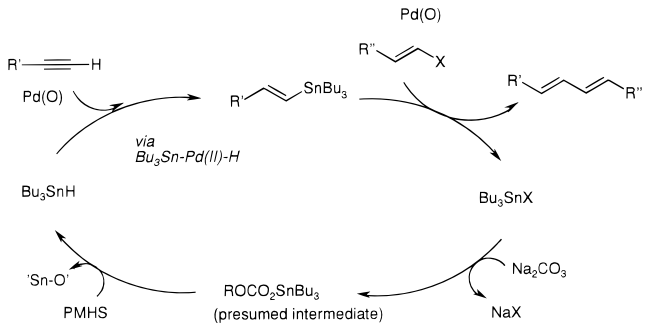
Organic Process Research & Development **2000**, *4*, 134–140

Highlights from the Literature

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

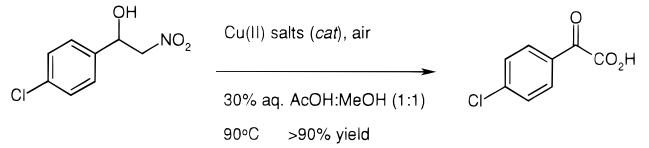
Stille reactions have proven useful in natural product synthesis, heterocycle preparation, and carbohydrate chemistry and involve the Pd-catalysed union of vinyl or aryl halides with vinylstannanes to form 1,3-dienes. Despite such synthetic utility, a historical drawback of this important reaction is the reliance on stoichiometric quantities of toxic, costly, and occasionally unstable organostannanes. Robert Maleczka, Jr., and co-workers at the Michigan State University have recently reported (*J. Am. Chem. Soc*. **2000**, *122*, 384) Stille reactions that are catalytic in tin. In their protocol the reaction sequence is run in the presence of aqueous Na_2CO_3 and polymethylhydrosiloxane (PMHS) affecting in situ conversion of the trialkyl halide Stille byproduct into a tin oxide species which is subsequently reduced, regenerating the R_3SnH. The catalytic cycle is shown in Scheme 1. The group have shown improved reaction with trimethyltin chloride at 6 mol % loading coupled with 1 mol % $PdCl_2(PPh_3)_2$, 1 mol % Pd_2dba_3, and 4 mol % $(2\text{-furyl})_3P$.

Scheme 1



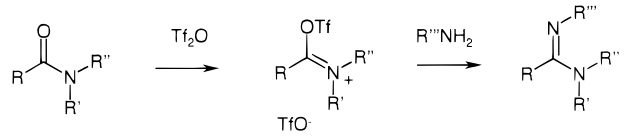
Sudalai and co-workers (*Tetrahedron Lett.* **2000**, *41*, 959) have recently demonstrated that catalytic Cu(II) salts in 30% aqueous AcOH:MeOH (1:1) can be used for the conversion of aryl nitroaldol adducts (prepared by the Henry reaction) to aryl α-keto acids (Scheme 2). The group have used $Cu(OAc)_2 \cdot H_2O$, $CuCl_2$ and $CuSO_4 \cdot 5H_2O$ with good success.

Scheme 2



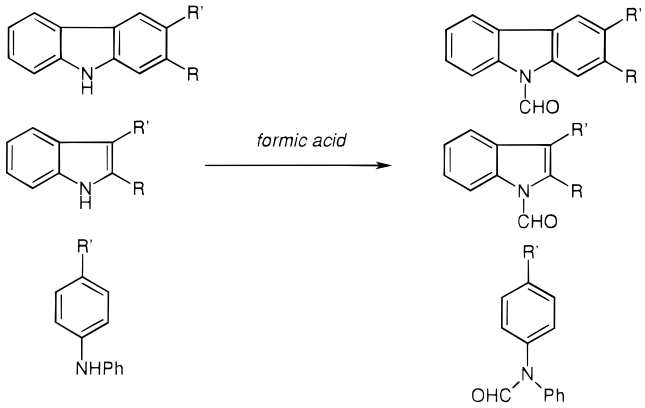
Amidines are useful intermediates in the preparation of heterocyclic compounds. Conventional strategies for amidine synthesis include addition of metal amides or amines to nitriles, addition of amines to imido ester intermediates, and the condensation of amides with amines in the presence of halogenating reagents. Charette and Grenon (*Tetrahedron Lett*. **2000**, *41*, 1677) have demonstrated that amidines may be prepared by activating secondary or tertiary amides with trifluoromethanesulphonic anhydride (triflic anhydride) to generate the corresponding iminium salts which undergo reaction with nucleophiles (Scheme 3). The amine nucleophile may conveniently be added as the hydrochloride salt and the product amidine subsequently isolated as its salt.

Scheme 3



Chakrabarty and co-workers (*Synth. Commun*. **2000**, *30*, 187) have demonstrated that neat formic acid alone efficiently *N*-formylates carbazoles, 3-alkylindoles, diphenylamine, and even moderately weak nucleophilic anilines to generate the *N*-formyl derivatives in 72−87% yields. Formic acid is inexpensive and readily available, and the reaction byproducts are environmentally friendly. This efficient reaction is testimony that the simplest reagents should be tried before the more elaborate and costly ones (Scheme 4)!

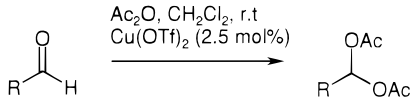
Scheme 4



Acylals are efficient protecting groups for aldehydes as they are stable in neutral and basic media. Usually they are prepared by treatment of aldehydes with acetic anhydride in the presence of strong protic or Lewis acids. Singh and co-workers have reported (*Synlett* **2000**, 359) the use of $Cu(OTf)_2$ as an efficient catalyst for the acylation reaction of aldehydes with acetic anhydride in CH_2Cl_2 (Scheme 5). Their postulated mechanism involves the reaction of Ac_2O with $Cu(OTf)_2$ to generate in situ Cu(OTf)(OAc) and the acyl triflate. The aldehyde then can react with the Cu(OTf)-(OAc) to give RCH(OCuOTf)(OAc) which in turn reacts with the acyl triflate to generate the acylal.

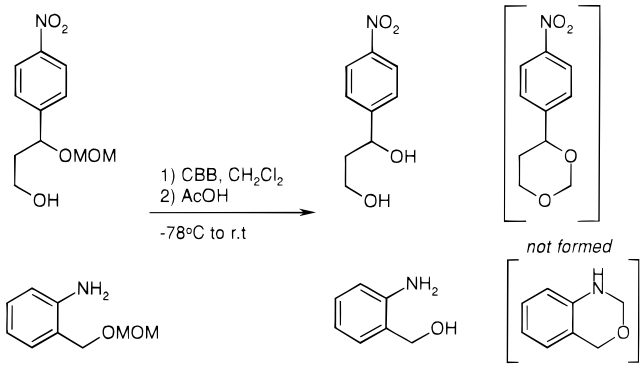
 10.1021/op0000374 CCC: $19.00
Published on Web 04/18/2000

Scheme 5



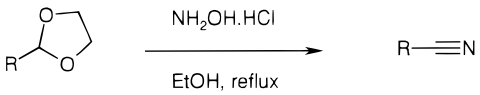
Hu has recently reported (*Tetrahedron Lett*. **2000**, *41*, 819) a modified procedure for the deprotection of the robust methoxymethyl ether (MOM) protecting group using a combination of catechol boron bromide (CBB) with acetic acid. In particular this method circumvents the formation of cyclic formyl acetals when the MOM protected substrates contain proximate hydroxyl or amino functionalities. Deprotection of the substrates shown in Scheme 6 using this method affords the diol and amino alcohol products in >91% yield.

Scheme 6



It is not only the current literature that contains smart ways of doing simple organic reactions. The less recent literature provides a wealth of synthetic tricks, procedures, and preparations! Yamauchi reported (*Chem. Pharm. Bull*. **1993**, *41*, 2042) that acetals may be easily converted to nitriles using hydroxylamine hydrochloride in refluxing ethanol for ~2 h. This interesting conversion makes use of an acetal "protecting group", circumvents a deprotection, and formally performs an oxidation from the aldehyde oxidation state to that of a carboxylic acid—all in one pot (Scheme 7)!

Scheme 7



Nishi and co-workers have described (*Tetrahedron Lett*. **2000**, *41*, 1785) a versatile method for the preparation of 2,2-disubstituted morpholine analogues as shown in Scheme 8. In their approach, treatment of a styrene derivative with *N*-iodo succinimide in the presence of *N*-BOC-aminoethanol in acetonitrile at 70 °C gave the iodoether which was ring closed by treatment with NaH in DMF. Acid mediated deprotection followed by resolution using (D)-tartaric acid gave their key chiral building block.

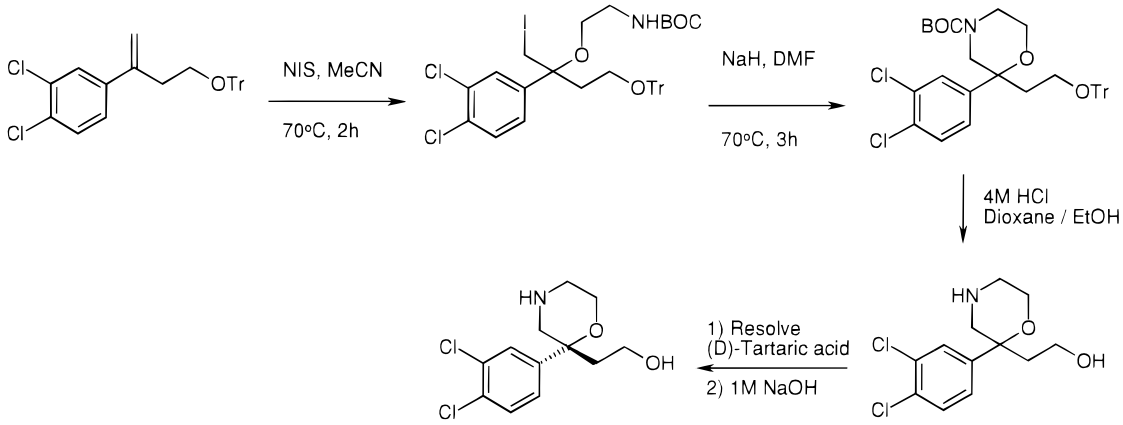
Antibiotic 1-β-methylcarbapenems have been the subject of much investigation because of their chemical and metabolic stability as well as potent and broad antibacterial activity. Orally active carbapenems are still rare and in great demand. Researchers at Tanabe in Japan have discovered a promising candidate TA 949 and now report an efficient and economic synthesis (Seki, M. *J. Org. Chem*. **2000**, *65*, 517).

The key building block, (*R*)-4-mercaptopyrrolidine-2-thione was quite tricky to make since Mitsunobu reactions of the known (*S*)-4-hydroxypyrrolidine-2-one were low-yielding, and alternatives were deemed unsuitable for large-scale work. The rather long but high-yielding route from aspartic acid was preferred (Scheme 9).

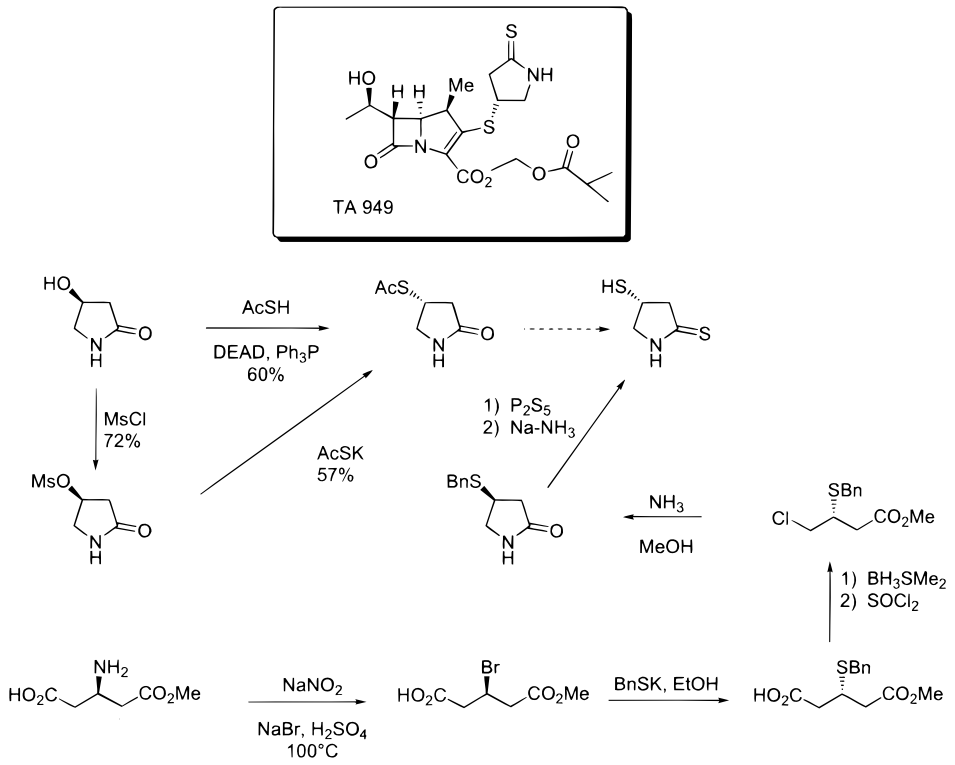
The choice of solvent for the displacement of the bromide by potassium benzenemethylthiolate was crucial, since in THF and DMF much racemisation occurred, even at 25 °C. Ethanol proved to be the solvent of choice, accelerating the reaction from 96 h in THF to 3 h in EtOH but with no racemisation.

Strobilurin analogues are a relatively new class of agricultural fungicides with a wide spectrum of activity and a new mode of action. It is not surprising that agrochemical companies have examined modifications to the basic structure to seek to differentiate their products and to obtain patentable compounds. Zeneca (with ICI A 5504) and BASF (with BAS-490F) already have products on the market in this area. The Mitsubishi candidate (*S*)-MA20565 (Scheme 10) has a slightly different pharmacophore (*N*-methylmethoxyimino-acetamide) and a substituted aldoxime ether side chain. It shows potent fungicidal activity against a wide range of crop diseases, and thus, a practical asymmetric synthesis of the compound was required, as reported by Tanaka et al (*J. Org. Chem*. **2000**, *65*, 432)—see Scheme 10. The synthesis of the chiral component was carried out using 3-trifluoromethyl-

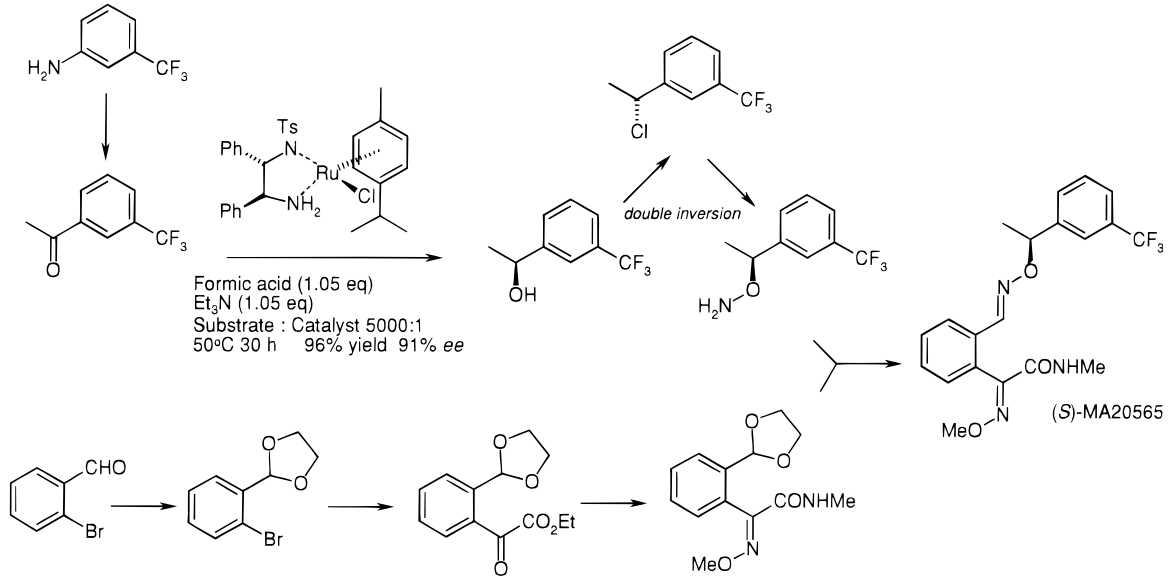
Scheme 8



Scheme 9



Scheme 10



aniline as raw material, by diazotisation and reaction with acetaldoxime followed by hydrolysis, giving the required trifluoromethylacetophenone. The alternative route via a trifluoromethylphenyl Grignard reagent was ruled out because of the well-known explosibility of these derivatives.

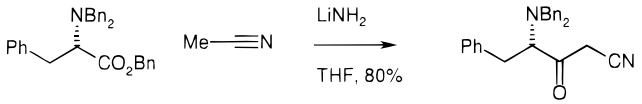
The asymmetric reduction was a modification of Noyori's ruthenium(II)-catalysed procedure using formic acid in preference to 2-propanol. The problem of removal of acetone byproduct was cited as the main reason for the choice. With formic acid/Et_3N, a substrate-to-catalyst ratio of 5000:1 can be achieved, but the slow reaction necessitates reduction at 50 °C which lowers the enantiomeric excess to 91%. In the conversion of the chiral alcohol to the chloride using MsCl/pyridine, the choice of solvent was crucial to get a high yield, to avoid product racemisation, and to get the reaction to proceed at a reasonable rate. The use of a DMF/heptane mix of 2:5 was the best compromise and had the further advantage of simple workup and low effluent loading.

In the preparation of the other half of the molecule, the choice of protection group was crucial to the success of the chemistry. The dioxolane group was preferred; the diethylacetal derivative decomposed in the reaction of the ketoester with methoxyamine hydrochloride, whereas a dioxan group as aldehyde protection gave poorer E/Z ratios.

The final condensation of the two halves was carried out in acetic acid/water as solvent which caused acceleration of the reaction and direct crystallisation of the product from the reaction mixture.

In the synthesis of the Abbott protease inhibitor Ritonavir, Chang and Stuk report (*Synth. Commun*. **2000**, *30*, 955) the use of lithium amide in preference to sodium amide in the nucleophilic addition of acetonitrile to *N*,*N*-dibenzyl L-phenylalanine benzyl ester. The lithium amide gave little racemisation (Scheme 11) and is non-pyrophoric.

Scheme 11



The use of oxygen or air as a co-oxidant in the asymmetric dihydroxylation of olefins is briefly reviewed (Wirth, T. *Angew. Chem., Int. Ed.* **2000**, *39*, 334). There have been a number of reports in 1999 of the use of co-oxidants, but the group of Beller has shown that oxygen at 50 °C gives good yields of diols in high yield and good enantiomeric excess. Both oxygen atoms are utilised, in contrast to many other systems. The importance of pH control is emphasised, with high conversions at pH 10.4 in *tert*-butyl alcohol containing a phosphate buffer.

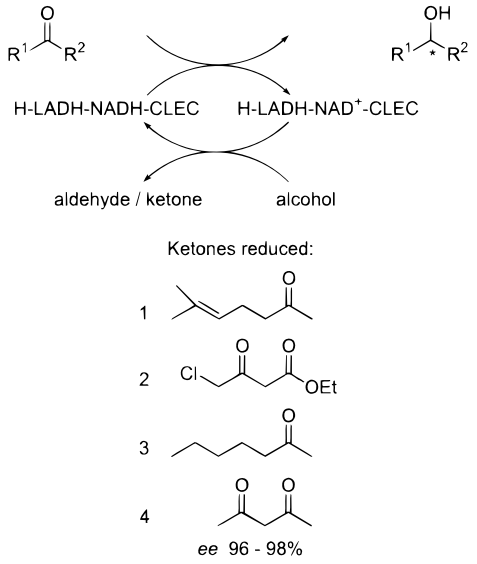
Whilst green chemical alternatives to chromium-based oxidising agents would be preferred, it is useful to have a method of recovering the chromium from waste water when this metal has to be used. A new method has been described by workers at the Central Leather Research Institute in India (Sreeram, K. J. et al. *Green Chem*. **2000**, *2*, 37).

Green oxidations are reviewed in the perspectives section of the latest issue of *Green Chem.* (**2000**, *2*, G28).

A review of the use of room-temperature ionic liquids, solvents for synthesis and catalysis, has appeared (Welton, T. *Chem. Rev*. **1999**, *99*, 2071). The author points out that these are not new—the first ionic liquid ($EtNH_3^+NO_3^-$) which has a melting point of 12 °C, was first described in 1914. Ionic liquids are useful solvents for many industrial processes, and the catalytic cracking of polyethylene to light alkanes has recently been described (Adams, C. J. et al. *Green Chem*. **2000**, *2*, 21).

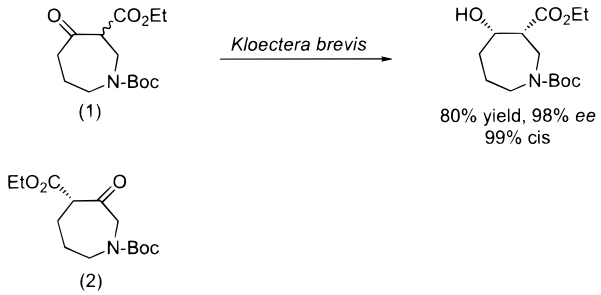
The use of enzymes in asymmetric reduction has often been limited by the instability of the enzymes and cofactors, and by the need for efficient cofactor regeneration. In a recent report, the group of Margolin at Altus Biologics in Cambridge, MA, U.S.A. (*Angew. Chem., Int. Ed*. **2000** *39*, 380) have shown that the cross-linked enzyme crystals (CLECs) approach, previously successful in stabilisation of a number of enzyme classes, can also be used to stabilise the cofactor NADH. Thus, the enzyme horse liver alcohol dehydrogenase (HLADH) in its CLEC form can now be used for the asymmetric reduction of ketones in high enantiomeric excess, using a simple alcohol (2-propanol, butanediol) as the reducing agent to regenerate the cofactor. Some reactions are a little slow at room temperature, but the turnover number for cofactor regeneration was calculated to be 12000. This suggests that this process has the potential for high catalyst productivity. The stability of the HLADH-CLEC towards organic solvents is important in these reduction processes, allowing high concentration of organic alcohols to be used in the cofactor recycling (Scheme 12).

Scheme 12



In a paper describing synthesis of drugs and their intermediates using enzyme-catalysed processes Hans-Georg Leuenberger of Hoffmann-La Roche, Basel shows the atom economy of some of these biotransformations. Examples include the biosynthesis of lipostatin, the penultimate intermediate in the synthesis of the anti-obesity drug Xenical, the use of microbial fermentation to produce quinic acid or shikimic acid, precursors of the new anti-influenza drug Tamiflu (RO 64-0796), and a novel microbial hydrogenation (Leuenberger, H.-G. W. et al. *Chimia* **1999**, *53*, 536). In the latter example the yeast *Kloeckera brevis* can not only convert a racemic mixture of ketoesters (**1**) to a single product in high enantiomeric and diastereomeric excess but can also distinguish between the desired substrate (**1**) and its isomer (**2**). This allows the use of crude **1** containing 25% of **2**, eliminating the need to purify the substrate (Scheme 13).

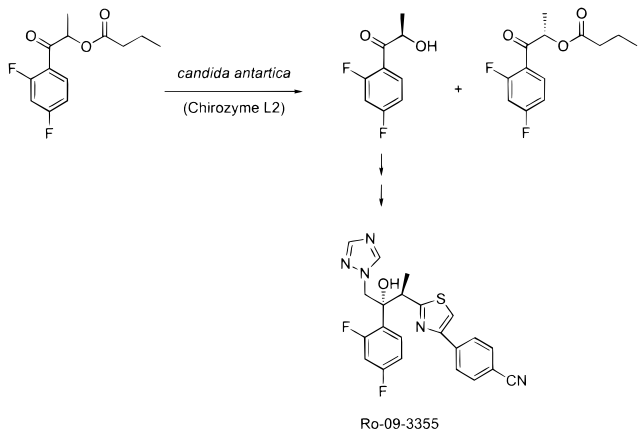
Scheme 13



In the same paper the kinetic resolution of the butyrate ester in a biphasic system is described. Whereas the corresponding acetate was hydrolysed to α-hydroxyketone in 70% enantiomeric excess, the butyrate ester gave 78%

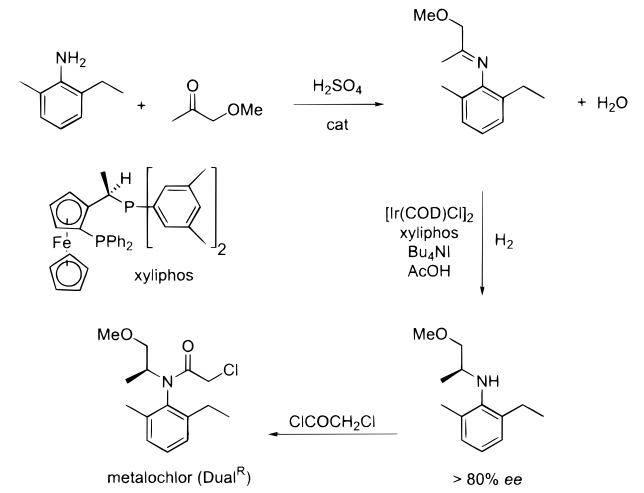
enantiomeric excess, and the product was easier to isolate from unreacted ester by a distillative workup (46 kg scale). Presumably the unreacted butyrate ester was racemised in a recycle step (Scheme 14).

Scheme 14



The development of the large-scale process for the production of metalochlor, the active ingredient of the herbicide, Dual, is described in a lecture transcript (Blaser, H.-U. et al. *Chimia* **1999**, *53*, 275). The article describes the development work involved in the production of a process for 10 000 t/a manufacture, using an enantioselective catalytic process. Whilst some aspects of this work have already been reported, the interest in this article is the thinking behind the ideas, the reasons for the choice of synthetic route, the assessment and screening of the proposed routes, the screening of ligands and catalysts, the optimisation of the reaction conditions, and the synthesis of the ligand known as xyliphos. The first stage of the process to form the key imine looks trivial but was quite tricky, since significant byproducts occurred when the process was pushed to 100% conversion. It was also very sensitive to the quality of methylethylaniline used, so a multistep continuous distillation process was required to purify the air-sensitive imine. The purity of the imine affects the subsequent hydrogenation step (Scheme 15).

Scheme 15

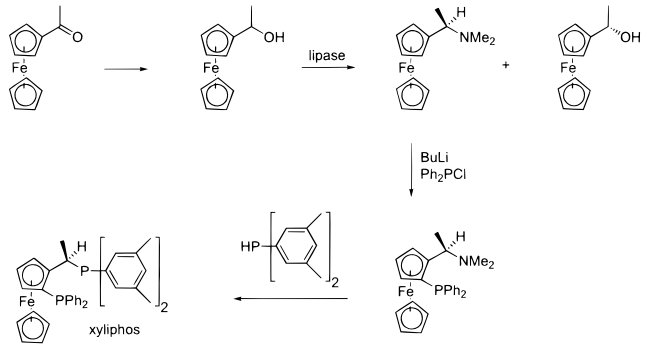


In contrast to many similar ligands, xyliphos showed high turnover numbers (1,000,000 initially optimised to 2,000,000) and turnover frequency. Interestingly, adding 30% acetic acid to the process resulted in a rate increase by a factor of 5, while the time for 100% conversion was reduced by a factor of 20 once all additives were used. The enantioselectivity was slightly temperature sensitive but not sensitive to the hydrogen pressure. However, a high-pressure reactor is required.

The addition of a solid multicomponent catalyst mixture to a high-pressure reactor is time-consuming so a stable liquid formulation was produced. The hydrogenation was performed in a loop reactor at 50 °C and 80 bar since the exothermic reaction can best be controlled using large external heat exchangers. The product is isolated by distillation and the iridium recovered; the expensive ligand, xyliphos, however is lost during this process. The high turnover number, however, ensures that the process is economic, despite this loss.

The xyliphos ligand is prepared by a six-step process, shown in Scheme 16. It is interesting that the displacements

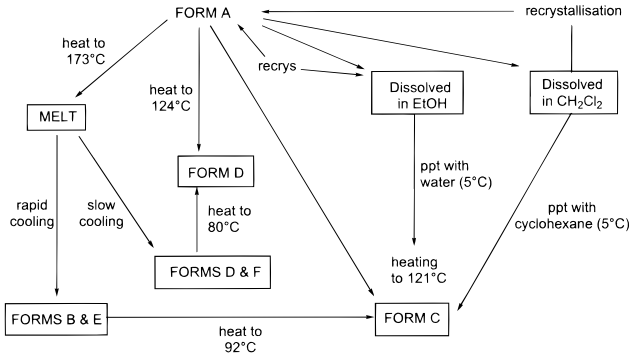
Scheme 16



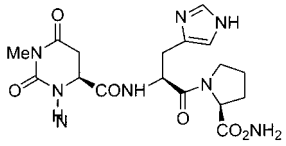
all occur with retention of configuration. The process has been operated on 2500 L scale to produce hundreds of kilograms of catalyst.

The merging of large chemical and pharmaceutical companies occasionally leads to the spin-off of some smaller units into separate organisations, which can then offer services to the whole industry. A good example is Novartis, which spun off the Scientific Services section which includes Analytical Chemistry, Physics, and Catalysis. In an article in *Chimia* **1999**, *53*, 261. Hans-Ulrich Blaser and Martin Studer describe the services offered with some case studies. One case study involves the solid-state characterisation of Iufeniron, a drug marketed as a racemate. Form A is the stable modification, but Form C is also considerably stable and is stable in the solid state for months at room temperature when dry. In slurries, Form A transforms to Form C within a short period of time. The complex interconversions are shown in Scheme 17, which demonstrates the importance of understanding the stability of the polymorphs and interconversion of the polymorphs as an aid to controlling their production.

Scheme 17



A group at Tanabe Seiyaku in Japan (Maruyama, S. et al. *Chem. Eng. J.* **1999**, *75***,** 193) describe the solution to a potential polymorphism problem in the manufacture of the drug taltireline (**3**), a central nervous system activating agent. The chosen form for the formulated product, the α-form, was metastable at its crystallisation temperature, 10 °C. To suppress the transformation to the *β*-form, the critical parameters that influence the crystallisation process were examined. Both forms crystallise as hydrates, with the α-form being less soluble—and therefore more stable—above 39 °C in both methanol/water and water, as demonstrated by examination of the solubility curves. Thus, at the crystallisation temperature of 10 °C, the undesired *β*-form was the stable form.



(3)

To control the production of the α-form, it is necessary to crystallise from methanol−water but to remove methanol from the crude precipitate in a drying step before recrystallisation from water. Any methanol, which remains behind, promotes the formation of the *β*-form. The stirring rate also increases the rate of conversion from α to *β*. Interestingly the transformation from α to *β* ***decreases*** with an increase in temperature, and thus it is important not to have the temperature too low in the crystallisation—this is obviously driven by solubility factors! My guess is that to get the correct polymorphic form, the authors must accept a lower yield of product in the isolation process—the mother liquors, of course, could always be recycled.

The control of pollution is an important issue in the design of chemical processes and can be achieved in many ways such as:

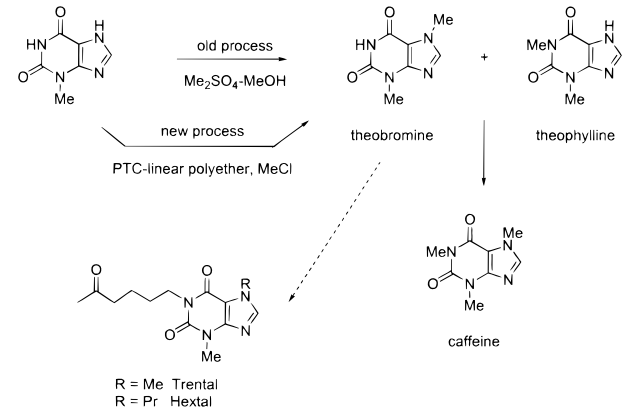
- atom efficient synthetic routes
- catalytic processes
- replacing toxic reagents and solvents
- clean chemistry/production
- recycling waste
- end-of-pipe solutions

End-of-pipe solutions usually result in high capital expenditure and do not reduce the consumption of raw materials, and an integrated approach to pollution prevention and control is recommended by C. Christ of Hoechst AG, Germany (*Chem. Eng. Technol.* **1999**, *22*, 642). Some examples are given below.

In the production of *n*-valeraldehyde and amyl alcohol, the old process used a cobalt catalyst to hydroformylate a mixture of butanes to produce valeraldehyde, part of which is hydrogenated to amyl alcohol. In the new process a selective rhodium catalyst allows the conversion of only 1-butene so that in a second stage the unreacted 2-butene can be converted to valeraldehyde using Co catalysis. The modification increases the yield of *n*-valeraldehyde and reduces the iso content. The waste water pollution is cut from 3.4 t COD to 1.1 t COD, and the amount of waste from 785 t to 100 t (per 1000 t in valeraldehyde).

In the production of theobromine, an intermediate in the synthesis of the drugs Trental and Hextol, 3-methylxanthine is methylated (Scheme 18), but the byproducts are theophylline and caffeine. In the old process using dimethylsulphate and methanol, the yield is 81.5%, but 7400 kg of waste for incineration per 1000 kg of theobromine is produced. In the new PTC process using methyl chloride, an 88% yield is also accompanied by a reduction in waste to 50 kg per 1000 kg theobromine. Waste water pollution drops from 400 kg COD to 60 kg COD, and the energy requirement is one tenth of the former process. Pollution prevention pays for itself, since process costs are down by 15% in the new process.

Scheme 18



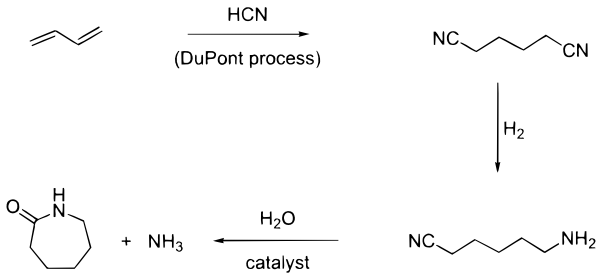
In a change to an enzyme process for the production of 7-aminocephalosporanic acid (ACA), the waste requiring incineration was reduced from 3100 kg to 30 kg (per 100 kg ACA) and the fraction of the process costs accounted for by environmental protection reduced from 21 to 1%. The absolute environmental protection costs are reduced by 90% per tonne of ACA.

In conclusion, the author points out that production integrated environmental protection is cost-effective, benefiting both ecology and economy. Both of these terms derive from the Greek “Oikos” meaning house, and thus we are concerned with both nature’s and societies “housekeeping” in the aims of sustainable development.

The latest issue of *Green Chemistry* contains an editorial (by Roger Sheldon of Delft University) which describes some new environmentally friendly processes. The production of caprolactam using the Beckmann rearrangement of cyclohexanone oxime gives a large amount of salt byproduct: 4.5 kg salt per kg caprolactam; thus, companies have looked at alternative routes.

The Rhodia process (Scheme 19) involves the hydrolysis/cyclisation of aminoadiponitrice, using an alumina catalyst in the vapour phase at 3000 °C (*Green Chem.* **2000**, *2*, G3). The ammonia can be recycled. Sixty tonnes were made by this process in 1999, and it is scheduled to have a 100,000 tonne plant by 2003.

Scheme 19



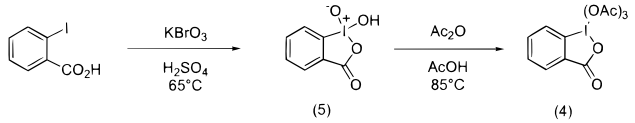
In an article entitled "Process and Product Engineering − achievements, present and future challenges", K. Wintermantel of BASF, Germany describes the key issues facing chemists and chemical engineers in the future (*Trans. I Chem. E* **1999**, *77A*, 175). One case study refers to the importance of trace additives to control crystallisation of a carboxylic acid. If trace impurities in the product occurred, the small size and needle shape of the crystals caused isolation difficulties, and subsequent drying was difficult. A more compact form had been produced in the lab by crystallising from pure water. However, addition of just 10 ppm of an anionic surfactant gave a further improvement in particle size and shape, which was beneficial.

BASF use computer simulation to study the most important crystal surfaces, using data obtained from X-ray examination. In the simulation, contaminant molecules as well as molecules which are expected to have a beneficial effect on the crystallisation process are "placed" on the surface, and their absorption energy is calculated. The hypothesis is that the growth rate of a surface is lower as the absorption energy increases, and this was confirmed experimentally,

In the conclusion to the article, Wintermantel discusses the role of chemical engineers in industry and the academic needs of the chemical engineering profession. One statement could equally apply to any discipline—"...university scientists and engineers should not focus narrowly on meeting the needs of industry but rather on extending our fundamental knowledge". He indicates that it is useful if industrial scientists return to academia to study fundamental research and pass the industrial knowledge on to students. The importance of basic research in both academia and industry is emphasised.

And finally, a hazard warning which comes from the latest edition of *Org. Synth.* (**2000**, *77*, 141) relating to a multigram synthesis of the Dess Martin reagent, 1,1,1,-triacetoxy-1,1-dihydro-1,2 benziodox-OI-3(1H)-one (**4**), via oxidation of *o*-iodobenzoic acid with potassium bromate followed by acetylation of the intermediate (**5**). Both the intermediate and Dess Martin reagent are heat- and shock-sensitive (Scheme 20).

Scheme 20



Samples of the intermediate exhibited exotherms upon heating to >130 °C in a DSC characteristic of an explosive material. The periodinane reagent is explosive when impure, but pure samples are less sensitive. When handling these materials on large scale, appropriate rigorous thermal hazard evaluation is essential.

Trevor Laird*
Editor

Stephen A. Hermitage
Glaxo Wellcome Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY, UK

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