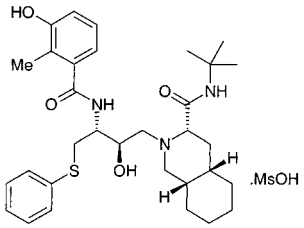
Organic Process Research & Development **2003**, *7*, 226–236

Highlights from the Literature

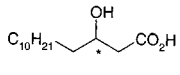
Some Items of Interest to Process R&D Chemists and Engineers

A Process in Need Is a Process Indeed...

The concept article written by Ikunaka (*Chem.-Eur. J.* **2003**, *9*, 379) ends with the quote of Albert von Szent-Gyorgyi, "Discovery consists of seeing what everybody has seen and thinking what nobody has thought." It is this quote that begins our series of highlights for this issue of OPRD which will again hopefully inspire, educate, and provide interest to process R & D chemists and engineers.



Viracept (Nelfinavir mesylate)

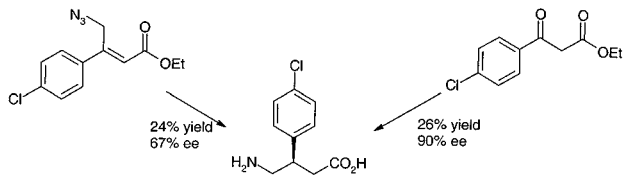


3-hydroxytetradecanoic acid

Ikunaka's report deals with enantioselective synthesis of viracept (nelfinavir mesylate, AG 1343), a potent HIV protease inhibitor, and 3-hydroxytetradecanoic acid, a component of lipid A comprising lipopolysaccharide embedded in the cell surface of Gram-negative bacteria, from both strategic and practical perspectives. Examples where molecular symmetry has helped streamline synthetic strategy, chiral methodologies (resolution via diastereomeric salt formation, lipase-catalyzed kinetic resolution, asymmetric synthesis, and chiral pool approaches) are all discussed.

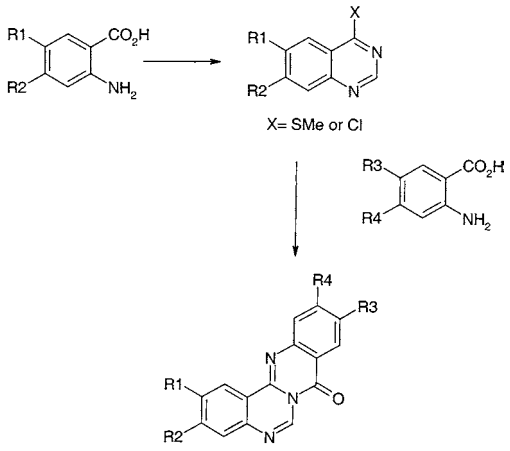
(*R*)-(−)-Baclofen

A short and efficient enantioselective synthesis of (*R*)-(−)-baclofen, a selective $GABA_B$ agonist has been described by Sudalai and colleagues (*Tetrahedron: Asymmetry* **2003**, 581) with an overall yield of 26% and 90% ee. Ru(II)-(*S*)-BINAP catalyzed asymmetric hydrogenations of the C=C in ethyl 4-azido-3-(4-chlorophenyl)-2-butenoate and C=O in ethyl 4-chlorophenylbenzoyl acetate constitute key steps in introducing the chirality into this molecule.



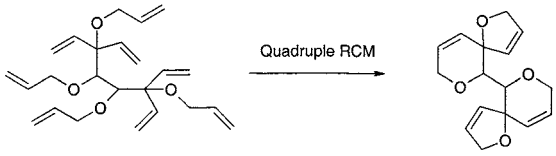
8*H*-Quinazolino[4,3-*b*]quinazolin-8-one

Besson and co-workers describe (*Tetrahedron* **2003**, *59*, 1413) how microwaves can assist the multistep synthesis of 8*H*-quinazolino[4,3-*b*]quinazolin-8-one. The quinazoline motif is found in a variety of alkaloid and biologically active compounds, and their synthesis has been described utilising two Niementowski condensations from anthranilic acids.



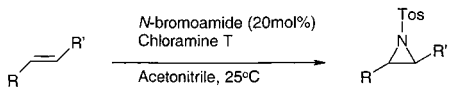
Quadruple Ring-Closing Metathesis

The first example of a quadruple ring-closing metathesis (RCM) reaction has been reported by Wallace (*Tetrahedron Lett.* **2003**, *44*, 2145). The reaction of the C2 symmetric octaene with Grubbs catalyst afforded bis-spirocyclic compounds in high yield and provides intriguing use of RCM and a convenient route into highly functionalised substrates.



Aziridination

Aziridines are versatile building blocks in organic synthesis and have provided entry into many biologically active molecules such as amino acids, β-lactam antiobiotics, and alkaloids. Sudalai and Thakur contribute to the area and have recently published (*Tetrahedron Lett.* **2003**, *44*, 989) how *N*-bromoamides can catalyze the aziridination of electron-deficient as well as electron-rich olefins using chloramine-T (*N*-chloro-*N*-sodio-*p*-toluenesulfonamide) as a nitrogen source under ambient conditions to afford the corresponding aziridines in good to excellent yields.



R = aryl, H
R' = H, alkyl, aryl, acyl, CH_2OH, CO_2R

A proposed catalytic cycle for the NBS-catalysed aziridination of olefins has been described in their publication.

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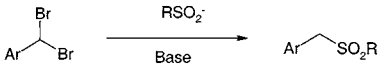
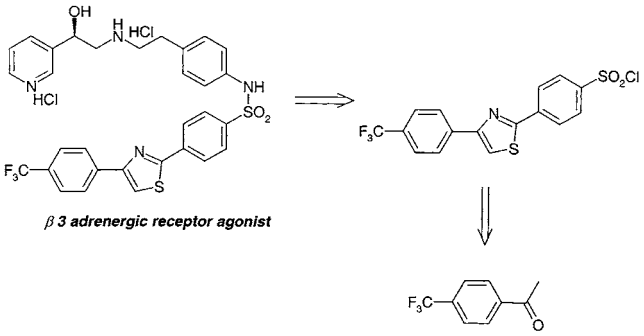
Sulfones from Dibromomethyl Aromatics

A novel, high-yielding preparation of sulfones from dibromomethyl aromatics through reaction with a sulfinate salt has been reported by Xu and colleagues from Merck (*Tetrahedron Lett.* **2003**, *44*, 1283). This method is high-yielding on a variety of simple aromatic substrates.



A β_3 Adrenergic Receptor Agonist

The synthesis of a β_3 adrenergic receptor agonist on a multikilogram scale and in high yield and purity via convergent syntheses has been described by Ikemoto and colleagues at Merck (*Tetrahedron* **2003**, *59*, 1317). The arylthiazolylbenzenesulfonyl chloride (shown in the scheme) was assembled at the thiazole ring via coupling of an α-haloketone and thiobenzamide precursors (Hantzsch synthesis). The Merck group have synthesised the target β_3 adrenergic receptor agonist in six steps starting from trifluoromethylacetophenone with an overall yield of 50%.



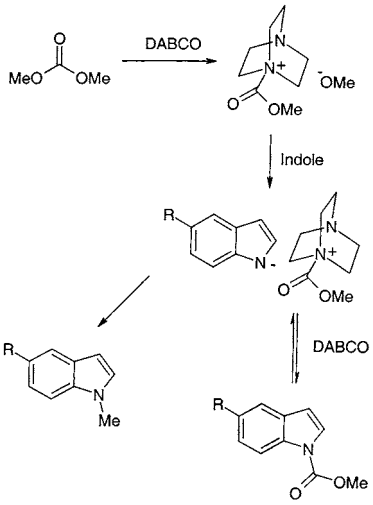
β 3 adrenergic receptor agonist

N-Methylation of Indoles

DABCO has found to be an extremely active catalyst for the methylation of indoles in conjunction with dimethyl carbonate (DMC) by Shieh and co-workers at Novartis (*J. Org.Chem.* **2003**, *68*, 1954). This chemistry is highly effective and produces *N*-methylindoles in nearly quantitative yields. The reaction sequence consists of competing alkylation and acylation pathways and involves 1,4-diazabicyclo[2.2.2]octane (DABCO) dually as a nucleophilic catalyst, ultimately resulting in a single product: the *N*-methylated indole.

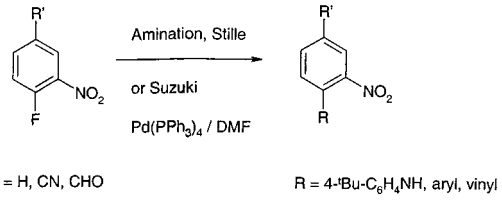
Pd(0)-Catalysed Amination, Stille Coupling, and Suzuki Coupling of Electron-Deficient Aryl Fluorides

Pd(0)-catalysed amination, Stille Coupling, and Suzuki coupling of electron-deficient aryl fluorides have been investigated by Yu and Mi Kim at Pfizer and recently reported (*J. Am. Chem. Soc.* **2003**, *125*, 1696). The amination of 2-fluoronitrobenzene was Pd(0)-catalyzed at 65 °C in DMF, and the effectiveness of the catalysis found to be ligand-dependent. Among the five catalyst systems investigated, $Pd(PPh_3)_4$ was the most effective catalyst. The control experiments revealed that $Pd(OAc)_2$ or PPh_3 was not responsible for the catalysis. 4-Fluoro-3-nitro-benzonitrile and 4-fluoro-3-nitro-benzaldehyde also underwent Stille coupling and Suzuki coupling in the presence of $Pd(PPh_3)_4$,



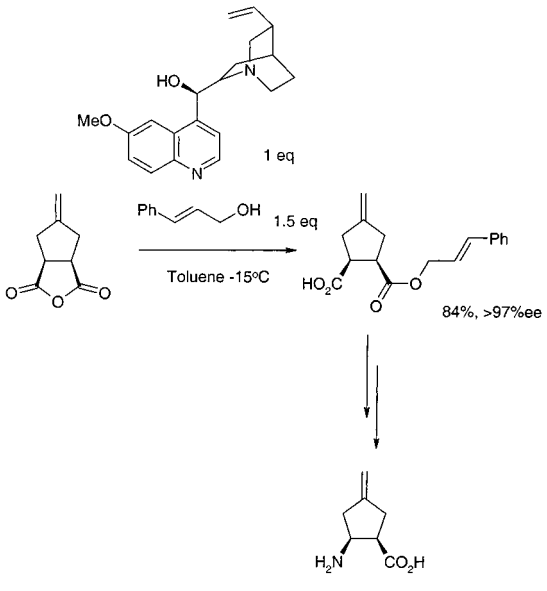
Methylation of indoles

and the reactions afforded the coupling products in 28−86% yields. The control experiments showed no sign of reaction in the absence of palladium.



Asymmetric Synthesis of BAY 10-8888/PLD-118

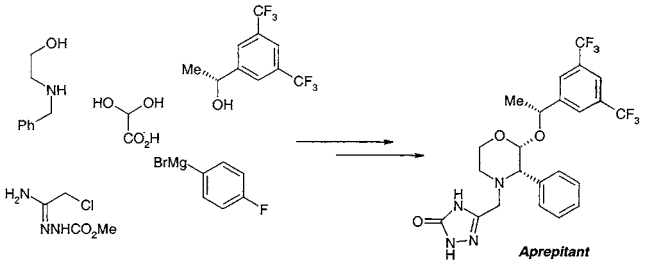
The β-amino acid BAY 10-8888/PLD-118 is currently being investigated in phase II clinical studies as a novel antifungal for the treatment of yeast infections. An efficient asymmetric synthesis of this compound is described by Mittendorf (*Synthesis* **2003**, 136). The key step employed in their approach involved a highly enantioselective, quinine-mediated alcoholysis of a meso-anhydride intermediate which has been demonstrated on a pilot-plant scale.



BAY 10-8888 / PLD-118

Aprepitant Synthesis

An efficient stereoselective synthesis of the orally active NK_1 receptor antagonist Aprepitant is described by Brands and a number of colleagues from Merck (*J. Am. Chem. Soc*. **2003**, *125*, 2129). A direct condensation of *N*-benzyl ethanolamine with glyoxylic acid yielded a 2-hydroxy-1,4-oxazin-3-one which was activated as the corresponding trifluoroacetate. A Lewis acid-mediated coupling with enantiopure (*R*)-1-(3,5-bis(trifluoromethyl)phenyl)ethan-1-ol afforded a 1:1 mixture of acetal diastereomers which was converted into a single isomer via a novel crystallization-induced asymmetric transformation. The resulting 1,4-oxazin-3-one was converted via a unique and highly stereoselective one-pot process to the desired α-(fluorophenyl)morpholine derivative. Interesting and unexpected [1,2]-Wittig and [1,3]-sigmatropic rearrangements were identified by the group during the optimization of these key steps. In the final step, a triazolinone side chain was appended to the morpholine core. Aprepitant was obtained in 55% overall yield over the longest linear sequence.

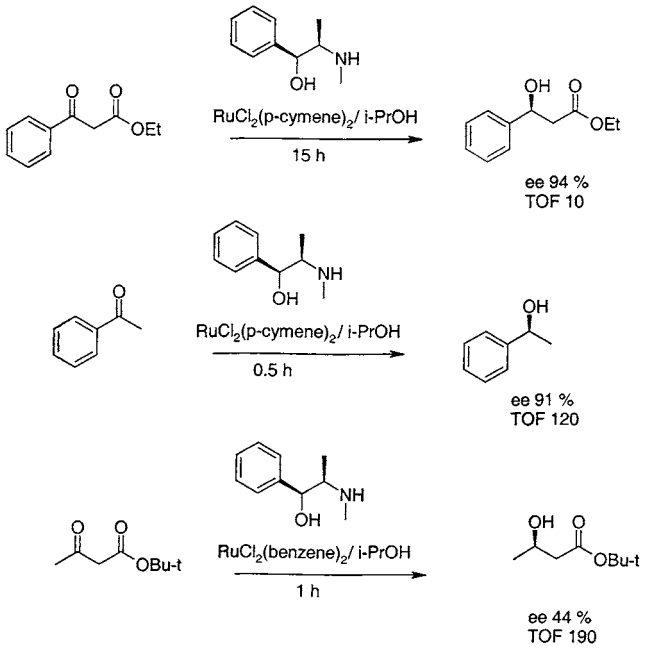


Selective Hydrogenation: Recent Trends And New Development

The group around H.-U. Blaser at Solvias AG (*Adv. Synth. Catal*. **2003**, *345*, 103) has summarized recent trends and new developments of selective hydrogenation reactions. This excellent review is divided into the following: the design and preparation of ligands and catalyst, design of enantioselective homogeneous hydrogenations, new effective monodentate phosphines, successful bidentate phosphine ligand families (with axially chiral biaryl- and ferrocenyl-based backbones, new phospholanes and with stereogenic phosphorus), novel bidentate ligands with P−O and P−N bonds and oxazoline-based ligands. A short overview on immobilized chiral complexes and of the toolbox of heterogeneous catalysis is also given. In a second part, progress for selected catalytic transformations and generic selectivity problems is described, intended mainly for organic chemists who need to solve specific synthetic problems.

Ruthenium (II)-Catalyzed Asymmetric Transfer Hydrogenation Of Carbonyl Compounds With 2-Propanol And Ephedrine-Type Ligands

The group of J.-F. Carpenter (*Adv. Synth. Catal*. **2003**, *345*, 67) has summarized the development and application of Noyori-type catalysts based on ruthenium−arene complexes and simple chiral β-amino alcohols derived from ephedrine, for the asymmetric transfer hydrogenation of 2-propanol to carbonyl substrates. The catalytic precursors and the true active species have in a special case been isolated. This leads to a more precise structural description of the catalytic cycle and of probable deactivation pathways. Highly effective applications are summarized. The method is very selective for aromatic ketones while aliphatic ketones still remain problematic. In particular, the deactivation of catalytic species by β-dicarbonyl compounds constitutes an intrinsic limitation of the Ru-catalyzed transfer hydrogenation process, which thus far cannot compete, in this case, with classical hydrogenation.

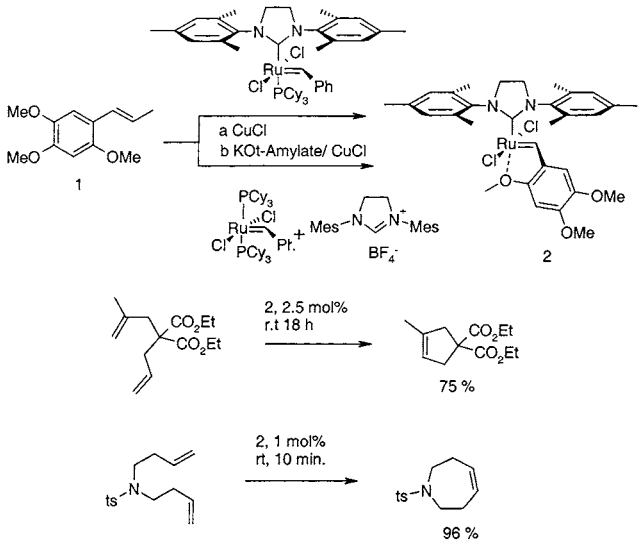


A Good Bargain: An Inexpensive Air-Stable Ruthenium Metathesis Catalyst from α-Asarone

K. Grela and M. Kim have studied the effects of an increase in electron density in the benzylidene part of Hoveyda-type ruthenium metathesis catalysts. Starting from the inexpensive and readily available α-asarone (**1**), which is the major component of European ginger, a new metathesis catalyst **2** was synthesized through two different high-yielding routes from either second- or first-generation Grubbs catalysts. The new catalyst was found to be highly air stable and slightly more active than parent catalyst systems in some selected metathesis reactions of different standard substrates. The catalyst is also easily recycled through chromatography.

Silica-Supported Palladium Nanoparticles Show Remarkable Hydrogenation Catalytic Activity

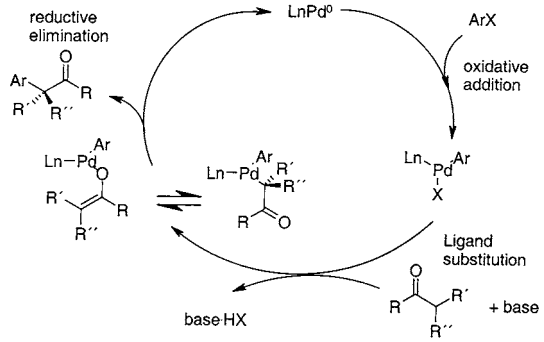
Palladium nanoparticles (1.9 nm) stabilized on silica obtained from the reduction of Pd(II)dba with hydrogen were investigated by O. Domínguez-Quintero et al. (*J. Mol. Catal. A: Chem.* **2003**, 3850,1). In the hydrogenation catalysis of different substrates (1-hexene, cyclohexene, benzene, 2-hexanone, cyclohexanone, and benzonitrile) the highest hydrogenation rate was found with 1-hexene with a TOF of 38250 mol of product/mol of Pd/h at 25 °C and 30 psi. The Pd/SiO_2 nanocatalyst showed also very high turnover frequencies for the other substrates. During the catalytic cycle an aggregation of the nanoparticles was observed. The mean particle size went up from 1.9 to 2.8 nm during the



hydrogenation of benzene at 140 °C for 2 h at 120 psi hydrogen pressure.

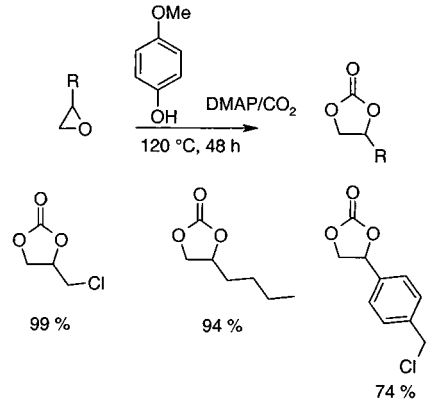
Palladium-Catalyzed α-Arylation of Carbonyl Compounds and Nitriles

D. A. Culkin and J. F. Hartwig (*Acc. Chem. Res.* **2003**, *36*, 234−245) have summarized the knowledge about the palladium-catalyzed α-arylation of carbonyl compounds. The observation of phenyl acetone as an impurity of an aryl halide amination in acetone as solvent inspired the development of this new practical synthetic method for the α-arylation of a variety of ketones and carboxylic acids derivatives. The design and use of electron-rich alkylphosphines and N-heterocyclic carbenes has been essential to achieve high selectivity and efficiency of these transformations with a broad range of enolates and related anions, including those from amides, esters, aldehydes, nitriles, nitroalkanes, sulfones, and lactones. In the proposed mechanism for this reaction, the carbon−carbon bond of the product is formed by reductive elimination from an aryl palladium enolate intermediate.



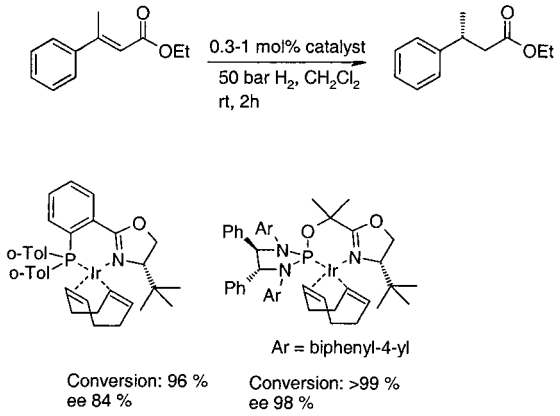
Phenol and Base Cocatalyzed Addition of CO_2 To Terminal Epoxides for the Formation of Cyclic Carbonates

Y.-M. Shen et al. (*Adv. Synth. Catal.* **2003**, *345*, 337) have reported a new catalytic method for the ring-opening of terminal epoxides to cyclic carbonates with carbon dioxide. The reaction is cocatalyzed from a phenol (pK_a 7−10) and an amine base, preferably DMAP. Both catalysts are used in 0.4 mol %. None of the catalysts can achieve the transformation alone, and other acidic catalyst in combination with the amine base give low yields of the cyclic carbonates. The reaction is very efficient, giving the cyclic carbonates as the sole product after 48 h reaction time at 120 °C.



Iridium-Catalyzed Enantioselective Hydrogenation of Olefins

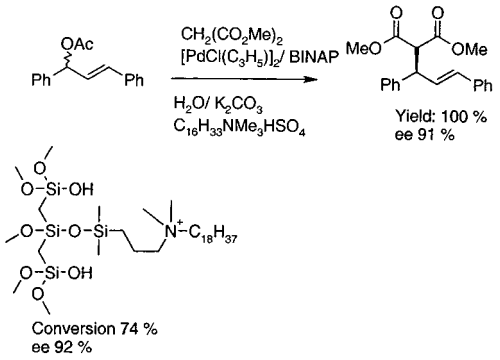
Pfaltz et al. (*Adv. Synth. Catal.* **2003**, *345*, 33) have summarized their results from enantioselective hydrogenations with cationic iridium complexes with chiral P,N-ligands. The complexes are readily prepared, air-stable, and easy to handle. In contrast to chiral rhodium or ruthenium-phosphine catalysts, they do not require the presence of a polar coordinating group near the C−C double bond. These new ligands fill a gap in the application range of enantioselective hydrogenation. Several types of olefins, for which no suitable catalysts were previously available, can now be hydrogenated with high efficiency and good-to-excellent enantioselectivity as, for instance, α,β-unsaturated esters.



Catalytic Asymmetric Alkylation in Water in the Presence of Surfactants

Asymmetric palladium-catalyzed alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate was found by D. Sinou et al. (*Adv. Synth. Catal.* **2003**, *245*, 357) to occur in water in the presence of surfactants and a base. The efficiency and the enantioselectivity of the coupling reaction depend strongly on the nature and the concentration of the surfactant. The highest yield and enantioselectivity was

obtained with BINAP as ligand in the presence of a cationic surfactant, neutral or zwitterionic gave bad results, and anionic caused no reaction at all. Carbonates were found to be the best bases. A supported cationic surfactant was also successful, allowing a simple separation of the product. A recycling of the supported surfactant, however, was not possible.

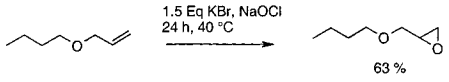


A Simple and Convenient Method for Epoxidation of Olefins without Metal Catalysts

The group of M. Beller (*Adv. Synth. Catal*. **2003**, *345*, 389) have reported a simple epoxidation of various nonactivated olefins using bleach and a bromide salt. Aromatic olefins furnish the corresponding epoxide with high selectivity at room temperature to 40 °C in a short time (<1−2 h). Aliphatic olefins react more sluggishly with up to 24 h reaction time. The method can be performed safely without addition of transition metal catalysts and is also a cheap and simple method.

Entry	Eq. KBr	Eq. NaOCl	Time (h)	Co-Solvent	Yield(%)	Conv. (%)	Selec. (%)	pH
1	-	1.1	1	t-BuOH	15	55	28	10.4
2	1.5	1.1	1	t-BuOH	82	100	82	10.4
3	1.5	1.1	1	CH_3CN	90	100	90	10.4
4	0.2	1.1	21	t-BuOH	78	100	28	10.4

Conditions: 2 mmol α-methyl styrene, t-BuOH (10 ml), Buffer solution (10 ml), 1.1 Eq. NaOCl, 25 °C 1000 rpm.
Yields determined by GC

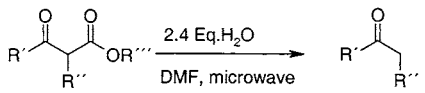


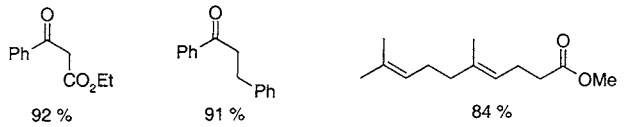
Microwave Heating Effects Rapid and Selective Decarboalkoxylation of Mono-Alkylated Malonates and β-Ketoesters

D. Curran and Q. Zhang (*Adv. Synth. Catal.* **2003**, *345*, 329) have found that brief microwave irradiation of monoalkylated malonates and β-ketoesters at 160−200 °C in wet DMF induces smooth and selective decarboalkoxylation. It is suggested that water attacks the ester and causes hydrolysis followed by a decarboxylation of the resulting acid. The reaction occurs readily with monoalkylated derivatives but not dialkylated.

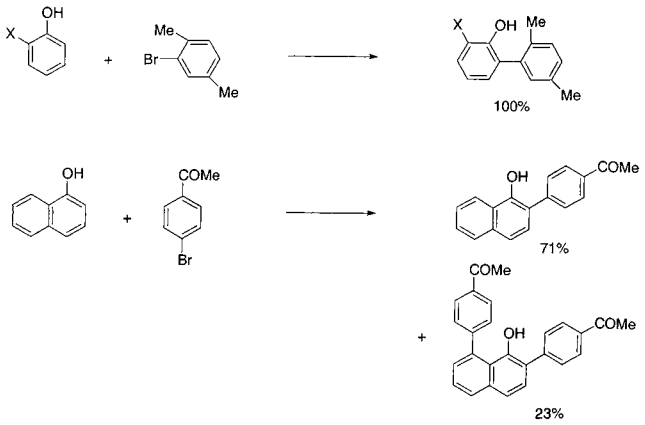
Ortho Arylation of Phenols

Intermolecular arylation of phenols occurs when a mixture of an ortho-substituted phenol, an aryl halide, cesium carbonate, Wilkinson's catalyst, and a phosphinite are



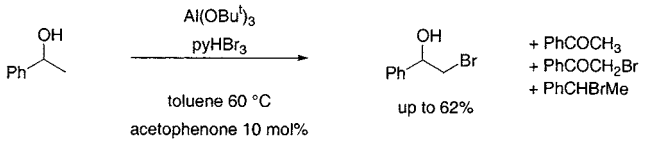


refluxed in toluene for 18 h (Bedford, R. B. et al. *Angew. Chem., Int. Ed.* **2003**, *42*, 112). The bulkier the alkyl substituent in the ortho position, the better the yield.



Indirect β-Bromination of Alcohols

A novel process has been conceived which involves reversible oxidation of an alcohol to a ketone, halogenation, then reversible reduction back to the alcohol (Cami-Kobeci, G. et al. *Synlett* **2003**, 124). The result is a one step β-bromination of the alcohol.



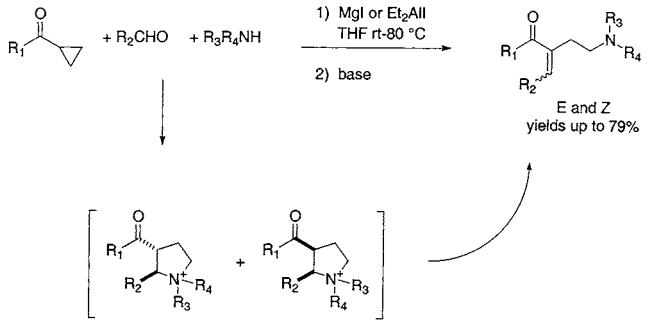
A One-Pot Reaction for the Synthesis of α-Aminoethyl-α,β-enones

Multicomponent reactions are an attractive concept for high-throughput chemistry and for scale-up, if they can be controlled for selectivity. The reaction of a cyclopropyl ketone, aldehyde, and amine has now been shown to give a pyrrolidine, under metal catalysis, and on elimination an α-aminoethyl-α,β-enone is produced (Bartozzi, F. et al. *Org. Lett.* **2002**, *4*, 4333).

It is, however, quite difficult to control the *E*/*Z* stereochemistry in this reaction, and *E*/*Z* ratios varied from 1:1 to 6:1, depending on substrate.

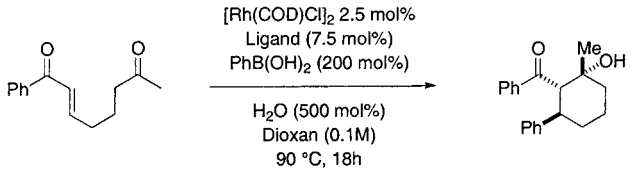
Tandem Conjugate Addition−Aldol Cyclisation

There is much current interest in the generation of enolates from enones by reduction (for review, see: Huddleston, R. R. et al. *Synlett* **2003**, *12*). These enolates can be trapped in a number of ways, and a recent report describes the



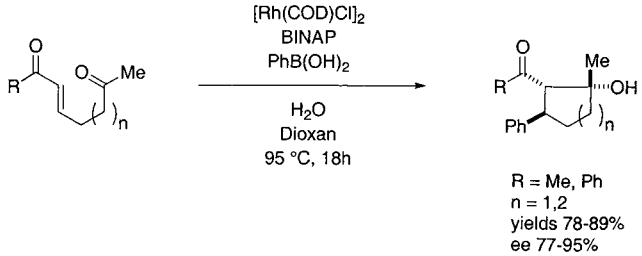
subsequent aldol reaction of an enolate generated in a carbometalation (Cauble, D. F. et al. *J. Am. Chem. Soc.* **2003**, *125*, 1110).

The intramolecular reaction produces five- and six-membered carbocycles and heterocycles in stereospecific manner—no epimers were detected.



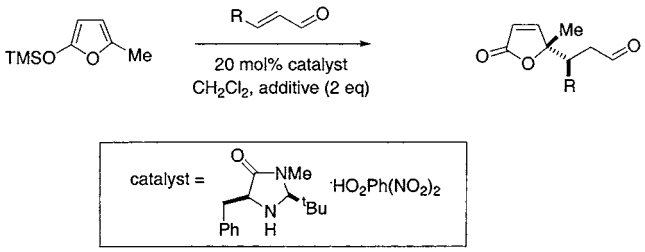
Ligand	Yield
PPh_3	Trace
biphep	24%
dppf	33%
dppa	44%
dppb	72%
dppb (+ TEA)	87%
dppb (+ KOH)	87%

The reaction also proceeded enantioselectively when some chiral ligands were used. Although JOSIPHOS and MeDuPhos gave racemic product, ligands in the BINAP series gave ee's in the 80−94% range. The methodology creates three continguous centres, one of which is quaternary, in a single manipulation with high levels of relative and absolute stereochemistry.



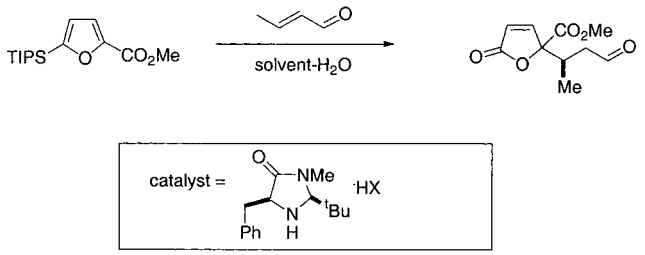
First Enantioselective Organocatalytic Mukaiyana−Michael Reaction

Iminium organo catalysis using chiral imidazolinones has emerged as a powerful strategy for C−C bond formation. The group of MacMillan at Pasadena has now found (Brown, S. P. et al. *J. Am. Chem. Soc.* **2003**, *125*, 1192) that the addition of unsaturated aldehydes to silyloxyfurans takes place not in a 1,2-sense (as with Lewis acids) but in a 1,4-sense—the Mukaiyama−Michael addition.



R	Additive	Temp	Time(h)	% Yield	Syn/anti	% ee
Me	-	-40	10	31	10:1	85
Me	1-PrOH	-40	10	83	10:1	84
Me	H_2O	-40	10	93	16:1	85
Me	H_2O	-70	11	84	22:1	92
Pr	H_2O	-50	20	87	31:1	84
iPr	H_2O	-20	30	80	7:1	98
Ph	H_2O	-40	30	77	1:6	99
CH_2OBz	H_2O	-70	24	86	20:1	90
CO_2Me	H_2O	-60	22	84	11:1	99

No products of 1,2-addition were detected in these reactions. The selectivity can be varied by use of an appropriate catalyst salt. From a practical viewpoint, all these reactions are performed under an aerobic atmosphere, using wet solvents and a pre-prepared, stable catalyst (which presumably could be easily recycled or reused). These reactions should be readily scaleable.



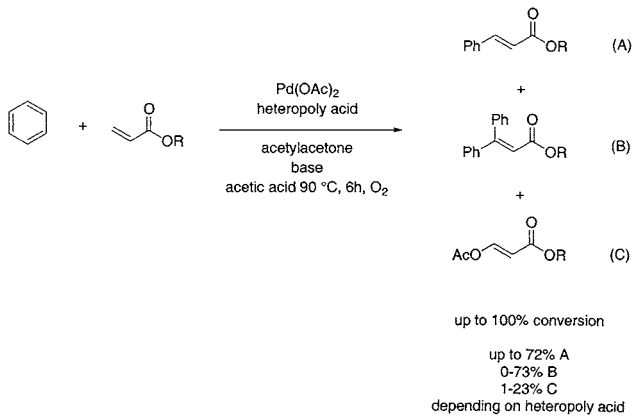
Solvent	HX	% Yield	Syn/anti	% ee
THF	TFA	86	6:1	98
$CHCl_3$	TfOH	83	1:7	98

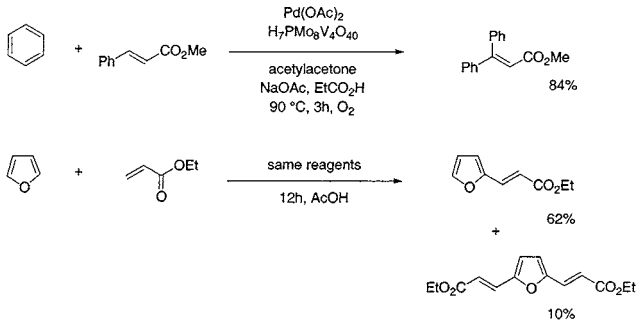
Direct Coupling of Olefins with Aromatics

The Heck−Mizoroki arylation of olefins is a versatile transformation but not so atom efficient. A new reaction has been described which allows direct reaction of arenes with olefins (Yokota, T. et al. *J. Am. Chem. Soc.* **2003**, *125*, 1476).

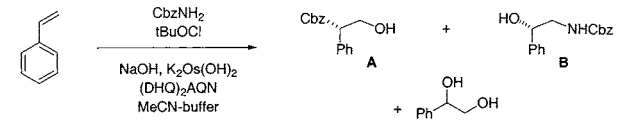
Influence of pH on Asymmetric Aminohydroxylation (AA)

When styrene is used in an AA reaction, the regio chemical outcome is influenced by solvent, nitrogen source,

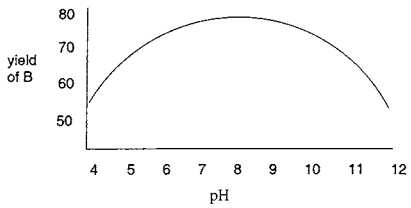




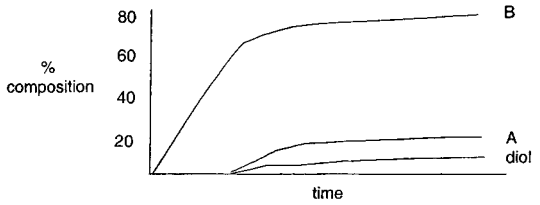
substrate, and ligand. Typically, the major product is the 2-aryl-2-amino ethanol regioisomer (A). It is now reported that the opposite regioisomeric product 2-amino-1-phenylethanol derivative (B) can be obtained in good enantiomeric excess when the pH is controlled—best results are in the range 7.5−8.5, where the opposite isomer and byproduct diol are suppressed. (Nesterenko, V. et al. *Org. Lett.* **2003**, *5*, 281).



Ligand	Solvent	A:B	Yield of B	Enant Ratio
$(DHQ)_2AQN$	MeCN	1:10	82	87.13
$(DHQ)_2AQN$	ProOH	1:4	57	75.25
$(DHQ)_2AQN$	THF	1:4	53	58.42
$(DHQ)_2PHAL$	MeCN	1:5	52	85.15
$(DHQ)_2PYR$	MeCN	1:3	38	70.30
$(DHQD)_2AQN$	MeCN	1:10	78	11.89



The reaction works well for a number of para-substituted styrenes, but a kinetic investigation reveals that the B:A ratio changes with time. In the early stages of the reaction B is very much the dominant product, but after a certain time (∼30 min) the rate of formation of isomer A starts to become significant. When purified isomer A is added at the start, the composition changes from 1:10 to 1:1.6, whereas adding isomer B had little effect on the selectivity. This effect is currently being investigated.

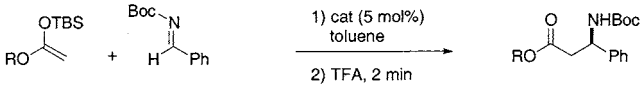


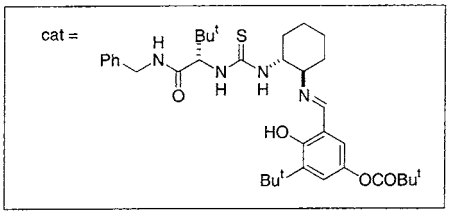
buffered asymmetric aminohydroxylation of p-acetoxystyrene

Asymmetric Catalytic Mannich Reactions Catalysed by Urea Derivatives

The Mannich reaction is an excellent method for forming β-aminocarbonyl compounds, and recent interest in asymmetric versions has proved challenging (for reviews, see Benaglia, M. et al. *Eur. J. Org. Chem.*, **1999**, *99*, 1069; Kobayashi, S. et al. *Chem. Dev.* **1999**, *99*, 1069). Progress has been made with zirconium catalysts (see previous Highlights, *Org. Process Res. Dev.* **2003**, *7*, 124−134), but these systems are restricted to imine substituents bearing aryl groups with a pendant chelating group.

A new methodology (Wenzel, A. G. et al. *J. Am. Chem. Soc.* **2002**, *124*, 12964) provides efficient access to *N*-Boc-protected β-amino acids via addition of silyl ketene acetals to *N*-Boc-aldimines under thiourea catalysis.

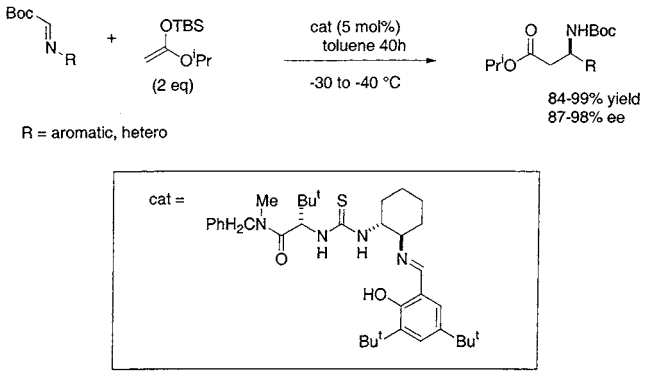




R	Temp	Time(h)	Conv(%)	ee(%)
Me	23	5.5	90	54
Et	23	3.5	90	63
^{i}Pr	23	2	93	68
^{i}Pr	-40	48	90	91
^{t}Bu	23	21.5	91	51

The rate of the uncatalysed reaction was found to be significant when urea, rather than thiourea, catalysts were used, and changes to the ester group and temperature allowed the background reaction to be eliminated.

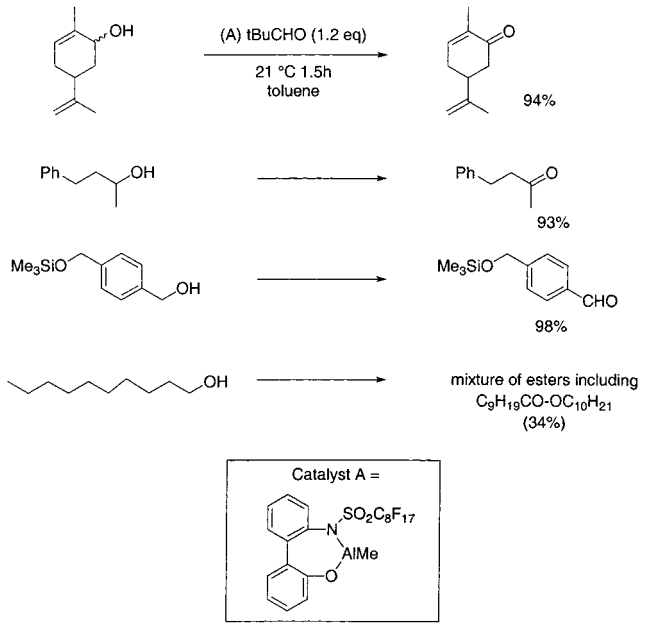
Further catalyst optimisation was carried out via a library optimisation strategy, and an increase in ee to over 90% was achieved with most substrates with the optimised catalyst.



New Catalyst for Oppenauer Oxidation

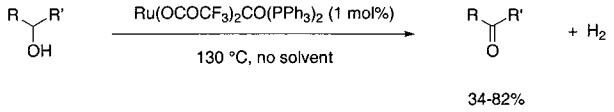
The catalyst (A) was found to be highly effective in the Oppenauer oxidation of alcohols under mild conditions. This oxidation method, although classical, is effective and practical on large scale, but suffers from the disadvantage of requiring large amounts of catalysts such as $Al(OPr)_3$ or $Al(OBu^t)_3$ which can cause side reactions such as dehydration of alcohols or aldol condensation (Ooi, T. et al. *Org. Lett.* **2002**, *4*, 2669). The new catalyst, A, is used in only catalytic quantities (1 mol %), works well in a variety of solvents (CH_2Cl_2 ethyl acetate, toluene, cyclohexane, THF), and gives high yields of ketones with secondary alcohols, allylic alcohols, and benzyl alcohols. Primary alcohols give the Tischenko reaction rather than oxidation to an aldehyde.

Although pivaldehyde was used as the hydrogen donor in the early work, it was found, in contrast to other aluminium-based catalysts, that the much cheaper acetone works just as well and no aldol products are formed.



Catalytic Dehydrogenation of Alcohols with Evolution of Hydrogen Gas

The most atom-efficient process for oxidation of alcohols is a simple dehydrogenation, but often this needs a hydrogen acceptor. Prompted by earlier work which had indicated that hydrogen could be produced from alcohol by a ruthenium catalyst, workers at Eindhoven (The Netherlands) have found that secondary alcohols are dehydrogenated in high selectivity in short reaction times (Ligthart, G. B. W. L. et al. *Tetrahedron Lett.* **2003**, *44*, 1507).



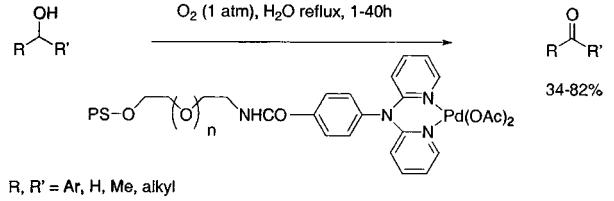
The catalyst was generated from $RuH_2(CO)(PPh_3)_3$ and acid—other acids such as acetic or toluenesulphonic can be used but TFA gives the best selectivity.

Primary alcohols give some H_2, but the reaction is not useful since the resultant aldehydes decarbonylate and the CO poisons the catalyst. For the ketones synthesis, the catalyst could be recycled.

An earlier paper (Arita, T. et al. *Tetrahedron Lett.* **2003**, *44*, 1083) had established that hydrogen could be generated from ethanol in supercritical water *without a catalyst*. Of course temperatures are in the range 450−500 °C, and at this temp the product is decarbonylated to methane.

Catalytic Oxidation of Alcohols in Water

Oxygen can be used to convert alcohols to aldehydes and ketones using a polystyrene−poly(ethylene glycol) resin-supported palladium phosphane complex. The catalyst can be recycled (Uozumi, Y. et al. *Angew Chem., Int. Ed.* **2003**, *42*, 194).



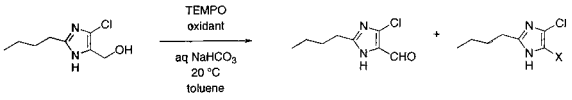
Primary aliphatic alcohols gave the corresponding carboxylic acid rather than aldehyde—these oxidations were carried out on the presence of potassium carbonate to dissolve the product.

Iodine as a Chemoselective Reoxidant for TEMPO

Oxidation of alcohols to carbonyl/compounds can be achieved with TEMPO, either stoichiometrically or catalytically in conjunction with a reoxidant. For the oxidation of imidazolyl alcohol to the corresponding aldehyde a key intermediate in Merck's losartan synthesis, TEMPO could be used, but if reoxidants such as positive chlorine or bromine reagents were used, dihalogenated derivatives were obtained. It is now reported that iodine is an excellent reoxidant for TEMPO without the side-reaction of electrophilic substitution (Miller, R. A. et al. *Org. Lett.* **2003**, *5*, 285).

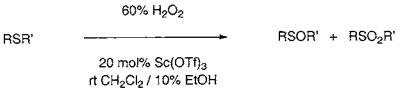
Catalytic Chemoselective Oxidation of Sulphides to Sulphoxides

Catalytic scandium triflate greatly increases the efficiency of hydrogen peroxide-mediated monooxidation of alkylaryl



Reoxidant	Yield	Yield
2 eq Br_2	-	<50%
1 eq Br_2	-	80%
1 eq NBS	-	85%
1 eq NCS	-	85%
2 eq I_2	93%	not detected

sulphides and methylcysteine-containing peptides (Matteucci, M. et al. *Org. Lett.* **2003**, *5*, 235). The method is suitable for solid-phase applications and is compatible with a wide range of protection groups.



R	R'	H_2O_2 (eq)	Time (h)	Sulphoxide	sulphone
Ph	dimethylallyl	1.2	5	95	3
Ph	dimethylallyl	5.0	2	98	2
4-BrC_6H_4	Me	1.2	5.5	94	2
4-BrC_6H_4	Me	5	3	98	2
4-$MeOC_6H_4$	Me	1.2	2.3	98	2
4-$MeOC_6H_4$	Me	5.0	1.3	98	2

Aerobic Oxidations Catalysed by Chromium Corroles

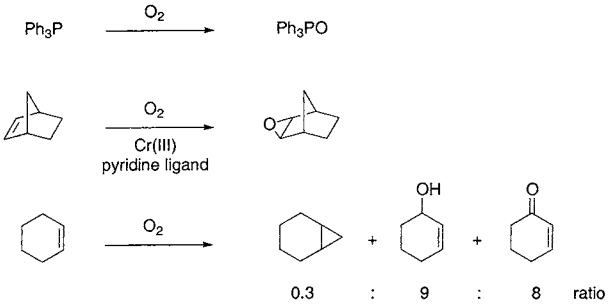
Selective oxidation of organic molecules by O_2 is a holy grail, but there is one problem with processes that rely on metal−oxo intermediates. When the reducing power of a given metal complex is sufficient to activate O_2, the oxidising power of its higher valent form is not great enough to allow oxidation of most organics.

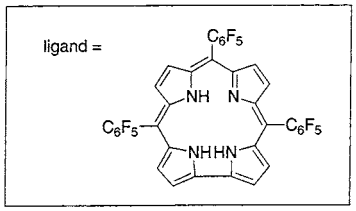
Nature has a way round this, as exemplified by cytochrome P-450 enzymes, but this is hard to mimic in synthetic systems. Use of the ligand tris(pentafluorophenyl) corrole, however, has allowed catalytic air-based oxidations to take place on simple substrates (phosphine to phosphine oxide). These reactions are fast in MeCN, much slower in methanol, and take weeks in toluene and THF (Mahammed, A, et al. *J. Am. Chem. Soc.* **2003**, *125*, 1162).

Activation of N_2O as an Oxidising Agent

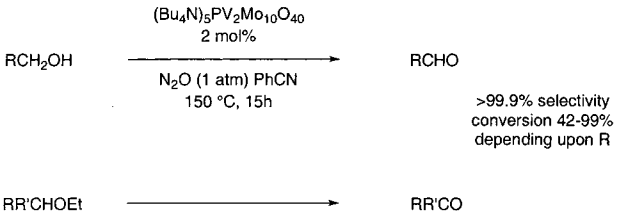
N_2O is a potentially interesting oxidising agent since it contains 36 wt % oxygen and the byproduct of oxidation should be nitrogen. The main reasons these advantages are not exploited is that N_2O is inert and is a poor ligand. Thus, few catalysts have been reported for the activation of N_2O and its use as a selective oxidant.

The group of Neumann in Israel has been examining activation methods and has already published some results (Ben-Daniel, R. et al. *J. Am. Chem. Soc.* **2002**, *124*, 8788)





on manganese activation. The latest paper (Ben-Daniel, R. et al. *Angew Chem., Int. Ed.* **2003**, *42*, 92) describes the use of vanadium-containing keggin-type polyoxomolybdates to activate N_2O in the oxidation of alcohols to aldehydes or ketones.

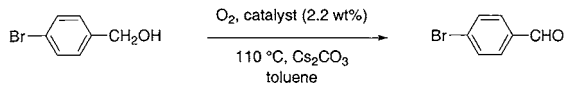


It is suggested that activation occurs by electron transfer of N_2O by the catalyst, followed by H abstraction from the substrate. For alcohols a second H abstraction must follow to give the aldehyde or ketone.

Aromatic CH_2 or CH_3 groups are also oxidised, but only activated groups work—toluene, for example, is not oxidised.

Oxidation Catalyst

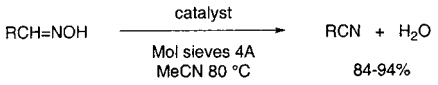
A heterogeneous ruthenium catalyst, easily prepared by absorption of $RuCl_2$ (*p*-cymene)$_2$ on activated carbon KB (100 mesh) is effective in catalysing the oxidation of alcohols to aldehydes and ketones by oxygen. (Choi, E. et al. *Org. Lett.* **2002**, *4*, 2369). The group had previously established that the Ru catalyst works homogeneously in the same reaction, but the advantage of the heterogeneous version is that the catalyst could be recycled and reused.



	1	2	3	4	5	6	7	8	9
time (h)	6	7	8	8	8	8	8	8	9
yield	89	92	97	92	94	89	93	85	81

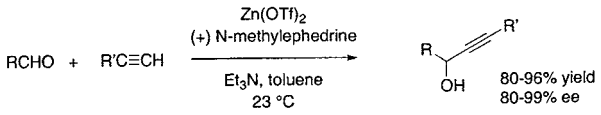
Leaching of ruthenium into the organic layer is negligible.

The catalyst also works for the dehydration of oximes to nitriles.



Enantioselective Addition of Terminal Alkynes to Aldehydes

The reaction of alkynes with aldehydes in the presence of zinc triflate and *N*-methyl ephedrine has been recently reported (see work of Carreira at ETH such as Amand, N. et al. *J. Am. Chem. Soc* **2001**, *123*, 9687). They found that, in general, exclusion of oxygen and rigorous drying of solvents was required, but one case did not require such dry conditions. It has now been found that in reagent-grade toluene, which has a water content of 84−1000 ppm H_2O, reaction of alkynes with aromatic, aliphatic, and α,β-unsaturated aldehydes can proceed even in the presence of small amounts of water. It is suggested that the monoalkynyl zinc intermediates are much more stable to water than typical dialkylzinc compounds (Boyall, D. et al. *Org. Lett.* **2002**, *4*, 2605).



Enantioselective Catalysis in Fine Chemicals Production

In a recent focus article in *Chemical Communications*, Hans-Ulrich Blaser of Solvias discusses the reasons why the advances in enantioselective catalysis, for which the Nobel Prize was awarded in 2001, have not been as widely implemented on-scale. Costs, time scales, and catalyst productivity are all discussed in the thought-provoking article. (Blaser, H.-U. *Chem. Commun.* **2003**, 296).

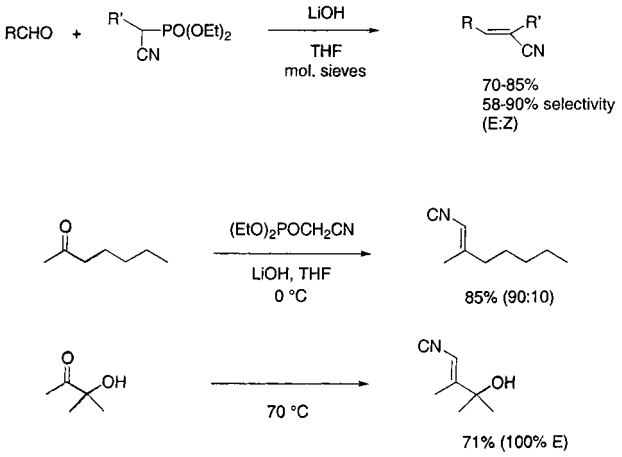
A useful survey of all catalytic enantioselective processes appeared last year in a chapter by Blaser and co-workers in *Applied Homogeneous Catalysis with Organometallic Compounds*, 2nd ed.; Cornils, B., Herrmann, W. A., Eds.; Wiley VCH: Weinheim, New York, 2002; pp 1131 ff. Blaser's opinion is that enantioselective catalysis has not yet achieved its appropriate position in the production of fine chemicals and has the potential for greater economic and environmentally attractive production processes.

Convenient Procedure for Horner−Wadsworth−Emmons (HWE) Olefination

One of the best bases to use for the HWE olefination is a mixture of lithium hydroxide and molecular sieves (4 Å), which allows mild reaction conditions to be used (Bondies, F. et al. *Tetrahedron Lett*, **1996**, *37*, 1899; **1995**, *36*, 2839; and Takacs, J. M. et al. *J. Org. Chem*. **1998**, *63*, 6757). It is generally superior to classical bases such as LDA, LiHMDS, and NaH and is presumably cheaper. Good control of stereochemistry is achieved.

It has now been reported that this method can also be used to make α,β-unsaturated nitriles (Lattamzi, A. et al. *Tetrahedron Lett.*, **2003**, *44*, 1333) from aldehydes *and* ketones, with moderate to good *E*/*Z* selectivity. It was also found that for ketones, the reactions worked just as well in the absence of molecular sieves.

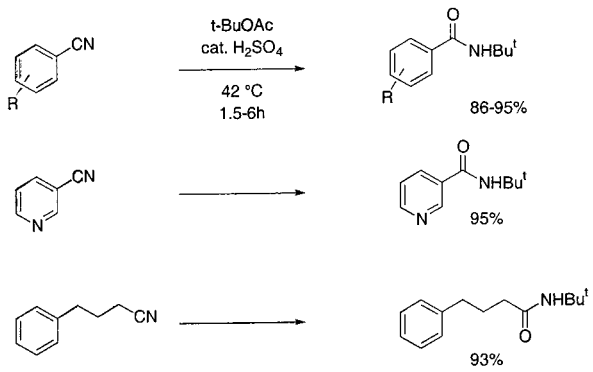
Dicarbonyl compounds could be converted to mono- or diolefins by suitable choice of reaction conditions. α-Hydroxyketones can also be reacted and give exclusively the *E* stereochemistry.



Efficient Procedure for the Ritter Reaction

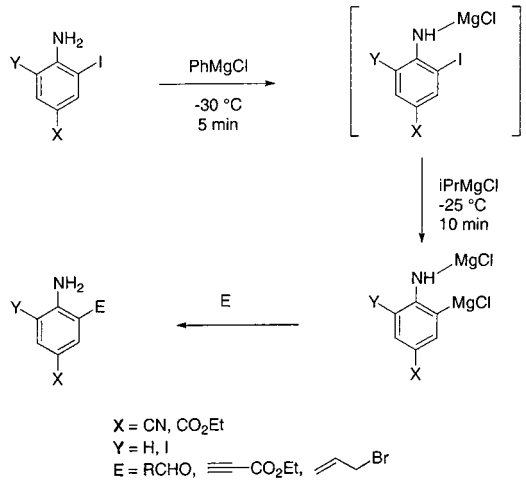
A simple procedure for the conversion of a nitrile to a *tert*-butylamide has recently been reported by chemists from the Process R & D group at Bristol-Myers Squibb (Laxma Reddy, K. et al. *Tetrahedron Lett*. **2003**, *44*, 1453). Only a catalytic quantity of sulphuric acid is required, which makes work-up and product isolation much easier. The source of the *tert*-butyl cation is crucial, with *tert*-butyl acetate giving the best results. The reaction works well for aromatic and heteroaromatic nitriles, and few examples of other nitriles are provided.

In the introduction to the paper, the author indicates that the Ritter reaction works well only for tertiary alcohols, but I believe that Merck have published data (and scaled-up processes) for Ritter reactions on secondary alcohols in two different processes.



Amino-Substituted Aryl Grignard Reagents

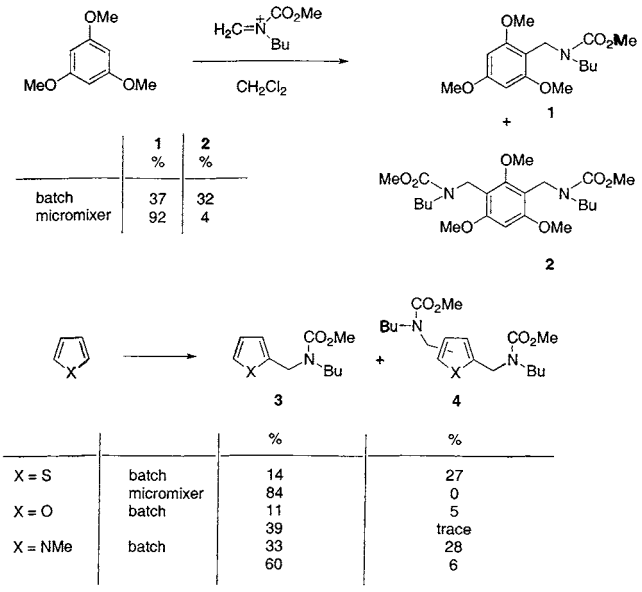
Treatment of various iodoanilines sequentially with PhMgCl (to remove the H on NH_2) and *i*-PrMgCl (to form the Grignard at the iodine position) allows *o*-iodoanilines to be reacted without NH_2-protection (Vardis, G. et al. *Chem. Commun.* **2003**, *396)*.



Highly Selective Alkylation Reactions Using a Micromixer

Alkylation of electron-rich aromatics by iminium salts is a fast reaction, and in a batch reactor, considerable over-reaction occurs. By using a microreactor, however, good selectivity could be achieved (Suga, S. et al. *Chem. Commun.* **2003**, *354*). The Japanese chemists used a multilamination-type microreactor produced by the Institut fur Microtechnik Mains GmbH, where the fluids to be mixed are introduced into the mixing element as two counter-flows and the fluids stream into an interdigital channel configuration (channel width 25 μm) In the next stage, a periodical flow configuration consisting of the lamellae of two fluids is generated by means of the slit-shaped interdigital channel.

Compared to a batch reactor, where a 1:1 mixture of mono- and bis-adducts is obtained, high selectivity to mono-adduct (>90%) occurs in the microreactor. The reaction also works well with heteroaromatics.



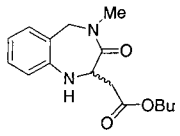
	1 %	2 %
batch	37	32
micromixer	92	4

		%	%
X = S	batch	14	27
	micromixer	84	0
X = O	batch	11	5
		39	trace
X = NMe	batch	33	28
		60	6

Continuous Chromatographic Separation of Isomers: The VARICOL Process

Varicol is a new multicolumn continuous process which has some similarities to simulated moving bed (SMB) chromatography. In SMB, the inlet/outlet lines are shifted simultaneously, whereas in Varicol they are never shifted at the same time. This means that, in contrast to SMB, the column distribution between zones does not stay the same. This gives the Varicol system more flexibility than SMB, particularly when a small number of columns is used. (Ludemann-Hombourger, O. et al. *J. Chromatogr., A* **2002**, *947*, 59).

The methodology has been applied to the separation of SB-55 3261 isomers and is shown to be more efficient than SMB, with increased specific productivity and lower eluent consumption.



SB 553261

Phase-Vanishing Reactions

When a fluorous solvent such as perfluorohexane is mixed with a heavier reagent, two phases result with the reagent in the bottom layer. When a mixture of an organic solvent and substrate is added, a third upper layer is obtained, screened from the reagent by the middle fluorous phase. This phase prevents good mixing but permits "passive" transport of reagents from the bottom layer to the top layer and regulates the reaction (without stirring). The reaction is thus diffusion controlled.

The methodology has been used for bromination with Br_2 and demethylation with BBr_3 and gives good yields. One phase vanishes as the reaction proceeds (Ryu, I. et al. *J. Am. Chem. Soc.* **2002**, *124*, 12946). Other three-phase systems, such as brominations in hexane−MeCN−water are less efficient. It is suggested that this methodology can be used to control exothermic reactions on large scale. The question is whether this concept will turn out to be really practical or just a curiosity!

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