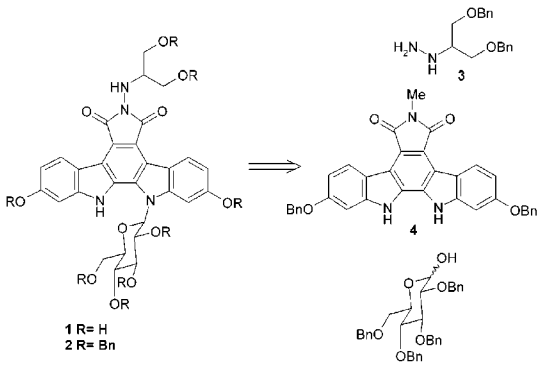
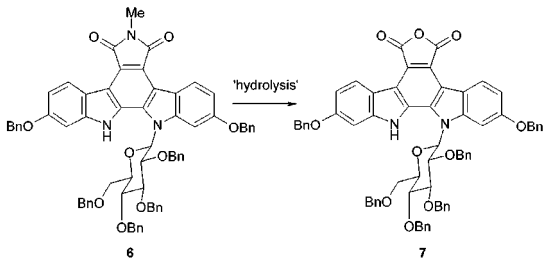
Some Items of Interest to Process R&D Chemists and Engineers as Selected by Trevor Laird, Stephen A. Hermitage, and Ulf Tilstam

DNA Topoisomerase Inhibitors: Synthesis. DNA topoisomerase I inhibitors are currently under investigation as cancer chemotherapy agents of which indolocarbazole glycoside **1** has been identified as a promising candidate. Workers at the Banyu Pharmaceutical company and Merck have reported a practical scalable synthesis of **1** that limits the isolation of cytotoxic compounds to only that of the final product (Akao and Weissman et al. *Tetrahedron*, **2001**, *57*, 8917). Their disconnection is shown in the scheme and in the convergent forward synthetic pathway features a novel phase-transfer-promoted glycosylation of aglycone core **4** with **5**.



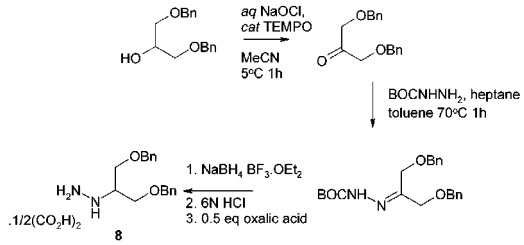
Retrosynthetic analysis

Hydrolysis of **6** to the anhydride **7** followed by coupling to the hydrazine fragment **3** gave an advanced intermediate which could be hydrogenated to the target **1**.



Anhydride formation

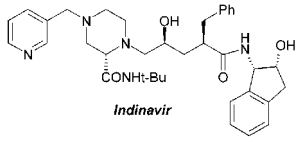
Interestingly, the hemioxalate salt **8** could be prepared from the commercially available 1,3-dibenzyloxy-2-propanol. A TEMPO-catalysed oxidation with bleach as the co-oxidant in MeCN/aqueous $NaHCO_3$ afforded the ketone analogue which was reacted directly with BOC−hydrazine. Subsequent reduction of the hydrazone was found to be most effective with borane formed in situ from $NaBH_4/BF_3{\cdot}OEt_2$. BOC-deprotection and salt formation completed the synthesis of **8**. Interestingly, the free base of **8** was found to be unstable on exposure to air, forming hydrazine which complicated subsequent steps.



Hemioxalate salt preparation

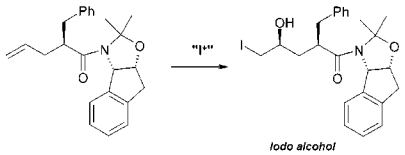
The groups have used this chemistry to prepare large quantities of material and describe their experimental procedures in the paper.

Diastereoselective Iodohydroxylation. Indinavir or Crixivan is the well-known HIV protease inhibitor from Merck.



Indinavir

A recent publication from the group describes (Sun et al. *Tetrahedron Lett.* **2001**, *42*, 8603) how the "evasive" hypoiodous acid (generated in situ from NaOCl and NaI) can be used efficiently for clean iodohydroxylation to produce the iodo alcohol in high yield with efficient 1,3 asymmetric induction. Few methods of producing HOI are



Diastereoselective iodohydroxylation

currently available, and they either require strongly acidic conditions or utilise molecular iodine. Since acidic conditions are incompatible with the substrate, the Merck group have developed a pH-tunable process which allows HOI generation at a pH optimal for suppressing byproduct formation in pH-sensitive iodohydroxylation reactions. They found that the best iodohydroxylation results are achieved when the NaOCl (2 equiv) and NaI (1.8 equiv) solutions are fed concurrently *but separately* into an agitated mixture of substrate, IPAC/$NaHCO_3$ biphase over 1 h with the reaction pH controlled in the 8−9.5 range by on-demand addition of dilute sulphuric acid.

Resolution Techniques. (*S*)-1,4-Benzodioxan-2-carboxypiperazine is a key building block in the synthesis of Doxazosin mesylate, indicated for the treatment of hypertension and more recently proven effective in the treatment of benign prostatic hyperplasia (BPH).

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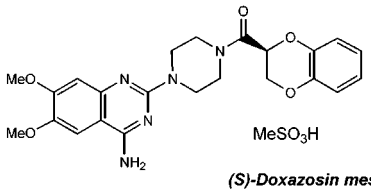
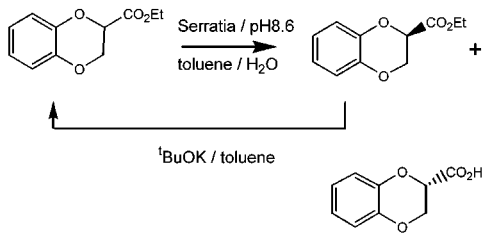


(S)-Doxazosin mesylate

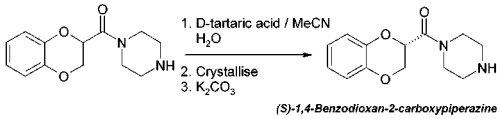
Fang and co-workers have described (*Tetrahedron Asymmetry* **2001**, *12*, 2169) two methods for the preparation of this intermediate.

First an enzymatic resolution of ethyl 1,4-benzodioxan-2-carboxylate with an esterase (Serratia) followed by amide formation



Enzymatic resolution

and second, direct resolution of 1,4-benzodioxan-2-carboxypiperazine with D-tartaric acid.

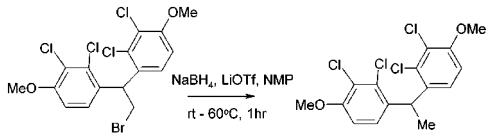


(S)-1,4-Benzodioxan-2-carboxypiperazine

Classical resolution

Interestingly, the classical resolution provided the most practical and economical solution to the problem.

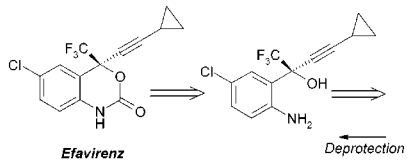
$NaBH_4$ in *N*-Methyl Pyrrolidinone. The explosive nature of $NaBH_4$ and DMF is well-known. Torisawa and co-workers have, however, reported (*Bioorg. Med. Chem. Lett*. **2001**, *11*, 2787) the use of $NaBH_4$ in *N*-methylpyrrolidinone as a reducing agent for the debromination of alkyl halides. They also report the use of $NaBH_4$−LiOTf−NMP which works as an alternative to $NaBH_3CN$ for the S_N2 type reduction, and an example is shown in the following:



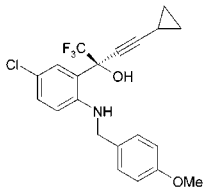
Debromination using $NaBH_4$ in NMP

Although the potential advantage of this method lies in the solubilising nature of NMP for a variety of organic compounds **the authors of OPRD strongly recommend a comprehensive safety evaluation and review of any new synthetic methodology prior to scale up or use in the laboratory.**

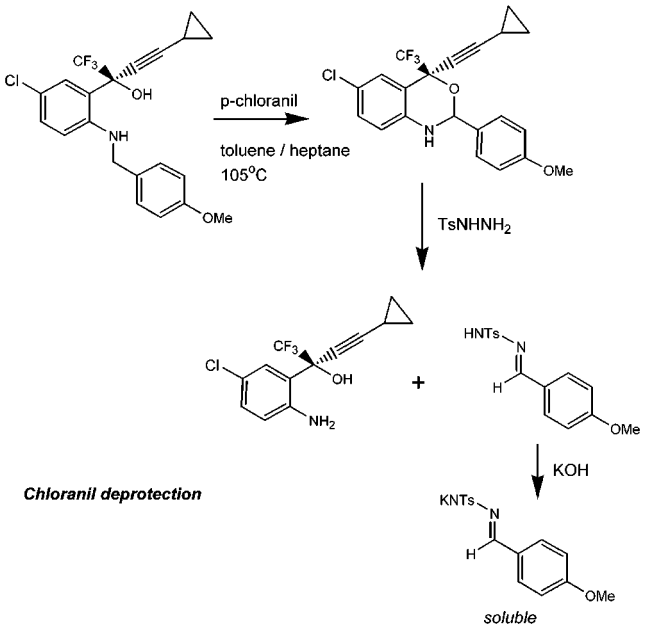
Oxidative Deprotection of a *p*-Methoxybenzylamino-Protecting Group. Workers at DuPont chemical process R&D department have reported an oxidative deprotection of a *p*-methoxybenzylamino-protecting group in the presence of a proximal hydroxyl functionality as a solution to a process problem in the Efavirenz synthesis (Choudhury et al. *Synth. Commun*. **2001**, *31*, 3707). In their deprotection sequence



Efavirenz *Deprotection*



p-chloranil was used to oxidatively convert the PMB group into a hemiaminal which could be subsequently converted into a mixture of the desired amino alcohol and tosylhydrazone derivative. Although both compounds coprecipitated from solution the addition of 1 M KOH in 9:1 H_2O:MeOH solubilised the anisaldehyde hydrazone as its potassium salt. This method provided high purity product (>99.5%) in 82.5% isolated yield.

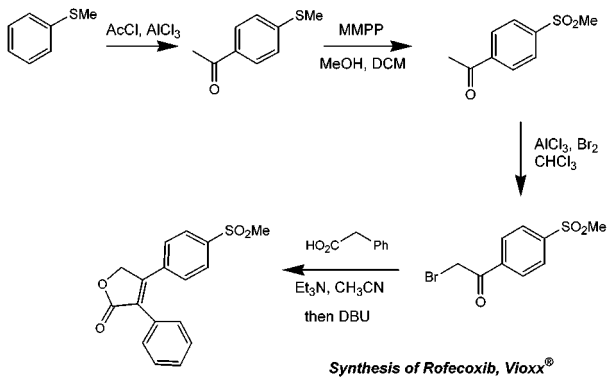


Chloranil deprotection

soluble

Synthesis of Rofecoxib (MK 0966, Vioxx). Workers at the Merck Frosst Centre for therapeutic research have described (Therien et al. *Synthesis*, **2001**, 1778) their synthesis of a selective and orally active inhibitor of cyclooxygenase-2, rofecoxib (MK 0966, Vioxx). This compound has been approved recently in the US and several other countries for use in humans as an antiinflammatory to relieve the signs and symptoms of osteoarthritis, for the treatment of acute pain and for the treatment of primary dismenorrhea.

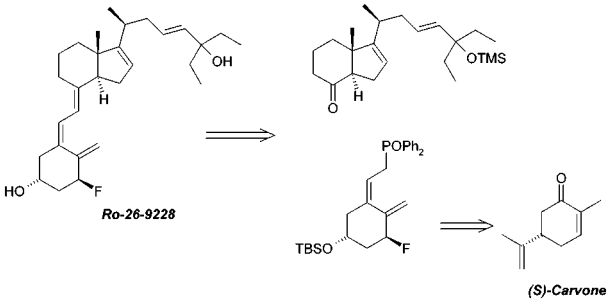
Their synthesis is shown in the following scheme



Synthesis of Rofecoxib, Vioxx®

and begins with Friedel−Crafts acetylation of thioanisole to give the acetophenone compound. Oxidation of the methyl thioether with magnesium monoperoxyphthalate hexahydrate (MMPP) gave the sulphone which was treated with Br_2 and $AlCl_3$ to give the α-bromoketone. Treatment of this derivative with phenylacetic acid in the presence of triethylamine followed by intramolecular cyclisation with DBU gave the target COX-2 inhibitor. The group outline their preparative method on multigramme-scale in the paper.

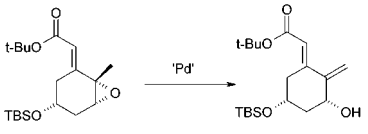
Synthesis of 1α-Fluoro A-ring Phosphine Oxide. 1α-Fluoro A-ring phosphine oxide (shown in the following scheme) is a useful building block for the preparation of vitamin D analogues (for example, Ro 26-9228). Workers at Hoffmann-La Roche have reported its synthesis (Radinov et al. *J. Org. Chem.*, **2001**, *66*, 6141) from (*S*)-carvone in 13 synthetic steps and only five isolations, in 22% overall yield.



Ro-26-9228

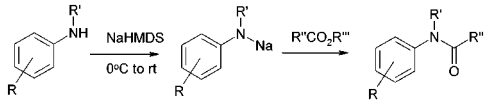
(S)-Carvone

In the key synthetic step the group describe their synthetic efforts in developing a highly selective palladium-catalysed isomerisation of epoxide to the dienol (shown in the following scheme). Virtually complete selectivity was obtained by performing the isomerisation using 1 mol % of a palladium catalyst prepared in situ from 0.5 mol % $Pd_2dba_3(CHCl_3)$, 5 mol % triphenylphosphine, and 2 mol % of 1,3-$C_6H_4[C(CF_3)_2OH]_2$ in toluene.



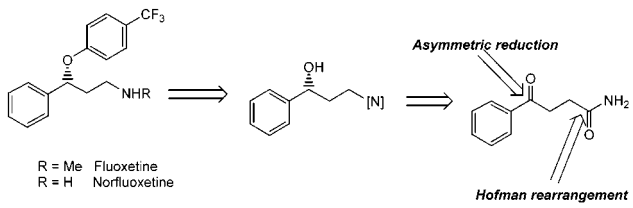
Isomerisation

Aminolysis of Esters and Lactones. The most common method for the preparation of *N*-aryl amides is by reaction of anilines with carboxylic acids, anhydrides and acyl halides. Although esters and lactones are stable and easily handled, preparation of *N*-aryl amides via aminolysis has not been widely employed because of poor nucleophilicity of *N*-arylamines. Wang and co-workers from the Bristol Myers Squibb Co. have addressed this issue and have recently disclosed (*Synlett* **2001**, 1485) an efficient method for the preparation of *N*-aryl amides from anilines, esters or alcohols promoted by NaHMDS. The advantages of this simple method include high yields and mild reaction conditions which they have shown as tolerating functional groups such as ketones and halides on simple systems.



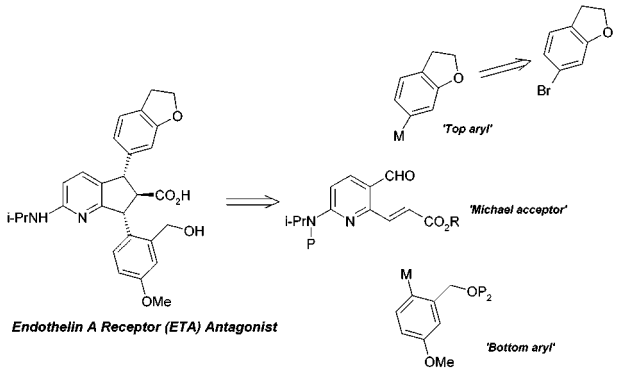
Amide formation

(*R*)-Fluoxetine Synthesis. A practical asymmetric synthesis of the potent and selective inhibitor of neural serotonin-reuptake, fluoxetine (Prozac), has been reported by Senanayake and co-workers from Sepracor (*Tetrahedron Lett.* **2001**, *42*, 8919). Their chromatography free synthesis relies on the use of the asymmetric CBS ketone reduction and a Hofman rearrangement (see below). Optical purity of the final product could be enriched by crystallisation of tartrate salt.



Hofman rearrangement

Endothelin A Receptor Antagonist. Workers from the Banyu Pharmaceutical Co. and Merck have reported their asymmetric synthesis (Song et al. *Org. Lett.* **2001**, *3*, 3357) of the selective endothelin A receptor antagonist (see below), a compound that is currently being evaluated as a therapeutic agent for the treatment of hypertension, congestive heart failure, and renal disease. In their report they describe the development of a chromatography-free synthesis including a new efficient process for the preparation of 6-bromo-2,3-dihydrobenzofuran. Their key synthetic approach is to protect



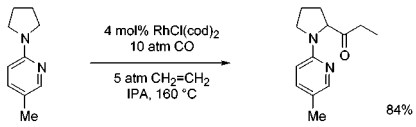
Endothelin A Receptor (ETA) Antagonist

an aldehyde in the presence of a "Michael acceptor" using a chiral amino alcohol, thus providing the source of stereo-

induction in a subsequent conjugate organometallic addition. The aldehyde is unmasked and then reacted with a "top aryl" Grignard reagent. An aminophosphate-mediated stereospecific intramolecular enolate alkylation reaction gave the five-membered ring bearing three contiguous chiral centres in the target compound.

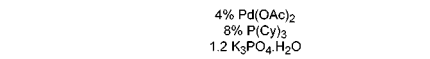
Catalytic Asymmetric Arylation Reactions Reviewed. A comprehensive review of catalysed asymmetric arylation reactions has appeared (Bolm, C. et al. *Angew. Chem. Int. Ed.* **2001**, *40*, 3285). The review includes cross-coupling reactions, aryl additions to carbonyls and heterocarbonyls, conjugate additions, oxidative couplings, and asymmetric ring-opening of epoxides and aziridines.

Catalytic Activation of C−H Bonds. A short review of recent work on catalytic procedures for activation of C−H bonds adjacent to a nitrogen atom has been published (Doye, S. *Angew. Chem. Int. Ed.* **2001**, *40*, 3351); for an example see below:



Microencapsulated Palladium Catalysts for Coupling Reactions. The group of Kobayashi at Tokyo has previously reported on microencapsulated scandium and osmium catalysts for organic synthesis. This has now been extended to palladium catalysts for allylic substitution and Suzuki coupling (Akiyama, R. et al. *Angew. Chem. Int. Ed*. **2001**, *40*, 3469). In both cases the microencapsulated triphenylphosphine palladium was quantatively recovered and reused. It is noteworthy that the air sensitivity of the palladium complex is suppressed by immobilisation on polystyrene.

Room-temperature Alkyl−Alkyl Suzuki Cross Coupling. Suzuki coupling of alkyl halides (containing β-hydrogens which may have been expected to eliminate) with alkyl boron derivatives takes place at room temperature under very specific conditions. The phosphine ligand of choice is tricyclohexylphosphine, whereas the butyl and phenyl derivatives give poor results. Phosphites and arsines are also ineffective. (Netherton, N. R. et al. *J. Am. Chem. Soc.* **2001**, *123*, 10099).

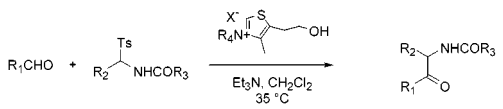


R	R'	Yield (%)
n-hexyl	n-dodecyl	93
$BuC{\equiv}C-(CH_2)_3$	$EtO_2C(CH_2)_5Br$	58
$TESO(CH_2)_5$	$Me_2CH(CH_2)_2$	72
$MeOC_6H_4(CH_2)_3$	n-hexyl	80
$MeO_2C(CH_2)_{10}$	$NC(CH_2)_6$	81
$TES(CH_2)_5$	$Cl(CH_2)_8Br$	81

The process is selective for alkyl bromides over alkyl chlorides. The reactions are *not* moisture-sensitive; in fact, if anhydrous K_3PO_4 is used, the reactions do not work! Addition of 1 equiv of water, however, starts the reaction, and yields comparable to those obtained from adding $K_3PO_4 \cdot H_2O$ are obtained. The role of water is believed to be via reaction with the alkyl BBN to give hydroxy-bound "ate" complexes, which are known to play a key role in transmetalation.

Are Heterogeneous Catalysts Precursors to Homogeneous Catalysts? This is the title of an important paper from the Merck Process R&D group (Davies, I. W. et al. *J. Am. Chem. Soc.* **2001**, *123*, 10139)—the paper should be read by all process chemists carrying out organometallic reactions. Process chemists often prefer heterogeneous catalysts for scale up since the catalysts are easily removed from the product and the product remains free from metal—or so we used to believe. This myth was probably derived from the use of heterogeneous catalysts in catalytic hydrogenation, where leaching rarely occurs. When heterogeneous catalysts are used in other processes, such as coupling reactions, for example, the catalyst becomes converted to another species which may dissolve in the solvent. Often during product isolation and work up the organometallic is deposited back on the heterogeneous support, and we assume that it has always been there. This does not appear to be true. The Merck workers report a simply unambiguous test to determine the presence of a homogeneous catalyst in the reaction mixture. This allows additional mechanistic information to be obtained.

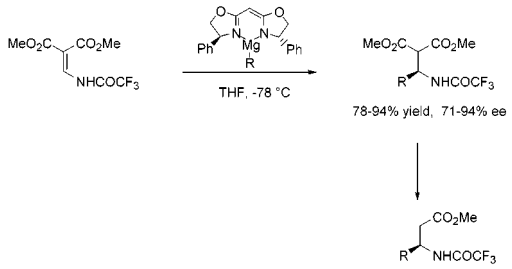
Addition of Aldehydes to Acylimines To Give α-Amido Ketones. The use of thiazolium-catalysed processes (e.g., benzoin reaction, Stetter reaction) to add acyl anion equivalents is a powerful synthetic methodology. This approach has now been extended to addition of "acyl anions" to acylimines to give α-amido ketones by workers at Merck (Murry, J. A. et al. *J. Am. Chem. Soc*. **2001**, *123*, 9696). The acylimines are generated from stable arylsulphonylamides, which can eliminate sulphinic acid under mild conditions. The reaction works with both alphatic and aromatic aldehydes, and surprisingly, α,β unsaturated aldehydes also work—in the Stetter reaction, 1,4-addition takes place. The reaction is tolerant of the amide portion of the tosylamide, and common amine-protecting groups (Boc, Cbz) can be used. Surprisingly, the benzoin reaction does not seem to compete, and benzoins themselves are not substrates for the reaction, indicating that the product of kinetic control is obtained.



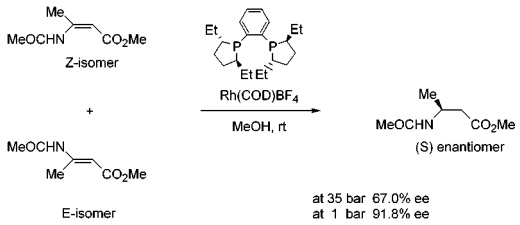
R_1 = aryl, alkyl, α–β unsat
R_2 = aryl, H
R_3 = H, alkyl, aryl, OBu^t, OCH_2Ph
R_4 = Me, CH_2Ph

New Method for Synthesis of β-Amino Acid Derivatives. The development of new methods of synthesis of β-amino acids continues to be of interest. An attractive method is the enantioselective addition of nitrogen nucleo-

philes across enoates; however, previous reports have been limited to hydroxylamines and azides, and other side reactions can occur. A recent report uses conjugate addition of carbon nucleophiles to β-enamino carbonyl derivatives, readily available from β-dicarbonyl compounds. (Sibi, M. P. et al. *J. Am. Chem. Soc.* **2001**, *123*, 9708).

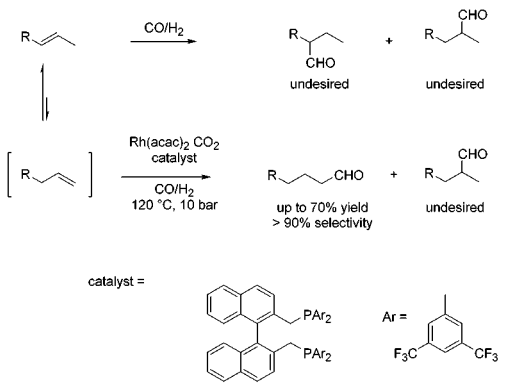


Pressure-Dependent Enantioselective Hydrogenation Of Unsaturated β-Amino Acid Precursors. Asymmetric reduction of Z and E β-acylaminoacrylates is normally successful for only the E isomer with the Z isomer giving poor enantioselectivity. Since the methods of preparation usually give Z/E mixtures, separation before reduction is advisable. A recent report (Heller, D. et al. *J. Org. Chem.* **2001**, *66*, 6816) indicates that in polar solvents such as methanol and at atmospheric pressure, Z isomers are reduced quickly and enantioselectively. With decreasing pressure, enantioselectivity increases. In contrast, under similar conditions the reduction of the E isomer is less pressure-dependent, but still gives high enantioselectivity and in the same sense as the Z isomer. Thus, mixtures of E/Z isomers can be enantioselectively reduced using rhodium S S Et DuPhos as catalyst.

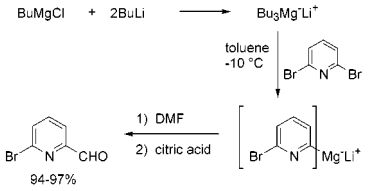


Hydroformylation of Internal Olefins to Linear Aldehydes. The conversion of internal olefins by hydroformylation to linear aldehydes would be an important industrial process, since many olefins occur as mixtures and since terminal olefins can already be hydroformylated. The group of Beller at Rostock, Germany, has now reported that NAPHOS ligands in conjunction with rhodium allowed the desired process to take place (Klein, H. et al. *Angew. Chem. Int. Ed.* **2001**, *40*, 3408). This provides useful methodology, although for an industrial process the activity and long-term stability of the catalysts will need improvement.

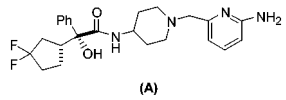
Synthesis of 6-Bromo-2-formylpydridine. In an excellent paper from the Process R&D groups at Banyu and Merck on the synthesis of the muscarinic receptor antagonist (**A**), a scaleable synthesis of 6-bromo-2-formylpyridine is reported (Mase, T. et al. *J. Org. Chem.* **2001**, *66*, 6775). The selective monometalation of 2,6-dibromopyridine at −78 °C followed by addition of DMF gives excellent yields, but the low



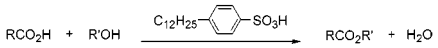
temperature and the pinpoint accuracy of the BuLi charge were essential for good yield, and scale up problems were envisaged. After much experimentation and some excellent mechanistic reasoning, the process chemists used a mixture of BuLi and BuMgBr to generate an ate complex (Bu_3MgLi) which reacts at −10 °C to give a species which reacts readily with DMF. This reaction is not sensitive to the accuracy of the reagent charge.



The paper also includes other improved procedures of value to the process chemist, for example, for the difluorination of ketones using Deoxofluor [$F_3SN(CH_2CH_2OMC)_2$] in which the amount of the expensive fluorinating agent has been considerably reduced.



Dehydration Reactions in Water! Direct Esterification of Acids and Alcohols in an Emulsion System. It has previously been found that emulsion droplets in water are hydrophobic enough to protect water-labile substrates from hydrolysis. It has now been discovered (Manabe, K. et al. *J. Am. Chem. Soc.* ***2001***, *123*, 10101), contrary to conventional wisdom, that esterification reactions between an acid and an alcohol in a 1:1 ratio can be carried out in the presence of 10 mol % *p*-dodecylbenzene sulphonic acid at 40 °C in water. The reaction works best with hydrophobic sub-



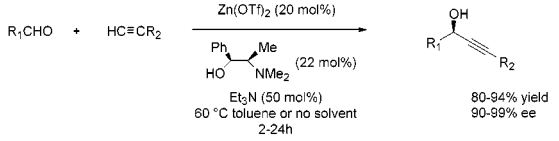
R	R'	yield (%)
$CH_3(CH_2)_{10}$	$Ph(CH_2)_3$	89
$CH_3(CH_2)_{10}$	$(CH_2)_{11}CH_3$	97
$Ph(CH_2)_4$	$(CH_2)_{13}CH_3$	97
cyclohexyl	$(CH_2)_{13}CH_3$	96
$CH_3(CH_2)_5$	$Ph(CH_2)_3$	61
$CH_3(CH_2)_2$	$Ph(CH_2)_3$	31
CH_3	$Ph(CH_2)_3$	6

strates—acetic acid does not work well. The reaction mixtures become white, turbid emulsions as the reaction proceeds—hopefully this will not impact on product isolation. The method may have application in the speciality chemicals industry as a mild—though slow—esterification method.

An earlier reference to the condensation of equimolar amounts of alcohols and acids using hafnium IV salts is probably more widely applicable (Ishihara, K. et al. *Science* **2000**, *290*,1140; *Synlett* **2001**, 1117).

Use of Chiral HPLC-MS for Rapid Screening of Yeasts in a Bioreduction of a Diaryl Ketone. One of the problems in evaluating aryl ketone bioreductions by chiral HPLC with UV detection is that residual ketone, with its high UV absorbance, may complicate determination of alcohol enantiomeric excess, resulting in long assay times to avoid peak overlap. This makes screening very time-consuming. However, by resolving ketone and alcohol peaks using MS the rapid enantiopurity analysis needed for high-throughput reaction screening can be achieved (Welch, C. J. et al. *J. Org. Chem.* **2001**, *66*, 6836).

Mild Catalytic Enantioselective Addition of Terminal Acetylenes to Olefins. A simple way to add acetylenes enantioselectivity to aldehydes has been reported by the group of Carreira at ETH, Zurich (Anand, N. K. et al. J. *Am. Chem. Soc.* **2001**, *123*, 9687). The reaction uses zinc triflate in conjunction with a chiral amino alcohol. The conditions tolerate air and moisture and can even be carried out without solvent. The reaction works best at 60 °C but can be carried out at 100°, if desired, without loss of enantioselectivity.

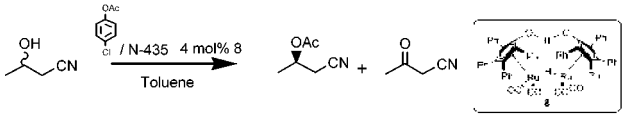


Industrial Scale Up of Countercurrent Chromatography (CCC). A paper entitled "Industrial Scale Up of Countercurrent Chromatography" may be of interest to process chemists and engineers trying to separate complex mixtures, for example, those from a fermentation process. (Sutherland, I. A. et al. *J. Liq. Chromatogr. Relat. Technol.* **2001**, *24*, 1533; *J. Chromatogr. Sci.* **2001**, *39*, 21). The methodology allows purification of compounds in a single operation from crude extract and has high loading capacity (compared to HPLC). It has potential for scale up, which is why the work is being funded by a number of pharmaceutical companies and pilot-plant trials are presently being carried out.

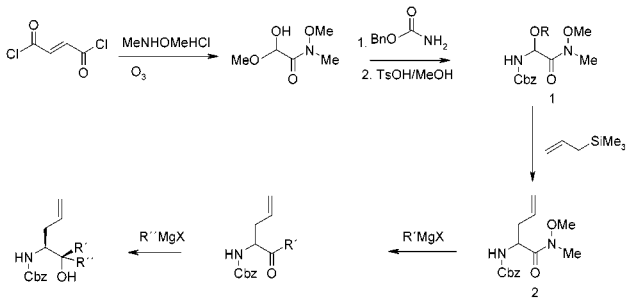
Failed Reactions. The database contains 5000 "reactions" which are known to fail and aims to help chemists avoid duplication of these experiments. For further details see www.accelrys.com.

***Organic Syntheses* Goes Electronic.** *The Organic Syntheses* (OS) website, www.orgsyn.org, contains all nine collective as well as annual volumes and indices, and, more importantly, is free of charge. The OS website allows structural searches as well as conventional search terms and goes far beyond the scope of the printed version.

Dynamic Kinetic Resolution of β-Hydroxy Nitriles. The importance of optically active amino alcohols as versatile building blocks in asymmetric synthesis is well established. The group of J.-E. Bäckvall (O. Pàmies and J.-E- Bäckvall (*Adv. Synth. Catal.* **2001**, *6*−*7*, 343) has now published a variation of their dynamic kinetic resolution of racemic α- and β-hydroxy carbonyls (see also J.-E. Bäckvall et al. *Org. Lett.* **2000**, *2*,1037 and **2001**, *3*, 1209) to β-hydroxy nitriles for an efficient synthesis of γ-amino alcohols. A variety of racemic alkyl-, aryl-substituted β-hydroxy nitriles was efficiently transformed to the corresponding enantiomerically pure acetates through a *Candida antartica* lipase (N-435)-catalyzed transesterification in combination with a ruthenium-catalyzed alcohol racemization (yields in the range 72−85% and ee > 94%) the sole impurity being the corresponding keto compound. This new method could be highly interesting for large-scale synthesis of chiral α- and β-hydroxy carbonyl compounds and their derivatives.



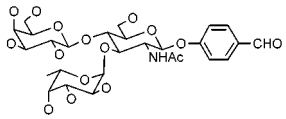
A New Method for the Synthesis of Highly Substituted β-Amino-Alcohols. H. Hiemstra et al. (*J. Chem. Soc., Perkins Trans. 1* **2001**, 2909) have reported the synthesis of several substituted β-amino alcohols in a diastereoselective manner via the novel highly versatile intermediate **1** involving a combination of *N*-acyliminium ion and Weinreb amide chemistry (see below).



The novel Weinreb amide **1** contains both precursor functionalities for *N*-acyliminium ion and Weinreb amide chemistry. Hence, via this species three different functionalities can be introduced (one via *N*-acyliminium ion chemistry and two by organometallic additions) in three subsequent reaction steps resulting in highly functionalized compounds.

After a Lewis acid-catalyzed nucleophilic substitution with the allyl silane the Weinreb amide **2** was used as a substrate in the diastereoselective double addition of Grignard reagents to obtain β-amino alcohols. Primary Grignard reagents gave reasonable-to-high yields, whereas the use of secondary Grignard reagents resulted in low yields of 20−30%.

Zirconium Alkoxides in Catalysis. M. Shibasaki et al. (*Chem. Eur. J.* **2001**, *7*, 4067) have presented the recent advances of zirconium alkoxide-catalyzed reactions in a comprehensive review. Not only Lewis acid-catalyzed reac-



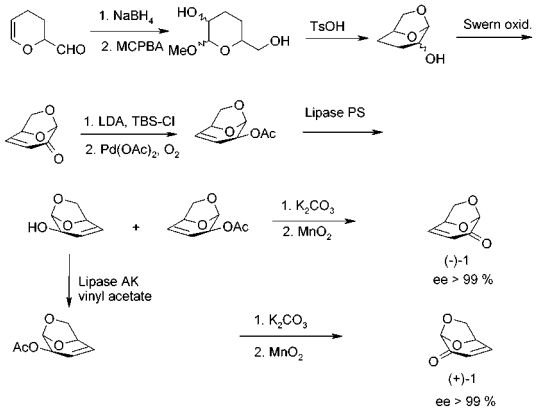
1

tions, even enantioselective variations with BINOL ligands, but also other types of reactions such as enantioselective Mannich-type reactions and aza-Diels−Alder as well as asymmetric aldol reactions have been developed. Zirconium alkoxides have also been used in redox reactions such asa Oppenauer oxidations or Meerwein−Ponndorf−Verley reductions. Lately, also a direct synthesis of *trans*-β-cyanohydrins from olefins catalyzed by zirconium alkoxides has been reported.

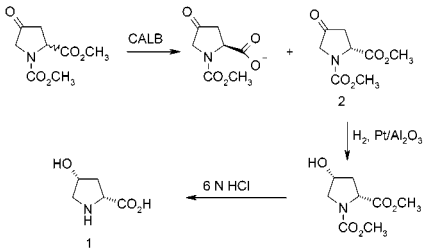
Continuous Asymmetric Transfer Hydrogenation in a Membrane Reactor. Continuous manufacturing processes gain a growing interest in the pharmaceutical and fine chemical industry. S. Laue et al. (*Adv. Synth. Catal*. **2001**, *343*, 711) have presented the first example for a transfer hydrogenation process in a continuously operated membrane reactor utilizing a chemzyme based on Gao and Noyoris (*Organometallics* **1996**, *15*, 1087) ruthenium-based transfer hydrogenation catalyst linked to a polysiloxane. In the reaction 2-propanol was used as source of hydrogen. With the chemzyme the use of the cofactor NADH is not necessary. It was possible in the reactor during the investigation of the transfer hydrogenation of acetophenone to get a space time yield of 578 g $L^{-1}d^{-1}$ which is about 4 times what is possible with an oxidoreductase. From the hydrogenation an ee of 94% was received which is somewhat lower than with the enzyme (>99%). Despite the lower enantioselectivity this is very promising approach for future continuous manufacture of chiral alcohols.

Homogeneous Enzymatic Synthesis Using a Thermoresponsive Water Soluble Polymer Support. D. Bergbreiter et al. (*Adv. Synth. Catal*. **2001**, *343*, 675) have reported a new support for enzymes which is soluble in cold water but precipitates out of solution once the temperature is higher than their lower critical solution temperature (LCST). The LCST of these *N*-*i*-propylacrylamide polymers can be readily tailored by modifying the side chain as well as the ratio of NIPAm to the functionalized monomer. The group has previously reported the use of these thermoresponsive polymers as support for ligands which can quantitatively remove noble metals from water as well as organic solvents (see Highlights from the Literature. *Org. Process Res. Dev*. **2000**, *4*, 306.). In the report polymers with LCSTs between 20 and 30 °C are used for the immobilization of enzymes. After immobilization of the enzyme on the polymer it was found that they are nearly as active as in solution. With subtilisin the activity after recovery was determined; after three rounds the activity was about 50%. It was found that the loss of activity was not due to loss of enzyme from the support as the supernatant solution showed no enzymatic activity at all.

The polymer was also used as the solid support for the solid-phase synthesis of oligosaccharides. The trisaccharide Le^x (**1**) was synthesized in 60% yield without chromatographic purification of intermediates.



Lipase-Mediated Synthesis of Both Enantiomers of Levoglucosenone. (−)-Levoglucosenone (**(−)-1**) is a molecule with high chemical potential exhibited by an enone functionality and a masked formyl and 1,2-glycol functionalities; however its utilization is still limited as its preparation from cellulose affords only the (−)-enantiomer in very low yield (<10%). The group of K. Ogasawara reports a synthesis of both enantiomers of levoglucosenone based on kinetic lipase-mediated hydrolysis of the corresponding acetoxy derivative. The synthesis of the racemic levoglucosenone was based on the readily available acrolein dimer (*Adv. Synth. Catal.* **2001**, *343*, 618). Both enantiomers could be obtained in an enantiomeric excess >99%.

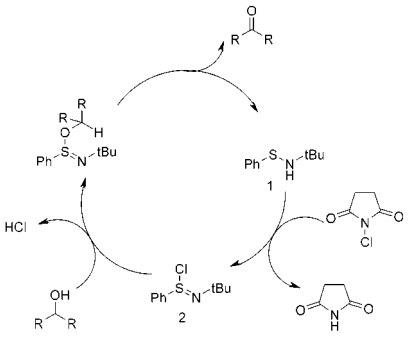


Chemoenzymatic Synthesis of *cis*-4-Hydroxy-D-proline. *trans*-(2*S*,4*R*)-4-Hydroxy-L-proline (L-Hyp) is present in plants and animals. It has been used as starting materials for numerous pharmaceuticals, including antibacterials, antibiotics, analgesics, to mention just a few (P. Remuzon, *Tetrahedron* **1996**, *52*,13803). *cis*-4-Hydroxy-D-proline (**1**) is one of four possible diastereomers of L-Hyp which also has been used for the synthesis of pharmaceuticals and agrochemicals. Until recently, it has been obtained through epimerization of L-Hyp. Now an efficient total synthesis has been reported based on the synthesis of racemic 4-oxopyrrolidindicarboxylic acid dimethylester from fumaric acid dimethylester (see below) and followed by treatment with *C. antartica* lipase B (CALB) which selectively hydrolyses the unwanted L-4-oxoprolinester, giving the wanted product (**2**) in 97% ee at 51% conversion. After catalytic hydrogenation over platinum (yield 97.9%) and hydrolysis with HCl (yield 98%) *cis* 4-hydroxy-D-proline was obtained (R. DiCosimo et al. *Adv. Synth Catal*. **2001**, *343*, 587).

The Sonochemical Effect in Heterogeneous Sonochemistry. Sonochemistry is a field of chemistry which has over the last 10 years received a steadily growing interest from

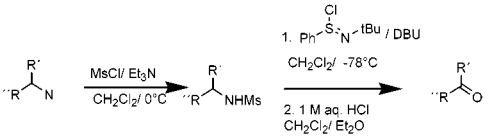
process research. During this period there has also been an ongoing discussion about the sonochemical effect in heterogeneous sonochemistry. Numerous papers have described this special effect during agitation with ultrasound. As agitation is an important theme in industrial chemistry it is an active research subjects for chemical engineers. Y. Kegelaers et al. (*Eur. J. Org. Chem.* **2001**, 3683) has investigated the described sonochemical effect in heterogeneous sonochemistry on reported examples in comparison to that of effective agitation using an UltraTurax system providing adjustable rates between 8000 and 24000 rpm. Under their sonochemical conditions the stirring was equivalent to 14 000 rpm. The authors found that there is no special sonochemical effect. The effect of ultrasound is comparable to other types of good agitation in comparison to the normally used stirring bar which for an heterogeneous mixture gives an insufficient agitation.

Sulfenamide-Catalyzed Oxidation of Alcohols with NCS as Primary Oxidant. The group of T. Mukaiyama had previously published an oxidation of primary and secondary alcohols with *N-tert*-butylphenylsulfinylimidoyl chloride (**2**) in the presence of DBU or zinc oxide (T. Mukaiyama et al. *Chem. Lett*. **2001**, 150.) The group now reports a catalytic variation of this method with NCS as the stoichiometric oxidant and a catalytic amount of *N-tert*-butylbenzenesulfenamide (**1)** (5 mol %) and potassium carbonate as solid base and molecular sieves for the dehydration (T. Mukaiyama et al. *Chem. Lett.* **2001**, 846). The reaction is performed in methylene chloride at 0 °C. Using this new method it was possible to obtain the corresponding carbonyl compound in good to excellent yields. *N-tert*-butylbenzenesulfenamide is easily obtained from benzenesulfenyl chloride and *tert*-butylamine. The authors have proposed a catalytic cycle for the reaction (see scheme below).



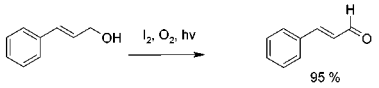
Oxidative Deamination of Primary Amines with *N-tert*-buTylphenylsulfinylimidoyl Chloride. The oxidation of primary amines to the corresponding carbonyl compound is a difficult, and known processes are not applicable to various types of primary amines.

For a more applicable process the use of *N-tert*-butylphenylsulfinylimidoyl chloride for the oxidative deamination of primary amines as part of a three-step process has been reported (T. Mukaiyama et al. *Chem. Lett.* **2001**, 712). The three-step procedure is as following; initial formation of the *N*-mesylate or *N*-cyclohexylate followed by oxidation with *N-tert*-butylphenylsulfinylimidoyl chloride with DBU as base to the imine and subsequently acidic hydrolysis to the corresponding carbonyl compound (see scheme below). Using the method it was possible to obtain ketones and aldehydes in good to excellent yields (73−98%).



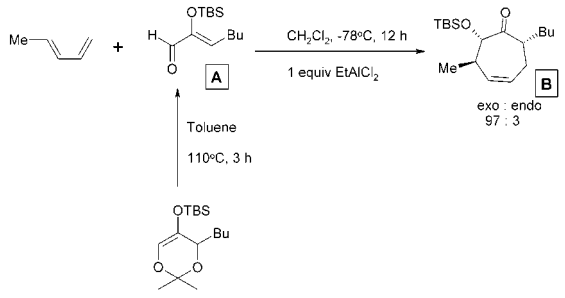
An Iodine-Catalyzed Photooxidation of Benzylic and Allylic Alcohols. Benzylic and allylic alcohols were found to be oxidized to the corresponding aldehydes in the presence of iodine and air under photoirradiation (A. Itoh et al. *Chem. Lett*. **2001**, 686). The corresponding aldehydes were obtained in good-to-excellent yields. The method was found to be highly selective for benzylic and allylic alcohols. *tert*-Butyl cyclohexanol was quantitatively recovered after 66 h of irradiation; also electron-poor benzylic alcohols were inert under the reaction conditions.

Due to the high selectivity of the method it could be of interest for a selective oxidation of benzylic and allylic alcohols in highly functionalized molecules.



Puzzle!

In a continuation of our puzzle section run in the last issue of OPRD we have selected an example of an interesting cycloaddition. This chemistry is taken from a paper by Aungst and Funk (*Org. Lett*. **2001**, *3*, 3553). They report that retro-cycloadditions of 4*H*-4-alkyl-5-(trialkylsilyoxy)-1,3-dioxins proceed smoothly in refluxing toluene to afford (*Z*)-2-(trialkylsiloxy)-2-alkenals with complete stereoselectivity. These enals undergo Sasaki-type [4 + 3] cyclisations with dienes in the presence of Lewis acids, in many instances with excellent regio- and stereoselectivity. The puzzle is to think about the mechanism and rationalisation of stereoselectivity—good luck!



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