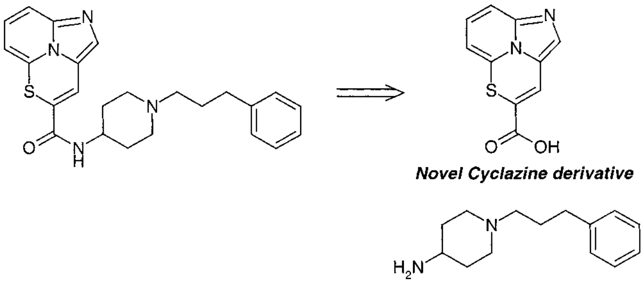
Organic Process Research & Development **2002**, *6*, 90–97

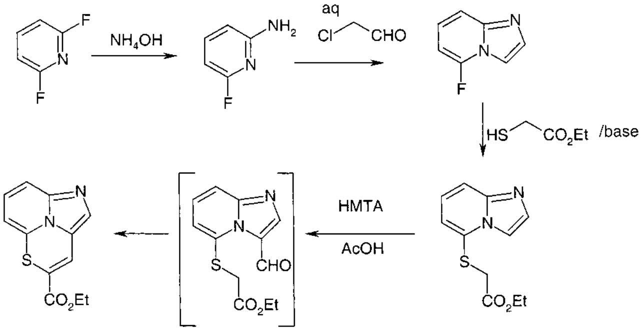
Highlights from the Literature

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

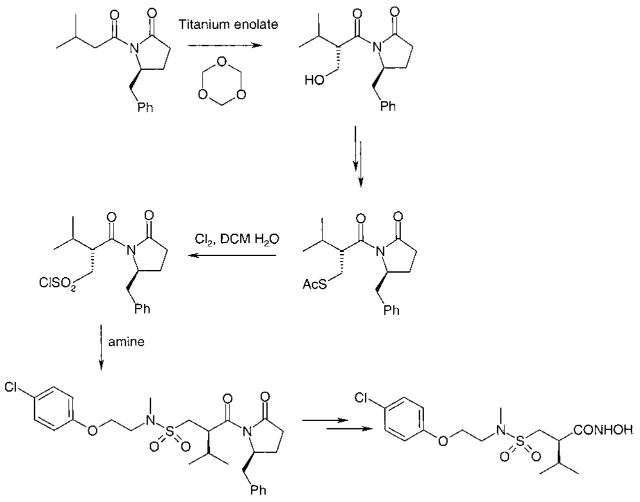
Synthesis of New Cyclazines. Interesting heterocycles are commonplace in the pharmaceutical industry and often require inventive chemical syntheses based on fundamental organic chemistry. *N*-[1-(3-Phenylpropan-1-yl)piperidin-4-yl]-5-thia[1,8-*b*]diazaacenaphthylen-4-carboxamide (shown below) is an example of a compound that has been shown to reduce the amount of low- and very low-density lipoprotein cholesterol and triglycerides in hamsters and has potential for preventing atherosclerosis.



Three convenient methods for the construction of the fused tricyclic ring system derivatives of "cyclazine" 5-thia[1,8-*b*]diazaacenaphthylene-4-carboxylic acid have been reported by Ikemoto and co-workers (*Tetrahedron* **2002**, *58*, 489). In particular the group report reaction of 5-fluorimidazo[1,2-*a*]pyridine hydrochloride (from 2,6-difluoropyridine as shown in the following scheme) with thioglycolate followed by treatment with hexamethylethylenetetramine (HMTA) at 90–100 °C in AcOH to be an effective method for the synthesis of the tricycle. Experimental conditions are given in the paper for the multigramme chromatography-free synthesis.

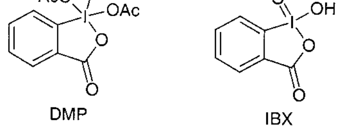


Enantioselective Synthesis of Sulphonamide Hydroxamic Acids. Excess proteolytic activity of matrix metalloproteinase enzymes (MMPs) has been implicated in a wide range of disease states including cancer, arthritis, and inflammatory bowel disease. Watson and co-workers have recently described (*Tetrahedron Lett.* **2002**, *43*, 683) their high-yielding and enantioselective approach to α-substituted hydroxamic acids as inhibitors of matix metalloproteinases. In their approach Evans oxazolidinone chemistry was used to set the stereochemistry, the titanium enolate being quenched with trioxane to give the chiral hydroxymethylated derivative.



Conversion of this primary alcohol to the sulphonyl chloride was achieved via the thioacetate after oxidation using chlorine. Reaction with the required amine gave the sulphonamide which was converted to the carboxylic acid after removal of the Evans auxiliary. The desired hydroxamic acid product was prepared by simple treatment of the acid with oxalyl chloride followed by aqueous hydroxylamine with no loss of ee.

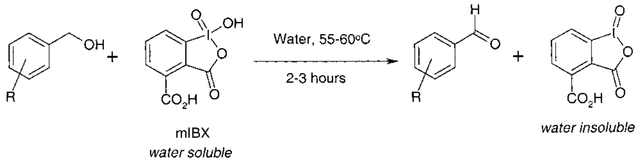
Hypervalent Iodine Compounds as Oxidants. Hypervalent iodine reagents, due to their low toxicity and ready availability, have attracted considerable attention recently as mild and selective oxidizing agents. The Dess–Martin periodinane (DMP) and *o*-iodoxybenzoic acid (IBX) are amongst the most commonly used. Despite the nontoxicity and ease of preparation these reagents do have drawbacks—both reagents are potentially explosive.


DMP IBX

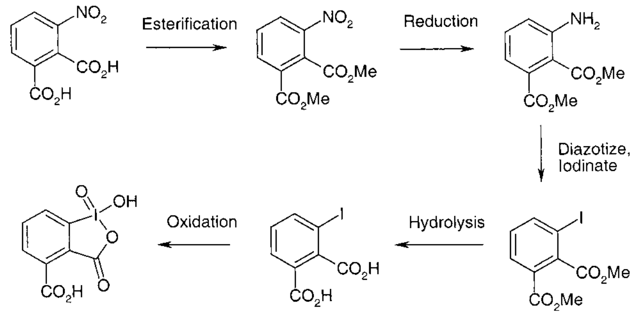
Vinod and Thottumkara report (*Tetrahedron Lett.* **2002**, *43*, 569) the synthesis and oxidation reactions of a "user- and eco-friendly" modified water soluble derivative of IBX (mIBX). They have demonstrated that allylic and benzylic alcohols can be cleanly oxidised to the corresponding carbonyl compounds in water or water/THF mixtures using this reagent. In addition, the byproduct (the reduced form

10.1021/op020018p CCC: $22.00

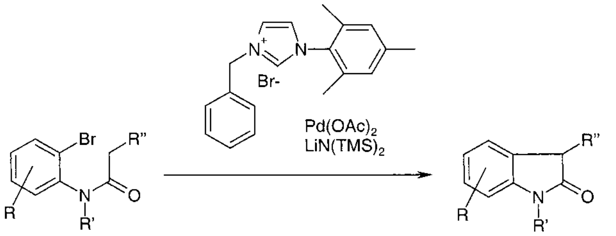
of mIBX, see below) is nearly completely insoluble in the aqueous reaction media and can be removed by simple filtration. An easy reoxidation of the byproduct using $KBrO_3$ makes the procedure cost-effective.



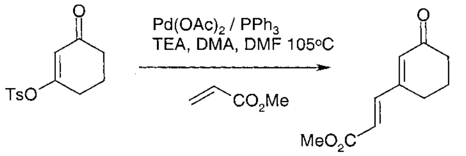
mIBX was prepared in five chemical steps from 3-nitrophthalic acid as shown the following scheme:



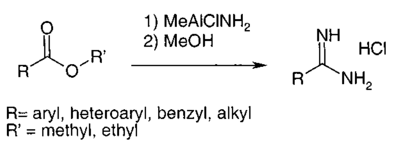
Imidazol-2-ylidine: A Ligand for Palladium-Catalysed Synthesis of Oxyindoles from *o*-Haloanilides. Zhang and Zhang from Lilly have described (*Tetrahedron Lett.* **2002**, *43*, 193) how oxyindoles were prepared in good yields from 2-bromo or chloroanilides in the presence of a base and a novel palladium imidazoyl-2-ylidene complex through a process of *metal-catalysed intramolecular arylation of amide enolates*. In particular the group note the ease of preparation of the ligand from readily available starting materials and its stability towards air and prolonged storage. This novel metal/ligand system may find application to other transition-metal catalysed processes where more traditional systems fail.



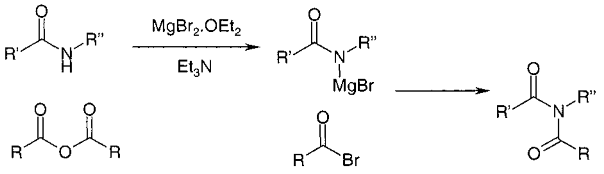
Tosylates in the Palladium-Catalysed Heck Reaction. Fu and co-workers report (*Tetrahedron Lett.* **2002**, *43*, 573) the first examples of a tosylate in the palladium-catalysed Heck cross-coupling reaction. In the example shown in the following scheme the tosylate is reacted with methyl acrylate using palladium acetate as catalyst to provide 3-(3-oxo-1-cyclohexen-1-yl)-2-propenoic acid methyl ester in excellent yield. The effect of reaction parameters such as temperature and catalyst as well as the ratio of palladium acetate to triphenyl phosphine on the reaction rate is described. In addition, the group describe an experimental procedure on multigramme scale.



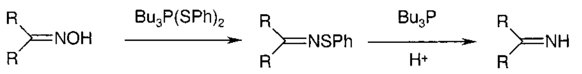
Amidines from Esters. A method for directly converting esters to amidines in moderate-to-high yields has been described by Gielen and co-workers (*Tetrahedron Lett.* **2002**, *43*, 419). In their procedure esters are treated with methyl chloroaluminium amide (prepared from trimethyl aluminium and ammonium chloride) followed by methanol as the quenching agent to give the amidine hydrochlorides. The method is based on a procedure used by Weinreb where he quenches the reaction mixture with 5% HCl to obtain amides from esters.



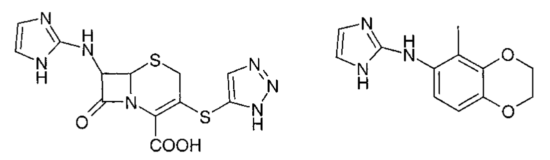
N-Acylation of Amides. A new practical method for the N-acylation of amides has been described by Yamanda and co-workers (*Tetrahedron Lett.* **2002**, *43*, 647). Their protocol involves the treatment of amides with acid anhydrides in the presence of $MgBr_2{\cdot}OEt_2$ to give the corresponding *N*-acyl amides. The method is applicable to amides that are labile to acids and bases, which tend to receive O-acylation or that could be susceptible to racemisation and *O*,*N*-acyl migration.



Reduction of Oximes to Imines. Conversion of ketones to oximes represents a useful protection strategy for the functionalisation of this type of carbonyl compound. However, this methodology remains under-utilized, owing to the harsh conditions needed for the reverse reaction that are often incompatible with sensitive organic substrates. Lukin and Narayanan report (*Tetrahedron* **2002**, *58*, 215) the reduction of oximes to imines with a tributylphosphine−phenyldisulphide reagent combination via the formation of a phenylthioimino intermediate which is subsequently reduced to the imine with tributylphosphine in the presence of a proton source. Under hydrolytic conditions this provides a practical and general method for the conversion of oximes to ketones.

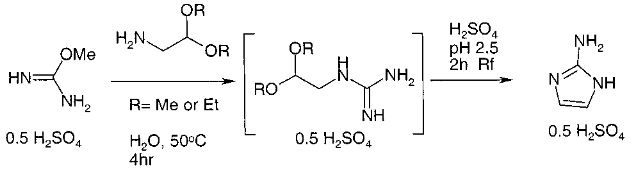


2-Amino Imidazole. Weinmann and co-workers have reported (*Tetrahedron Lett.* **2002**, *43*, 593) an efficient and environmentally friendly preparation of 2-amino-imidazole, a heterocyclic substructure found in many pharmacologically active substances:

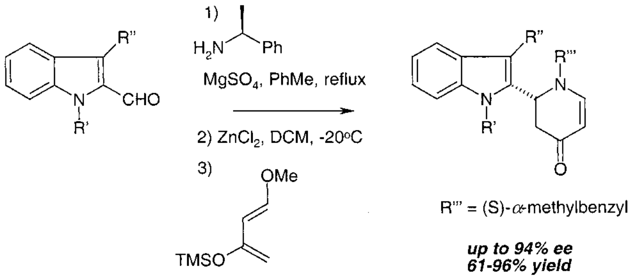


Pharmacollogically active substances containing the 2-amino imidazole unit

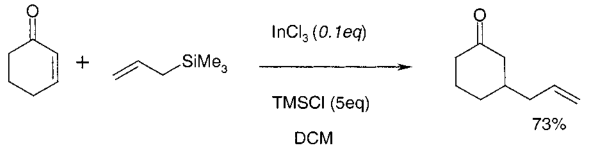
Their method uses the cheap starting materials, *O*-methyl-iso-urea sulphate and 2-aminoacetaldehyde acetals with the desired product being isolated through a simple work-up. A multigramme preparation is outlined in the paper.



Asymmetric *aza*-Diels−Alder Reaction. The asymmetric aza-Diels−Alder reaction of substituted indole 2-carboxyaldehydes with Danishefsky's diene has been investigated by Kuethe and co-workers at Merck (*Tetrahedron Lett.* **2002**, *43*, 29). In their report, they describe how the reaction proceeds with a high degree of diastereoselectivity providing highly functionalised 2-(2-piperidyl)indoles which were further elaborated into novel polycyclic heterocycles. Asymmetric induction was achieved by utilising α-methyl benzylamine as the chiral auxiliary due to low cost and availability in either enantiomeric form.



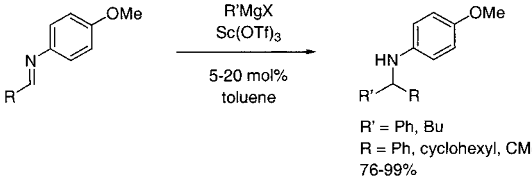
Catalytic Sakurai Reaction. Lee and co-workers have shown (*J. Org. Chem.* **2001**, *66*, 8646) that catalytic amounts of $InCl_3$ promote inter- and intramolecular Sakurai reactions (see below) in the presence of TMSCl. This method complements existing synthetic methodology due to its mild reaction conditions and some of the advantageous properties of indium metal over other metals (such as ease of handling, high reactivity and selectivity, low toxicity, and operational simplicity).



Catalytic Sakurai reaction

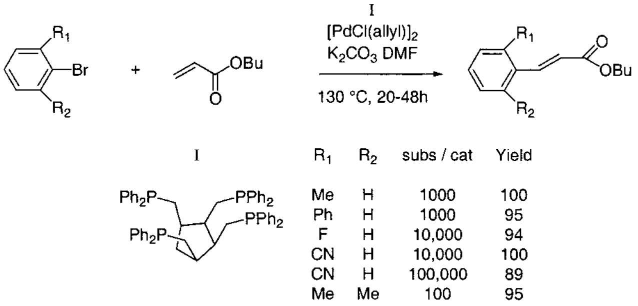
Addition of Grignard Reagents to Imines Catalysed by Scandium Triflate. Compared to organlithium species, the reaction of Grignard reagents with imines gives complex mixtures of products, depending on the structure of the reagents/substrates. Although it has been shown previously that a *stoichiometric* amount of Lewis acid can accelerate the reaction and give selective 1:2 addition, a recent paper indicates that *catalytic* amounts of scandium triflate (Saito, S. et al. *Synlett* **2001**, 1858) will now work successfully.

The preferred solvent is toluene, but THF slows down the addition. Whereas normally the rate is concentration-dependent, in the presence of Sc(OTfl$_3$) the rate is concentration-independent.



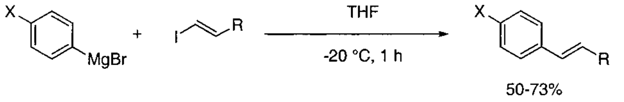
Heck Reaction with Hindered Substrates. The Heck reaction is very sensitive to steric effects on the aryl halide and olefin, possibly owing to faster decomposition of the catalysts. A few phosphine ligands have been found to work, but catalyst loadings are quite high for industrial use. The best ligands to date are Herrmann's palladacycle and Fu's P(*t*-Bu)$_3$ with palladium.

It is now reported (Feverstein, M. et al. *Synlett* **2001**, 1979) that a palladium complex of a tetraphosphine is more stable and gives a very high efficiency (substrate-to-catalyst ratios of up to 210 million!) for the reaction of 3,5-bis(trifluoromethyl)bromobenzene with acrylates. With hindered aryl halides, high turnover is also observed (see also *J. Org. Chem.* **2001**, *66*, 5923).



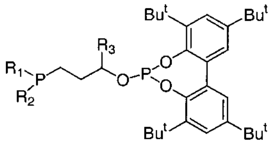
R_1	R_2	subs / cat	Yield
Me	H	1000	100
Ph	H	1000	95
F	H	10,000	94
CN	H	10,000	100
CN	H	100,000	89
Me	Me	100	95

Iron-Catalysed Cross-Coupling Reactions. Palladium-catalysed cross-coupling reactions are widely carried out, but coupling using low-cost metals is rare. Inspired by the work of Kochi, Cahiez et al. have previously reported cross-coupling between RMgX and alkenyl halides in the presence of Fe(acac)$_3$ (Cahiez, G. et al. *Synthesis* **199**, 1199; *Pure Appl. Chem.* **1996**, *68*, 669). His group, working with Knochel's group in Munich, now report that arylmagnesium halides undergo fast cross-coupling with alkenyl halides.

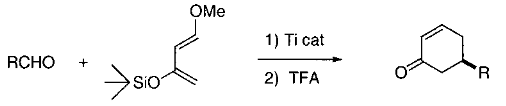


Better yields are obtained by carrying out the reaction on solid phase (Dohle, W. et al. *Synlett* **2001**, 1901).

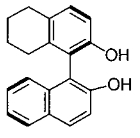
Chiral Phosphine−Phosphite Ligands for Asymmetric Hydrogenation. A recent report from the group of Van Leeuwen in Amersterdam shows that ligands which contain a phosphine *and* a phosphite group are better than ligands with two phosphines or two phosphites in the asymmetric hydrogenation of dehydroamino acid derivatives with rhodium metal complexes. It is suggested that the phosphine moiety does not influence the enantioselectivity, which is more affected by the backbone in the ligand and the phosphite. The phosphine affects the rate, however. The rate of reaction is first order in rhodium and hydrogen, zero in substrate (Deerenberg, S. et al., *J. Org. Chem.* **2001**, *66*, 7626)



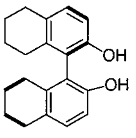
Discovery of Efficient Asymmetric Catalysts for Solvent-Free Hetero-Diels−Alder Reactions. Using a combinatorial approach, mixtures of chiral diols were screened singly and in pairs in the presence of titanium isopropoxide for catalysis of aldehyde addition to Danishesky's diene. By this approach catalysts which give high enantioselectivity and are active at 0.005−0.01 mol % were discovered (Long, J. et al. *J. Am. Chem. Soc.* **2002**, *124*, 10). Best results were achieved with ligands A and B with either two A or A and B together.



usually 99% yield
95-99% ee

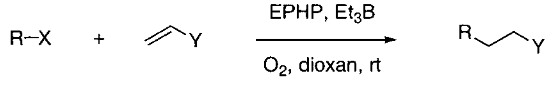


(A)



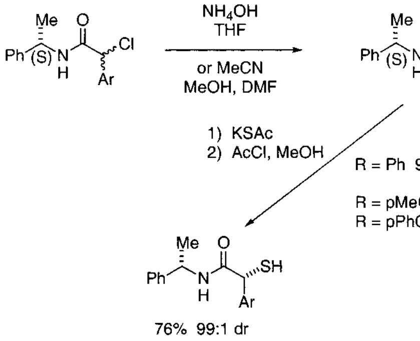
(B)

1-Ethylpiperidium Hypophosphite: A Radical Mediator for Carbon−Carbon Bond Formation. An Alternative to Tin Hydrides. Radical reactions are useful for C−C bond formation, but the use of organo tin compounds generally precludes use on a large scale. 1-Ethylpiperidium hypophosphite (EP HP) has previously been shown to work well in radical reductions and for intramolecular C−C bond formation, but a recent report indicates that its applicability is more widespread (Jan, D. O. et al. *Synlett* **2001**, 1923). The moderate cost, low toxicity, and ease of work-up should ensure that use on large scale will be tried in the future.



R	X	Y	O_2 (eq)	Time	Yield
cyclohexyl	I	SO_2Ph	0.015	1	98
cyclohexyl	I	SO_2Ph	0	3	90
adamantyl	I	SO_2Ph	0.015	1	94
adamantyl	I	CO_2Me	0.015	1	80
adamantyl	I	COMe	0.03	2	64
$C_{12}H_{23}$	I	SO_2Ph	0.045	3	86
adamantyl	Br	SO_2Ph	0.015	1	75 (at 100 °C)

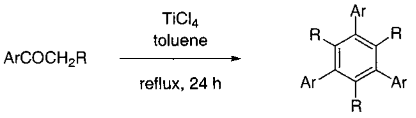
Crystallisation-Induced Dynamic Resolution of α-Chloro Acetamides. Treatment of α-chloro-α-phenylacetamide derivatives of, for example, (*S*)-1-phenylethyl-amine with aqueous ammonia causes a crystallisation-induced conversion to a single diastereoisomer. However, the addition of the ammonia must be very slow to get good results (Lee, S.-K. et al. *Synlett* **2001**, 1941).



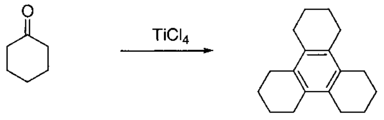
R = Ph 96% yield 96:4 ratio

R = pMeC$_6$H$_4$ 91% 90:10
R = pPhC$_6$H$_4$ 87% 75:25

Triple Self-Condensation of Ketones To Give Aromatics. Refluxing a ketone with 2 equiv of $TiCl_4$ in toluene leads to formation of hexasubstituted benzenes by triple self-condensation (Li, Z. et al. *Synlett* **2001**, 1947).

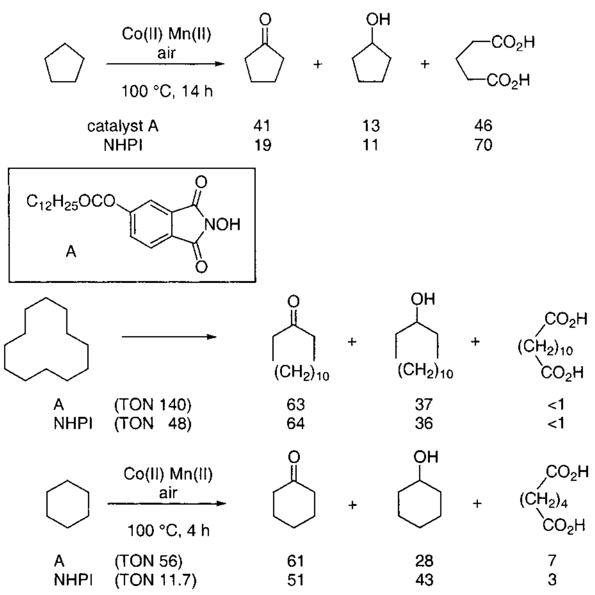


Ar	R	Yield
Ph	H	65
p-Cl-C_6H_4	H	77
p-Me-C_6H_4	H	83
2-naphth	H	45
Ph	Me	32

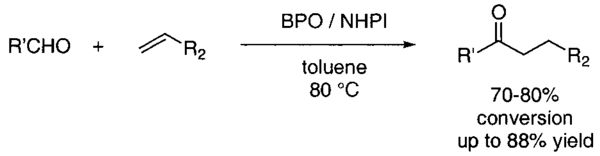


44%

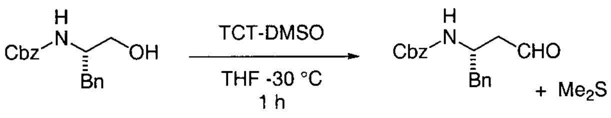
Alkane Oxidation with Air Catalysed by Lipopholic *N*-Hydroxyphthalimides in the Absence of Solvent. Oxidation of cyclohexane to a mixture of cyclohexanone and cyclohexanol is carried out industrially using a soluble cobalt catalyst but can be operated only at 3−6% conversion if high selectivity (75−80%) is required. Although introduced in the 1940s by DuPont for production of adipic acid, the process is still employed without major modification. The group of Ishii in Osaka have recently developed oxidation methods using *N*-hydroxyphthalimide (NHPI) as a catalyst under mild conditions (*Adv. Synth. Catal.* **2001**, *343*, 393). They have now developed NHPI derivatives which dissolve in the hydrocarbon and allow air oxidation under mild conditions without the need for a solvent and which lead to different results from NHPI itself (Sawatari, N. et al. *J. Org. Chem.* **2001**, *66*, 7869).



Addition of Aldehydes to Alkenes Using NHPI Catalyst. The group of Ishii (Tsujimoto, S. et al. *Chem. Commun.* **2001**, 2352) have also found that NHPI in the presence of dibenzoyl peroxide catalyses the radical addition of acyl radicals (generated from aldehydes) to alkenes in moderate-to-good yields.



A Mild and Efficient Alternative to the Swern Oxidation. DMSO has been widely used as an oxidising agent in conjunction with acetic anhydride, methane sulphonic anhydride, tosyl chloride, SO_3-pyridine, phosphorus pentoxide, thionyl chloride, oxalyl chloride, and other compounds. However, the DMSO activation step can be violent and exothermic, and there have been scale-up problems. Generally this step is carried out below −60 °C, a disadvantage for scale-up. Now it has been reported that 2,4,6-trichlorotriazine (TCT, cyanuric chloride) can be used to activate DMSO in THF at −30 °C, and the mixture oxidises alcohols efficiently (DeLuca, L. et al. *J. Org. Chem.* **2001**, *66*, 7907). The method is particularly suitable for making α-aminoaldehydes without racemisation at the chiral centre. For a review of TCT in organic synthesis, see future issues of OPRD.



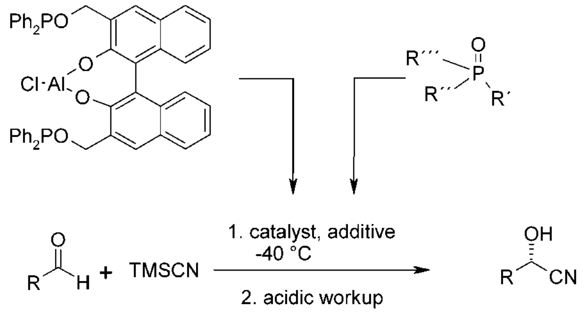
Biproducts Using TIPS Protection: A Warning. The group of Fleming at Cambridge UK (Barden, D. J. et al. *Chem. Commun.* **2001**, 2367) have found byproducts in reactions using triisopropylsilyl (TIPS) protection groups. The byproduct is a derivative with 2-isopropyl groups and one normal propyl group attached to silicon and is derived from an impurity in the supplied TIPS triflate. The amount of impurity in products varies with the excess of TIPS triflate used and may depend on whether the reaction goes to completion, presumably because the (*i*-Pr)$_2$ *n*-Pr Si OTf reacts faster than TIPS.

The motto is—always check for a byproduct when using TIPS protection. The problem is worse when:

- an inferior batch of reagent is used
- a large excess is used
- the reaction does not go to completion
- hindered alcohols are used
- the alcohol is added to TIPS triflate rather than the other way round.

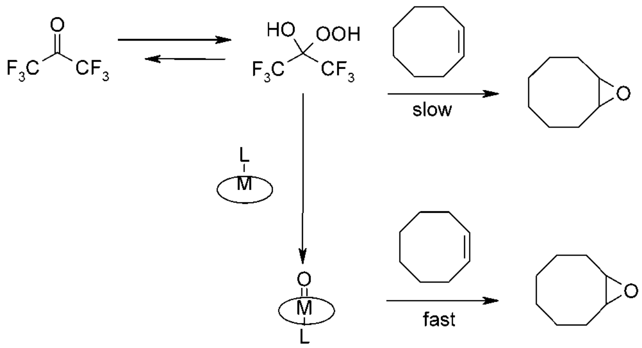
It is speculated that the contaminant arises in the preparation of TIPS triflate, presumably from reaction of isopropylmagnesium chloride with trichlorosilane. The *n*-propyl group may be a contaminant in the isopropyl chloride, or the Grignard may rearrange.

The Development of New Monometallic Bifunctional Catalysts with Lewis Acid and Lewis Base Properties. H. Gröger (*Chem. Eur. J.* **2001**, *7*, 5247) has summarized the latest development of chiral bifunctional catalysts developed in the Shibasaki group (see also Shibasaki, M.; Gröger, H. *Topics in Organometallic Chemistry*; Lanthanides: Chemistry and Use in Organic Synthesis, Vol. 2; Springer: Berlin, 1999) containing both Lewis acid and Lewis base moieties. These monometallic and bifunctional phosphinoyl-containing catalysts are able to coordinate both nucleophilic and electrophilic substrates in the transition state. Such a coordination of both substrates within an asymmetric space would lead to a stereodiscrimination and should result in a highly enantioselective process. In the design of the catalysts it was found important to prevent the internal coordination of the Lewis base to the metal. One of the best ligands was found to be **2**. Several successful applications of this new catalytic concept in the field of asymmetric cyanation reactions have been reported, including asymmetric hydrocyanation of aldehydes, ketones, and imines with high-to-excellent yields and stereochemical induction. Almost the same excellent results were obtained with an immobilized catalyst. Lately it was also found that replacing titanium by samarium or gadolinium in a sugar-based catalyst for the asymmetric cyanosilylation gives the opposite enantiomer as the sole product in up to 97% ee (see also K. Yabu et al. *J. Am. Chem. Soc.* **2001**, *123*, 9908).

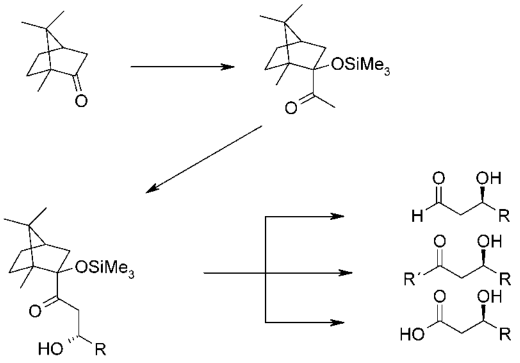


Catalytic Olefin Epoxidation with Hydrogen Peroxide in Supercritical CO₂. Among the various substances that can be employed at supercritical conditions, carbon dioxide ($scCO_2$) is a particularly attractive reaction medium as it is environmentally friendly and economical, nonflammable, nontoxic, and chemically inert under many conditions. $scCO_2$ has already been shown to be a clean and effective reaction medium for many catalytic processes including hydrogenations, hydroformylations, and enzymatic processes.

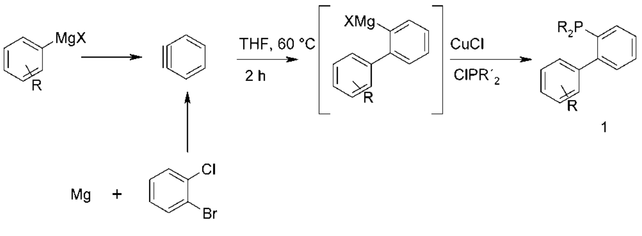
In the case of oxidation processes, $scCO_2$ is particularly well-suited being fully oxidized. S. Campestrini and U. Tonellato (*Adv. Synth. Catal*. **2001**, *343*, 819) have reported the first heterogeneous oxidation of cyclooctene with hydrogen peroxide catalysed by manganese 5,10,15,20-tetrakis(2′,6′-dichlorophenyl)porphyrinate, in the presence of hexafluoracetone hydrate as cocatalyst in $scCO_2$ at 40 °C and 20 MPa. The role of hexafluoroacetone is manifold; the perhydrate from hexafluoroacetone is more soluble in $scCO_2$, the perhydrate provides also a useful tool to preserve H_2O_2 from decomposition induced by the porphyrin, and finally the perhydrate is the better nucleophile which reacts with the manganese porphyrin. Without the porphyrinic catalyst the reaction is clean but very slow. To speed up the reaction a catalytic amount of 4-*tert*-butylpyridine as an axial ligand for the manganese porphyrin is also necessary. Under the best conditions a complete conversion of cyclooctene within 15 min with the epoxide as the only product was possible.



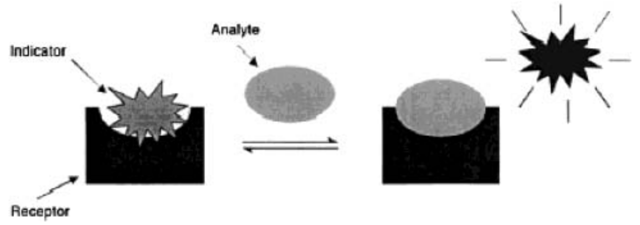
The Aldol Addition Reaction: An Old Transformation at Constant Rebirth. C. Palomo et al. (*Chem. Eur. J*. **2002**, *8*, 37) have summerized the latest development of the aldol addition reaction in connection with industrial implementation. The most elemental, simple, direct base- or acid-promoted aldol reactions usually suffer from reversibility, dehydration side reaction, and lack of chemo-, regio-, and stereoselectivity. To make the reaction practical, and therefore selective, "directed" stepwise aldol methodologies that use preformed nucleophiles have been developed. In this way impressive achievements in asymmetric aldol methodology have been reached, which basically rely on the use of chiral auxiliaries, ligands, and catalysts as the main stereochemical controllers. The Mukaiyama aldol reaction has represented a big breakthrough in the field, which has shifted much attention from the "stoichiometric" arena. Soon due to practical reasons this field will probably be dominated by direct catalytic asymmetric aldol methodologies useful also for large-scale industrial applications. Relative high degrees of chemo-, regio-, and stereocontrol have been achieved, but still they lack substrate generality. Despite the advances, two long-standing problems associated with the aldol reaction, the production of *anti*-aldol products and the "acetate" aldol reaction, are still challenges in the aldol field. The first nondestructive auxiliary for the use in the acetate aldol reaction has just recently been reported (see scheme).



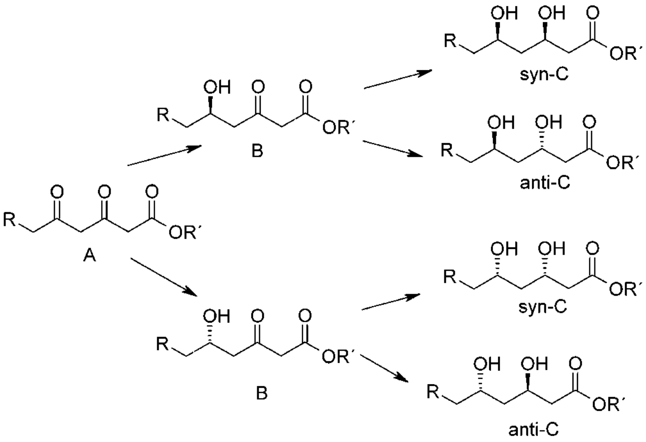
The Use of Catalytic Amounts of CuCl and Other Improvements in the Benzyne Route to Biphenyl-Based Phosphine Ligands. The combination of phosphines **1** with a source of Pd(0) gives catalysts for the formation of C−N, C−O, and C−C bonds that are exceptional in terms of activity and general utility. These ligands possess a number of attributes that make them attractive to the practising organic chemist: they are crystalline materials that are very stable to air oxidation—even in solution—and a number of derivatives are commercially available. S. L. Buchwald et al. (*Adv. Synth. Catal*. **2001**, *343*, 789) report that according to their studies the dimethylamino-substitued ligand is the most generally useful ligand for the Pd-catalyzed amination of aryl halides and sulfonates. It is also a very effective catalyst for the formation of α-aryl ketones, α-arylesters, and biaryls. The main drawback for the use of the ligand was its unavailability. To overcome this and to make the ligand accessible in large amounts, a new synthetic procedure was developed. The described preparation is based on the CuCl-catalysed addition of 2-(dimethylamino)phenylmagnesium bromide to benzyne generated from 2-chlorobromobenzene with a subsequent addition of dicyclohexylchlorophosphine. From this process it is possible to obtain the ligand in 56% yield.



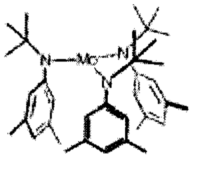
Teaching Old Indicators New Tricks. A significant thrust in chemical research has recently focused on the notion that molecular design can lead to practical sensors. To make a chemosensor, a compound must contain a "binding site" and a "signaling site", such as a chromophore, fluorophore, or redox active center. Furthermore, a mechanism to communicate between them must exist. Most synthetic sensors are designed with covalent attachment between a receptor and a reporter moiety. E. Anslyn et al. (*Acc. Chem. Res.* **2001**, *34*, 963) have reported the current progress of their use of noncovalently attached indicators to signal binding of analytes. With these systems, analyte binding leads to indicator displacement from the binding cavity, which in turn yields an optical signal modulation. The authors describes chemosensors for citrate, glucose-6-phosphate, nitrate, and tartate. This could be in the future an interesting approach for the screening of chemical reaction conditions. If the wanted product is obtained, it can attach to the binding site and release the indicator. The released amount of indicator is easily determined photometrically. To ascertain an easy reuse of these systems they should be added to a solid phase.



Biocatalytic Reduction of β,δ-Diketo Esters: A Highly Stereoselective Approach to All Four Stereoisomers of a Chlorinated β,δ-Dihydroxyhexanoate. Optically active β,δ-dihydroxy esters have found widespread application in the stereoselective synthesis of natural products, polyol fragments, and chiral drugs. The regio- and enantioselective reduction of β,δ-diketo esters is a straightforward and flexible approach for all four stereoisomers of the corresponding dihydroxy esters. M. Wolberg et al. (*Chem. Eur. J.* **2001**, *7*, 4562) have now reported a new biocatalytic method for the enantioselective synthesis of all four enantiomers from *tert*-butyl-6-chloro-3,5-dihydroxy-hexanoate. For the crucial first step, two enantiocomplementary biocatalysts are used, namely, recLBADH and Baker's yeast, which allow the highly regio- and enantioselective reduction of the δ-keto group of the diketo ester. The keto group of the products (*S*)-2 and (*R*)-2 can be reduced either syn-selective or anti-selective by application of known borohydride reduction protocols.



Alkyne Metathesis: Development of a Novel Molybdenium-Based Catalyst System. A. Fürstner et al. (*Chem. Eur. J.* **2001**, *7*, 5299) have reported that sterically hindered molybdenium(III)amido complexes upon treatment with CH_2Cl_2 or other halogen donors have been converted into highly effective catalysts for all kinds of alkyne metathesis reactions. Several applications illustrate the performance of the catalytic system $1/CH_2Cl_2$ which operates under mild conditions and tolerates an array of polar functional groups. Although the required complexes are rather sensitive towards oxygen and moisture, this new method outlines existing protocols for alkyne metathesis. To demonstrate the scope of the new method the authors used it for the total synthesis of epothilone A and C. The macrolide core of these targets is forged by ring-closing alkyne metathesis.



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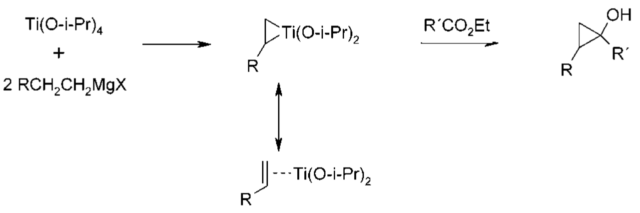
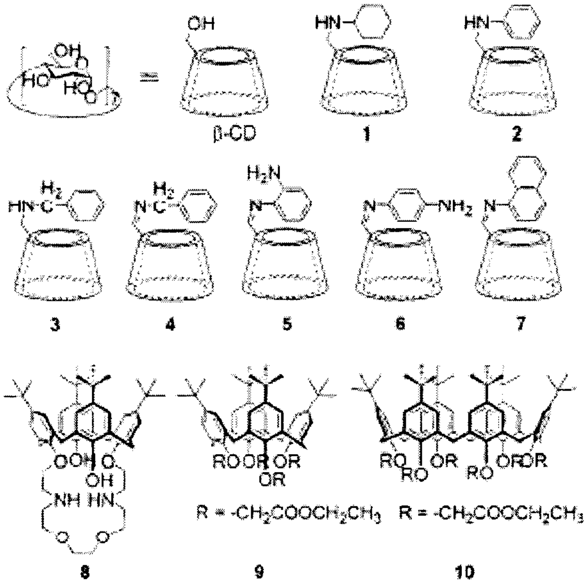
The Divalent Titanium Complex Ti(O-*i*-Pr)$_4$/2-*i*-PrMgX as an Efficient and Practical Reagent for Fine Chemical Synthesis. New efficient and sophisticated reagents and reactions for organic synthesis are being developed at steadily increasing speed, allowing organic chemists to prepare any targeted complicated molecule. However, it is also true that when there is a need for larger amounts of an agricultural or pharmaceutical ingredient most of the developed synthetic methods are more or less useless. In the development of new reagents much effort has been devoted to organometallics in a stoichiometric or a catalytic amount. Divalent group 4 metal complexes such as titanium(II) and zirconium(II) complexes have been widely accepted as useful synthetic reagents. However, because these reagents contain a cyclopentadienyl group, their application to large-scale production is somewhat limited. In 1989 Kulinkovich and co-workers presented a new Ti(O-*i*-Pr)$_2$-olefin complex by the reaction of Ti(O-*i*-Pr)$_4$ with 2 equiv of an alkyl Grignard reagent and showed that the reagent reacts with esters, giving cyclopropanols. After the first excitement and doubt had settled, this interesting reagent has been found to be very versatile, thus allowing a variety of synthetic transformations. F. Sato and S. Okamoto (*Adv. Synth. Catal.* **2001**, *343*, 759) have summarized the synthetic transformations developed with this interesting reagent, which is suitable for large-scale use, due to the low toxicity of Ti(O-*i*-Pr)$_4$ and *i*-PrMgX and their availability in bulk at low cost.



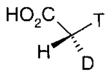
Supported Catalysts and Their Applications in Synthetic Organic Chemistry. Y. R. de Miguel et al. (*J. Chem. Soc., Perkin Trans. 1* **2001**, 3085) have gathered the latest results from the development of supported catalysts and their applications in organic chemistry. This is a field in organic chemistry which has in the past decade experienced a revival. This newly awaking interest has also spread to different process research groups in the industry. The review describes the development of new supported catalysts for enantioselective C−C bond formation, Diels−Alder reaction, hydroformylation, olefin metathesis, and Phauson−Khand reactions, just to mention a few. Most of the reported supported catalysts are transition metal complexes or chiral auxiliaries supported on polystyrene or silica. The methods used for catalyst immobilization range from copolymerisation of functionalised monomers to the more commonly used approach of covalent or ionic anchoring. Over the past years much progress has been made on the development of enantioselective supported catalysts with activities and selectivities comparable to those of their homogeneous counterparts. To this aim, many researchers have explored novel polymeric backbones. There have also been some reports on screening of catalyst libraries. Although this field is still new in the fine chemical and pharmaceutical industry, it has great potential to bring about new economical and ecological manufacturing procedures.

Synthesis of Novel β-Cyclodextrin and Calixarene Derivatives and Their Use in Gas Sensing on the Basis of Molecular Recognition. The molecular recognition behavior of synthetic receptors has been used extensively in various fields of science and technology. One of the most successful applications is in analytical chemistry. The piezoelectric chemical sensor is a widely employed analytical technique, including practical applications such as enviromental monitoring and gas supervision in factories. Y. Liu et al. (*Eur. J. Org. Chem.* **2002**, 607) have reported the synthesis and use of novel β-cyclodextrin and calixarene derivatives and their use as coating on piezoelectric sensors for aliphatic amines. The piezoelectric chemical sensors show considerable sensitivity and selectivity towards aliphatic amines. The β-cyclodextrin coated sensors showed a much higher frequence shift towards ethylenediamine than calixarene derivatives. It can be anticipated that the molecular recognition phenomenon will have an extensive application not only in enviromental monitoring but also in on-line monitoring of chemical reactions.



PUZZLE!

"Chiral methyl groups" in the form of chiral acetic acid are invaluable tools for the elucidation of numerous biochemical mechanisms. Therefore, here is the challenge for this issue—how would you prepare the chiral isotopically labeled acetic acid?



If you are stuck, have a look at the paper by Mulzer and co-workers (*J. Am. Chem. Soc.* **1999**, *121*, 10848) entitled "Highly Stereoselective Synthesis of a Chiral Methyl Group by a Facially Controlled Sigmatropic [1,5]-Hydrogen Shift"—Good luck!

Trevor Laird*
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