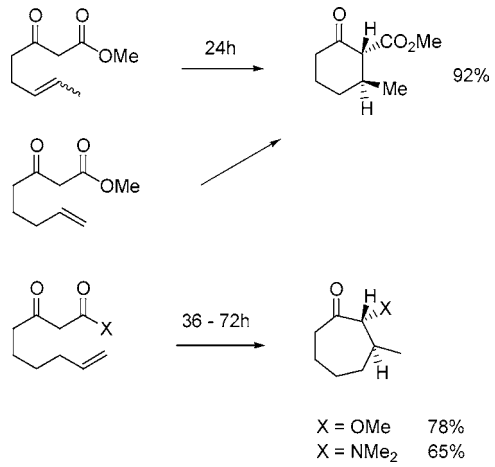


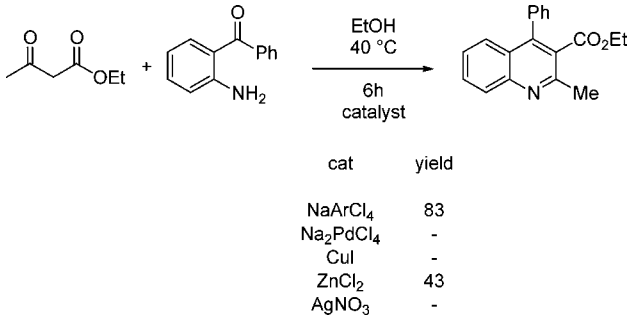
Lanthanide Triflate-Promoted, Palladium-Catalysed Cyclisations. Last year, it was reported that alkenyl-1,3-diketones would cyclise to six-membered rings in the presence of a palladium catalyst, the key being to have TMSCl present which forms an intermediate silylenol ether (Pei, T. et al. *Chem. Commun.* **2002**, 650). The group of Dan Yang in Hong Kong has now found that ytterbium triflate can be used instead of TMS chloride, and the rate and yields improve (Yang, D. et al. *Org Lett.* **2003**, *5*, 2869).



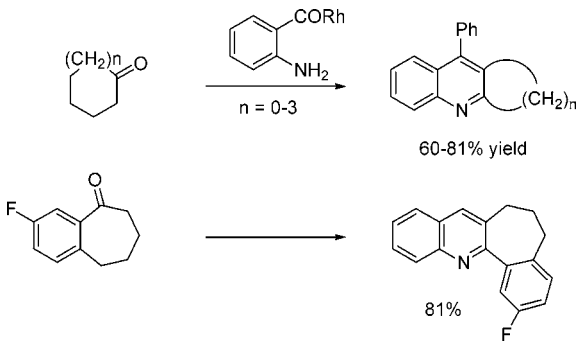
The reaction works best for six-membered rings, but seven- and eight-membered rings can be formed in lower yields. The ring junction is always trans in the final product, no matter what the stereochemistry of the starting olefin is.

A New Green Approach to the Friedlander Synthesis of Quinolines. The Friedlander synthesis of quinolines is an excellent method on small scale, but the harsh conditions required (high temperatures, acid catalysis, sometimes no solvent) often lead to reduced yields on scale-up. It has now been found (Arcadi, A. et al. *Syn. Lett.* **2003**, 202) that a catalytic amount of a gold catalyst allows the reaction to be carried out under milder conditions.



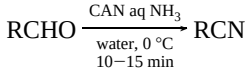


Cyclic ketones and diketones can also be used to generate interesting new fused heterocyclics.



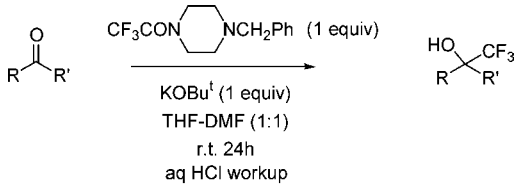
Preparation of Nitriles from Aldehydes. There are many methods of making nitriles from aldehydes, the most common being dehydration of oximes, but other methods which work well for aromatic aldehydes are not suitable for enolisable aliphatic aldehydes. Many researchers have tried to use ammonia in conjunction with an oxidising agent, but many of these methods are not general and have limitations. An Indian group (Bandgar, B. P. et al. *Syn. Lett.* **2003**, 262) have described a simple procedure involving treatment of an aldehyde with ammonia and ceric ammonium nitrate in water at 0°C. The procedure works for aliphatic, aromatic, heteroaromatic, $\alpha\beta$-unsaturated, and carbohydrate aldehydes—no protection of the alcohol groups is necessary. For

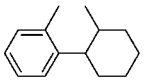
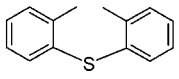
solid products the nitrile is simply filtered off after the reaction.



R	yield
Et	89
Pr	88
Bu	90
Ph	90
$HOC_6H_4^-$	94
furyl	90
PhCH═CH	87
deoxyribose	97 (after acylation)

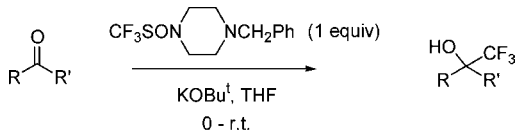
Trifluoroacetic Acid Derivatives as Nucleophilic Trifluoromethylating Agents. The introduction of the CF_3 group into organic molecules is commonly achieved by anionic means, often via the use of trifluoroacetaldehyde derivatives, such as aminals. Since trifluoroacetaldehyde (fluoral) is usually produced by reduction of the acid, it would be more useful if acid derivatives could be used for anionic trifluoromethylation. Treatment of secondary trifluoro acetamides and trifluoroacetate esters with base yields CF_3 anion, but initial experiments showed that on reaction with benzophenone, good yields could only be obtained with THF/DMF as solvent and potassium *tert*-butoxide as base (Jablonski, L. et al. *Syn. Lett.* **2003**, 230). Subsequently it was found that THF could be used as solvent if a crown ether was added. Best results were obtained with the *N*-benzylpiperazine amide of trifluoroacetic acid.



R	R'	Yield
Ph	Ph	95
Ph	2-pyridyl	95
		95
		60
Ph	2-thienyl	10
Ph	H	0

In the following paper (Inschauspe, D. et al. *Syn. Lett.* **2003**, 233) from the same group in Lyon, France, the reaction of the corresponding sulphinimides is reported to give excellent yields with some aldehydes, although poorer yields with benzophenone are obtained.

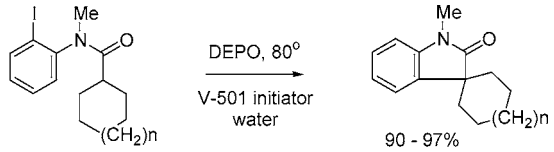
Radical Cyclisation without Tin. Carbon−carbon bond formation via radical intermediates is an attractive synthetic method, but the usual tin reagents are not suitable for large-scale synthesis for environmental reasons. Therefore, there has been a drive to find alternative reagents. Tris(trimethylsilyl)silane has a similar, but not identical, range of reactivity to tributyltin hydride, but it is expensive. Phosphorus compounds such as hypophosphorous acid and its salts are receiving attention, since they are cheap and can be used in water or organic solvents. However, they are often used in excess, and there can be an issue of waste products with these reagents.



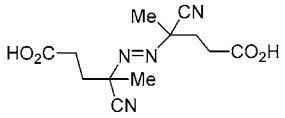
R	R'	Yield
Ph	Ph	75
Ph	2-pyridyl	80
PhCH=CH	Ph	53
Ph	H	80
2-quinolyl	H	40
6-methoxy-2-naphthyl	H	91
N-methylpyrrole	H	75

The group of Murphy at University of Strathclyde in Scotland has recently found that diethylphosphine oxide (DEPO) prepared by addition of ethylmagnesium bromide to diethyl phosphite is an excellent reagent for the cyclisation of *o*-iodoanilides to indolones (Khan, T. A. et al. *Org. Lett.* **2003**, *5*, 2971).

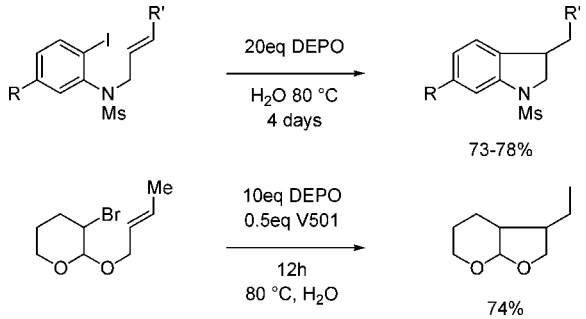
The byproduct, diethylphosphinyl iodide is easily converted to diethylphosphinic acid ($pK_a = 3.29$) and is easily separated from products and reagent DEPO ($pK_a = 6.0$).



V-501 is

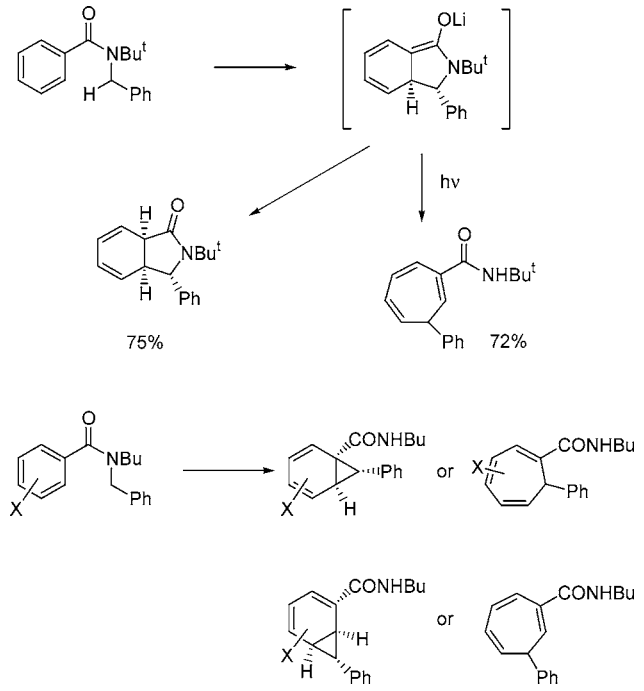


Radical cyclisations to olefins can also be accomplished, but the reactions are slow at 80°C in water and require a large excess of reagent. However, workup is relatively simple.

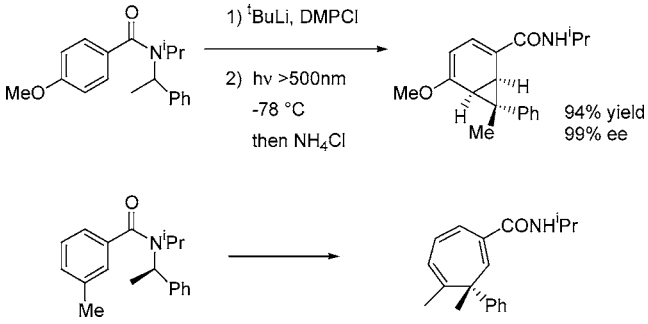


Perhaps a change of solvent, slightly higher temperatures, or microwave conditions may shorten the reaction time.

Ring Expansion of Lithiated Benzamides. The group of Clayden at the University of Manchester are producing some novel chemistry using simple molecules. An earlier communication (Ahmed, A. et al. *Chem. Commun*. **1999**, 231) reported on the cyclisation of lithiated benzamides to tetrahydroisoindolinones, whereas the most recent report (Clayden, J. et al. *J. Am. Chem. Soc*. **2003**, *125*, 9278) shows that the same lithiated benzamides can, under photochemical conditions, give ring expansion. Similar treatment of substituted derivatives led to related, but not always identical, rearrangements. The four classes of compounds fall into two pairs of regioisomers related by a disrotatory thermal electrocyclisation.

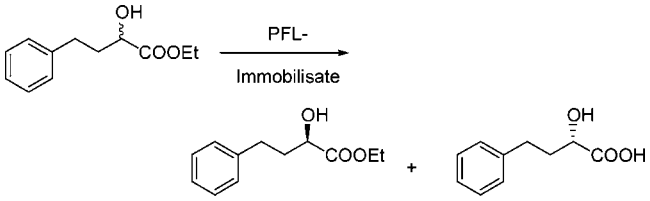


Introducing chirality into the system allowed the generation of complex molecules in simple enantiomer form in a simple manner.



Immobilising Enzymes: How to Create More Suitable Biocatalysts. A two-page Highlight article on this topic discusses ways in which enzymes, on immobilisation, can have substantially altered properties, with an increase in activity and enantioselectivity (Bornscheuer, U. T. *Angew. Chem., Int. Ed*. **2003**, *42*, 3336).

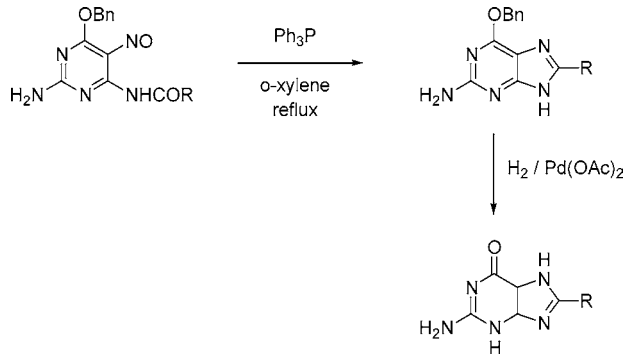
The table is a comparison of different "controlled" immobilisation techniques for a lipase from *Pseudomonas fluorescens* (PFL) in the resolution of a racemic carboxylic acid ester.



carrier	activity [U mg^{-1}]	ee [%]	enantioselectivity
- (native)	0.5	59	7
dextran-agarose	0.45	58	6.9
glyoxyl-agarose	0.35	74	20
IHA-octyl-agarose	3.5	92	79
IHA-decaoctyl-sepharose	3.4	92.5	86

Online Measurement of Crystalline Forms. Raman spectroscopy can now be used for the measurement insitu or online of the crystalline properties of molecules during manufacture, and this can give tremendous insight into how these processes operate on-scale. This improved understanding should lead to process improvement. For a short review of use of online Raman techniques see Clegg, I. et al. *Eur. Pharm. Rev.* **2003**, 56.

Improved Synthesis of Guanines. Purine and purine nucleosides continue to be of interest to the pharmaceutical industry, but their synthesis is not always straightforward, and yields can be low. It has now been found that phosphines can effect the cyclisation of nitroso amides in good yield (Xu, M. et al. *Chem. Commun*. **2003**, 1452).



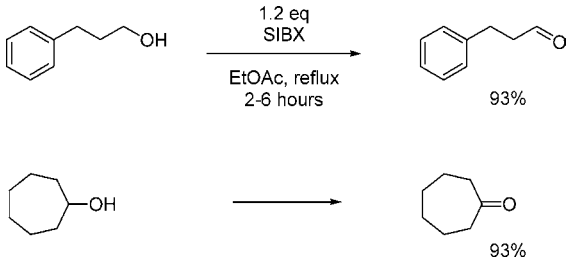
Stabilised Form of IBX for Safe Oxidation Reactions. Hypervalent iodine (V) reagents such as the Dess−Martin periodinane reagent and its precursor IBX continue to find new applications in synthesis. (For a review see Wirth, T. *Top. Curr. Chem*. **2003**, *224*, 185). Industrial applications, however, may be limited because both reagents suffer from major safety concerns related to their violent decomposition under impact and/or heating (see *Org. Lett*. **2002**, *4*, 3001). Modified IBX reagents have recently been introduced, but their preparation requires additional synthetic steps.

It has been found by workers at the French company Simafex, working with the University of Bordeaux, that a nonexplosive white powder formulation of IBX, composed of a mixture of benzoic acid (22%) isophthalic acid (29%)

and IBX (49%), can be produced and has been given the acronym SIBX (stabilised IBX) (Ozanne, A. *Org. Lett*. **2003**, *15*, 2903).

The new reagent allows the SAFE oxidation of alcohols to aldehydes and ketones in solvents such as NMP, THF, and ethyl acetate. Owing to the low solubility of SIBX, refluxing conditions are usually required. Most yields are comparable to the Dess−Martin reagent or IBX.

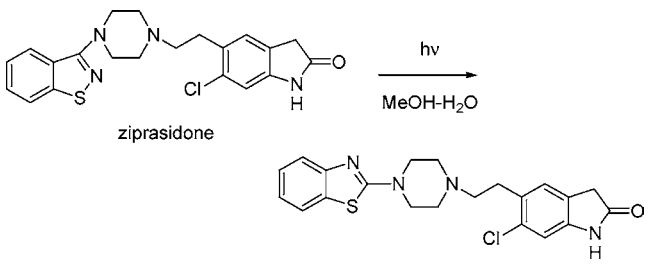
The new formulation is similar to IBX in that solvent oxidation (toluene → benzaldehyde and THF → ring-opened aldehydes) may occur on prolonged reflux. For less reactive substrates, ethyl acetate is often the best solvent.



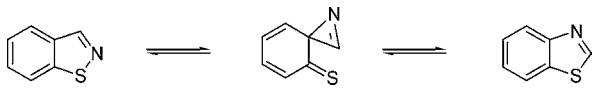
As with IBX, the byproduct, iodosylbenzoic acid, can be filtered off and recycled, using oxone as the oxidising agent.

For more details see the patent applications WO 02/057210 A1, PCT/FR02/00189 and U.S. 2002/0107416 (*Chem. Abstr*. **2002**, *137*, 109123). SIBX is available directly from SIMAFEX (contact Dominique.depernet@simafex.com or benoitj@simafex.com). Hopefully, smaller samples will become available via the "catalogue" companies.

Photoisomerisation of Ziprasidone. The antipsychotic drug substance, ziprasidone, recently approved by FDA and marketed by Pfizer, undergoes a clean conversion under photostability challenge to a new isomer, in which the benzisothiazole portion of the molecule converts to the corresponding benzthiazole (Sharp, T. R. et al. *Tetrahedron Lett*. **2003**, *44*, 1559). Analogues of the drug also undergo this isomerisation when irradiated.



The mechanism of this novel photo isomerisation is suggested below.



Diamond Formation by Reduction of CO_2 with Sodium. Perhaps industrial diamonds will become cheaper if a recent process reported by Chinese workers can be scaled (Lou, Z. et al. *J. Am. Chem. Soc*. **2003**, *125*, 9302). They have synthesised small diamonds (10−250 μm) by reduction of CO_2 with metallic sodium at 440 °C and 800 atm in a simple reaction autoclave. The reaction is sensitive to temperature, pressure, and stoichiometry—perhaps factorial designs should be used to optimise the process further.

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