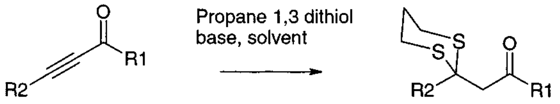
Organic Process Research & Development **2003**, *7*, 124–134

Highlights from the Literature

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

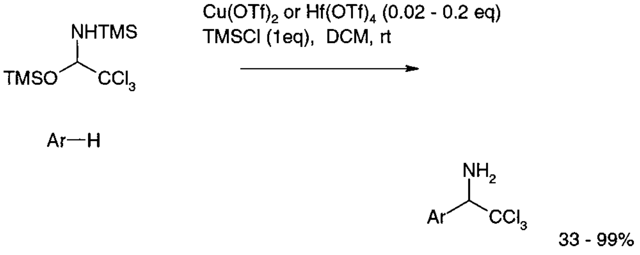
β-Keto 1,3-Dithianes As Versatile Synthetic Intermediates

In the first issue of *Organic & Biomolecular Chemistry* (formerly known as *Perkin Transactions 1 & 2*) Steve Ley and co-workers from the University of Cambridge have reported (*Org. Biomol. Chem.* **2003**, *1*, 15) how *β*-keto 1,3-dithianes can be generated by the double conjugate addition of dithiols to propargylic ketones, esters, and aldehydes in excellent yields. As masked 1,3-dicarbonyl systems these substrates can be converted to a range of functionalised oxygen-containing heterocycles that can be used in natural product synthesis.



Facile Synthesis Of Aromatic Primary Amines

An interesting paper by Sakai and co-workers (*J. Org. Chem.* **2003**, *68*, 483) describes a facile synthesis of aromatic primary amines via aminomethylation of electron-rich aromatics. The group have discovered that $Cu(OTf)_2$ and $Hf(OTf)_4$, in the presence of TMSCl, successfully catalyze the reaction of the *N*-silyl-*N,O*-acetal containing a trichloromethyl group with various indole derivatives leading to indolyl primary amines. It is noteworthy that the catalytic system using $Hf(OTf)_4$-doped TMSCl shows a higher activity and can be applied not only to electron-rich heterocycles other than indoles but also to electron-rich arenes to afford various 1-aryl-trichloroethylamine derivatives in good-to-excellent yields. Although the role of TMSCl is not clear, TMSCl is an essential activator for a smooth and complete conversion in the present reaction. The group propose a mechanism for the reaction.

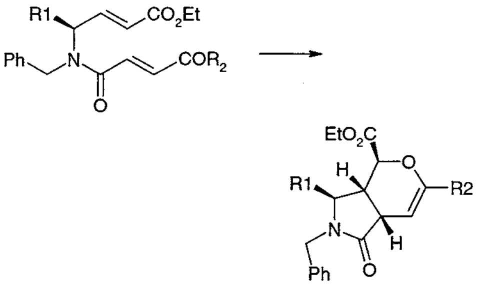


33 - 99%

Ar = pyrroloyl, furyl, thienyl, indolyl
naphthyl, dimethoxyphenyl

Intramolecular Diels Alder Reaction

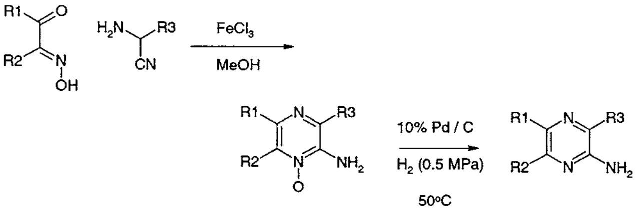
Preparation of densely functionalised pyrrolidinone templates is a challenge for synthetic chemists as they are important building blocks in peptidomimetic compounds. In a recent publication, *Tetrahedron Lett.* **2002**, *43*, 7389, Murray and co-workers at Johnson & Johnson have reported facile stereoselective intramolecular Diels–Alder reactions to generate densely functionalised cis fused pyrrolidinone templates.



Intramolecular Diels Alder reaction

Synthesis of 2-aminopyrazines

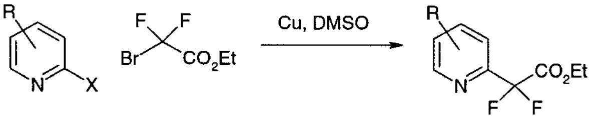
Itoh and colleagues from the process R&D labs at the Banyu Pharmaceutical Co. describe (*Tetrahedron Lett.* **2002**, *43*, 9287) the $FeCl_3$-promoted condensation of hydroxyiminoketones with aminoacetonitriles followed by catalytic hydrogenation to generate pyrazines in moderate-to-good yields. This protocol provides an efficient and practical synthesis of substituted 2-aminopyrazines.



R1 = alkyl, aryl
R2 = H, alkyl, halogen
R3 = H, alkyl, aryl, aryl, benzyl

Ethyl 2′-Pyridyldifluoroacetate Preparation

A facile process for the preparation of substituted ethyl 2′-pyridyldifluoroacetates has been described by Ashwood and colleagues at Merck (*Tetrahedron Lett.* **2002**, *43*, 9271) starting from readily available ethyl bromodifluoroacetate and substituted 2-bromo or 2-chloropyridines (see below). This process features a copper-mediated cross-coupling reaction in DMSO and is the first to utilise pyridylbromides or chlorides with ethyl bromodifluoroacetate in this reaction.

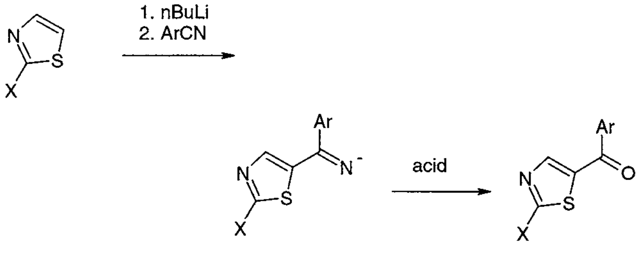


X = Cl, Br

10.1021/op034022s CCC: $25.00

2-Substituted 5-(Ketoaryl)thiazole Preparation

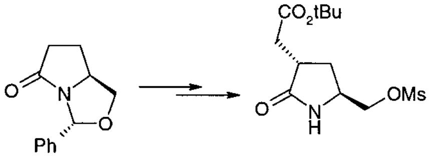
In an article by Marcantonio and co-workers (*Tetrahedron Lett.* **2002**, *43*, 8845) a facile synthesis of 2-substituted 5-(ketoaryl)thiazoles is outlined. A variety of 2-substituted thiazole anions were added to aryl nitriles to provide the desired ketones after aqueous hydrolysis. Thiazoles are classically assembled using the Hantzsch synthesis (condensation of a thiourea with an amide acetal to afford a thiocarbonylamidine, followed by a base-promoted cyclisation with a phenacyl halide). While the thiourea and formamide can be appended with alkyl groups to produce diversely substituted thiazoles, this method is limited in that it only produces thiazoles with an alkylamino group in the 2-position.



X = SMe, Si^tBuMe_2, $C(CF_3)_2OMOM$

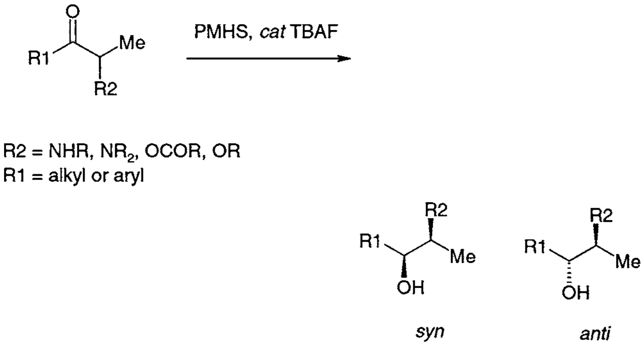
(*3S,5S*)-3-[(*tert*-Butyloxycarbonyl)methyl]-5-[(methanesulfonyloxy)methyl]-2-pyrrolidinone

Yee and colleagues from the chemical development department at Boehringer Ingelheim have reported (*J. Org. Chem.* **2002**, *67*, 8688) a practical and improved synthesis of (*3S,5S*)-3-[(*tert*-butyloxycarbonyl)methyl]-5-[(methanesulfonyloxy)methyl]-2-pyrrolidinone. The key transformations involve a highly efficient reaction sequence consisting of ethoxycarbonylation, alkylation, hydrolysis, and decarboxylation. The process is practical, robust, and cost-effective, and it has been successfully implemented in a pilot plant to produce a multikilogram quantity of the mesylate to support a project directed at the treatment of a variety of inflammatory diseases.



Reduction of α-Oxy- and α-Amino-substituted Acyclic Ketones with Polymethylhydrosiloxane

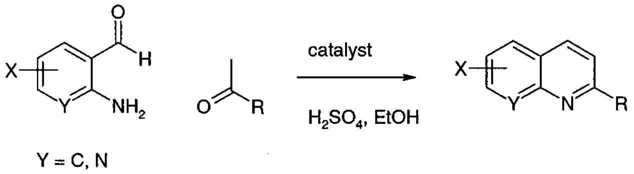
The diastereoselectivity in the reduction of α-alkoxy-, α-acyloxy-, and α-alkylamino-substituted ketones with polymethylhydrosiloxane (PMHS) in the presence of fluoride ion catalysis has been reported by Nadkarni, Hallissey, and Mojica from Pfizer (*J. Org. Chem.* **2003**, *68*, 594). High *syn*-selectivity was observed in the reduction of α-alkoxy, α-acyloxy, and α-dialkylamino ketones. Reduction of α-monoalkylamino ketone proceeded in anti-selective manner with moderate selectivity. The observed selectivity is explained based on Felkin–Anh and Cram-chelate models, and this is pictorially depicted in the publication.



R2 = NHR, NR_2, OCOR, OR
R1 = alkyl or aryl

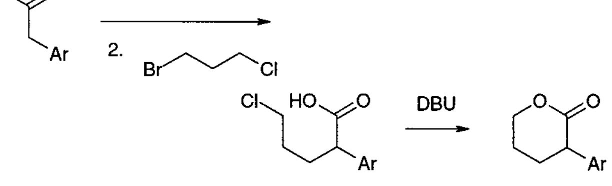
Frielander Annulation

A number of catalysts have been evaluated by McWilliams and colleagues from Merck (*J. Org. Chem.* **2003**, *68*, 467) in the preparation of 2-substituted quinolines, 1,8-naphthyridines, and chromone derivatives from unmodified methyl ketones and *o*-aminoaromatic aldehydes. The most reactive and regioselective catalyst was a bicyclic pyrrolidine derivative, TABO (1,3,3-trimethyl-6-azabicyclo[3.2.1]octane), yielding 1,8-naphthyridines with as high as 96:4 regioselectivity. Regioselectivity increased with slow addition of the methyl ketone substrate to the reaction mixture, and was positively related to temperature. Isolated yields of single regioisomers were typically 65–84%, while observed regioselectivities were 90:10 for 1,8-naphthyridines and 84:16 for quinolines.



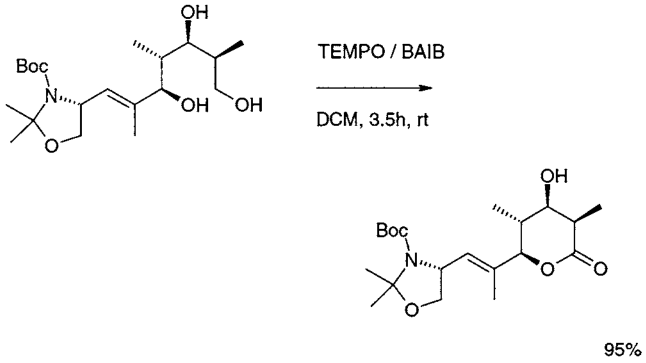
3-Aryl-δ-lactones

Various (±)-3-aryl-δ-lactones have been prepared from the corresponding arylacetic acids by Rosen and colleagues at Merck (*Tetrahedron Lett.* **2003**, *44*, 365). The lithium dianion of the acid is alkylated with 1-bromo-3-chloropropane, and the unpurified product is cyclised with DBU in typically 80% yield over both steps. The group have shown that lactones of this type can be converted to their corresponding 5,6-dihydropyran-2-ones and pyran-2-ones, which potentially provide useful sites for further functionalisation of the lactone ring.



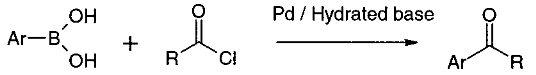
Oxidation of 1,5-diols to δ-lactones

Concerning δ-lactone synthesis, Forsyth has published (*Tetrahedron Lett.* **2003**, *44*, 57) the selective oxidative conversion of a variety of highly functionalised 1°,2°-1,5-diols into the corresponding δ-lactones. The reaction was effected simply and efficiently using a reagent system comprising catalytic 2,2,6,6-tetramethylpiperidinooxy (TEMPO) and excess bis-acetoxyiodobenzene (BAIB).



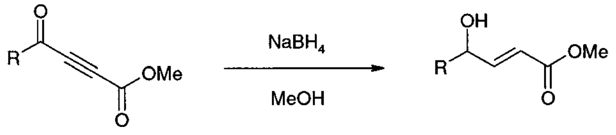
Aromatic Ketones from Acyl Chlorides

Aromatic ketones have been synthesised efficiently via palladium-catalyzed cross-coupling reaction of boronic acids with acyl chlorides in the presence of K_3PO_4 hydrate in toluene by Urawa and Ogura (*Tetrahedron Lett.* **2003**, *44*, 271). The authors report that hydrated water from the base plays a significant role as an H_2O source to activate the catalytic system.



γ-Hydroxy-,α,β-(*E*)-alkenoic Esters

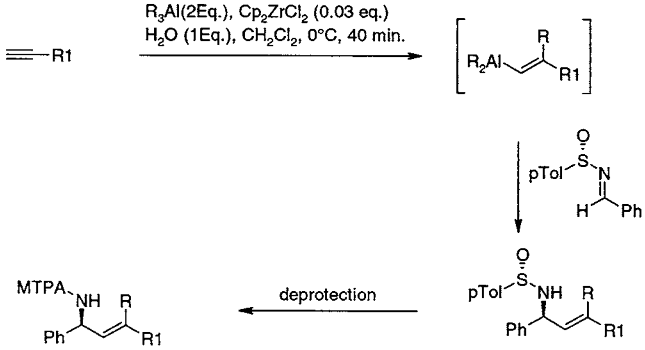
A method to convert γ-keto-alkynoic esters to γ-hydroxy-,α,β-(*E*)-alkenoic esters has been described by Naka and Koide (*Tetrahedron Lett.* **2003**, *44*, 443). This functional group transformation was accomplished in one step by means of $NaBH_4$ reduction in methanol and provides access to a useful and versatile synthetic intermediate.



Water-Accelerated Organometallic Chemistry: Carboalumination−Sulfinimine Addition and Asymmetric Synthesis of Allylic Amines

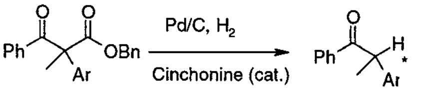
Due to their presence in many biologically important natural products and as building blocks in pharmaceuticals the synthesis of enantiomerically enriched α-branched amines has attracted considerable interest in recent years. Especially useful are allylic amines. The diastereoselective addition of organometallic reagents to the C═N bond of sulfimines that are N-substituted with chiral auxiliaries has been used for the synthesis of amines. The group of P. Wipf (*Helv. Chim. Acta* **2002**, 3478) has reported on a water-accelerated addition of organoaluminum reagents to sulfimines for the synthesis of enantiomerically enriched allylic amines.

The carboalumination of terminal alkynes is considerably accelerated through the addition of stoichiometric amounts of water and after the addition of (*p*-tolyl)sulfimines a 1,2-addition of the alkenylorganometallic intermediate provides the corresponding allylic sulfinimides in high yields and in good-to-excellent diastereoselectivities.



Catalyzed Asymmetric Protonation of Simple Linear Keto−Enolic Species

The enantioselective protonation of prostereogenic enol derivatives is conceptually simple, but the development of catalytic methods remains a challenge, especially in terms of rational design. The methods in use are largely empirical, and numerous parameters need to be considered. One general approach involves the generation of an enolate, which is protonated by a catalytic chiral protic source, which is in turn regenerated by an achiral stoichiometric proton donor. J. Muzart et al. (*Eur. J. Org. Chem.* **2002**, 3986), have developed a methodology based upon a palladium-induced cascade reaction to produce enolic species. The presence of a chiral amino alcohol promotes the enantioselective protonation of the enolic species. Thanks to the enol itself, the amino alcohol is regenerated and can be used in catalytic amounts. With this methodology optically active ketones have been prepared starting from racemic β-oxo acids protected as benzylic esters. Through the palladium-catalyzed hydrogenation of the benzyl esters is the cascade reaction started. When the reaction was carried out in the presence of cinchonine it was possible to obtain optically active α-aryl ketones with up to 75% ee.



Why Do Cosolvents Enhance the Solubility of Solutes In Supercritical Fluids?

Supercritical fluid (SCF) science and technology has rapidly developed in the past decade and will be even more important in the future with respect to clean and environmentally benign technology.

CO_2 is, though, a poor solvent for high-molecular weight or hydrophilic compounds. It is well-known that the addition of small amounts of polar solvents enhances the solubility significantly. A general explanation is that the interaction between solute and cosolvent is very strong, but the mechanism is still unknown. X. Zhang et al. (*Chem. Eur. J.* **2002**, 5107) have studied the solubility of 1,4-naphthoquinone in SC CO_2 with and without the addition of acetone

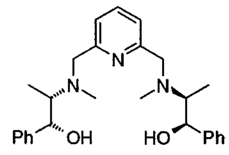
(0.5 or 1.1 mol %) or $CHClF_2$ (1.1 mol %). The addition of 1.1 mol % of acetone had the most pronounced effect on the solubility, raising the solubility of naphthoquinone by a factor of 4.4. All experiments were performed in the single-phase region. During the experiments the solubility and the enthalpy were determined as a function of the pressure. The density of the solution was also measured. It was surprisingly found that the negative enthalpy of solution decreases significantly on the addition of cosolvent. This means that the dissolution process becomes less exothermic. In conventional solvents, strong interaction between the solvents and solutes generally results in a more exothermic dissolution process. As the enthalpy effect decreases, the entropy effect becomes dominant, and the entropy change favors an increase in the solubility. This unusual phenomenon is related to the special solvation in SCF solutions. This is of course only true where the cosolvent associates preferentially with the solute.

Metal Catalysis Inside Polymer Frameworks: Evaluation of Catalyst Stability and Reusability.

Metal catalysts built up with metal nanoclusters supported on functional resins are currently used in a few industrial processes, which originated from Bayer technology in the 1980s. Despite this there has been little or no research within this field over the past decade. In conventional supported metal catalysts the support is typically a microstone with defined physical and physicochemical features, and its chemical ones are controllable to some extent. In the case of resin-supported metal nanoclusters, the support particles are micro sponges, the physical, physicochemical and chemical features of which can be designed and are controllable. M. Králik et al. (*Chem. Eur. J.* **2003**, *9*, 209) have investigated the stability of a heterogeneous palladium hydrogenation catalyst built up with Pd nanoclusters (ca. 3 nm) dispersed inside the nanoporous domains of a thermally stable gel-type polyacrylic resin. The resin is doped with $Pd(OAc)_2$ in methanol to afford complexation of the Pd^{2+} to the cross-linking dicarboxyhydrazine sites in the resin, which is thereafter reduced to Pd^0 with sodium borohydride giving widespread palladium nanoclusters. It was found that the resin has good chemical stability under hydrogen at 5 bar pressure and 40 °C for a reasonable time. For the reusability the hydrogenation of cyclohexene at 40 °C with 1.7−5.0 bar hydrogen pressure was studied. It was found that the catalyst is completely reusable for at least four consecutive runs. After several consecutive runs it was found that the size of the palladium particles had grown.

Asymmetric Cyclopropanation Catalyzed by C_2-Symmetric Bis-ephedrine−Cu(II) Complexes

The asymmetric cyclopropanation of styrene with alkyl diazoacetate was studied by J. Gao et al. (*J. Mol. Catal. A* **2003**, *191*, 23) with a series of Cu(II) complexes of chiral ligands, which were derived from 1*R*,2*S*-(−)-ephedrine. The prepared catalysts were found to give ee up to 89% with a trans/cis ratio of 86/14 in a total yield of 92%. The best catalyst was found to be the pyridine-derived dimeric catalyst **1** easily obtained from 2,6-bis (bromomethyl)pyridine and 1*R*,2*S*-(−)-ephedrine. This Cu(II) complex was also found to have the highest stability constant $10^{7.8}$ at 298 K.



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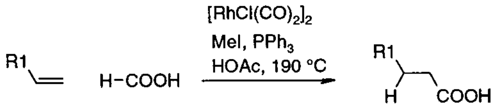
New Efficient Catalytic System for Hydroxycarbonylation without CO Gas

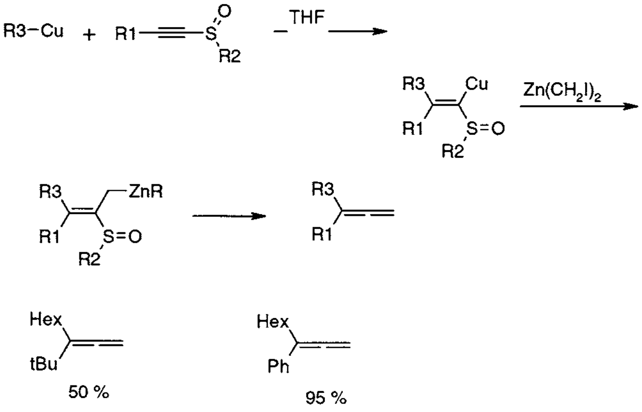
Alkyl formats have been focus of intensive researches in recent years for the direct synthesis of carboxylic esters from alkenes in the absence of carbon monoxide. Alkyl formamides, which lead to the corresponding amides have also been studied. Surprisingly, formic acid has not been thoroughly investigated although it may allow the direct synthesis of carboxylic acids from alkenes or alcohols. J.-P. Simonato (*J. Mol. Catal. A*, **2003**, in press) has studied the hydroxycarbonylation with formic acid using a rhodium catalyst. The source of rhodium was not important, but the addition of methyl iodide to stabilise the catalyst and the addition of triphenyl phosphine were found to be important. The reaction was performed in a pressure reactor at elevated temperatures. The system also functions without solvent. From the process, mainly linear carboxylic acids are obtained also from internal olefins. The yields obtained are moderate to good.



Carbocupration/Zinc Carbenoid Homologation and β-Elimination Reactions for a New Synthesis of Allenes: Application to the Enantioselective Synthesis of Chiral Allenes by Deracemisation of sp^3-Organometallic Derivatives

Allenes are an important class of molecules with high chemical reactivity, due to their cumulated double bonds. The most popular method for their preparation is the treatment of propargylic derivatives with organocopper reagents. In many cases, however, allenes are contaminated with alkenyl isomers resulting from direct S_N2 processes. I. Marek et al. (*Eur. J. Org. Chem.* **2002**, 4151) have developed a new method for the synthesis of polysubstituted allenes from acetylenic sulfoxides and sulfones in a straightforward manner as no isomeric alkynes can be formed in the procedure. The one-pot procedure involves a carbocupration followed by a zinc carbenoid homologation and finally a syn β-elimination reaction. The scope of the reaction is broad although the yield decreases slightly with more substituted substrates. Even aryl copper adds cleanly to both octynyl and ethynyl sulfoxides.

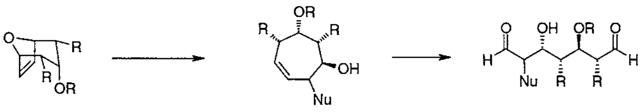
If the method is extended to a chiral sulfoxide, which was treated with butyl cuprate followed by the zinc homologation/β-elimination, a chiral allene was obtained in good yield and 51% enantiomeric excess. This is due to a deracemisation of the zinc chelate before syn elimination.

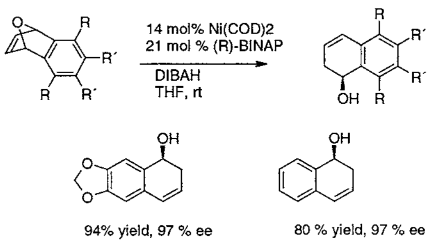


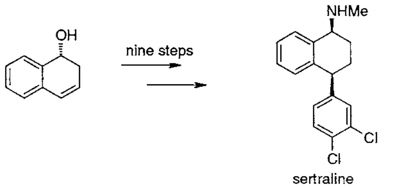
Transition Metal-Catalyzed Enantioselective Ring-Opening Reactions of Oxabicyclic Compounds

There is a continuing need for the discovery of new reactions that control the relative and absolute stereochemistry in cyclic and acyclic compounds. One approach that has attracted attention is to utilise desymmetrisation reactions of meso compounds since many stereo centers can be established rapidly and efficiently in one step. M. Lautens et al. (*Acc. Chem Res.* **2003**, *36*, 48) have summarised the research on enantioselective ring-opening reactions of oxabicyclic alkenes over the past five years. During this period several metal-catalyzed asymmetric ring-cleaving reactions have been developed that generate products in high yield and enantiomeric excess. These reactions can be carried out with a range of nucleophiles including hydride, stabilised and nonstabilised carbanions, alcohols, amines, and carboxylates.

The methods have found use in the total synthesis of several biological interesting molecules including sertraline.

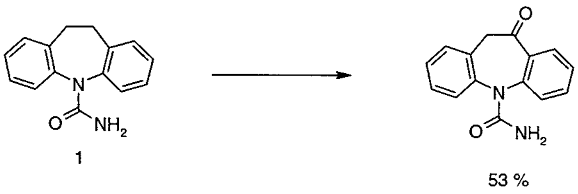






Low-Temperature High Conversion, Liquid-Phase Benzylic Oxidations with Oxygen and Metal/NHPI-Catalyzed Co-oxidation of Benzaldehyde

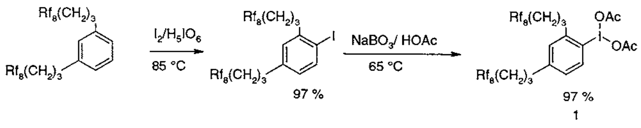
The group of P. Alsters at DSM fine chemicals (*Eur. J. Org. Chem.* **2003**, 578) has developed a new liquid-phase catalytic oxidation system for the low-temperature, benzylic mono-oxyfunctionalisation. The method is based on the co-oxidation of the substrate with benzaldehyde in the presence of a four-component catalyst system consisting of $Co(OAc)_2$ $Ni(OAc)_2$, $Cr(NO_3)_3$, and *N*-hydroxyphthalimide (NHPI). The mechanism and the influence of the different components were investigated, and the scope of this method for the oxidation of different substrates has also been studied. Yields depend on structure. Easily oxidised substrates are obtained in lower yield than with the Ishii method Co/NHPI; however, for more complex structures such as **1** and compounds not as easily oxidised the new method is superior although giving, in the best cases, modest yields.

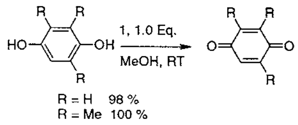


Convenient Syntheses of Fluorous Aryl Iodides and Hypervalent Iodine Compounds and Applications in Oxidations of Hydroquinones

Over the past decade many new compounds with high affinities for perfluoroalkane and perfluorodialkyl ether have been synthesised driven by the development of fluorous biphase chemistry. High fluorous phase affinities are achieved by appending sufficient numbers of “pony tails” of the formula $(CH_2)_m(CF_2)_n{-}CF_3$, The spacer segment $(CH_2)_m$ partially insulates the reactive site from the electronegative perfluoro groups.

Aryl iodides are very versatile synthetic organic building blocks as well as precursors to a variety of extremely useful hypervalent iodine reagents. J. A. Gladysz et al. (*Chem. Eur. J.* **2003**, *1*, 9) have developed a synthesis of fluorous aryl iodides and hypervalent iodine compounds. The fluorous arenes were iodinated under standard conditions with periodic acid and iodine in aqueous acetic and sulfuric acid in good-to-excellent yields. The perfluoroaryl iodides were oxidised with sodium perborate in acetic acid at 65 °C in high yield. The aryl iodides were insoluble in acetic acid under the standard reaction conditions at 40 °C. Diacetoxyiodobenzene is normally used for the oxidation of hydroquinones in methanol. However, the coproduct phenyl iodide is normally discarded. All of the perfluoro analogues performed this oxidation in excellent yield. After the reaction the perfluoroaryl iodides were extracted from the reaction mixture with perfluoro-heptane. The iodides were subsequently reoxidised and reused in the oxidation without any loss in yield of the iodide or the quinone.

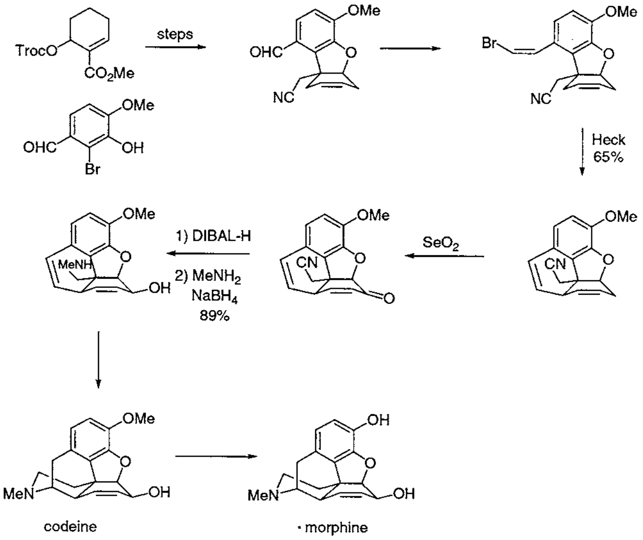




Enantioselective Synthesis of Morphine and Codeine

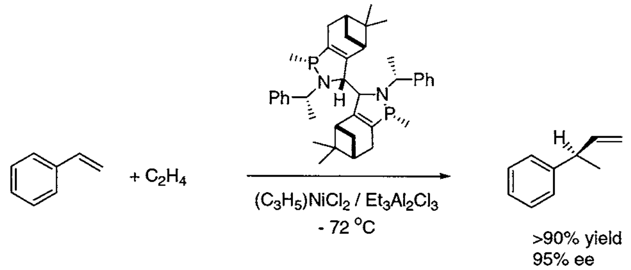
2002 was the 50th anniversary of the first synthesis of morphine (Gates, M. et al. *J. Am. Chem. Soc.* **1952**, *74,* 1109), but interest in these compounds and the related amaryllidaceae alkaloids such as galanthamine continues. A recent publication (Trost, B. M. et al. *J. Am. Chem. Soc.* **2002**, *124*, 14542), describes an enantioselective synthesis of codeine and morphine.

The successful synthesis uses a Heck vinylation reaction to build up one ring, followed by a hydroamination to form the piperidine ring.

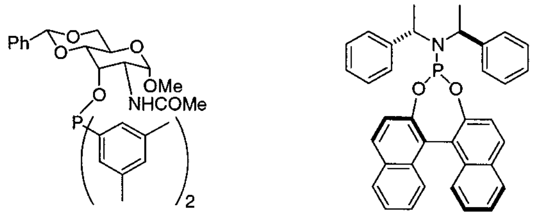


Asymmetric Hydrovinylation of Olefins

A short review of this important carbon−carbon bond-forming reaction has appeared (Goossen, L. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 3775). Hydrovinylation was first observed in 1953 when Ziegler, during his studies on polyethylene, observed that, in the presence of nickel, polymerisation was suppressed and ethylene dimerised to 1-butene. Asymmetric hydrovinylation was achieved as early as 1967 though it was not until 1988 that an excellent catalyst was found.

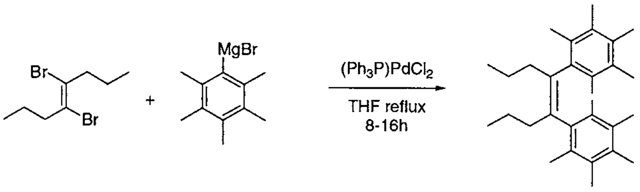


The limitation of this catalyst was, however, its complex structure and limited ability for fine-tuning. Recent work in the groups of Rajanbabu (Park, H. et al. *J. Am. Chem. Soc.* **2002**, *124,* 734) and Leitner (Francio, G. *J. Am. Chem. Soc.* **2002**, *124*, 736) has developed the new catalysts below. However, there is still room for improvement, and further developments will, no doubt, appear in the next few years.

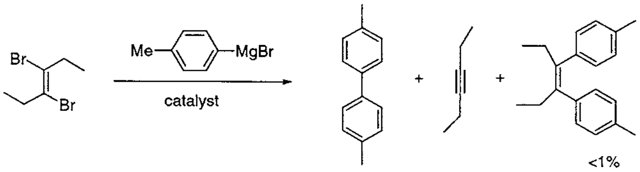


Synthesis of Pure CIS Stilbenoid Hydrocarbons from *trans*-Dibromoalkanes

The reaction of *trans*-dibromoalkanes with highly substituted aromatic Grignard reagents in the presence of a palladium catalyst results in the formation of highly hindered *cis*-stilbenes with *no trace* of the trans isomer (Rathore, R. et al. *J. Am. Chem. Soc.* **2002**, *124*, 14832).



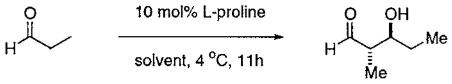
The success of this transformation depends on the presence of the ortho methyl groups and less than 1% yield of desired product is obtained with arylmagnesium halides lacking these substituents.



Whilst the mechanism of this unusual transformation is unclear, it is interesting to note that both aryl groups seem to go on simultaneously (or the second goes on much faster than the first) since a reaction in the presence of a 100-fold excess of *trans*-dibromohexene produced ONLY the *cis*-diarylolefin, with no trace of a mono-derivative. The *cis*-diarylolefins produced form molecular clefts which can trap small molecules such as NO and metal cations. They are also potentially useful as photochromic molecular switches for molecular electronics applications. This new methodology makes their synthesis relatively straightforward.

The First Direct and Enantioselective Cross-Aldol Reaction of Aldehydes

The enantioselective coupling of nonequivalent aldehydes is a formidable challenge because the aldehydes tend to polymerise under the metal-catalysed reaction conditions and because of the need for selectivity between the reaction "partners". It has now been shown by the group of MacMillan at Pasedena (Northrup, A. B. et al. *J. Am. Chem. Soc.* **2002**, *124*, 6798) that enamine catalysis results in efficient coupling of two aldehydes. Initial results showed promise with self-coupling of propionaldehyde in the presence catalytic quantities of proline in DMF.



Solvent	Conversion	Anti/Syn	% ee (Anti)
Benzene	32	5:1	>99
CH_2Cl_2	29	4:1	98
EtoAc	41	5:1	99
NMP	62	3:1	98
DMF	91	3:1	99

Byproducts arising from dehydration were at low levels (<4%). Slow addition of propionaldehyde to a series of aldehyde acceptors in the presence of an amine catalyst suppressed homo-dimerisation and gave good yields of the desired cross aldol product. The reaction tolerates a wide variety of structural variation and seems amenable to scale-up. I assume a patent application has been made!

R_1	R_2	Yield	Anti:Syn	% ee
Me	Et	80	4:1	99
Me	i-Bu	88	3:1	97
Me	cyclohexyl	87	14:1	99
Me	Ph	81	3:1	99
Me	i-Pr	82	24:1	99
n-Bu*	i-Pr	80	24:1	98
Benzyl*	i-Pr	75	19:1	91

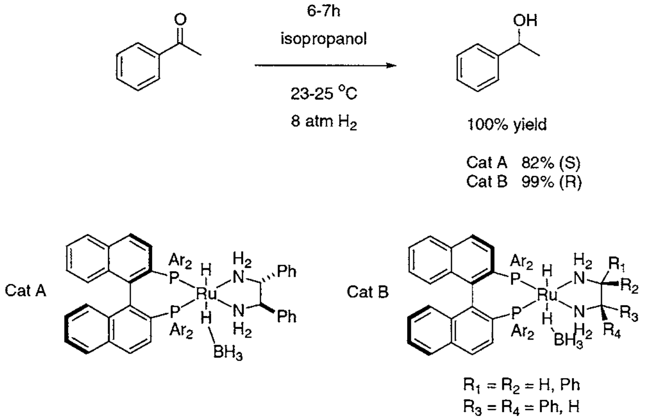
*At 23 °C

Asymmetric Hydrogenation

Normally, asymmetric hydrogenation of simple ketones in 2-propanol, in the presence of chiral diphosphine complexes of ruthenium, requires the presence of a base such as KOH, KOiPr, or KO tBu (Noyori, R. et al. *Angew. Chem., Int. Ed.* **2001**, *40*, 40). It has now been found that reactions can occur in the absence of base, provided the catalyst is designed carefully (Ohkuma, T. et al. *J. Am. Chem. Soc.* **2002**, *124*, 6508)—the catalysts are of the type Ru (η^1-BH_4) (binap) (1,2-diamine) and can give excellent productivity (substrate-to-catalyst ratio up to 100,000).

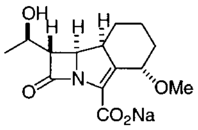
The old base-catalysed procedure had been used for selective hydrogenation of α-substituted ketones via dynamic kinetic resolution but was inappropriate for kinetic resolutions when the ketone was configurationally labile.

The new procedure allows the hydrogenation of, for example, 2-isopropylcyclohexanone to the alcohol, and the *R* enantiomer of the ketone is consumed 38 times faster than



the S isomer. Thus, after 53% conversion, the *S* ketone can be recovered in 91% ee.

The process can be used for resolution of enantiomers of 2-methoxycyclohexanone, which is a key intermediate in the synthesis of the potent antibacterial agent sanfetrinem.

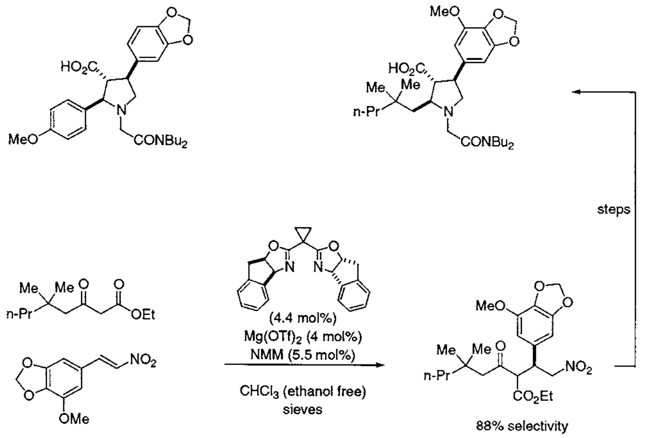


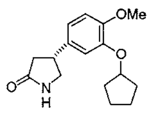
Sanfetrinem

Catalytic Enantioselective Conjugate Addition (1)

ABT 627 and ABT 546 are clinical candidates at Abbott and are being tested for prostate cancer therapies. Although synthetic routes based on resolution strategies were originally developed, these were very inefficient (20% yield), and new syntheses which are based on addition of ketoesters to nitro olefins (Barnes, D. M. et al. *J. Am. Chem. Soc.* **2002**, *124*, 13097) have been developed.

The methodology has also been used in a synthesis of another Abbott drug, the antidepressant Rolipram.

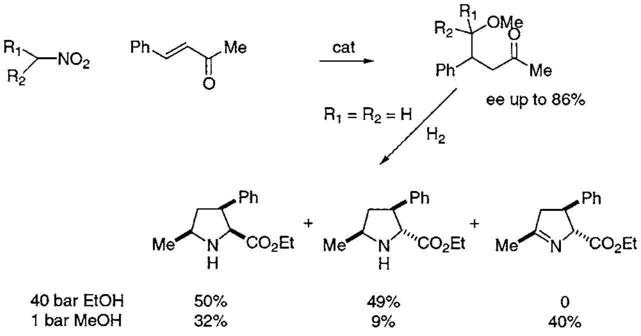


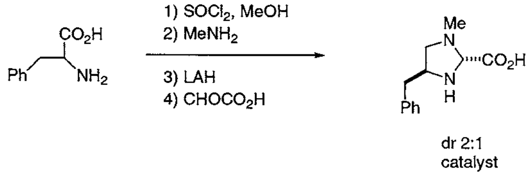


(R)-rolipram

Catalytic Enantioselective Conjugate Addition (2)

Enantioselective conjugate addition of nitroalkanes to α,*β*-unsaturated ketones yields products which can also be cyclised to pyrrolidines (Halland, N. et al. *J. Org. Chem.* **2002**, *67*, 8331). Novel imidazoline catalysts are used for this transformation, and their synthesis is also shown below.

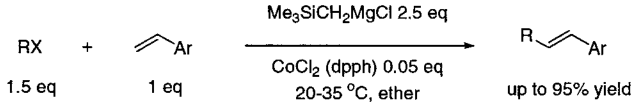




Cobalt-Catalysed Heck-Type Reaction

The major limitation of the Heck reaction is that one cannot use alkyl halides having a β hydrogen (with respect to the halide) because of competitive elimination (for a review see Beletskaya, I. P. et al. *Chem. Rev.* **2000**, *100*, 3009).

It has now been found that a cobalt−phosphine complex catalyses a Heck-type reaction of alkyl halides with styrenes in the presence of TMS CH_2MgCl (Ikeda, Y. et al. *J. Am. Chem. Soc.* **2002**, *124*, 6514).



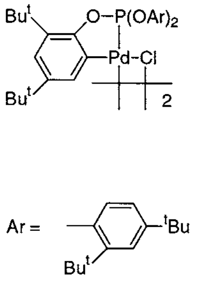
The reaction tolerates functionality such as ester, amide (in some cases), and halogen. Cyclopropylmethyl halides gave only ring-opened products.

It is suggested that the mechanism proceeds via alkyl radicals, quite different from the palladium-catalysed Heck reaction. Thus, the scope of the two processes should be different and, hopefully, complementary.

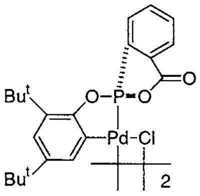
Extremely High Activity and Long-Lived Catalysts for Suzuki Coupling

There has been much interest in the coupling of aryl chlorides in the Suzuki reaction, owing to chloride's lower costs and greater availability. There have been many recent successes, but often the catalysts are used in relatively high loadings which negates the cost advantages of using chlorides. The group of Bedford at the University of Exeter, UK, has now found that phosphite-containing catalysts, formed from a mixture of PCy_3 and compound A, had long lifetime, possibly due to the π-acidity of the phosphite ligand. Increasing the π-acidity further, by using a salicylate residue as in B, leads to a much longer-lived catalyst (Bedford, R. B. et al. *Chem. Commun.* **2002**, 2610).

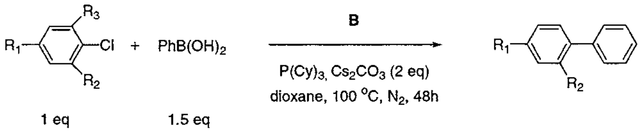
A range of substrates was studied and most give extremely high turnover numbers, which has high significance for industrial applications. Catalyst A is also active in the Stille coupling (see preceding paper, Bedford, R. B. et al. *Chem. Commun.* **2002**, 208).



A



B

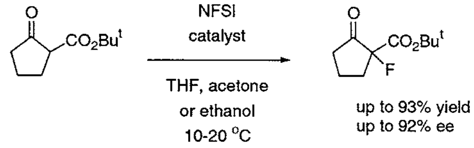


R_1	R_2	R_3	Pd loadings (mol %)	Conv	TON
MeO	H	H	0.001	90	90,000
MeO	H	H	0.00005	84	1,860,000
NO_2	H	H	0.00005	100	2,000,000
MeCO	H	H	0.00005	97	1,940,000
H	OMe	H	0.0005	84	168,000
H	Me	H	0.0005	82	174,000
H	Me	Me	0.0005	58	116,000

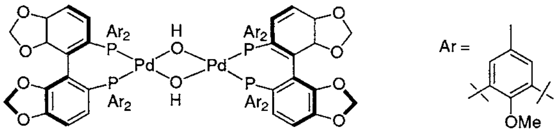
Enantioselective Fluorination

This topic seems to be attracting interest, and already two groups have published results (Paina, S. et al. *Angew. Chem., Int. Ed.* **2002**, *41*, 979; Kim, D. Y. et al. *Org. Lett.* **2002**, *4*, 545). Now it has been found that β-keto esters will react with *N*-fluorobenzenesulfonimide (NFSI) in the presence of a palladium catalyst. Interestingly, no reaction occurs with salt-type fluorine sources such as Selectfluor (Hamashima, Y. et al. *J. Am. Chem. Soc.* **2002**, *124*, 14530). Acyclic ketoesters also work, giving ees in the 83−94% range.

The keto esters can be converted into a number of useful compounds such as α-fluoroamino acids and esters.



catalyst is R-DTBM-SEGPHOS

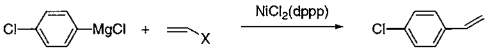


Large-Scale Grignard Cross-Coupling Reactions

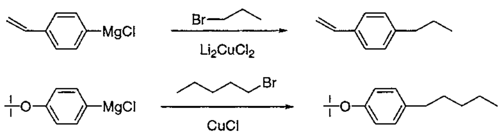
The reactions first reported by Kumada and Tamao in 1972 on the nickel catalyst cross-coupling of Grignard reagents with vinyl chloride have been scaled up and commercialised by Hokka Chemical Industry Company in Japan (Banno, T. et al. *J. Organomet. Chem.* **2002**, *653*, 288). Thus *p*-chlorostyrene is made on 5000 kg/annum and *tert*-butoxystyrene on 200,000kg/annum and increasing, because of potential use as a raw material for a photo resist.

A key problem to be overcome was a replacement solvent for ether. The table below shows the importance of using a mixed solvent since THF alone is a poor substitute for ether, possibly because it coordinates to the nickel catalyst better than vinyl chloride does.

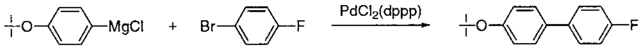
Copper can also be used as a catalyst for coupling between alkyl halides and Grignard reagents.



Solvent	Molar ratio THF/ArMgCl	X	Yield
Et_2O	6	Br	56
THF	6	Cl	5
THF/Toluene	2.2	Cl	63
THF/Toluene	2.2	Cl	68



Some biphenyl compounds, useful as intermediates for liquid crystals and pharmaceuticals are also manufactured on a large scale. In these cases an aromatic bromide has to be used, but Hokko are working on a lower-cost process using chlorides.



The report describes the plant for the manufacture of these molecules. Grignard reagents are prepared on 6000-L scale using 200−300 kg of magnesium, activated using Hokko's own proprietary know-how. The Grignard solution is transferred to a second reactor, where the halide and catalyst are added. If vinyl chloride is used, the gas is blown through the reaction mass. Work-up is very exothermic and requires careful control. The catalyst is removed in the aqueous layer, and solvent is recovered and reused, after concentrating the product.

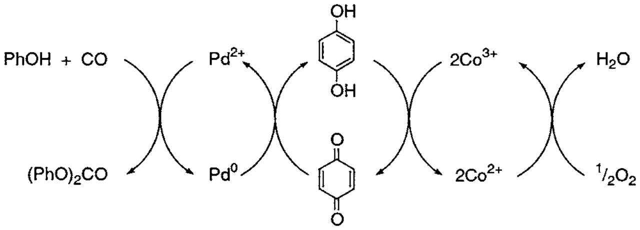
Chemically Modified Corn Starches Are Catalysts for Organic Reactions

The group of Clark at the University of York has prepared catalysts from a high-surface-area form of corn starch, made easily by heating starch in water at 100−130 °C, cooling, then keeping at 5 °C for an extended period, and washing with ethanol. The starch is then modified by direct reaction with (a) $ClCH_2CH(OH)CH_2SO_3Na$ and NaOH, (b) $ClSO_3H$ and pyridine, or (c) reaction with $(MeO)_3Si\ (CH_2)_3SH$ followed by oxidation with hydrogen peroxide. The resultant catalysts are very stable.

These catalysts can be reacted with a variety of amines to give new heterogeneous basic catalysts, and these are active in typical condensation reactions (Doi, S. et al. *Chem. Commun.* **2002**, 2632).

A New Heterogeneous Catalyst for the Oxidative Carbonylation of Phenol to Diphenyl Carbonate

The group of Jacobs at Leuven, Belgium, has reported a heterogeneous catalyst for the carbonylation of phenol (Linsen, K. J. L. et al. *Chem. Commun.* **2002**, 2728). The catalyst is prepared by immobilising a palladium sulfonated phenanthroline derivative on a magnesium−aluminium-layered double hydroxide. The catalyst has the advantage of also being the base so that the phenolate and carbon monoxide are brought into proximity. The catalyst works in conjunction with benzoquinone and cobalt (to reoxidise the palladium), in the presence of oxygen.



Role of Nucleation Inhibition in Resolutions with Families of Resolving Agents

The separation of enantiomers by diastereomeric salt formation, discovered by Pasteur in 1848, remains the most widely used industrial method for obtaining enantiomerically pure compounds. One hundred and fifty years later, the so-called Dutch resolution method, whereby a family of structurally related agents (families) are used SIMULTANEOUSLY, gave major improvements in success rate (Vries, T. et al. *Angew. Chem., Int. Ed.* **1998**, *37*, 2349; Eur. Pat. Appl. EP 0838448 to DSM). Thus, compounds can be resolved with a success rate of 90−95% compared to 20−30% when a single resolving agent is used.

In the original 1998 method, three related resolving agents from the same family were used in a 1:1:1 ratio, but the first salt which crystallised had all three agents in the crystal, but in a nonstoichiometric ratio. Of the 46 examples mentioned in the 1998 paper, 10 crystallised without one (or more) of the resolving agents, but the feeling was that these resolutions proceeded less well when these unincorporated resolving agents were absent. Experiments were designed to understand this phenomenon. Thus, in the resolution of mandelic acid by (*S*)-phenylethylamine, the first crystals have a de of only 14%. If, however 0.1 equiv of a 1:1 mixture of *o*- and *p*-nitro α-methyl benzylamines is added, the de increases to 55%, but no detectable nitro derivative is incorporated. It was shown that the presence of the nitro derivative enlarged the metastable zone width and this affects the nucleation temperature by nucleation inhibition.

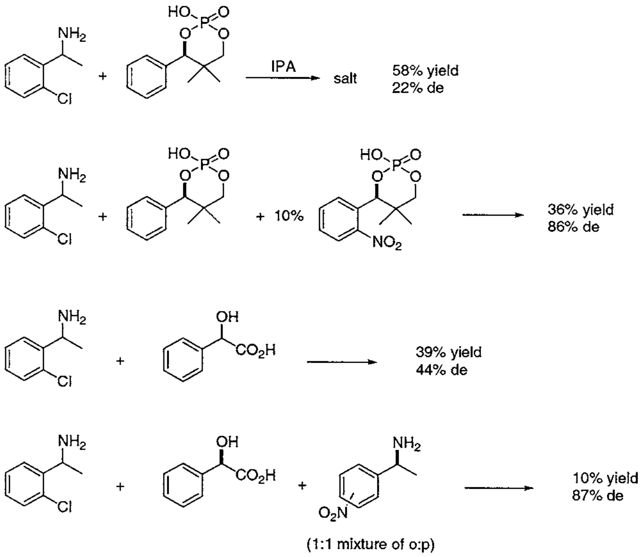
The main structural characteristics of these nucleation inhibitors are:

(1) substitution in the aromatic ring (nitro is very effective)

(2) position of substituent—ortho generally giving better results.

A two-component resolution, where the second minor component is not incorporated, is much more interesting from a large-scale manufacturing viewpoint that the original Dutch resolution with three components, and this recent study has provided an understanding of how the process proceeds.

A wide range of examples are given in this very important paper (Nieuwenkuijzen, J. W. et al. *Angew. Chem., Int. Ed.* **2002**, *41*, 4281). In some cases, "reverse" resolutions occur when the additive is a family member of the racemate. This may explain the difficulty of repeating experiments with starting materials of different purities, where the impurities can act as nucleation inhibitors.



Preferential Enrichment: A Way To Increase Enantiomeric Excess

The preferential crystallisation of conglomerates, whereby with the aid of enantiopure seed crystals a racemic mixture can be resolved (with alternate batches giving high ee but with alternating *R* and *S* chirality), is a useful industrial process and has been used in the past for drugs such as thiamfenicol and, I believe, for glutamic acid. It is not widely known that there is a complementary process, preferential enrichment, which has the following features:

(1) Repeated crystallisation of the racemate leads to alternating enrichment of ee in the mother liquors (up to 100% ee).

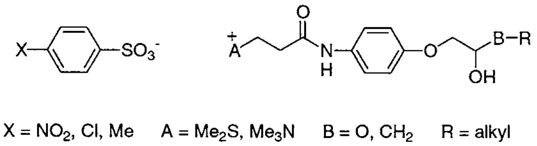
(2) At the same time, the deposited crystals display the opposite chirality, sometimes with slight enrichment of chirality.

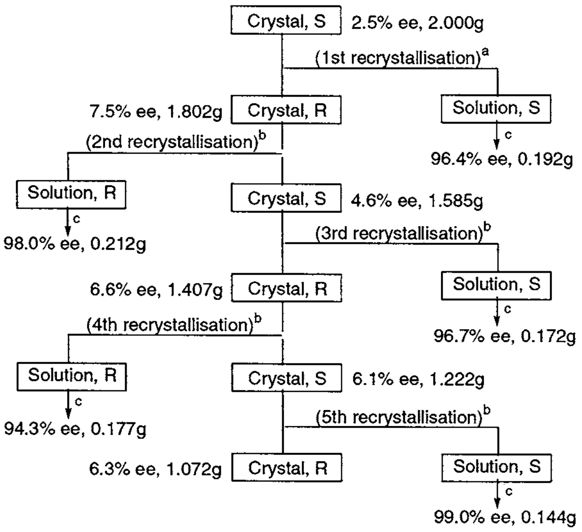
(3) The process works best with low ee values or racemates (<10% ee).

(4) No seed crystals are required.

The compounds showing this phenomenon are shown in the scheme (Tamura, R. et al. *J. Am. Chem. Soc.* **2002**, *124*, 13139).

These compounds are polymorphic,and a phase transition occurs during crystallisation from solution, in which the excess *R* or *S* enantiomer is liberated from the crystal into the solution. A chiral discrimination by the crystalline phase during crystal growth leads to enrichment of one enantiomer in the liquors. These transformations were studied by FTIR and, in the solid phase, by DSC to establish these detailed mechanisms.





Preferential enrichment conditions:

[a] EtOH (32 mL) at 25 °C for 4 days

[b] EtOH (32 mL) at 25 °C for 2 days

[c] removal of solvent by evaporation

Ten Years of Experience in Polymorphism Prediction: What Next?

The Royal Society of Chemistry has an electronic journal which has some interesting articles, often produced from papers given at conferences on crystallisation. Chemists and chemical engineers may be interested in a report on polymorph prediction (Gavesotti, A. *CrystEngComm* **2002**, *4*, 343) and also a report on Crystal Engineering Nucleation, The Key Step (Davey, R. J et al. *CrystEngComm* **2002**, *4*, 257); see the RSC website, http://www.rsc.org/cryst/eng/comm for more details and to download the files.

Metrics to Green Chemistry: Which Are the Best?

In a paper in *Green Chemistry*, a group from GlaxoSmithKline Pharmaceuticals compare and contrast metrics which are used by chemists and chemical engineers to evaluate "greenness" in a process (Constable, D. C. et al. *Green Chemistry* **2002**, *4*, 521).

A metric generally must be clearly defined, simple, and measurable, must be objective rather than subjective, and must ultimately "drive" the desired behaviour. Over the past 5−10 years a number of metrics for "greenness" have been suggested, and this paper reviews and critically analyses effective mass yield, *E* factor, atom economy, carbon efficiency, and reaction mass efficiency. The latter is a new metric, defined as, for a reaction A + B → C.

$$\text{Reaction mass efficiency} = \frac{\text{mass of product C}}{\text{mass of A + mass of B}} \times 100$$

$$\text{or} = \frac{\text{Mw of product C}}{\text{Mw of A + (Mw of B x molar ratio B/A)}} \times 100$$

It includes atom economy, yield, and the reaction stoichiometry.

The scheme shows that, depending on which metric is used, one gets different percentages, and it is important to understand why.

$$PhCH_2OH + TsCl + Et_3N \xrightarrow[\text{90\% yield}]{\text{toluene (500 mL)}} PhCH_2OTs$$

$PhCH_2OH$	TsCl	Et_3N	$PhCH_2OTs$
Mw 108.1 10.81g 0.1 mol	Mw 190.65 21.9g 0.115 mol	15g	Mw 262.29 23.6g 0.09 mol

$$\text{Atom efficiency} = \frac{262.29}{108.1 + 190.65} \times 100 = 87.8\%$$

$$\text{Carbon efficiency} = \frac{0.09 \times 14}{(0.1 \times 7) + (0.115 \times 7)} \times 100 = 83.7\%$$

$$\text{Reaction mass efficiency} = \frac{23.6}{10.81 + 21.9} \times 100 = 70.9\%$$

$$\text{Mass intensity} = \frac{10.81 + 21.9 + 500 + 15}{23.6} \times 100 = 23.2\ \text{kg/kg}$$

The atom economy is less than 100% because of the byproduct HCl. The carbon efficiency includes the excess TsCl, i.e., stoichiometry. The reaction mass efficiency takes account of the yield and stoichiometry. Mass intensity includes concentration.

The work includes an analysis of 28 different reactions on this basis. It is an interesting analysis which includes cost implications and costs calculated, assuming solvents are recovered. It concludes that pursuing atom economy on its own may not be a good economic driver.

Unfortunately, the report does not discuss space−time−yield, and when considering costs, particularly of lower-cost chemicals, this is a key consideration. The analysis, of course is focused on synthesis (and does not therefore deal with work-up) and is aimed at analysis of the synthetic route before the synthesis becomes a "process". However, since reaction mass efficiency does not include a concentration term, it has less value in measuring "greenness" than it could.

Treatment of Toxic Organic Effluent

A process, currently used for decontaminating nuclear waste and destruction of chemical weapons, may be useful for safely disposing of toxic organics. The process, marketed by Accentus, the UK subsidiary of AEA Technology, uses electrochemical oxidation, in which silver (II) ions are produced. These ions can form radicals which are very reactive and convert organics to CO_2, H_2O, and residual metal salts (*Chem. Br.* **2002**, 13).

Sources for Accident/Incident Data Bases

The December 2, 2002, issue of *Chemical & Engineering News* published a list of websites where process safety information may be obtained. These are reproduced below.

Chemical Safety and Hazard Investigation Board: http://www.csb.gov

Marsh Risk Consulting: http://www.marsh.com

Institute of Chemical Engineers (UK): http://www.ichem.org

American Institute of Chemical Engineers Center for Chemical Process Safety: http://www.aiche.org/ccps/

Mary Kay O'Connor Process Safety Center: http://mkopsc.tamu.edu

Other Highlights Pages

I know that these highlights pages are well used from the comments received from readers and from the large number of "hits" on the web editions and on the highlights published on the website (http://pubs.acs.org/oprd).

There are, however, other places where similar highlights also appear, and we try not to duplicate what is done although some overlap is inevitable. One of the first journals to publish Highlights was the magazine of the Society of Chemical Industry (SCI), *Chemistry in Industry* (free to members of SCI) and this is still a popular feature, containing not only "academic" highlights but also an applied section. In the front section of the journal *Green Chemistry*, the editors provide highlights of "environmentally friendly" reactions, many of which are relevant to the process chemistry community. The now defunct American Chemical Society magazine, *Chemical Innovation*, was also an early innovator (in its *CHEMTECH* days) with its "Heart Cut" section. It may not be realised that this section still continues and can be accessed via the website http://pubs.acs.org/ci.

Methods in Organic Synthesis is a comprehensive review of the literature for interesting organic transformations and is presented only in reaction-scheme format with reagents and yields, with an occasional one-line comment, but no Discussion. It is also available online as a searchable database, MOSonline (see http://www.rsc.org/mos).

Of interest to industrial chemists should be *Catalysts and Catalysed Reactions* of the Royal Society of Chemistry, which is in a format similar to that of MOS. However, it does cover more physical chemistry and surface science journals, which the average organic chemist may not read, as well as some chemical engineering journals (see http://www.rsc.org/catalysts).

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