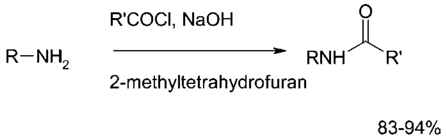
Organic Process Research & Development **2004**, *8,* 138–145

# *Highlights from the Literature*

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

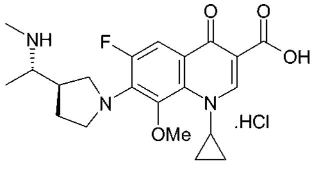
### Alternative to Dichloromethane

Although dichloromethane (DCM) continues to be an attractive and popular solvent for organic transformations, the increasing concerns over its environmental impact still need to be addressed. In a recent publication by Brown, Ripin. and Vetelino (*Synlett* **2003**, 2353) 2-methyltetrahydrofuran (MTHF) has been shown to be a superior solvent to DCM in some two-phase reactions. MTHF posesses many favorable physical characteristics. It is a nonreactive solvent with boiling point of 78−80 °C and forms an effective azeotrope with water (ca. 72 °C, ca. 1:9 $H_2O$/MTHF).



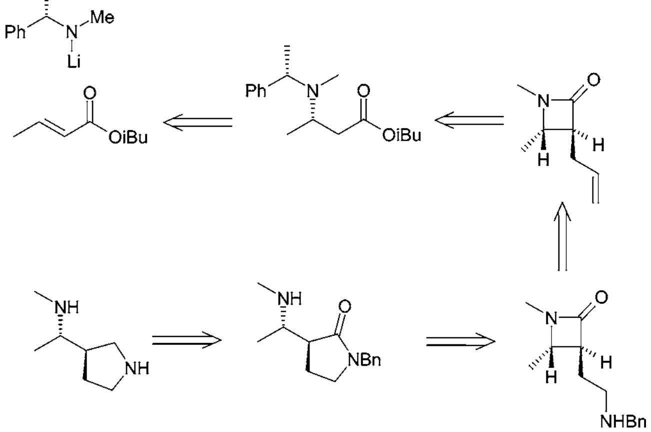
### Key Intermediate in the Preparation of Premafloxacin

*N*-Methyl-*N*-{(1*S*)-1-[(3*R*)-pyrrolidin-3-yl]ethyl}amine is a key intermediate in the preparation of premafloxacin which was under development in the Pfizer labs as an antibiotic for use against pathogens of veterinary importance.



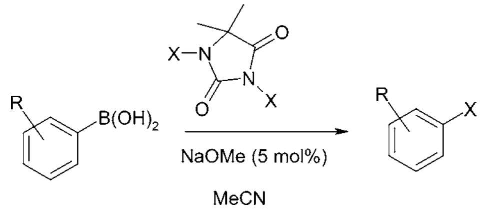
***Premafloxacin***

McWhorter and colleagues have recently disclosed (*J. Org. Chem*. **2003**, *68*, 9612) the synthesis of a key building block towards this molecule in nine steps from isobutylcrotonate in 38% overall yield. Notably the group use an asymmetric Michael addition of a chiral lithium amide (see scheme) to set the first stereocentre, followed by stereoselective alkylation, which gives (3*S*,4*S*)-3-allyl-1,4-dimethylazetidin-2-one. Conversion of this alkene to the benzylamine derivative was achieved using a series of functional group manipulations and the conversion of amino $\beta$-lactam to pyrrolidinone achieved in toluene at 80−90 °C.

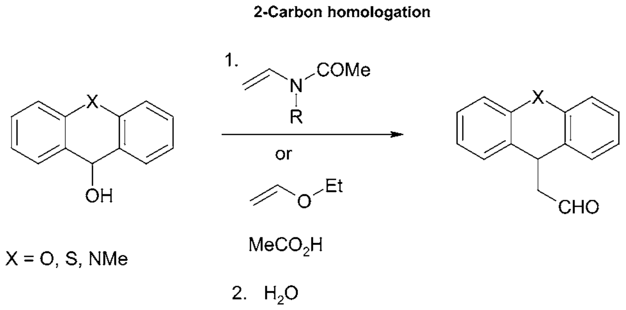


### Halodeboronation

Aryl halides are widely recognized as important synthetic intermediates. Their use has seen explosive growth in the past number of years as key components for the construction of new carbon−carbon and carbon−heteroatom bonds. A scaleable synthesis of 2-bromo-3-fluorobenzonitrile via a NaOMe-catalyzed bromodeboronation of 2-cyano-6-fluorophenylboronic acid has been developed by Szumigala and colleagues at Merck (*J. Org. Chem*. **2004**, *69*, 566). Their method serves to generate either aryl bromides or aryl chlorides in good to excellent yields when the corresponding aryl boronic acid is treated with 1,3-dihalo-5,5-dimethylhydantoin and 5 mol % NaOMe. Addition of base has beneficial effect on rate and yield, and the group propose from the data so far that it serves to assist in the breakdown of less reactive trimeric boronic acid anhydrides to a more reactive monomeric form. The generality of this transformation has been demonstrated through the halodeboronation of a series of aryl boronic acids.



### 2-Carbon Homologation



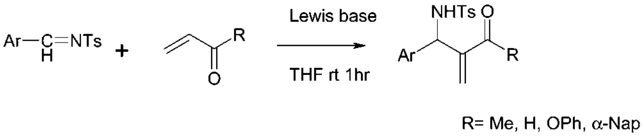
An efficient synthesis of 9H-xanthene-9-carboxaldehyde, 9H-thioxanthene-9-carboxaldehyde, and 9,10-dihydro-10-methyl-9-acridinecarboxaldehyde by a novel two-carbon homologation of xanthydrol, thioxanthydrol, and 9,10-

10.1021/op049963z CCC: $27.50

dihydro-10-methyl-9-acridinol, respectively, using *N*-vinylacetamides or ethyl vinyl ether as acetaldehyde anion equivalents has been reported by Prashad and co-workers at Novartis (*J. Org. Chem.* **2004**, *69*, 584). The proposed mechanism is thought to go through a cationic intermediate formed by loss of water from the secondary alcohol starting material under acid conditions followed by nucleophilic attack of the *N*-vinylacetamide followed by hydrolytic work up to generate the aldehyde.

### *aza*-Baylis−Hillman Reaction

Xu and Shi describe (*J. Org. Chem*. **2004**, *69*, 417) a number of highly efficient *aza*-Baylis-Hillman reactions of *N*-tosylated imines with methyl vinyl ketone, acrolein, and phenyl acrylate or α-naphthyl acrylate in the presence of a Lewis base. In most cases, the reaction was complete within 1 h. These reactions serve as an efficient method to synthesize *β*-amino ketones, aldehydes, and esters in high yields with short reaction time.



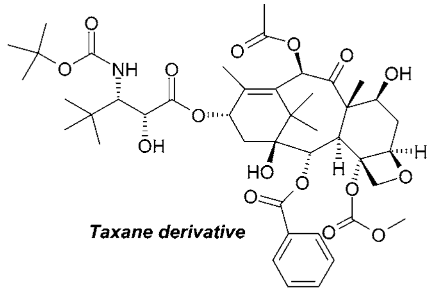
***aza* Baylis-Hillman reaction**

### Asymmetric Synthesis on a Process Scale

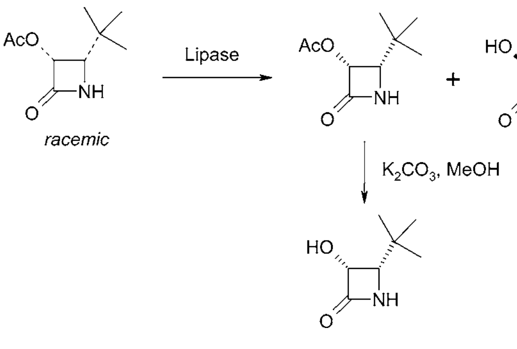
A whole issue of *Tetrahedron Asymmetry* (**2003**, p 3427 and following) is devoted to asymmetric synthesis on a process scale. The journal does a great job in pulling together a variety of asymmetic protocols that cover access to homochiral molecules tested on large scale.

### Synthesis of a Side Chain Synthon for an Orally Active Taxane

In efforts directed towards the synthesis of a new orally active water-soluble taxane derivative (see scheme) the chiral intermediate (3*R*)-*cis*-3-acetyloxy-4-(1,1-dimethylethyl)-2-azetidinone has been prepared by Patel and co-workers from Bristol Myers Squibb (*Tetrahedron Asymmetry* **2003**, 3673). The enantioselective enzymatic hydrolysis using immobilized lipase PS-30 or BMS lipase of racemic *cis*-3-acetyloxy-4-(1,1-dimethylethyl)-2-azetidinone to the corresponding undesired (*S*)-alcohol left the desired unreacted acetoxy compound. Reaction yields of >48% and enantiomeric excesses of >99% were obtained for the desired diastereomer which was converted to the hydroxy lactam derivative for use in the semi-synthesis of the anticancer taxane.

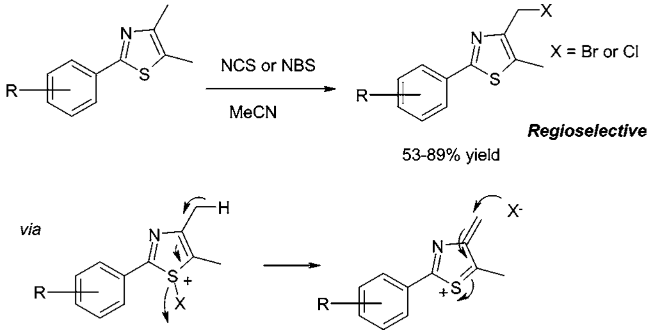


*Taxane derivative*

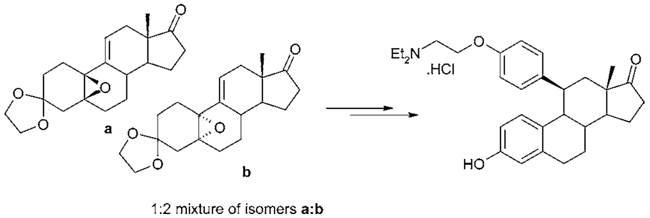


### Regioselective Halogenation

Substituted 1,3-thiazoles have an important place as structural motifs in the discovery of pharmaceutically interesting molecules. Yamane and colleagues at Takeda Chemical Industries, Ltd. report (*Tetrahedron Lett.* **2004**, *45*, 69) an unprecedented regioselective C4-methyl halogenation of 4,5-dimethyl-2-aryl-1,3-thiazoles. The reaction of the dimethyl starting material (see scheme) with *N*-chlorosuccinimide and *N*-bromosuccinimide under mild conditions provides a simple method for obtaining 4-chloromethyl-5-methyl-2-aryl-1,3-thiazoles and 4-bromomethyl-5-methyl-2-aryl-1,3-thiazoles, respectively, in good yields without the formation of 4-methyl-5-halomethyl regioisomers. The group postulate a Pummerer-type mechanism to explain the origin of the regioselectivity.



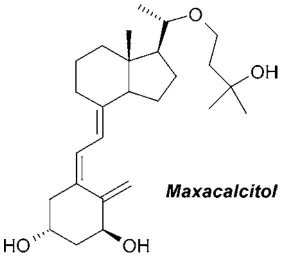
### 11*β*-Aryl-estrone Derivative

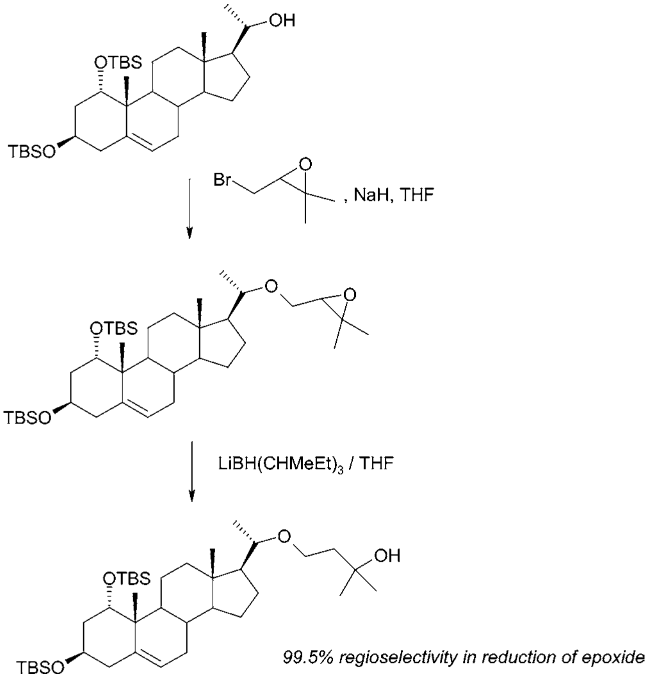


An industrial synthesis of 11*β*-aryl-estrone derivatives has been published by Prat and colleagues from Aventis (*Tetrahedron Lett.* **2004**, 765) based on the 1,4-addition of a cuprate aryl side chain to a mixture of allylic α- and *β*-epoxides, followed by hydrolysis and subsequent aromatization. Although good stereoselectivity was not achieved in the initial epoxidation reaction, both epoxides could be transformed to the desired product, thus significantly increasing the yield.

### Maxacalcitol

Shimizu and colleagues report (*Tetrahedron Lett.* **2004**, 1347) a one-pot method to modify a steroid 20*S*-hydroxy functionality to allow synthesis of the medicinally important 1α,25-dihydroxy-22-oxa-vitamin $D_3$, Maxacalcitol. Their method involves sequential alkylation (Williamson ether synthesis) followed by regioselective reductive cleavage of epoxy linkage to give the tertiary alcohol.

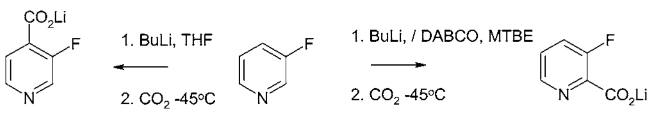

*Maxacalcitol*



*99.5% regioselectivity in reduction of epoxide*

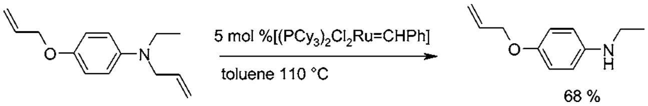
## Lithium 3-Fluoropyridine-2-carboxylate

A practical method amenable to kiloscale synthesis for the preparation of lithium 3-fluoropyridine-2-carboxylate as well as its 4-regioisomer has been reported by Emerson and colleagues at Merck (*Synth. Commun.* **2003**, 4235). 3-Fluoropyridine can be regioselectively lithiated on C-2 or C-4, depending on the reaction conditions, and the group have developed a quench protocol with carbon dioxide to conveniently give the lithium carboxylate in high yield and purity.



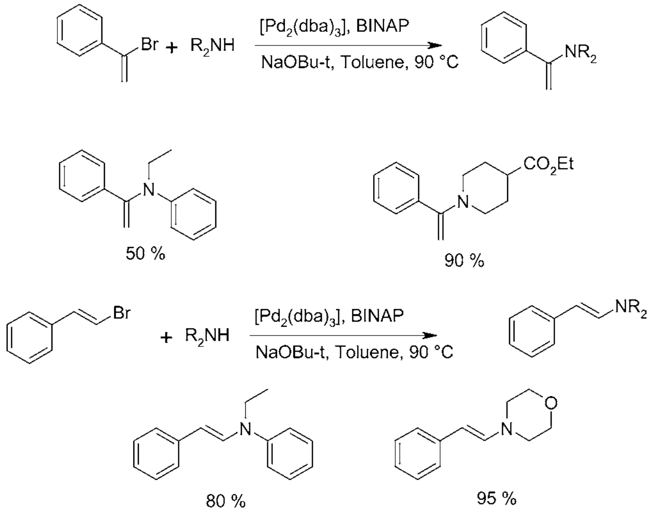
## Ruthenium-Catalyzed Chemoselective *N*-Allyl Cleavage with Grubbs Carbene Complex

The removal of allylic protecting groups has recently received growing attention not only in peptide chemistry but also in combinatorial chemistry. The most common methodology for this transformation is palladium π-allyl deprotection. As the coordination chemistry of ruthenium complexes has progressed, it has opened the way for a broad variety of catalytic transformations including olefin metathesis reactions. The chemistry of late-transition-metal carbene complexes has recently received much attention, primarily due to the high catalytic activity of phosphine and imidazolidine ruthenium carbene complexes in olefin metathesis. B. Alcaide et al. (*Chem. Eur. J.* **2003**, *9*, 5793) have now discovered a novel application of the Grubbs carbene complex $[(PCy_3)_2Cl_2Ru{=}CHPh]$. These are the first examples of the catalytic deprotection of allylic amines with reagents other than palladium catalysts. This new method is general, selective, and is more convenient than the palladium-catalyzed methodology, which requires not only the palladium catalyst but also a nucleophilic compound as an allyl group scavenger. The Grubbs carbene complex achieves chemoselective deprotection of allylamines in the presence of allyl ethers. This new method has the scope to extend the use of allyl protecting groups in synthesis.



## Palladium-Catalyzed Cross-Coupling Reactions of Amines with Alkenyl Bromides

The palladium-catalyzed cross-coupling reaction of alkenyl bromides with secondary and primary amines gives rise to enamines and imines, respectively. This new transformation (Barluenga, J. et al. *Chem. Eur. J.* **2004**, *10*, 494) expands the applicability of palladium-catalyzed C−N-forming reactions. The catalytic system which gave the best results in a broad screen was $Pd_2(dba)_3$/BINAP in the presence of NaOBu$^t$ in toluene. This system works as well for primary amines where it is possible to obtain the expected imines in very short times and with low catalyst loading. With secondary amines the corresponding enamines are obtained cleanly in nearly quantitative yield, but steric hindrance seems to be a limitation, as coupling partners with large substituents are not well converted.

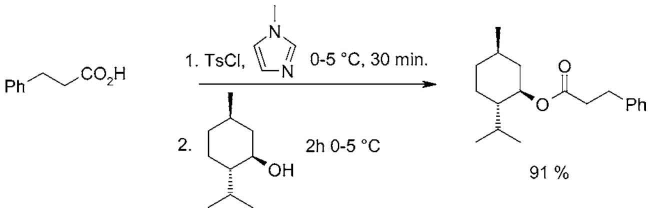


## Protons Can Be the Active Catalysts in Lewis Acid-Mediated Hetero-Michael Additions

J. B. Spencer et al. (*Chem. Eur. J.* **2004**, *10*, 484) have investigated the mechanism of Lewis acid-catalyzed hetero-Michael addition reactions of weakly basic nucleophiles to $\alpha,\beta$-unsaturated ketones. The authors found that protons, rather than metal ions, were the active catalysts. Other mechanisms were ruled out by analyses of side products and of stoichiometric enone-catalyst mixtures and by the use of radical inhibitors. No evidence for the involvement of $\pi$-olefin−metal complexes or for carbonyl−metal-ion interactions was obtained. The reactions did not proceed in the presence of the noncoordinating base 2,6-di-*tert*-butylpyridine. The authors also found a good correlation of catalytic activities with cation hydrolysis constants. The existence of Brønsted acid-catalyzed pathways has important implications for the development of enantioselective processes. Catalytic enantioselective reactions, which are sensitive to proton-mediated background reactions, cannot succeed when trace amounts of water cannot be excluded. These investigations provide useful information for the development of Lewis acid-catalyzed reactions of mono and dicarbonyl compounds under nonbasic conditions and are not limited to hetero-Michael reactions.

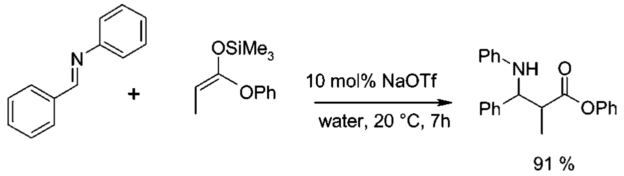
## Simple Mild and Practical Esterification, Thioesterification, and Amide Formation

Y. Tanabe et al. (*Adv. Synth. Catal.* **2003**, *345*, 1209) have developed an efficient method for the esterification or thioesterification of carboxylic acids through activation with *p*-toluenesulfonyl chloride and *N*-methylimidazole. The method can be applied to various types of carboxylic acids, alcohols, and thiols. The authors showed that *N*-Cbz-protected amino acids can smoothly be esterified without racemization using this new method. The obtained yields of esters or thioesters from alcohols or thiols, respectively, are good to excellent. The method is also efficient for the formation of amides from primary and secondary amines. The amides were obtained in excellent yields.



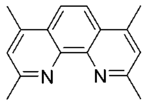
## Mannich-Type Reactions Catalyzed by Neutral Salts in Water

S. Kobayashi et al. (*Adv. Synth. Catal.* **2003**, *345*, 1187) have found that Mannich-type reactions of imines with silicon enolates can be catalyzed by neutral salts such as sodium triflate in water. In contrast to previous reported methods the present system does not need any acidic catalysts. The kinetic behavior of the reaction indicates that the product itself is involved in the catalytic system. Sodium triflate was found to be the best catalyst, whereas sodium dodecyl sulfate was not as efficient. It was found that sodium cation is crucial for the catalytic activity as the reaction was completely inhibited by the addition of [2,2,2]cryptand. The authors also applied the catalytic system to three-component reactions with aldehydes, amines and silicon enolates. From the reactions variously substituted $\beta$-amino acid derivatives were obtained in modest to good yields.



## Increased Substrate Scope in the Palladium−Neocuproine-Catalyzed Aerobic Oxidation of Alcohols in Aqueous Solvents

Neocuproine (**1**) and $Pd(OAc)_2$ was found by R. Sheldon et al. (*Adv. Synth. Catal.* **2003**, *345*, 1341) to be a highly active catalyst for alcohol oxidation with air in 1:1 water: DMSO. The catalyst is unique in that it tolerates water, polar cosolvents (DMSO, NMP, and DMAc), and a wide variety of functional groups in the substrate, for example double or triple bonds, halides, $\alpha$-carbonyls, ethers, thioethers, and amines. The optimum catalyst structure, reaction conditions and also substrate scope of the selected catalysts were quickly determined with the use of parallel experimentation. It should be noted that under these reaction conditions, 2-hexanol is converted at rates 2 orders of magnitude faster than with existing catalytic methods. With 0.025 mol % neocuproine/$Pd(OAc)_2$ catalyst the turnover frequency was found to be as high as 1800 $h^{-1}$.



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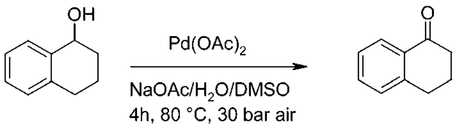
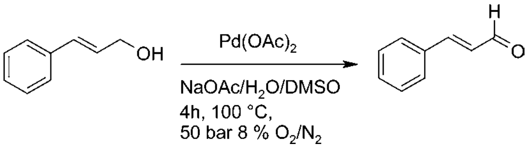
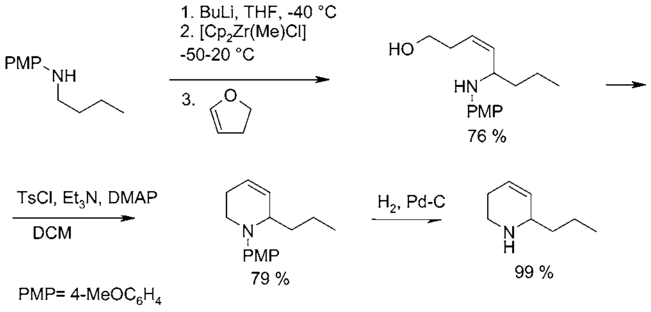




## Zirconium-Mediated Synthesis of Allyl and Homoallylamines

J. Barluenga et al. (*Chem. Eur. J.* **2004**, *10*, 109) have described an easy and efficient zirconium-mediated synthesis of allylamines from simple amines and enol ethers. This strategy allows the synthesis of amino alcohols containing a *Z* double bond in their structure when 2,3-dihydrofuran is used as enol ether. These amino alcohols can easily be converted to 2-substituted piperidine derivatives. The reaction between amines and allyl phenyl ethers furnishes homoallylamines or amino ethers, depending on the structure of the starting amine.



## Room-Temperature Air Oxidation of Primary Alcohols to Aldehydes using Copper Bromide, Bipyridyl, and TEMPO

A mixture of copper (II) bromide, bipyridyl, and TEMPO in the presence of base catalyses the air oxidation of alcohols to aldehydes at room temperature in acetonitrile−water. The reaction requires all components for efficient oxidation (Gamez, P. et al. *Chem. Commun.* **2003**, 2414).

Oxidation of Benzyl Alcohol to Benzaldehyde with $CuBr_2$

| Bipy | TEMPO | $KOBu^t$ | Conversion | |
|---|---|---|---|---|
| | | | 0.5h | 1.5h |
| No | Yes | Yes | <1 | 6 |
| Yes | No | yes | 0 | 0 |
| Yes | Yes | No | 10 | $27^b$ |
| Yes | Yes | yes | 38 | $83^{a,c}$ |

a 99% selectivity

b 100% conversion after 24h

c 100% conversion after 2.5h

The reagent catalyses the oxidation of primary alcohols but not secondary; benzylic alcohols can be preferentially oxidised in the presence of aliphatic alcohols.

| Alcohol | Time | Conversion |
|---|---|---|
| Benzyl | 2.5 | 100% |
| 1-Phenylethanol | 5 | 0 |
| Crotyl alcohol | 5 | 91% |
| Geraniol | 5 | 100% |
| Octan-1-ol | 24 | 61% |
| Octan-1-ol | 24 | 95% (at 40°C) |
| Octan-2-ol | 5 | no reaction |

Copper (II) bromide is more effective than copper chloride and nitrate. Copper perchlorate is slightly more active than copper bromide, but the hazards associated with this reagent outweigh the advantages. It is suggested that copper complexes with the bipyridyl, TEMPO, and the alcohol anion, and the weaker the coordinating anion on copper (e.g., $ClO_4$ etc.), the better.

At present, 5 mol % of each component is used. For a larger scale process, this would need to be reduced for economic oxidations. The method compares favourably with the few copper catalysed air oxidations reported previously.

## Oxidation of Alkanes to Chiral Alcohols

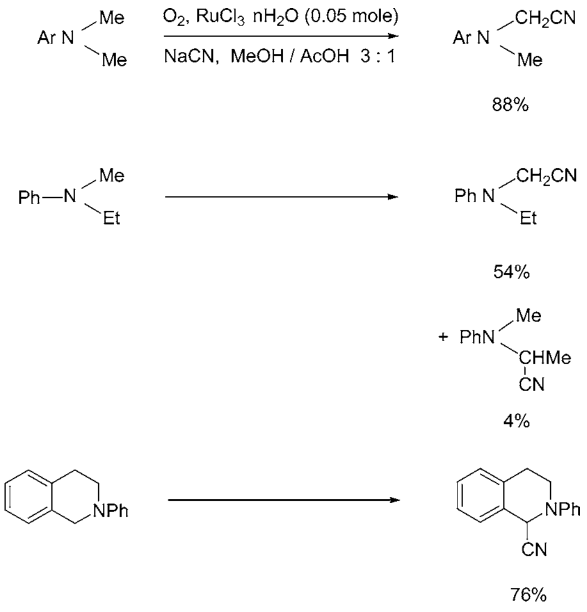
The direct oxidation of hydrocarbons to alcohols using oxygen and an enzyme is a dream which has now been brought to reality by Frances Arnold and colleagues at California Institute of Technology, Pasadena, CA (Arnold, F. H. et al. *J. Am. Chem. Soc.* **2003**, *125*, 13442). Using an engineered enzyme P450, optimised for performance by "directed" evolution, they carried out oxidation of nonane to *S*-3-nonanol in 84% ee. Regioselectivity still needs to be improved, but this is a remarkable result and shows the potential of directed evolution for developing economic industrial processes involving oxygen as oxidising agent.

A major limitation of these enzymes is the need to use an expensive cofactor, such as NADPH, which precludes their use without addition of a coupled cofactor−regeneration system. However Arnold's group have recently reported a self-sufficient, peroxide-driven hydroxylation catalyst (Cirino, P. C. et al. *Angew. Chem., Int. Ed.* **2003**, *42*, 3299). The TON for lauric acid hydroxylation is approximately 280.

## Oxidative Cyanation of Tertiary Amines

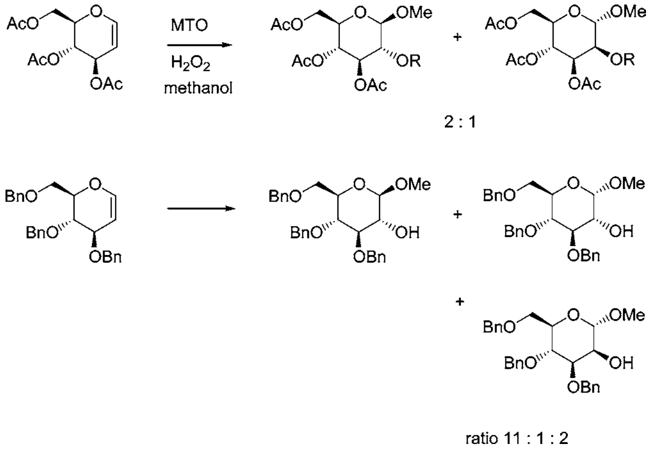
Although the ruthenium-catalysed oxidation of tertiary amines is well-known, the reagents are generally peracids or *t*-BuOOH. In a search for a more environmentally benign method of oxidative transformation of amines using oxygen (which occurs in nature using P450 enzymes), ruthenium catalysis was explored in the presence of trapping agents for the intermediate imine, such as cyanide ion. Acetic acid was found to be essential as a solvent or cosolvent, as in many oxidations with $O_2$ (Murahashi, S. et al. *J. Am. Chem. Soc.* **2003**, *125*, 15312). Interestingly *N*-methyl groups are oxidised in the presence of *N*-ethyl groups with reasonable selectivity.

Although the authors used a 3:1 mixture of methanol and acetic acid as solvent under $O_2$ at 60 °C, it should be pointed out that on scale-up this may be unsafe, and a pure acetic acid solvent may be preferred (or the use of a nonflammable cosolvent).



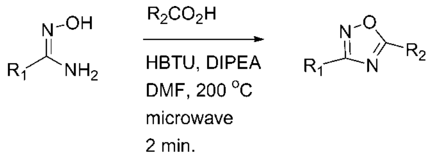
### "Green" Oxidations: Application to Carbohydrate Chemistry

Continuing the theme of green oxidations, the increasing use of methyltrioxorhenium (MTO) as catalyst in conjunction with hydrogen peroxide is attracting industrial attention. In a joint project between University of Manchester and Syngenta (Boyd, E. C. et al. *Green Chem.* **2003**, *5*, 679), glycals were directly oxidised to methyl glycosides. Hydrogen peroxide−acetonitrile could also be used. Protection of the alcohol groups on the carbohydrate is necessary. With acetate protection the reaction is not selective, giving a 2:1 mixture of products, whereas when benzyl protection is used, the reaction is more stereoselective.



### Accelerated Development of an Optimised Synthesis of 1,2,4-Oxadiazoles

The combination of microwave technology with statistical software (design of experiments) was shown to be a powerful tool in the optimisation of a process to prepare 1,2,4-oxadiazoles from amidoximes and carboxylic acids. The group of Nicewonger at ArQule, in collaboration with medicinal chemists from Pfizer, UK, showed that the reaction has a quadratic dependence on the equivalents of DIPEA used as base and that any deviation from the optimum of 2.85 equivalents of DIPEA leads to a substantial drop in yield. (Evans, M. D. et al. *Tetrahedron Lett.* **2003**, *44*, 9337).

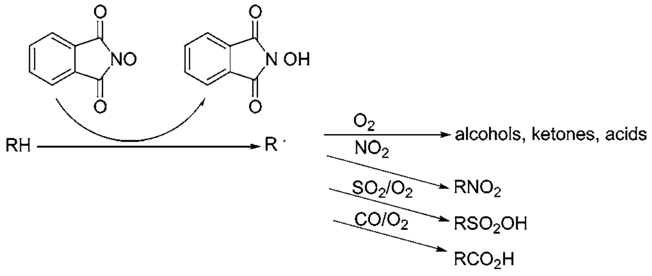


HBTU is O-benzotriazolyl, NNN'N' tetramethyluroniumhexafluorophosphate

### Catalytic Carbon Radical Generation and Its Application to Organic Synthesis

The journal, *J. Synth. Org. Jpn*, is normally published in Japanese, and therefore rarely read by Western scientists. However, each year, one issue is published in English and contains some useful short reviews, similar to *Accounts of Chemical Research*. In the 2003 issue, the work of Ishii, often highlighted in these pages because of its potential use in industrial processes, is reviewed (Ishii, Y. et al. *J. Synth. Org. Jpn.* **2003**, *61*, 1056).

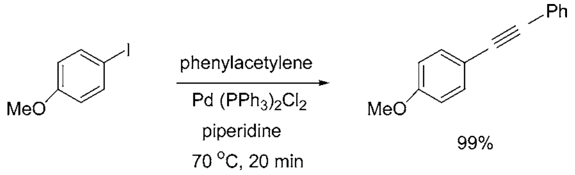
Many of Ishii's reactions are catalytic oxidations using oxygen, followed by further transformations.



In the previous volume, a paper you may have missed was on palladium catalysis in water (Uozumi, Y. et al. *J. Synth. Org. Jpn.* **2002**, *60*, 1063)

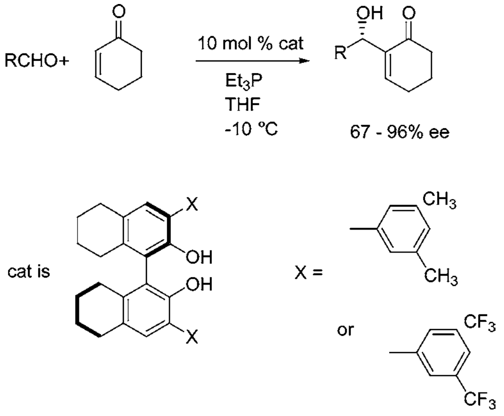
### Copper-Free Sonogashira Couplings

The Sonogashira reaction, the palladium- and copper-catalysed coupling of terminal alkynes with aryl and vinyl halides, is an efficient method which has been scaled up to kilogram scale. However, the use of two metals makes catalyst recovery more difficult; high palladium catalyst loadings are normally required in the absence of copper. Recently, a new procedure has been reported which, in the absence of copper, uses relatively low levels of palladium (0.5−1 mol %), (Leadbeater, N. E. et al. *Tetrahedron Lett.* **2003**, *44*, 8653).



### Asymmetric Morita−Baylis−Hillman Reactions

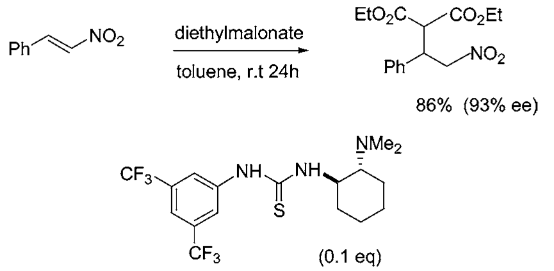
It has been shown that bisnaphthol-derived Brønsted acids can promote the Morita−Baylis−Hillman reactions using phosphane catalysts and that if chiral Brønsted acids are used, high ee of product is obtained (McDougal, N. T. et al. *J. Am. Chem. Soc.* **2003**, *125*, 12094).



### Enantioselective Michael Reaction

The reaction of malonates with nitroolefins has been shown to proceed, using novel, chiral thiourea catalysts with high enantiomeric excess (Okino, T. et al. *J. Am. Chem. Soc.*

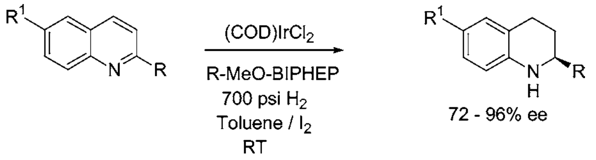
**2003**, *125*, 12672). Yields and ee were best in toluene as solvent; whereas ee was also high in THF and $CH_2Cl_2$, yield was considerably reduced.



### Asymmetric Hydrogenation of Pharmaceutically Interesting Substances

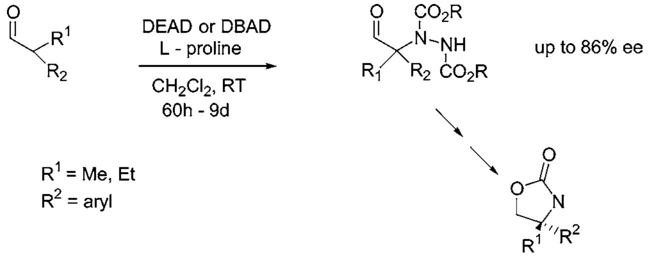
A review of this important area has recently appeared (Lennon, I. C. et al. *Curr. Opin. Drug Discovery Dev.* **2003**, *6*, 855−875). This review is an excellent, up-to-date summary but is also interesting for the many references to the patent literature and for the additional useful comments on certain literature references (e.g. “this paper describes the application of ...... on a multi-kilogram scale”).

A key example mentioned is the enantioselective reduction of quinoline rings (Wang, W. B. et al. *J. Am. Chem. Soc.* **2003**, *125*, 10536).



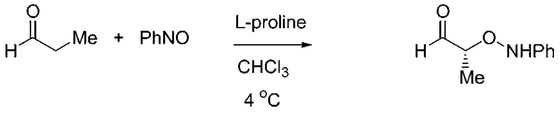
### Asymmetric Amination of Aldehydes

There is great interest in asymmetric amination at present, and recent publication from the groups of List (*J. Am. Chem. Soc.* **2002**, *124*, 5656) and Jorgensen (Bøgevig, A. et al. *Angew. Chem., Int. Ed.* **2002**, *41*, 1790; Marigo, M. et al. *Angew. Chem., Int. Ed.* **2003**, *42*, 1367) have shown the potential of this new methodology. A recent publication (Vogt, H. et al. *Chem. Commun.* **2003**, 2448) extends the scope to α,α-disubstituted aldehydes.



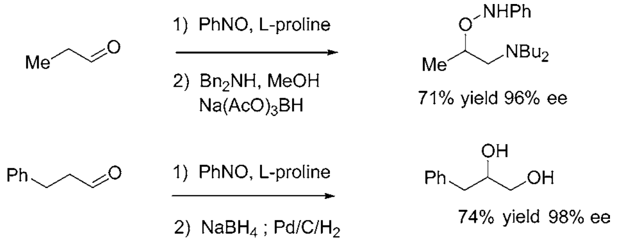
### Enantioselective Organocatalytic α-Oxidation of Aldehydes

The group of MacMillan at California Institute of Technology, Pasadena, CA, continues to expand the range of reactions which can be accomplished by organocatalysis. A recent publication announced the α-oxidation of aldehydes using nitrosobenzene as oxidant; since L-proline is the catalyst, the reaction can proceed in an enantioselective manner (Brown, S. P. et al. *J. Am. Chem. Soc.* **2003**, *125*, 10808). Although yield is dependent on solvent, high ee’s are obtained in all solvents used.



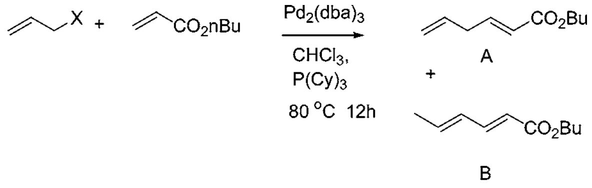
| Mol % proline | time | % yield | % ee |
|---|---|---|---|
| 10 | 20 min | 88 | 97 |
| 5 | 45 min | 86 | 97 |
| 2 | 2h | 88 | 97 |
| 1 | 8h | 83 | 97 |
| 0.5 | 18h | 68 | 94 |

A variety of aldehydes could be oxidised in high ee. The products are oligomeric in solution and are conveniently isolated by reduction to the alcohol. The aldehydes can be reacted further in standard reactions.



### Palladium-Catalysed Allylic Alkenation of Allylic Alcohols

1,4-dienes can now be prepared easily from allylic alcohols and acrylates in a palladium-catalysed reaction (Tsukuda, N. et al. *Chem. Commun.* **2003**, 2404). The reaction proceeds with high regioselectivity.



| X | Additive | Solvent | Yield | A : B |
|---|---|---|---|---|
| OTs | - | benzene | 42% | 75 : 25 |
| OTs | - | AcOH | 69% | 99 : 1 |
| OTs | - | butyl acrylate | 90% | 98 : 2 |
| OH | $Ts_2O$ | butyl acrylate | 63% | 96 : 4 |
| OH | $Tf_2O$ | butyl acrylate | 9% | 65 : 35 |

The reaction has been applied to a wide variety of allylic alcohols using the in situ tosylate generation protocol, since many allylic tosylates are difficult to isolate.

### Safety Warning

We have highlighted many examples of oxidations in this issue. There is a tendency in the literature to use oxidising agents which may pose a hazard on scale-up, and caution is urged when using IBX and Dess Martin reagents (use stabilised IBX instead−see December Highlights [*Org. Process Res. Dev.* **2003**, *7*, 776−783]). Nicolaou et al. (*Angew. Chem., Int. Ed.* **2002**, *41*, 1386) have suggested a mixture of iodic acid or $I_2O_5$ and DMSO as mild and selective oxidising agents. The reagents were prepared by heating the two components together at 80° for 1 h. However when this was repeated at the University of Nottingham (Woodward, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 3981) on a 42 mmol scale, the reaction exploded after 30 min heating at 80 °C. No abnormalities were found in the reagents used.

A search of Bretherick's *Handbook of Reactive Chemical Hazards* did not reveal any prior incompatibility, but periodic acid ($HIO_4$) and DMSO are known to explode when in concentrated solution, although more dilute solutions appear stable (Rowe, J. J. M. et al. *J. Am. Chem. Soc.* **1968**, *90*, 1924).

### Chemical Safety in a Vulnerable World

The title of this article is the motto of an International Forum on Chemical Safety which met in Bangkok in November 2003. This overview covers current developments in the field of chemical safety policy (Gartner, S. et al. *Angew. Chem., Int. Ed.* **2003**, *42*, 4456).

### Diamonds are Forever (in the Literature!)

I mentioned in the December Highlights (*Org. Process Res. Dev.* **2003**, *7*, 776−783) how to make diamonds. The good news is that you can now make them by reduction of magnesium carbonate with metallic sodium. However the bad news is that a temperature of 500 °C and a pressure of 860 atm is required (Che, Q. et al. *Angew. Chem., Int. Ed.* **2003**, *42*, 4501).

Trevor Laird*
*Editor*

Stephen A. Hermitage
*GlaxoSmithKline, Gunnels Wood Road,*
*Stevenage, Hertfordshire SG1 2NY, United Kingdom*

Ulf Tilstam
*Lilly Development Centre S.A.,*
*B-1348 Mont-Saint-Guibert, Belgium*

OP049963Z