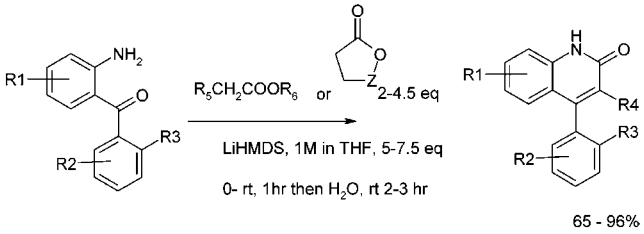
Organic Process Research & Development **2003**, *7*, 450−458

Highlights from the Literature

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

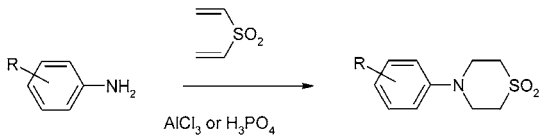
4-Aryl-quinolin-2(1*H*)-ones Synthesis

Wang and colleagues from Bristol Myers Squibb describe (*Tetrahedron Lett.* **2003**, *44*, 4271) how using LiHMDS as the base, a tandem amidation/Knoevenagel condensation of 2-aminobenzophenones with α-methylene esters or lactones gives 4-aryl-quinolin-2(1*H*)-ones in 65−96% yield. This method is mild, highly efficient, and amenable to scale-up.



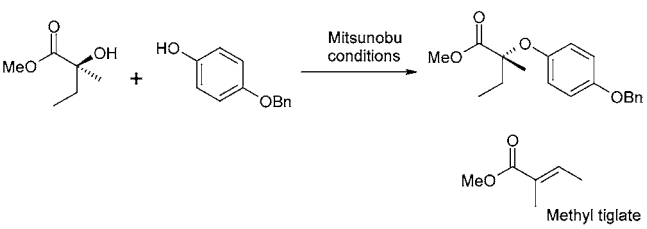
Double Michael Addition

Substituted anilines and vinyl sulfone have been found by Chen and colleagues at Pharmacia (*Tetrahedron Lett.* **2003**, *44*, 3459) to undergo a facile double Michael addition to form substituted phenylthiomorpholine dioxide, catalyzed with $AlCl_3$ or H_3PO_4 providing a useful synthetic tool for the preparation of this functional moiety.



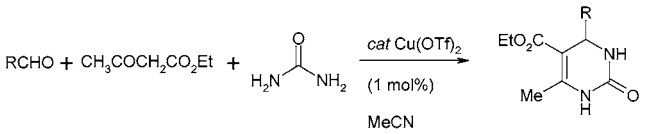
Inversion using Mitsunobu Chemistry

Shi and colleagues describe (*Tetrahedron Lett.* **2003**, *44*, 3609) how the Mitsunobu reaction of chiral tertiary alcohol with phenol derivatives provides the desired ethers in moderate yields at elevated temperatures (80−100°C). The S_N2 displacement pathway is evident by complete inversion of the (*S*)-alcohol to (*R*)-ether, but was accompanied by elimination to give the tiglate side product.



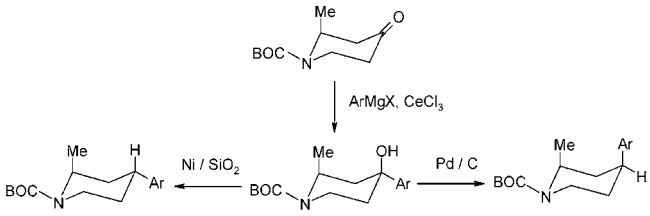
Copper (II) Triflate as a Reusable Catalyst

Copper (II) triflate has been found by Sudalai and coworkers (*Tetrahedron Lett.* **2003**, *44*, 3305) to catalyze the three-component condensation reaction of an aldehyde, β-ketoester and urea in acetonitrile to afford the corresponding 3,4-dihydropyrimidin-2(1*H*)-ones in high yields. In this modified Biginelli synthesis, the catalyst exhibited remarkable reusable activity and was recovered in solution once the product had been filtered from the mixture.



cis- and *trans*-2-Methyl-4-aryl Piperidines

A stereoselective approach has been developed for the synthesis of *cis*- and *trans*-2-methyl-4-arylpiperidines from a common intermediate by Merschaert and colleagues at Lilly (*Tetrahedron Lett.* **2003**, *44*, 4531). The Ni-catalyzed hydrogenolysis of *N*-Boc-2-methyl-4-aryl-4-piperidinols, obtained by addition of organometallic reagents on *N*-Boc-2-methyl-4-piperidone, afforded the *trans* derivatives with up to 95% selectivity whereas the corresponding *cis* isomers were obtained in the presence of palladium catalysts. In both cases the reaction was found to be sensitive to electronic as well as steric effects.



Cinnamic Acid Derivatives

A variety of (*E*)-cinnamic acid derivatives have been prepared (Seki et al. *Syn. Commun.* **2003**, *33*, 427) in high yields through the Claisen−Schmidt condensation in the presence of sodium metal and a catalytic amount of methanol with toluene employed as the cosolvent.

Synthesis of 4(5)-Alkylacyl-1H-imidazoles

A convenient synthesis of 4(5)-acyl-1H-imidazoles from 4(5)-imidazolecarboxaldehyde *without* an *N*-protecting group has been reported by Kawakami and colleagues from the chemical development laboratories at the Takeda Chemical Industries Ltd. (*Synthesis* **2003**, 677). 4(5)-Cyanoimidazole could be synthesized from commercially available 4(5)-imidazolecarboxaldehyde in one-pot reaction using hydroxylamine hydrochloride followed by acetic anhydride treatment.

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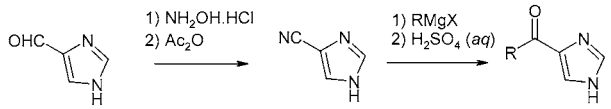
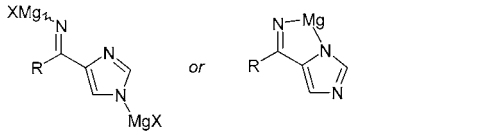
Treatment of 4(5)-cyanoimidazole with various alkylmagnesium bromides followed by addition of aqueous sulfuric acid afforded 4(5)-acyl-1H-imidazoles in good yields (79−96%).



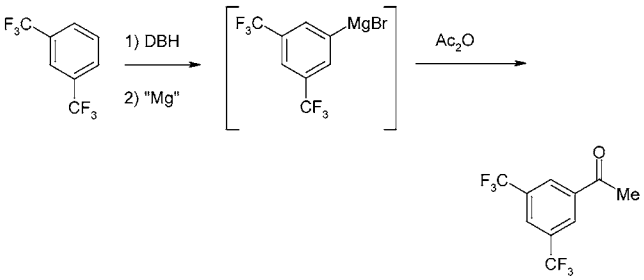
Although the group have not fully investigated the mechanism for the organometallic addition they propose reaction progression via one or both of the following intermediates:



proposed intermediates

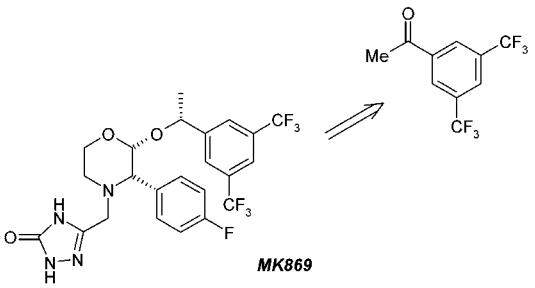
Preparation of 3,5-Bis(trifluoromethyl)acetophenone

An improved and efficient bromination of 3,5-bis(trifluoromethyl)benzene using 1,3-dibromo-5,5-dimethylhydantoin (DBH) has been developed by Leazer and co-workers at Merck (*J. Org. Chem.* **2003**, *68*, 3695). The group then



Thermally unstable, potentially explosive intermediate

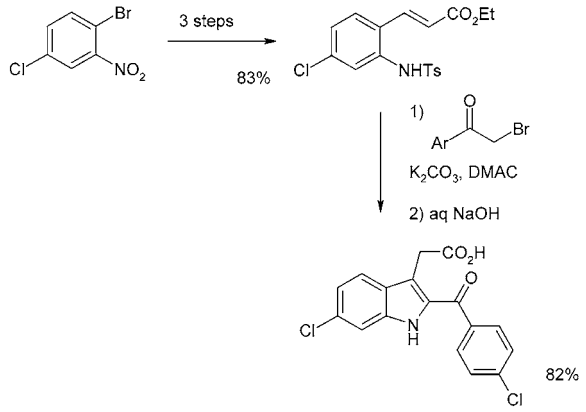
go on to describe how a safe and reliable preparation of the potentially explosive 3,5-bis(trifluoromethyl)phenyl Grignard and 3-trifluoromethylphenyl Grignard reagents, from the precursor bromides was achieved. They found the Knochel halogen−magnesium exchange protocol (THF, 0 °C, 1.1 equiv of *I*-PrMgBr, 30 min) to be the best method for Grignard formation. Reaction system screening tool (RSST) and differential thermal analysis (DTA) studies were used to suggest these trifluoromethylphenyl Grignard reagents can detonate on loss of solvent contact or upon moderate heating. When prepared and handled accordingly, these Grignard reagents can be safely prepared and carried on to advanced intermediates en route to the novel neurokinin 1 receptor antagonist MK869.



MK869

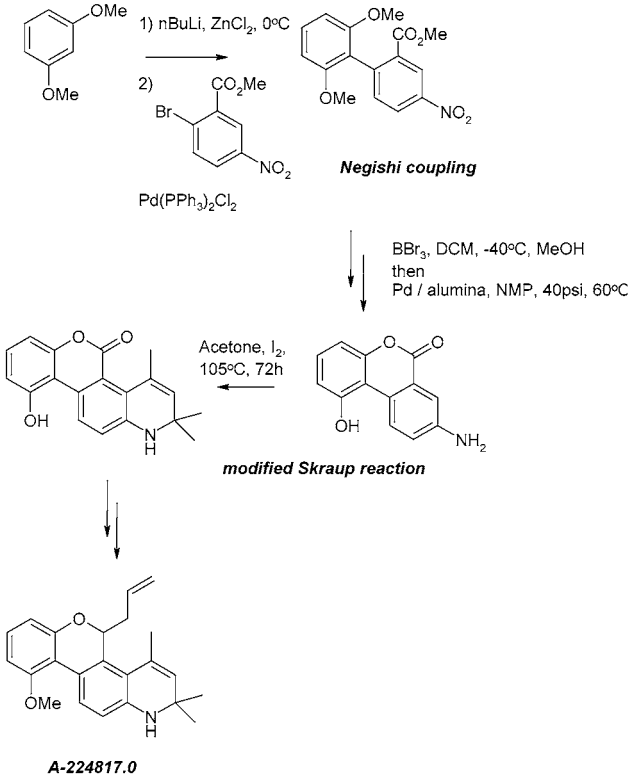
Efficient Synthesis of a Novel COX-2 Inhibitor

The synthesis of 6-chloro-2-(4-chlorobenzoyl)-1*H*-indol-3-ylacetic acid, a selective cyclooxygenase 2 (COX-2) inhibitor, is described by Caron and colleagues from Pfizer (*J. Org. Chem.* **2003**, *68*, 4104). The synthesis utilises a novel indole formation involving a tandem alkylation/1,4-addition/elimination/isomerization cascade. It was demonstrated that the entire sequence from sulfonamide ene ester and bromoketone (see below) to the desired indole product could be executed in a single pot.



Practical and Scaleable Synthesis of A-224817.0

A practical and scaleable synthesis of a novel nonsteroidal ligand for the glucocorticoid receptor A-224817.0 has been reported by Ku and co-workers from Abbott Laboratories (*J. Org. Chem.* **2003**, *68*, 3238). The synthesis is executed in seven steps starting from 1,3-dimethoxybenzene. The biaryl intermediate was prepared by an optimized high-yielding Negishi protocol (see below). The quinoline core

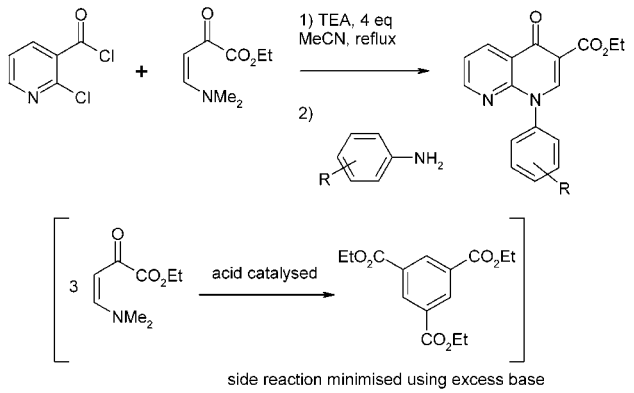


A-224817.0

was constructed using a modified Skraup reaction and the final product obtained by a direct allylation reaction of the lactol derived from the lactone with allyltrimethylsilane. The process was accomplished efficiently to produce the target molecule in 25% overall yield and >99% purity using simple and practical isolation and purification procedures.

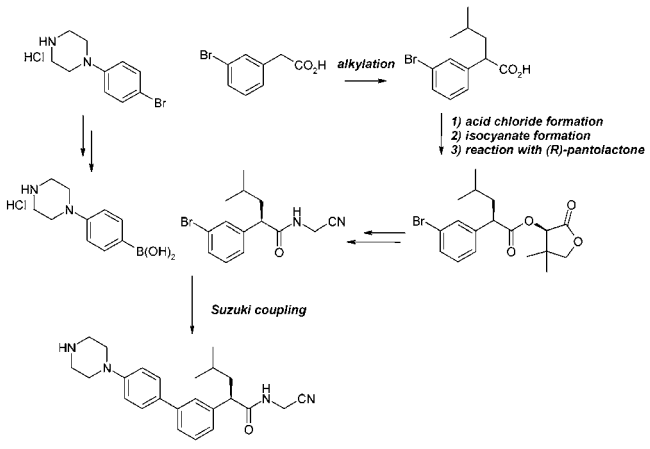
One-Pot Synthesis of 1,8-Naphthyridones

Springfield and colleagues from Merck have recently disclosed an efficient one-pot procedure for the preparation of substituted 1,8-naphthyridin-4-one analogues (*J. Org.Chem.* **2003**, *68*, 4598). Previous efforts to effect this type of transformation were complicated by the formation of benzene tricarboxylate however the group have found that using excess base, the impurity formation was completely inhibited. This allowed for the clean preparation of the desired intermediate and subsequent formation of naphthyridone analogues in a single flask, which could then be crystallized directly from the reaction mixture in good yield and high purity.



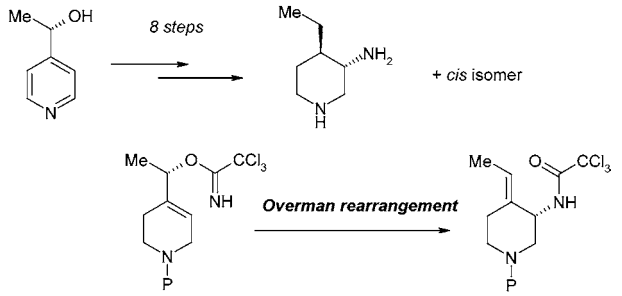
Asymmetric Synthesis of a Potent Cathepsin K inhibitor: Efficient Pd Removal

A large-scale, chromatography-free synthesis of a potent and selective cathepsin K inhibitor has been reported by O'Shea and colleagues at Merck (*J. Org. Chem.* **2003**, *68*, 2633). The key asymmetric center was installed by addition of (*R*)-pantolactone to the in situ-generated ketene followed by chiral protonation. The final step of the convergent synthesis was completed via Suzuki coupling of aryl bromide and the unprotected aryl piperazine boronic acid. Residual palladium and iron generated in the Suzuki coupling were efficiently removed from the crude product via a simple extractive workup using lactic acid.



Enantiospecific Synthesis of (3*S*,4*R*)-3-Amino-4-ethylpiperidine

An enantiospecific, eight-step synthesis of (3*S*,4*R*)-3-amino-4-ethylpiperidine starting from readily available (*S*)-(−)-α-methyl-4-pyridinemethanol has been achieved utilizing an Overman rearrangement of a chiral allylic trichloroacetimidate as the key step by Reilly and co-workers (*Tetrahedron Lett.* **2003**, *44*, 2927). A diastereoselective hydrogenation of the resulting chiral allylic amine product afforded predominantly the desired *trans*-substituted piperidine.



The Power of High-Throughput Experimentation in Homogeneous Catalysis Research for Fine Chemicals

The use of high-throughput experimentation (HTE) in homogeneous catalysis for the production of fine chemicals has received much attention over the last 3−4 years. De Vries, J. G. and de Vries, A. H. M. (*Eur. J. Org. Chem.* **2003**, 799) have summarized their achievements using this methodology. Whereas in the past stoichiometric chemistry was often preferred because of time-to-market constraints, HTE allows catalytic solutions to be found within a short time frame. At the same time, a reliable process can be achieved because extensive optimization can be undertaken. The authors give examples of lead generation and optimization, and scope determination, based on their basic research aimed at developing low-cost aromatic substitution reactions (C−H activation, Heck and Suzuki reactions). The authors also give an example of HTE in mechanistic research.

The use of HTE in the entire R&D process is expected to lead to increased reliability of implemented processes, yet with lower development costs. For the development of homogeneous catalytic processes there is even more incentives for the use of HTE. One of the more problematic aspects of homogeneous catalysis research is the almost complete lack of useful structure−activity relationships. One of the reasons for this lack of data is that most catalytic cycles consist of several consecutive discrete steps, and the chemical nature of each intermediate may be quite different. Although there are many parameters that effect the outcome of the reaction, the effects that they have on each discrete step may differ widely and may even be opposing. This thwarts most attempts to rationalize the choice of parameters based on analogies, which is the common approach in process

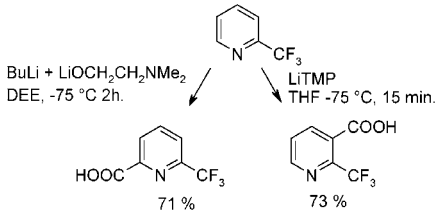
optimization. Thus, a slow step-by-step approach to lead finding and optimization was common practice prior to HTE. A legendary example is the discovery of a catalyst for the asymmetric imine hydrogenation in the production of Metolachlor, which took 12 years (see further, Some Items of Interest to Process R&D Chemists and Engineers *Org. Process Res. Dev.* **2002**, *3*, 207). The authors summarize that through the use of HTE they have been able to increase the output and the quality of their R&D. They have also been able to reduce the time necessary to find a catalyst and conditions for a given transformation to about three weeks, given availability of the starting materials. The HTE approach works for lead discovery as well as for optimization.

A Review of the Problem of Distinguishing True Homogeneous Catalysis from Metal-Particle Heterogeneous Catalysis

Widegren, J. A. and Finke, R. G. (*J. Mol. Catal. A: Chem.* **2003**, *198(1−2)*, 317) have reviewed the latest findings on the problem of distinguishing true homogeneous catalysis from soluble or other metal-particle heterogeneous catalysis. The various experiments that have been developed to distinguish homogeneous and heterogeneous catalysis have been outlined and discussed. The authors have found that (1) in-situ reduction of transition-metal complexes to form soluble metal-particle heterogeneous catalysts is common; (2) the formation of such catalyst is easy to miss because colloidal solutions often appear homogeneous to the naked eye; (3) a variety of experiments have been used to distinguish homogeneous from heterogeneous catalysis, but there is no single definitive experiments to make the distinction; (4) experiments that provide kinetic information are key to the correct identification of the true catalyst. The authors also suggest a procedure for the clear distinction of homogeneous and heterogeneous catalysis involving catalyst isolation and characterization, especially by TEM studies, kinetic studies, and quantitative catalyst poisoning experiments, and the decision should be consistent with all experiments.

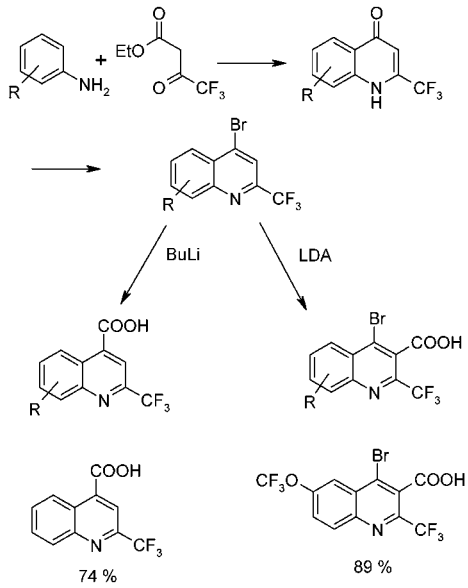
The Metalation and Functionalization of Trifluoromethyl-Substituted Pyridine And Quinolines

Over the last years fluorine has gained popularity as a heteroatom in pharmaceutical drugs and agrochemicals. Due to this popularity there is a growing need for the selective introduction of fluorine atoms or trifluoromethyl groups or the selective derivatization of the fluorine-substituted molecules. Trifluoromethyl-substituted heterocycles are relatively rare, especially if the simultaneous presence of other functional groups is required. Schlosser, M. and Marull, M. (*Eur. J. Org. Chem.* **2003**, 1569) have shown that, depending on the reagent, 2-(trifluoromethyl)pyridine can be selectively metalated and subsequently carboxylated or otherwise functionalized either at the 3- or the 6-position. This can also be achieved with 4-(trifluoromethyl)pyridine, which may be deprotonated either at the 2- or 3-position. In contrast 3-(trifluoromethyl)pyridine undergoes nucleophilic addition and ensuing decomposition whatever the base.



Selective And Efficient Structural Elaboration of 2-(Trifluoromethyl)Quinolinones

The acid-catalyzed cyclization-condensation between anilines and ethyl 4,4,4,-trifluoroacetoacetate affords 1,4-dihydro-2-trifluoromethyl-4*H*-4-quinolinones in fairly good yields with ortho- and para-substituted anilines (Schlosser, M.; Marull, M. *Eur. J. Org. Chem.* **2003**, 1576). 1,4-Dihydro-2-trifluoromethyl-4*H*-4-quinolinones have been shown to be easily converted into 4-bromo-2-(trifluoromethyl)quinolines with phosphorus oxytribromide in generally high yields. Through a metal−halogen exchange with butyllithium it is possible to obtain 4-substituted 2-(trifluoromethyl)quinolines. The 4-carboxylic derivatives were obtained in high yields. Through a hydrogen/metal exchange 3-substituted derivatives are obtained from 4-bromo-2-(trifluoromethyl)quinoline except for 5-substituted derivatives, which were found to be totally inert against lithium dialkylamides.



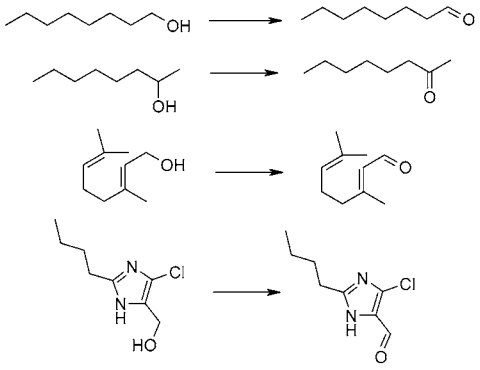
Automated Enzyme Screening Methods

In a pharmaceutical environment, the need for efficient and practical screening techniques has become vital in the search for ideal enzymes that can be used in the synthesis of drug intermediates. The group at Pfizer La Jolla Laboratories (Yazbeck, D. R. et al. *Adv. Synth. Catal.* **2003**, *345*, 524) has described a general high-throughput screening (HTS) protocol. The protocol has been validated within a number of projects within Pfizer. The protocol is based upon procedures for the preparation of screening kits, as well as protocols for reaction setup, optimization and analysis. The need for such protocols in routinely evaluating the use of solvent engineering in enzymatic hydrolysis reaction is also discussed with several examples. A great advantage gained

by using this protocol also is that it requires very small amounts of enzymes and substrates as the final reactions are performed on 100 μL scale with 1 mg/mL of substrate and 10 mg/mL enzyme. The advantages and disadvantages of a number of complementary analytical tools that are being used in the analysis of the enantiomeric excess of enzymatic reactions are also discussed. The authors found that the implementation of these universal screening and optimization protocols including the one-time preparation of screening kits with enzymes in 96 well-plates, which can be stored at −80 °C for months or years, have translated into not only reduced screening time but also significant cost savings. In cases where anhydrous conditions are required, the plates are lyophilized and stored in a refrigerator. The majority of the enzymes retain >85% of their activity. Furthermore, these techniques have facilitated the application of a routine comprehensive solvent screen, which has led to the discovery of a number of processes exhibiting dramatic solvent effects. If the initial screen uncovers a mildly enantioselective enzyme, a solvent screen can dramatically enhance the enantioselectivity.

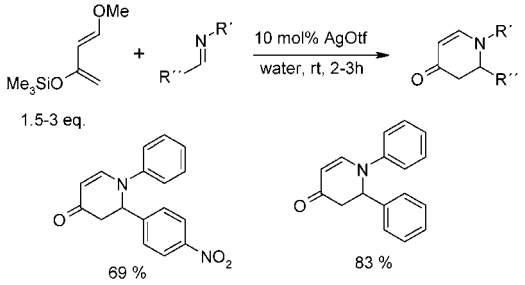
Selective Oxidation of Alcohols with Platinum Group Metal Catalysts

High-throughput screening (HTS) has been used by Griffin, K. et al. (*Adv. Synth. Catal.* **2003**, *345*, 517) to identify trends in catalyst activity and product selectivity, using air or hydrogen peroxide as oxidant and water as solvent. The platinum group metal catalysts are effective for the selective oxidation of 1-octanol and 2-octanol, geraniol and 2-*n*-butyl-4-chloro-5-hydroxymethylimidazole (an intermediate in the production of angiotension II inhibitors) using air as oxidant. The ratio of aldehyde to carboxylic acid in the oxidation of 1-octanol depends on the nature of the catalyst and the reaction conditions employed. The best selectivity found was around 15% carboxylic acid at 89% conversion. In the case of geraniol and 2-*n*-butyl-4-chloro-5-hydroxymethylimidazole the air oxidation was very selective for the aldehyde giving only traces of overoxidation. It was also found that in all cases hydrogen peroxide could be a good substitute for air as a primary oxidant giving around the same selectivities.



Aza-Diels−Alder Reactions of Danishefsky's Diene in Water

Kobayashi, S. et al. (*Adv. Synth. Catal.* **2003**, *345*, 475) have developed an aza-Diels−Alder reaction of imines with Danishefsky's diene in water catalyzed by Lewis acids at room temperature. The best catalyst for the reaction was found to be AgOTf. The reaction gives fairly good yields of dihydro-4-pyridones. Furthermore, silver triflate also catalyses the three-component reaction starting from aldehydes, amines, and Danishefsky's diene when the diene is slowly added to the mixture. In the three-component reaction with benzaldehyde the addition of a nonionic surfactant improved the yield.

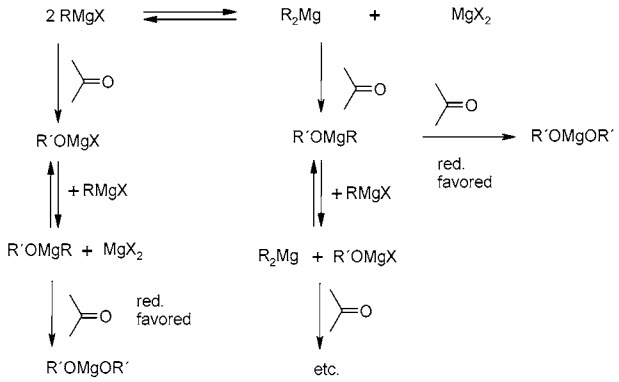


Solvation Effects in the Grignard Reaction with Carbonyl Compounds

Sassian, M. and Tuulmets, A. (*Helv. Chim. Acta* **2003**, *86*, 82) have studied the influence of the content of different ethereal solvents on the ratios of the yields of addition and reduction products for the reactions of butylmagnesium chloride with diisopropyl ketone, methyl 2-methylpropanoate, and isopropyl 2-methyl propanoate in toluene.

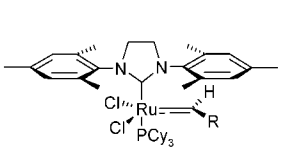
The ratio addition/reduction is minimal for small additions of ethers. In this region only a minor portion of the species are solvated, thus largely favoring the reduction of the ketone. However, growing solvation or solvation ability of the ether involves shifts in all equilibria, thus favoring, again, reduction of the ketone. As a result, the ratio Add/Red passes a maximum, expectedly located at higher amounts of weaker donors.

Replacement of the alkoxy group in the ester leads to strikingly different results for very small additions of the different donor solvents THF, diethyl ether, and *tert*-butyl methyl ether. In the region of insufficient solvation the reactions of esters are strongly governed by the nature of the alkoxy group. Susceptibility of the process to steric effects is unexpectedly high. The key step of the reaction appears to be complexation between a Grignard reagent and the alkoxymagnesium compound. Replacement of the methyl-group by the bulkier isopropyl group makes complexation unfavorable and switches the reaction to another pathway.

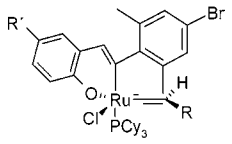


Easily Accessible and Robust Olefin-Metathesis Catalysts

Opstal, F. and Verpoort, F. (*J. Mol. Catal. A.: Chem.* **2003**, *200* (1−2), 49) have synthesized new ruthenium vinylidene complexes of the general formula **1** and **2** from $[RuCl_2(p\text{-cymene})]_2$, terminal olefins, imidazolium salts or salicylaldimine salts. The complexes were found to serve as good catalyst precursors for ring-opening metathesis polymerization (ROMP) of substituted norbornene, polycyclic alkenes, and cyclooctene and ring-closing metathesis (RCM) of α,ω-dienes. Furthermore, the complexes were found to be highly stable toward air, heat, and moisture in comparison with other metathesis precatalysts. Although the activity is lower than for the corresponding benzylidene analogues, these new catalysts can be interesting from a practical purpose as they are easily made from commercial products in high yields and they are stable in solution as well as in solid form.



1 R= Ph, $SiMe_3$, t-Bu

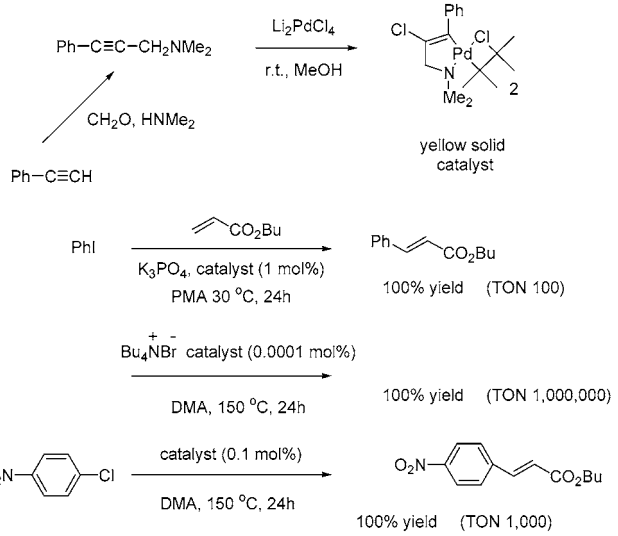


2 R= Ph, $SiMe_3$, t-Bu
R´=H, NO_2

Chloropalladated Propargylamine: A Highly Efficient Phosphine-Free Catalyst for the Heck Reaction

Palladocycles are among the simplest and most efficient precursors to promote the arylation of olefins (Heck reaction). All palladocycles reported up to now only promote the Heck reaction at 80 °C or above. The palladocycle generally acts as a "reservoir" of catalytic Pd species, the key step being the slow release of low-ligated active Pd(0). The most efficient palladocycles should therefore be where the release of Pd(0) is neither too fast (leading to inactive Pd metal) nor too slow (requiring higher temperatures typical of "robust" pallodocycles).

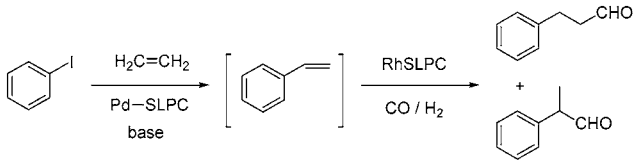
A group from Brazil has now reported (Consorti, C. S. et al. *Org. Lett.* **2003**, *5*, 983) that palladocycles can be easily prepared from alkynes, and these compounds (which are stable to air and water) are among the most effective catalysts for the Heck reaction with turnover numbers in the range of 10^4-10^6.



Simultaneous Application of Two or More Organometallic Catalysts

It is often desirable, especially in a large-scale production environment, to combine synthetic steps (telescope) to minimise the number of product isolations. When these steps involve organometallic catalysts, this may not be easy since when catalysts are mixed their performance may deteriorate. The idea of supported liquid-phase catalysis (SLPC) was proposed many years ago (Davis, M. E. *CHEMTECH* **1992**, 498; see also *Aqueous Phase Organometallic Catalysis, Concepts and Applications*; Cornils, B., Herrmann, W. A., Eds.; Wiley VCH, Weinheim, 1998; p 241). In SLPC a thin hydrophilic liquid film containing the catalyst(s) is supported on the surface of a high-surface-area solid and used in a hydrophobic solvent (for ease of separation).

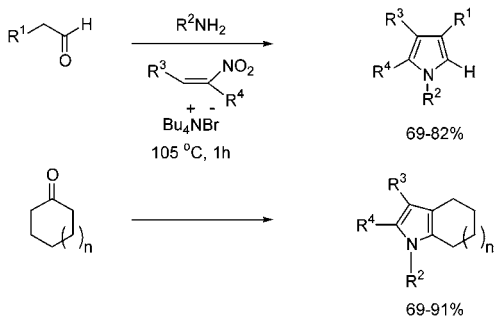
It has now been shown that SLPC can be used to carry out reactions with two or more catalysts with each SLPC catalyst retaining its own activity, thus allowing recycling (Bhanage, B. M. et al. *Tetrahedron Lett.* **2003**, *44*, 3505).



The catalysts are prepared from $PdCl_2$ or $Rh(CO)_2acac$ using triphenylphosphinetrisulphonate and reduced with H_2 before being absorbed on silica.

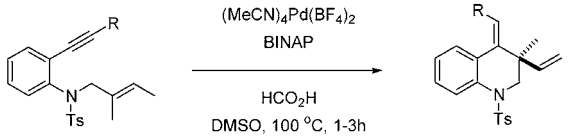
Novel Synthesis of Pyrroles

The synthesis of pyrroles via the classical Knorr and Hantzsch procedures may often give mixtures, and more selective methods for large-scale work are still required. A new process involves condensation of a carbonyl compound, an amine, and a nitro alkene. The reaction is at present carried out in a molten quaternary salt (which suggests that ionic liquids may also be appropriate) at 105 °C (Ranu, B. C. et al. *Tetrahedron Lett* **2003**, *44*, 2865). Surprisingly, open chain ketones do not work, stopping at the intermediate imine stage, whereas cyclic ketones work well.

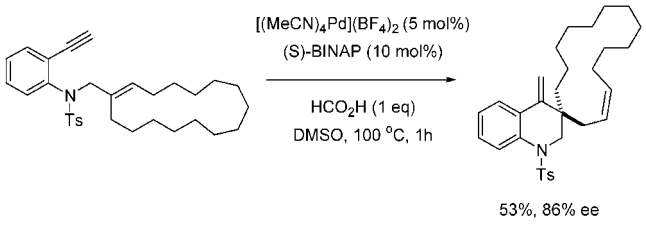


Enantioselective Ene-Type Cyclisation To Give Quinolines

The ene reaction of 1,7 enynes is promoted by a Pd(II) catalyst and a chiral bidentate phosphorus ligand such as BINAP in DMSO containing 1 equiv of formic acid. Products are produced in high yield and enantioselectivity (Hatano, M. et al. *J. Am. Chem. Soc.* **2003**, *125*, 4704).



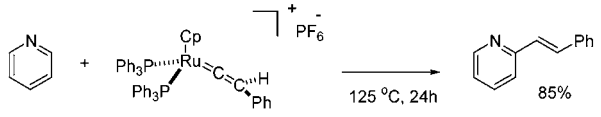
The reaction can be used to create spirocyclic compounds and even works when 15-membered rings are used.



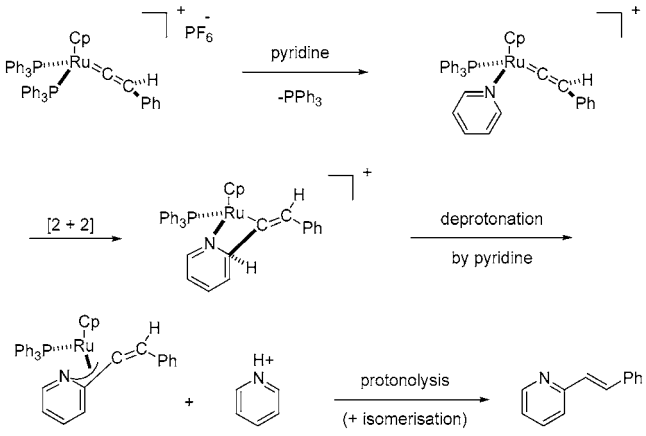
53%, 86% ee

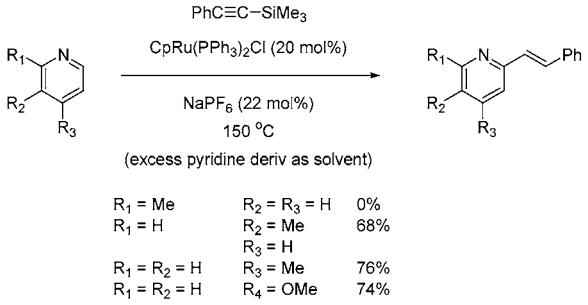
Stereoselective Alkenylation of Pyridine

Direct introduction of a carbon side chain to an aromatic or heteroaromatic ring under mild conditions remains a challenging problem. A new reaction has been discovered which allows the direct 2- or 6-substitution of pyridine derivatives. (Murakami, M. et al. *J. Am. Chem. Soc.* **2003**, *125*, 4720). Since the vinylidene complexes are generated from trimethylsilylacetylenes, it has now been found that direct reaction of these compounds with pyridine takes place in the presence of ruthenium catalysts.



The mechanism is shown below



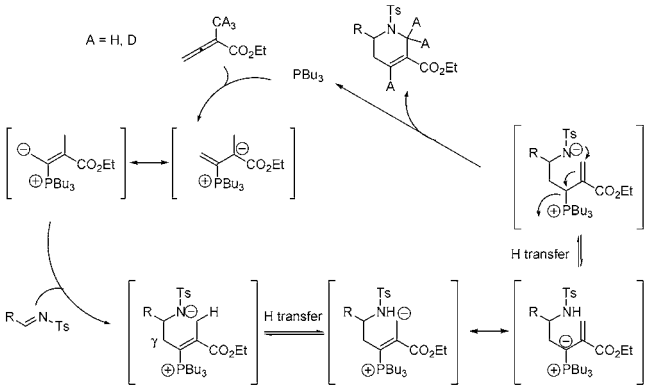


R_1 = Me	$R_2 = R_3$ = H	0%
R_1 = H	R_2 = Me, R_3 = H	68%
$R_1 = R_2$ = H	R_3 = Me	76%
$R_1 = R_2$ = H	R_4 = OMe	74%

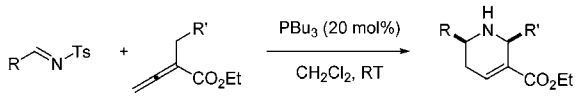
Synthesis of Highly Functionalised Tetrahydropyridines

Whereas the reaction of 2,3-butadienoates with imines in the presence of a phosphine catalyst gives pyrroline derivatives, it has now been found that when a methyl group is at the 2-position, a different transformation occurs (Zhu, X.-F. et al. *J. Am. Chem. Soc.* **2003**, *125*, 4716). The initially formed zwitterions rearrange to a new zwitterion with the negative charge on a methyl group. This attacks the imine, resulting eventually in the formation of a six-membered ring.

The mechanism shown below has been established from deuterium studies.



A wide variety of aromatic substituents are tolerated, and high diastereoselectivity is achieved. The only alkyl group (on the imine) which is tolerated is *tert*-butyl.



82-100%
(dr 90:10 to 98:2)

In a footnote, the authors indicated that the use of a chiral diphosphine (*S*,*S*)-DIPAMP resulted in moderate ee (34% ee), which is a promising result. Hopefully, further optimisation will give a truly enantiospecific process.

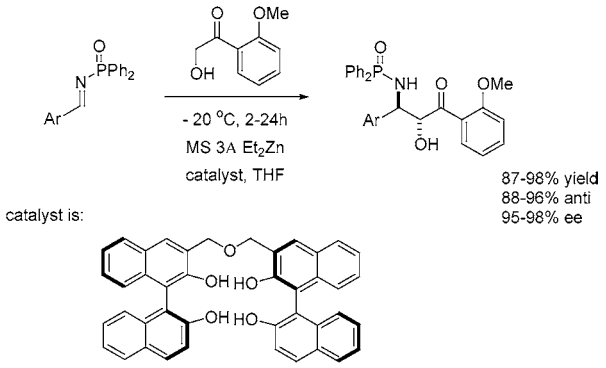
The reaction has some similarities to the Baylis−Hillman reaction, and one wonders whether amine catalysts would also be effective.

anti Selective Direct Catalytic Asymmetric Mannich-type Reactions

The direct addition of unmodified α-hydroxy-ketones to imines has been reported by several groups (Trost, B. M. et al. *J. Am. Chem. Soc.* **2003**, *125*, 338; List, B. et al. *J. Am. Chem. Soc.* **2002**, *124*, 827, and Cordova, A. et al. *J. Am.*

Chem. Soc. **2002**, *124*, 1842 and 1866; *Tetrahedron Lett* **2002**, *43*, 7749). These reactions are very selective but produce *syn*-amino alcohols.

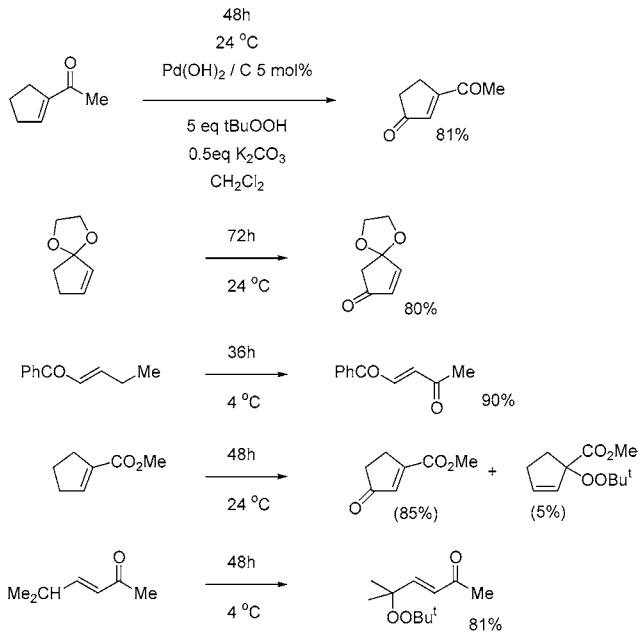
It has now been found by the group of Shibasaki in Tokyo that *anti*-amino alcohols can be produced when a catalyst formed from Et_2Zn and a linked BINOL derivative is used. The *anti*-selectivity is believed to be due to the bulky diphenylphosphinyl group used on the nitrogen of the imine (Matsunaga, S. et al. *J. Am. Chem. Soc.* **2003**, *125*, 4712).



For a recent review on the asymmetric Mannich reaction see Taggi, A. E. *Acc. Chem Res.* **2003**, 36, 10.

A Mild Catalytic Oxidation of Enones to Enediones

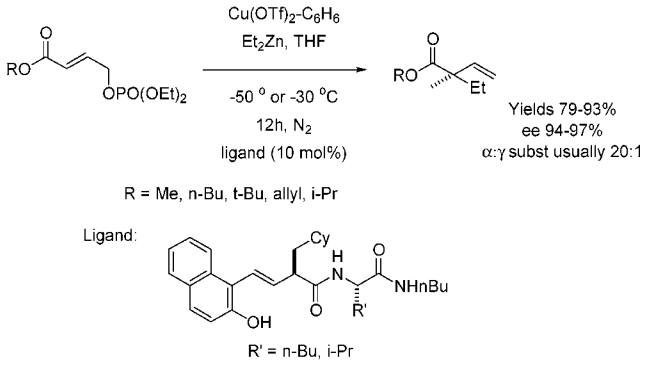
α,*β*-Unsaturated ketones and esters have a methylene group in the *γ* position are readily oxidised by a combination of *tert*-butyl hydroperoxide (stoichiometric oxidant), Pearlman's catalyst, and potassium carbonate in good yield (Yu, J. Q. et al. *J. Am. Chem. Soc.* **2003**, *125*, 3232). The $Pd(OH)_2$ catalyst initiates the reaction by activating the tBuOOH. The procedure is remarkably simple and amenable to large-scale work. If there is only a methine in the *γ* position, then a peroxide product will be formed. It is suggested that the reaction proceeds via tBuOO radicals. Oxygen gas is generated from the combination of tBuOOH, Pearlman's catalyst, and potassium carbonate, and there may be some



ditertiarybutyltetroxide formed in the system—these factors need to be taken into account in any scale-up work.

Copper-Catalysed Enantioselective Alkylations

Catalytic methods for the introduction of a group α to a carbonyl, where C−C bond formation proceeds by alkylation of an enolate, have been published by several groups in the past few years. An alternative approach relies on allylic alkylation of an α,*β*-unsaturated carbonyl with a leaving group on the *γ* position. This has now been demonstrated by the addition of Et_2Zn under copper catalysis (Murphy, K. E. et al. *J. Am. Chem. Soc.* **2003**, *125*, 4690). After screening a variety of ligands, the best results were those found below.

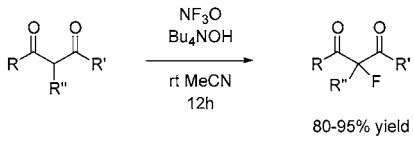


Other dialkyl zincs can be used but are not always as selective. The chiral ligand can be isolated in 98% yield and recycled.

Novel Fluorination Using NF_3O

Industry uses a wide variety of organofluoro compounds, and there is a need for novel fluorination methods. Recently novel N−F reagents have become commercially available (e.g., Selectfluor from Air Products) on kg scale.

It has now been shown that a simpler N−F reagent, NF_3O, is an effective fluorinating agent (Gupta, O. D. et al. *Tetrahedron Lett.* **2003**, *44*, 2799).

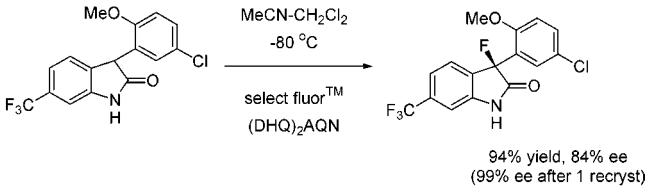


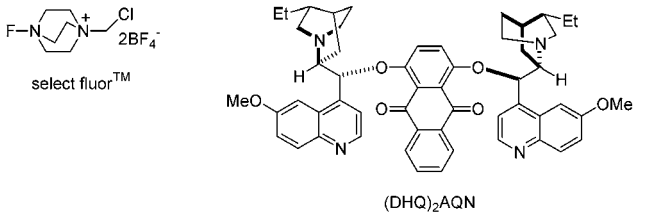
Difluorination could be achieved (R = H) by using twice the amount of NF_3O. The authors caution that NF_3O is a strong oxidiser and that mixtures of NF_3O and organics are potentially explosive. Therefore, scale-up should not be carried out without rigorous safety testing.

Enantioselective Fluorination

Enantioselective fluorination is also of current interest, partly because compounds such as the novel fluoroxindole BMS-204352 (MaxiPost) are being developed for stroke therapies. Use of Selectfluor in combination with specific cinchona alkaloid derivatives has given the first enantiose-

lective synthesis of MaxiPost (Shibata, N. et al. *J. Org. Chem.* **2003**, *68*, 2494).

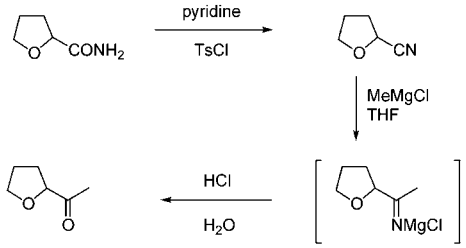




(DHQ)$_2$AQN

Microreaction Technology in a Continuous Process for Making (*S*)-2-Acetyl THF

A process for making (*S*)-2-acetyl THF by SK Corporation in Korea uses (*S*)-2-tetrahydrofurylamine as raw material. The latter is produced from the corresponding acid by standard methods, the chiral acid being made via an enzyme process (Kwak, B.-S. *Chim. Oggi* **2003**, Jan/Feb, 23−26). The amide is converted to the nitrile using pyridine/TsCl, but standard reaction of methylmagnesium chloride to the nitrile in THF in a batch process, followed by acidic work up leads to byproducts and considerable racemisation. Using a continuous microreactor, however, where good mixing occurs, (*S*)-acetyltetrahydrofuran can be obtained in high purity and with ee above 98%.



Process Intensification

Dow Chemicals in Freeport, Texas is using process intensification at pilot scale for production of hypochlorous acid from chlorine and sodium hydroxide. The gas−liquid reaction requires short residence time and good mass transfer; otherwise, byproducts such as sodium chlorite are formed. Dow use a rotating packed bed (RPB) reactor to give improved performance and a 40-fold reduction in equipment size compared to that for the existing process. The RPB reactor has now been operating for $2^1/_2$ years with >10% higher yields than those for previous processes. (Trent, D. *Chem. Eng.* **2003**, April, 30−31).

In the same issue in the following paper (Holl, R. pp 32−34) a spinning tube-in-tube (STT) Couette reactor is described which gives faster processing in a variety of reactions including polymerisation, saponification, hydrosilylation, etc. The STT reactor provides perfect intensification in plug flow, coupled with very efficient heat removal.

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