Organic Process Research & Development **2001**, *5*, 342−349

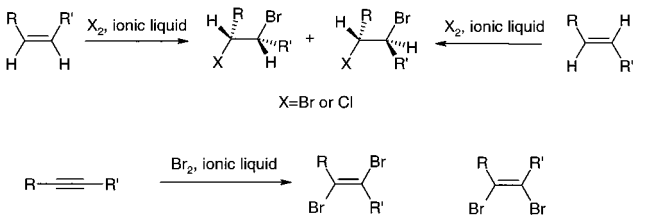
Highlights from the Literature

Some Items of Interest to Process R&D Chemists and Engineers as Selected by Trevor Laird and Stephen A. Hermitage

In the last issue of OPRD "Highlights" we outlined some work in the area of ionic liquids. During the past few weeks there seem to have been a flourish of publications in this area. Clearly there is much work to be done to make ionic liquids common-place in the industrial synthetic world but notably good headway is being made.

In particular Chiappe and co-workers (*Org. Lett.* **2001**, *3*, 1061) have used a variety of ionic liquids (1-butyl-3-methylimidazolium hexafluorophosphate, 1-butyl-3-methylimidazolium tetrafluoroborate, 1-butyl-3-methylimidazolium bromide and 1-butyl-3-methylimidazolium chloride (Scheme 1) as alternatives to the more common-place chlorinated solvents in the halogenation reactions of alkenes and alkynes.

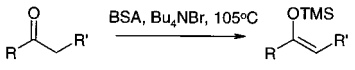
Scheme 1



Bromination

Mioskowski and Smietana (*Org. Lett.* **2001**, *3*, 1037) have used ionic liquids for the preparation of silyl enol ethers from aldehydes and ketones using bis(trimethylsilyl)acetamide (BSA) in good yields (Scheme 2). They have demonstrated their chemistry using molten salts (e.g., Bu_4NBr) and generate the products without the use of base and have also found that the nature of the salt (especially that of the cation) to be a particularly important parameter.

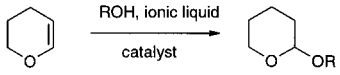
Scheme 2



Silyl enol ether formation

Afonso and Branco (*Tetrahedron* **2001**, *57*, 4405) have used ionic liquids as recyclable reaction media for the tetrahydropyranylation of alcohols. They have used pyridinium *p*-toluenesulphonate (PPTS) and triphenyl phosphine hydrobromide (TPP·HBr) as acid catalysts under nonreversible conditions to form the protected alcohol products (Scheme 3). The ionic media can be recycled on at least 22 occasions without appreciable loss in activity.

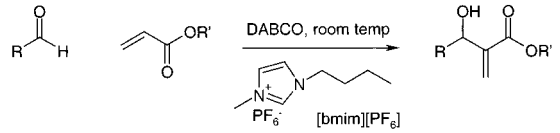
Scheme 3



Protection

In a more complex chemical example, Rosa, Afonso, and Santos (*Tetrahedron* **2001**, *57*, 4189) promote ionic liquids as a recyclable medium for the Baylis−Hillman reaction (Scheme 4). By using DABCO as the catalyst the reaction was shown to be 33.6 times faster in the ionic liquid ([bmim][PF_6]) than in acetonitrile. Low yields (14−20%) of adducts were obtained from aliphatic aldehydes, but higher yields (39−72%) were obtained from aromatic aldehydes. Again the recycling and reuse of the reaction medium was demonstrated.

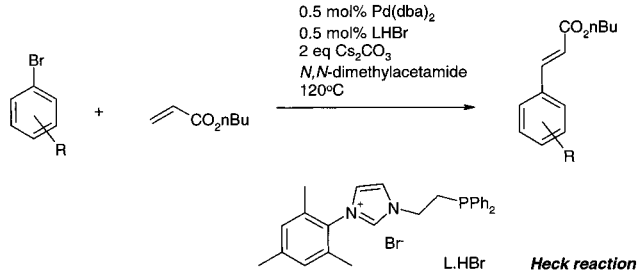
Scheme 4



Baylis-Hillman reaction

On the theme of imidazolium salts, Nolan and co-workers have prepared (*Org. Lett.* **2001**, *3*, 1511) a new phosphine−imidazolium salt, L.HBr (Scheme 5) for use as a catalyst in the Heck reaction between aryl bromides and *n*-butyl acrylate. $Pd(dba)_2$ (0.5 mol%) and of L·HBr (0.5 mol %) in the presence of 2 equiv of Cs_2CO_3 were used in *N*,*N*-dimethylacetamide to give high yields of the coupled products.

Scheme 5



Heck reaction

An improved and cost-effective synthesis of the *N*-aryl hydantoin LFA-1 antagonist BIRT-377 (Figure 1) has been reported by Frutos and co-workers from Boehringer Ingel-

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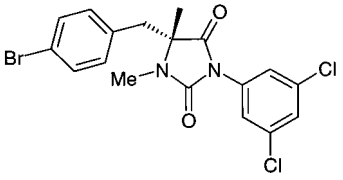
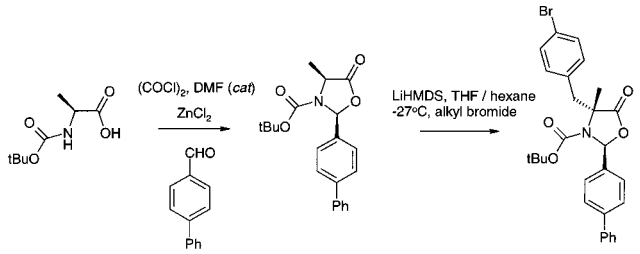


BIRT-377

Figure 1.

heim (*Tetrahedron Asymmetry* **2001**, *12*, 101). In another publication (*Tetrahedron Lett.* **2001**, *42*, 3231) Napolitano and Farina report the condensation of *N*-isobutoxycarbonyl-protected L-alanine with 4-phenylbenzaldehyde in a *crystallisation-controlled* process to give the corresponding *cis*-oxazolidinone derivative as the sole product in high yield. This compound was subsequently manipulated (Scheme 6) using "self-regeneration of stereocentres (SROSC)" to give BIRT377. The group have devised a high-yielding alkylation strategy at −27 °C rather than −78 °C, providing the enolate was formed in the presence of the electrophile.

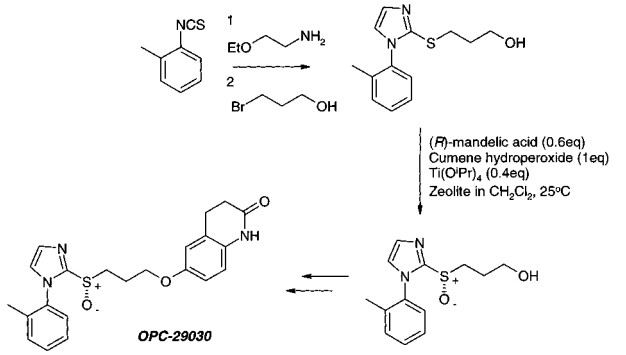
Scheme 6



ABT-271 (Figure 2) has been identified as a promising anti-cancer agent, and the process research group at Abbott Laboratories have reported their synthetic efforts towards its multigram synthesis. (*J. Org. Chem.* **2001**, *66*, 3330).

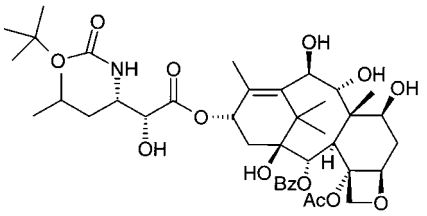
An effective catalytic asymmetric oxidation of a prochiral sulphide (Scheme 7) has been reported by Matsugi and co-workers (*Tetrahedron* **2001**, *57*, 2739) using a titanium−mandelic acid complex. The group discovered that the enantioselectivity was not influenced by moisture, and good selectivity (76% ee) was obtained at room temperature (25 °C). In addition the group have used this method to produce multikilogram quantities of an intermediate en route to an inhibitor of platelet adhesion, OPC-29030.

Scheme 7



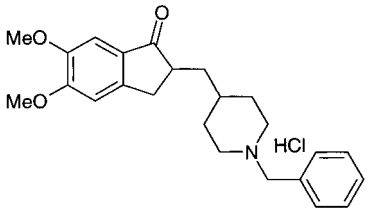
OPC-29030

Abe and co-workers have described (*Tetrahedron* **2001**, *57*, 2701) a large-scale synthesis of *N*-benzyl-4-formylpiperidine through partial reduction of esters using sodium bis(2-



ABT-271

Figure 2.

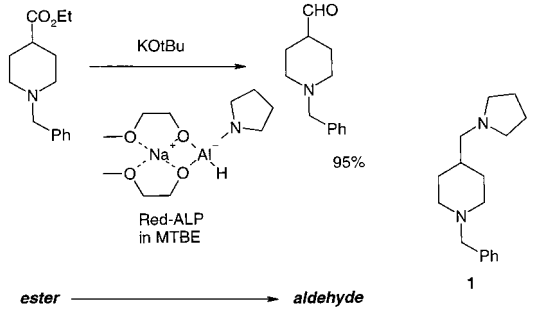


Aricept (Donepezil hydrochloride)

Figure 3.

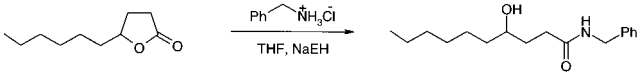
methoxyethoxy)aluminium hydride (SMEAH) reagents modified with pyrrolidine. Although this modification produced significant amounts of *N*-benzyl-4-(pyrrolidin-1-ylmethyl)piperidine **1** (due to an intersting over-reduction reaction discussed in the paper) this could be suppressed by the addition of potassium *tert*-butoxide (Scheme 8). The group have used this synthesis to prepare a key intermediate in the synthesis of Donepezil hydrochloride (Figure 3) and have applied the reduction protocol to a variety of other substrates.

Scheme 8

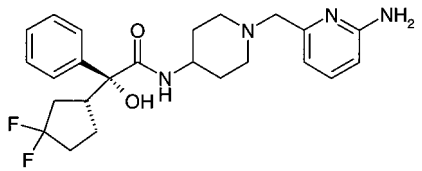


A mild method for the ring opening aminolysis of lactones has been described by Xu et al. from Novartis (*Tetrahedron Lett.* **2001**, *42*, 2439). In their method (Scheme 9) sodium 2-ethylhexanoate (NaEH) was found to serve as both base and catalyst in aminolysis of a variety of lactones using benzylamine hydrochloride. These nearly neutral pH conditions make this method applicable to many acid/base-sensitive substrates.

Scheme 9



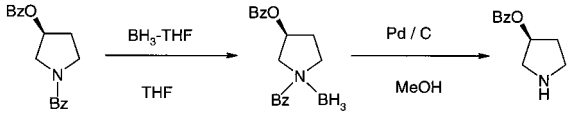
The use of borane−amine adducts in methanol as versatile palladium-catalysed hydrogen-transfer reagents has beendescribed by Couturier and co-workers from Pfizer in a recent publication (*Tetrahedron Lett.* **2001**, *42*, 2763). In the reaction depicted in Scheme 10 the group have used this method to chemoselectively deprotect an *N*-benzoyl-protecting group in the presence of an *O*-benzoyl group.



Muscarinic (M3) antagonist

Figure 4.

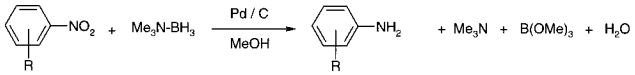
Scheme 10



Selective deprotection

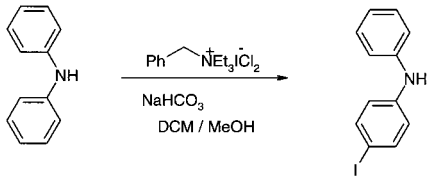
In an additional publication (*Tetrahedron Lett.* **2001**, *42*, 2285) the group report that stable borane−amine adducts can be activated through palladium catalysis and act as hydrogen transfer reagents for the reduction of nitrobenzenes to anilines. Their method is high-yielding and compatible with a variety of other functional groups. More importantly, the safety and handling convenience of borane−amines coupled with an operationally simple and straightforward work-up makes this protocol an attractive alternative to the more traditional methods for reduction of a nitro group to an amine (Scheme 11).

Scheme 11



Monoiodinated anilines have been prepared in good to excellent yields by Tour and Kosynkin (*Org. Lett.* **2001**, *3*, 991) by the action of benzyltriethylammonium dichloroiodate on anilines in the presence of sodium bicarbonate and methanol. In this communication they report an environmentally friendly preparation of the iodinating reagent without the use of organic solvents (Scheme 12).

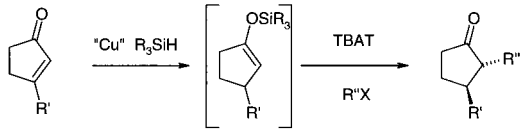
Scheme 12



Monoiodination

A one-pot synthesis of enantiomerically enriched 2,3-disubstituted cyclopentanones via copper-catalysed 1,4 reduction followed by alkylation has been reported by Buchwald and Yun (*Org. Lett.* **2001**, *3*, 1129). Their method, outlined in Scheme 13 involves 1,4 reduction using a mixture of 0.53 eq Ph_2SiH_2, 5%CuCl, 5% NaO^{t}Bu and 5% (*S*)-*p*-tol-BINAP. The intermediate silyl enol ether was treated with triphenyldifluorosilicate (TBAT) (an easily handled nonhygroscopic commercially available fluoride source) and the electrophile to give the *trans* substituted cyclopentanones in ca. 60−70% yield (range of 73:27 to 94:6 dr).

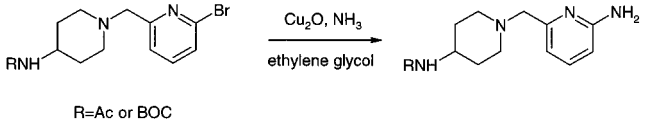
Scheme 13



One pot reduction / alkylation

Bromopyridines were converted into aminopyridines using Cu_2O catalysis with an ethylene glycol solution of ammonia by Lang and co-workers of Merck (*Tetrahedron Lett.* **2001**, *42*, 3251) in excellent yields (90%). The amination reaction (Scheme 14) features low (0.5%) catalyst loading, mild reaction temperature (80 °C), and low reaction pressure (50 psi) and offers a method for the preparation of a key building block in the synthesis of a muscarinic (M3) antagonist (Figure 4).

Scheme 14

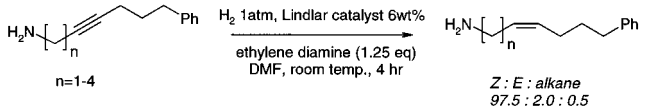


R=Ac or BOC

Amination

Ethylenediamine has been used to poison Lindlar's catalyst (*J. Org. Chem.* **2001**, *66*, 3634) by Campos and coworkers from Merck to allow for the clean, controlled semi-hydrogenation of alkynes to alkenes (Scheme 15).

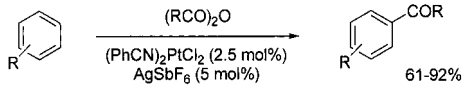
Scheme 15



Controlling hydrogenation

A catalytic version of Friedel−Crafts acylation has been described by a group at the Max-Planck Institute in Mulheim (Fürstner, A. et al. *Org. Lett.* **2001**, *3*, 417). A mixture of a platinum complex and silver hexafluoroantimonate is required to catalyse the acylation of aromatics and heteroaromatics by anhydrides. It is suggested that cationic Pt(II) reversibly activates the anhydride as well as the arene, and NMR and ESI-MS data is provided as evidence. With better catalyst utilisation and turnover, this could be of industrial significance for complex aromatic ketone synthesis (see Scheme 16).

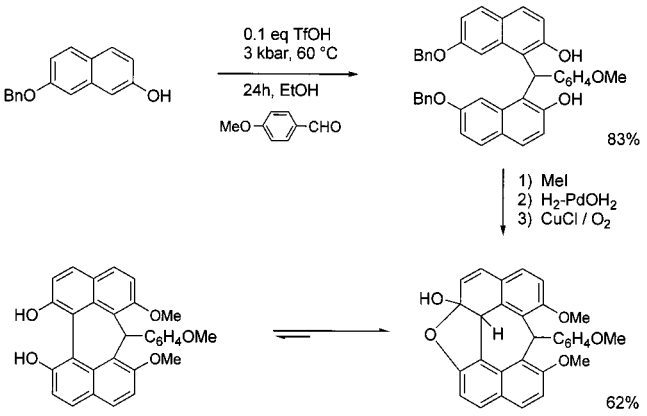
Scheme 16



A highly selective reaction between substituted phenols (and naphthols) and aromatic aldehydes has been reported (Ohishi, T. et al. *Tetrahedron Lett.* **2001**, *42*, 2493). Unfortunately the reaction takes place only under high pressure (3 kbar). The reaction has been used to provide a simple and efficient route to complex photoreceptor pigments (see Scheme 17).

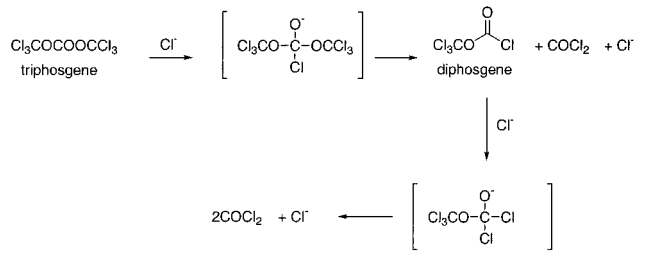
Increasing use of the solid reagent triphosgene (for a review, see Cotarca, L. et al. *Synthesis* **1996**, 553) can be ascribed to the ease of handling compared to that of phosgene and the specific reactivity that enables synthesis of unsym-

Scheme 17



metrical ureas and carbonates, carbamoyl chlorides, isocyanates, and carbamates. A recent paper from a group of chemists from Italy (Pasquato, L. et al. *J. Org. Chem.* **2000**, *65*, 8224) shows that triphosgene is decomposed quantitatively to 3 mol of phosgene by chloride ions (3−5 mol %) in hexane (using a phase-transfer catalyst) and confirms that the phosgene produced reacts faster with nucleophiles than the triphosgene or intermediate diphosgene (see Scheme 18).

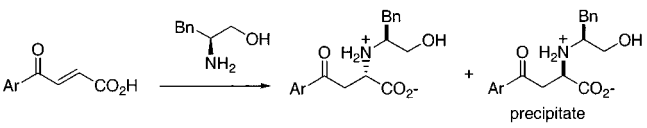
Scheme 18



The solid triphosgene can therefore be used as a safe alternative to phosgene, having the advantage of controlled generation of the phosgene in a closed environment, suitable for small-scale manufacturing operations.

Crystallisation-induced dynamic resolution is a useful, practical way to obtain enantiomers or diastereomers from simple reagents (for a review, see Caddick, S. et al. *Chem. Soc. Rev.* **1996**, 447). A recent paper demonstrates the importance of studying a range of solvents to find one where the desired diastereomer or enantiomer crystallises, and the equilibration between diastereomers (enantiomers) is relatively fast (Kolorovic, A. et al. *Tetrahedron Lett.* **2001**, *42*, 2579)—see Scheme 19.

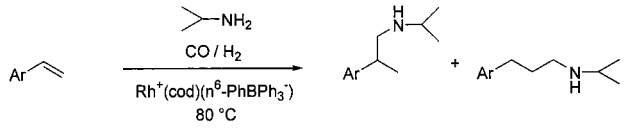
Scheme 19



Solvent	Diastereoisomer Ratio	
	Ar = Ph	Ar = 4-MeOC$_6$H$_4$
EtOH	no ppt	97:3
CH_2Cl_2	no ppt	96:4
THF	65:35	88:12
Dioxan	91:9	84:16

Hydroaminomethylation of arylethylenes takes place under relatively mild conditions in high selectivity in a new process reported by a Canadian group (Lin, Y.-S. et al. *Tetrahedron Lett* **2001**, *42*, 2423)—see Scheme 20.

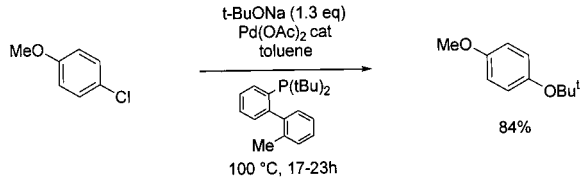
Scheme 20



Ar =	yield / %	ratio
H	92	11.5:1
4-MeC$_6$H$_4$	85	5.7:1
4-MeOC$_6$H$_4$	90	9.0:1
4-ClC$_6$H$_4$	77	5.5:1
4-PhC$_6$H$_4$	87	6.7:1

An improved procedure for the conversion of unactivated arylhalides to ethers (mainly *tert*-butyl ethers) has been discovered in the group of Buchwald at MIT (Parish, C. A. et al. *J. Org. Chem.* **2001**, *66*, 2498)—an example is shown in Scheme 21. The ligand, however, is not commercially available but can easily be synthesised in a one-pot procedure by a method reported earlier (Tomori, H. et al. *J. Org. Chem.* **2000**, *65*, 5334).

Scheme 21



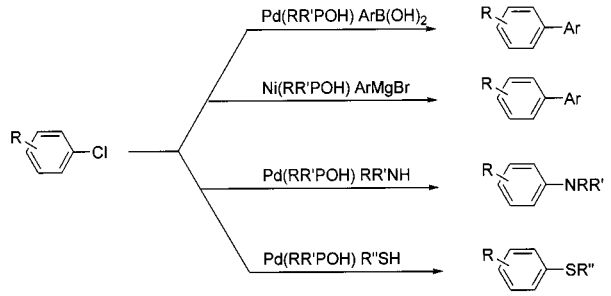
Each quarter, the *Journal of Organic Chemistry* publishes a list of recent reviews. The latest is in *J. Org. Chem.* **2001**, *66*, 2538 and is worthwhile scanning for reviews and monographs of interest. This list is also available free on the web (http//pubs.acs.org).

Weinreb amides (*N*-methoxy-*N*-methyl amides) are versatile building blocks in organic synthesis, but for the process chemist, their preparation usually involves expensive reagents such as carbodiimides or similar materials. A recent report (De Luca, L. et al. *J. Org. Chem.* **2001**, *66*, 2534) suggests that the relatively cheap 1,3,5-triazene derivatives work well in the conversion of a range of carboxylic acids to Weinreb amides. The method can also be applied to hydroxamic acid synthesis. Adjacent chiral centres are *not* racemised.

We normally think of phosphine oxides as waste products from Wittig reactions. If the phosphorus has a hydrogen attached, however, these oxides—tautomeric with phosphinic acids—can form complexes which may be useful catalysts. George Li from DuPont has now found the first example of a phosphine oxide−platinum complex which is useful for cross-coupling reactions with unactivated aryl chlorides (Le, G. *Angew. Chem., Int. Ed.* **2001**, *40*, 1513). Typical reactions are shown in Scheme 22. Yields are high for C−C bond formation but lower for C−N and C−S formation.

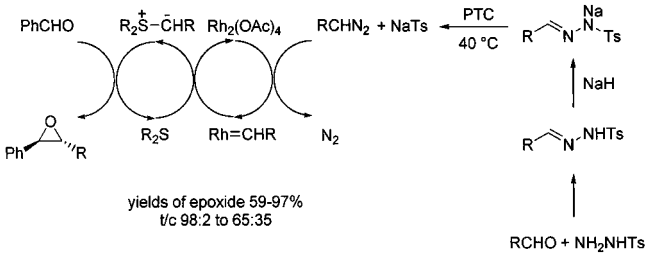
A valuable reaction of sulphur ylides is in epoxide formation (discovered by Corey), and a modification of his

Scheme 22



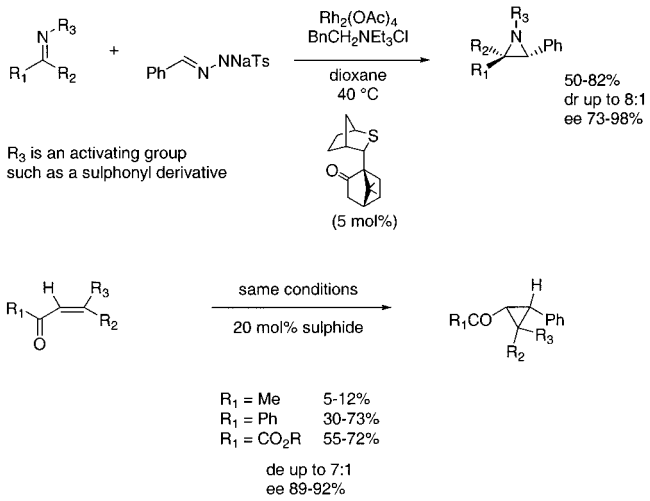
methodology is used industrially. In previous publications, a group at the University of Sheffield has generated sulphur ylides in a catalytic cycle from diazo compounds to produce the appropriate ylides "in situ" giving good yields of epoxides. They mention that they have had three explosions in 5 years when distilling phenyldiazomethane, however, and were looking for safe methods of generating diazo compounds using the Bamford−Stevens tosylhydrazone methodology. Even this can be generated "in situ", and this now produces a remarkable series of reactions which means that epoxides can be generated cleanly from two aldehydes (Aggarval, V. K. et al. *Angew Chem., Int. Ed.* **2001**, *40*, 1430)—see Scheme 23. Yields are usually better if the tosylhydrazone is isolated first.

Scheme 23



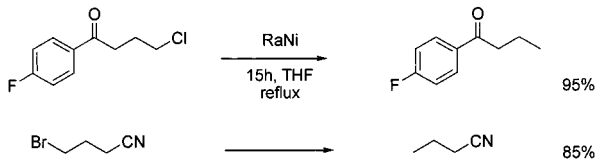
Using 5 mol % of an optically active bicyclic sulphide, asymmetric epoxidation can be achieved in 87−94% ee. In the following paper (Agganval, V. K. et al. *Angew Chem., Int. Ed.* **2001**, *40*, 1433) the same methodology is used to effect asymmetric aziridination and the cycloproparation of unsaturated ketones and esters (Scheme 24).

Scheme 24



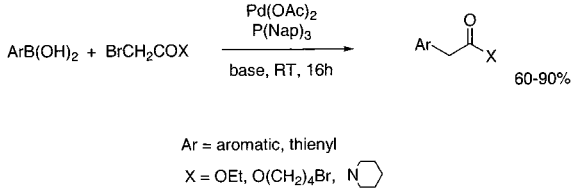
The removal of halogen from organic molecles can be effected in a number of ways, including zinc in acetic acid, hydride reduction, stannanes, and catalytic hydrogenolysis. A recent report suggests that Raney nickel is also a useful reagent for a wide variety of organic halides such as α-haloketones, aromatic halogen, alkyl halides (see Scheme 25). Fluorine is not removed, nor are vinylic halogens (Barrero, A. F. et al. *Synlett* **2001**, 485).

Scheme 25



Coupling reactions continue to dominate the synthetic chemistry literature, but the coupling of aryl boronic acids with α-haloesters has not previously been reported as a useful synthetic method. Under normal Suzuki conditions, biaryls and reduction products are obtained. By fine-tuning the ligand on the Pd metal, yields of around 90% can be obtained (Goossen, L. J. *Chem. Commun.* **2001**, 669). A wide range of substrates can be used (Scheme 26).

Scheme 26

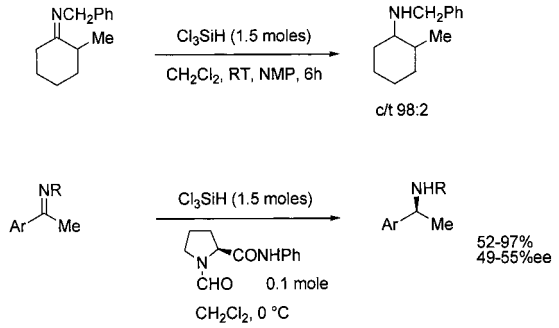


Industrial interest in use of environmentally friendly oxidising agents is high, and chemists will find much of interest in a review entitled "Hydrogen Peroxide and Air as Inexpensive Oxidants in Phase-Transfer Catalysis" (Schrader, S. et al. *Org. Prep. Proced. Int.* **2000**, *32*, 123). From the same journal an efficient and scalable synthesis of methyl-3-hydroxymethyl-benzoate is described by chemists from Warner Lambert (now Pfizer) (Chem, M. H. et al. *Org. Prep. Proced. Int.* **2000**, *32*, 381).

Trichlorosilane has previously been shown to be a useful reducing agent for imines. The latest paper from a combined industrial/academic team from Japan (Iwasaki, F. et al. *Tetrahedron Lett.* **2001**, *42*, 2525) shows that imine reduction is preferred in the presence of carbonyl groups (suggesting in situ generation?) and that an asymmetric reduction can be achieved, although as yet with moderate ee's in the range 49−66%. The reagent is activated by simple amides such as DMF and NMP—for the chiral reduction, a chiral amide is used. (Scheme 27).

An unusual set of conditions for reduction of nitriles to amines in the presence of Boc-protected amino groups has been reported (Klenke, B. et al. *J. Org. Chem.* **2001**, *66*, 2480). Whereas neither Raney nickel nor palladium on charcoal were effective catalysts for hydrogenation of the nitriles, a mixture of the two catalysts—*in the presence of water and base*—allowed hydrogenation to take place. Other catalyst mixtures were not effective. No comment is made on the reason for the success of the combination. Of course, catalyst

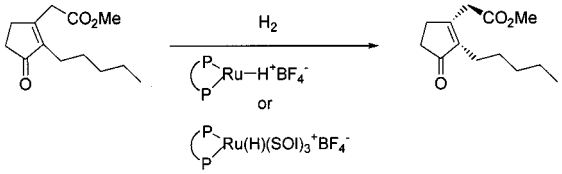
Scheme 27



recycle on large scale would probably be more difficult, but reuse may be an alternative way to keep catalyst cost down.

Novel catalysts have been discovered during the development of an industrial process to make the fragrance chemical (+)-*cis*-methyl dihydrojasmonate by enantioselective reduction of a tetrasubstituted alkene (see Scheme 28). Further mechanistic details of these active catalysts, obtained by hydrogenation at atmospheric pressure of simple precursors have now been published (Wiles, J. A. et al. *Angew Chem., Int. Ed*. **2001**, *40*, 914; Dobbs, D. A. et al. *Angew Chem., Int. Ed*. **2000**, *39*, 1992).

Scheme 28

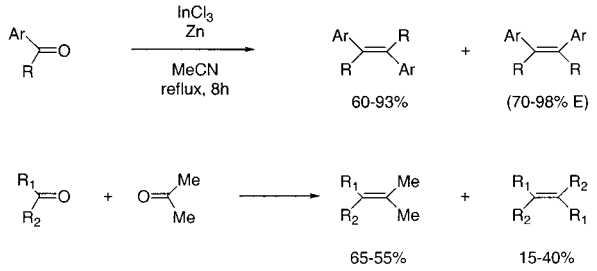


We have highlighted in these pages the trend towards using chiral monodentate ligands (usually phosphorus) in asymmetric hydrogenation. A short critique of the recent literature has been published (Komarov, I. V. et al. *Angew Chem., Int. Ed*. **2001**, *40*, 1197) in which the authors suggest that the mechanism of chiral transfer in asymmetric hydrogenation does not fundamentally differ between mono- and diphosphorus ligands (i.e., that catalysts should be conformationally rigid) and the choice of catalyst comes down to simple questions such as (1) Is it enantioselective? (2) How easy is it to obtain or synthesise? For the latter reason, monophosphorus may be preferred.

The asymmetric Strecker reaction has attracted a lot of attention recently, almost 150 years after Strecker's original publication (Ishitani, H. et al. *J. Am. Chem. Soc*. **2000**, *122*, 762; *Chirality* **2000**, *12*, 540; Vachal, P. et al. *Org. Lett*. **2000**, *2*, 867; Krueger, C. A. et al. *J. Am. Chem. Soc*. **1999**, *121*, 4284). A short review of recent developments highlights the progress and discusses the limitations for industrial scale work (Yet, L. *Angew Chem., Int. Ed*. **2001**, *40*, 875).

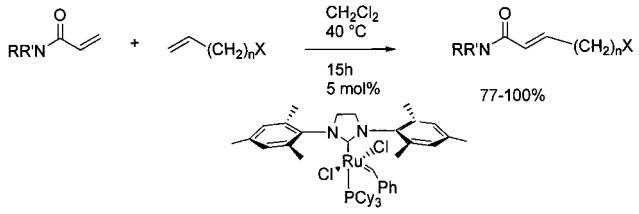
The deoxygenative coupling of carbonyl compounds to olefins is a potentially useful reaction (McMurray, J. E. *Chem. Rev*. **1989**, *89*, 1513) but sometimes suffers from a lack of reproducibility, probably owing to slight differences in the method of preparation of the reagent. Many new reagents have been suggested in the last 20−30 years, but a recent report (Barman, D. D. et al. *Synlett* **2001**, 515) suggests that indium trichloride in the presence of zinc is a simple and efficient reduction system—comparable to McMurry's reagent—for the conversion of aldehydes and ketones to olefins with high E-selectivity. Reaction of aldehydes or ketones with acetone can give moderate yields of cross coupled products (Scheme 29).

Scheme 29



Ring-closing metathesis (RCM) and ring-opening metathesis polymerisation (ROMP) have potential industrial applications and have received a lot of attention, whereas cross-metathesis (CM) has been less well-studied, although for organic chemists it could be an extremely valuable process for forming C═C bonds under mild conditions. The synthesis of functionalised alkenes has been made possible by the discovery of new catalysts by the group of Grubbs (Chatterjee, A. K. et al. *Org. Lett.* **1999**, *1*, 1751; *J. Am. Chem. Soc.* **2000**, *122*, 3783; Scholl, M. et al. *Org. Lett*. **1999**, *1*, 953). A recent publication from the same group (Choi, T.-C. *Angew Chem., Int. Ed.* **2001**, *40*, 1277) reports useful reactions of acrylamides and Weinreb amides with terminal olefins—see Scheme 30.

Scheme 30



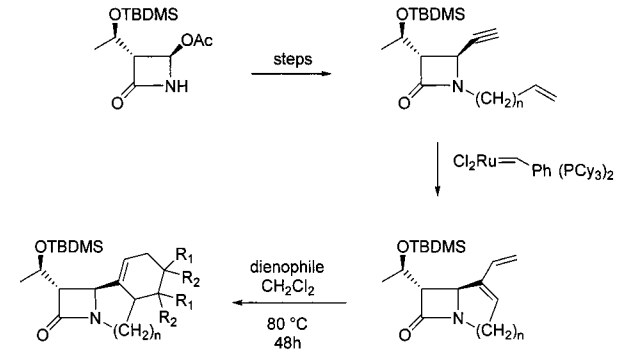
R, R' = alkyl, H, aryl, MeO, COR_2

X = OTBS, OTHP, OAc, CO_2Me, CONHOMe, $CONMe_2$

n = 2-7

Since the discovery by the Merck group in the early 1980s of thienamycin, carbapenem antibiotics have been of great interest. Tribactams have been shown by GlaxoWellcome scientists to have outstanding chemical and metabolic stability and a number of similar products (see Scheme 31) are in

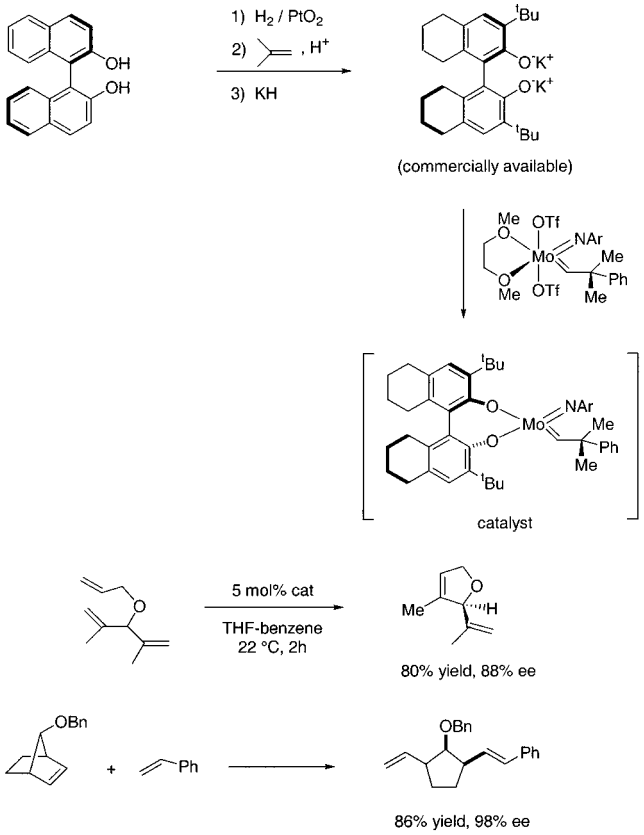
Scheme 31



clinical trials. The synthesis of these molecules is challenging, but a recent report by a group of French chemists, using olefin metathesis, looks attractive. (Duboc, R. et al. *Tetrahedron Lett*. **2001**, *42*, 2461).

Catalystic asymmetric olefin metathesis continues to be of interest, and a brief overview has appeared (Hoveyda, A. H. et al. *Chem. Eur. J*. **2001**, *7*, 945; see also Fürstner, A. *Angew Chem., Int. Ed*. **2000**, *39*, 3012). For many chemists the availability of catalysts is an issue, and simple preparative methods from commercially available raw materials would encourage more industrial chemists to use the methodology. A recent report from the groups of Schrock (at MIT) and Hoveyda (Boston College) describes a simple method of making chiral molybdenum catalysts "in situ" and use in enantioselective olefin metathesis (Aeilts, S. L. et al. *Angew Chem., Int. Ed*. **2001**, *40*, 1452)—see Scheme 32.

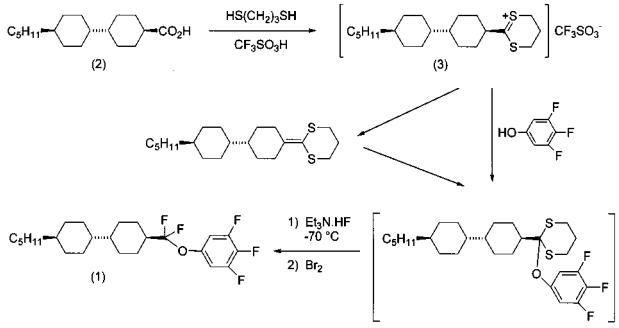
Scheme 32



The structure of liquid crystals becomes more complex and places a challenge for the synthetic—and particularly the process—chemist. A group at Merck AG, Darmstadt (Kirsch, P. et al. *Angew Chem., Int. Ed*. **2001**, *40*, 1481), report on a novel method of synthesising compound (**1**) by oxidative alkoxydifluorodesulphuration. The carboxylic acid (**2**) is converted to a dithianylium satt (**3**) which reacts with a phenol, $Et_3N{\cdot}HF$ and bromine to give the desired product (Scheme 33).

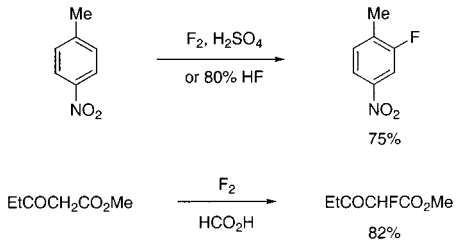
There seems to be an increase in interest in fluorine chemistry these days, although many chemists would be reluctant to handle fluorine itself. Nevertheless, there are companies who handle elemental fluorine, and a review of selective fluorination using F_2 has been published (Moilliet,

Scheme 33



J. S. *Chim. Oggi* **2001** (Jan/Feb), 41). When fluorination of organic molecules is carried out by a 10% F_2 in nitrogen mixture in an acidic reaction medium (formic, sulphuric, or hydrofluoric acid), selective fluoronation of aromatics and aliphatics can occur—see Scheme 34.

Scheme 34



Industrial chemists and engineers are looking for the ideal catalyst system which combines the advantages of homogeneous catalysis (higher selectivity, tunability, range of catalysts) with the obvious advantage of heterogeneous systems (removal of catalysts, recycling). A recent report from the University of Leuven, Belgium, describes a continuous process involving an homogeneous catalyst which is retained by a nanofiltration (NF) membrane (MW cutoff in the range 200−700; conditions below 40°). The methodology has been used in the enantioselective hydrogenation of dimethylitaconate and methylacetamidoacrylate with TOF of 1950 and 930 using Rh−BINAP and Rh−EtDUPHOS catalysts. Whilst the ee in the latter case is not as good as the reported value of 99.4%, it is suggested that these preliminary results demonstrate the general concept of a "hybrid" process with catalyst retention in the membrane.

Recent progress on anchored transition metal catalysts for hydroformylation of olefins has also been reported (Nowotny, M. et al. *Angew Chem., Int. Ed.* **2001**, *40*, 955). See also "Rhodium-Catalysed Hydroformylation" (van Leevwen, P. W. M. N. and Claver, C.), Kluwer, Dordrecht, 2000.

Sulpha drugs such as sulphathiazole are well-known to form many polymorphs (see Apperley, D. C. et al. *J. Pharm. Sci.* **1999**, *88*, 1275), and they often form solvates with most solvents. A recent study, which was originally intended to search for new polymorphs by recrystallising sulphathiazole from less common solvents, found that the compound crystallises as a solvate from many solvents. (Ann L. Bingham et al. *Chem. Commun.* **2001**, *7*, 603) A more detailed examination found more than 100 solvates of the drug. In general the solvates form two types; clathrates, or

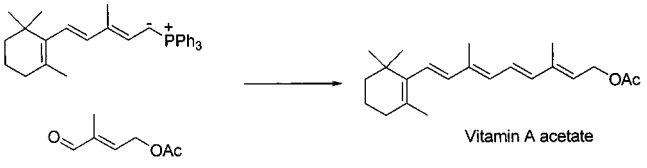
inclusion phases where the solvent essentially fills the cavities, and cocrystals, where the solvent forms an essential part of the hydrogen-bonded network in the lattice. All of the solvates were fully characterised by spectroscopic microscopy and thermochemical measurements.

A short review on novel catalysts for atom economic aromatic nitration from the group of Braddock and Barrett at Imperial College is in the latest issue of *Green Chem.* (**2001**, April, G26). The methodology, highlighted in these pages a couple of years ago, involves the use catalytic quantities of lanthanide triflate in the nitration of aromatics. The review describes results of an in-depth mechanistic study which led to the development of superior catalysts, which may be recycled and reused. The same group, as a spinoff from this work have described scandium triflate-catalysed acetylation of primary, secondary, and tertiary alcohols and nitric acid oxidation of alcohols to aldehydes.

It is over 100 years since Baeyer and Villiger discovered the reaction which bears their name, and it is an important large-scale methodology, using cheap reagents to achieve a high-yielding and usually very selective process. Recently, there has been interest in developing catalytic methods using, for example, H_2O_2, as oxidant to reduce the amount of waste generated (see Strukel, G. *Angew. Chem., Int. Ed*. **1998**, *37*, 1198). Catalysts based on Se, As, Mo, Re, Pt, and Zr have been reported. The group of Sheldon in Delft, The Netherlands, suggest that an excellent catalyst is bis(3,5-bis(trifluoromethyl)phenyldiselenide, which is transformed to the corresponding seleninic acid in solution (ten Briak et al. *J. Org. Chem.* **2001**, *66*, 2429). This catalyst had previously been shown to be useful in epoxidation reaction by the same group (Ten Brioche, G. J. et al. *J. Chem. Soc*., *Perkin Trans 1* **2000**, 224).

Chemists will be fascinated by a short essay on the life of Georg Wittig and his accomplishments (Hoffmann, R. W. *Angew Chem., Int. Ed.* **2001**, *40*, 1411). Of course Wittig is mainly known for the olefination of ketones, a reaction which bears his name. This reaction was so useful that it was immediately applied, for example, in the synthesis of vitamins A and D. Horst Pommer at BASF was able to devise an alternative route to vitamin A (Scheme 35), and this was quickly scaled up and taken into commercial production.

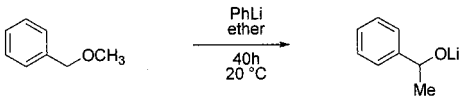
Scheme 35



It is worthwhile remembering that Wittig did not conceive the reaction—it arose out of unexpected observations and the ability to recognise their potential. The article describes the background to the discovery and makes very interesting reading.

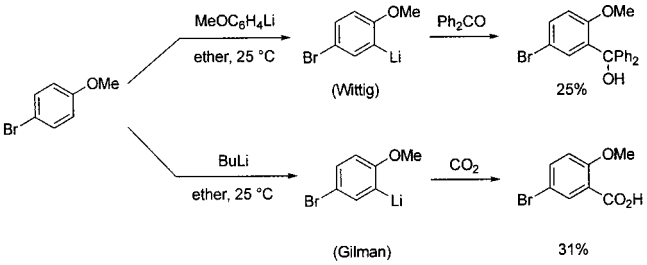
Wittig also discovered an anionic ether rearrangement which also bears his name (Scheme 36). Despite the

Scheme 36



commercial potential of this C−C bond forming reaction, this has not—as far as I know—been commercialised. He was also responsible—along with Gilman—for metal−halogen exchange (discovered in 1938) and the directed orthometalation of aromatics (Scheme 37). This reaction, whose scope

Scheme 37



was explored widely by others, is now used in a number of industrial processes.

He was also the first person to generate benzyne, to use complex bases (when a mixture of two bases is more reactive than the individual components), and one of the first to carry out asymmetric reduction of ketones (60% ee in 1969). Wittig received the Nobel Prize in 1979 for his work in the area of ylides and carbanion chemistry.

The account illustrates the value of serendipity in chemical discovery (funding agencies, please note!) and that simple techniques can often be used to discover new reactions—the rearrangement of penta-arylphosphoranes to triarylphosphines was found after taking a melting point! The melted solid was resolidified and remelted and the difference in melting point noted—this indicated a rearrangement had taken place on heating.

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