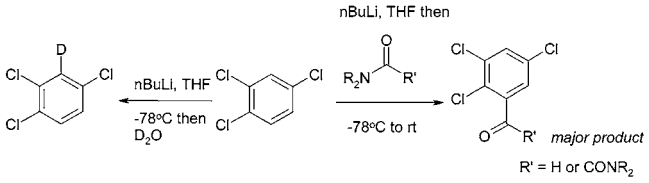
Organic Process Research & Development **2003**, *7*, 614–621

# *Highlights from the Literature*

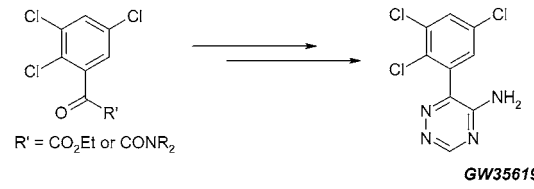
## Some Items of Interest to Process R&D Chemists and Engineers

### Syntheses of the Amino-1,2,4-Triazine, GW356194

In two back-to-back papers, Burton and co-workers at GSK describe (*Tetrahedron Lett*. **2003**, *44*, 5653) how unusual regiochemistry is observed in the products arising from the reaction of lithiated 1,2,4-trichlorobenzene with *N*,*N*-dimethylformamide and tetraalkyloxamides.




The group go onto describe (*Tetrahedron Lett*. **2003**, *44*, 5657) how new syntheses of the amino-1,2,4-triazine, GW356194 have been developed. The use of different amidrazones in cyclisations with α-keto and α-amido carbonyl compounds (see below) as the key step for the synthesis of the 1,2,4-triazine core was evaluated.

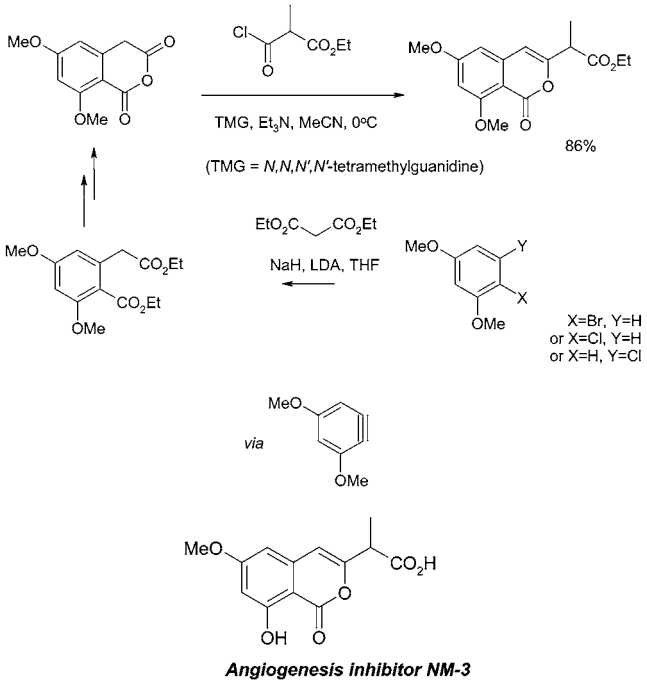



### Formal Synthesis of the Angiogenesis Inhibitor NM-3

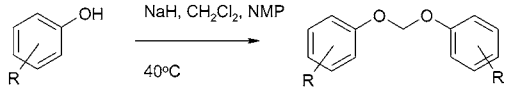
Bauta and co-workers from Ilex Oncology Inc., report (*J. Org. Chem.* **2003**, *15*, 5967) the formal synthesis of angiogenesis inhibitor NM-3 in six steps from either of the 2,4-dimethoxyhalobenzenes or 3,5-dimethoxychlorobenzene as shown in the scheme. The first key reaction is the regiospecific alkylation/rearrangement between the aryne derived from the dimethoxybenzene derivatives with sodium diethylmalonate in THF to produce diester, which after hydrolysis and cyclization affords homophthalic anhydride. The second is the reaction of anhydride with either ethyl 2-methylmalonate, in the presence of 1,1′-carbonyldiimidazole, or ethyl-2-methylmalonyl chloride under basic conditions to afford key isocoumarin.

### Diaryloxymethanes

Waykole and co-workers from Novartis publish an interesting paper (*Synth. Commun*. **2003**, 1751) where they report how diaryloxymethanes were prepared by treating phenols with sodium hydride and dichloromethane in *N*-methyl-pyrrolidinone (NMP) at 40°C. The paper not only serves as a useful preparation of this class of compound but

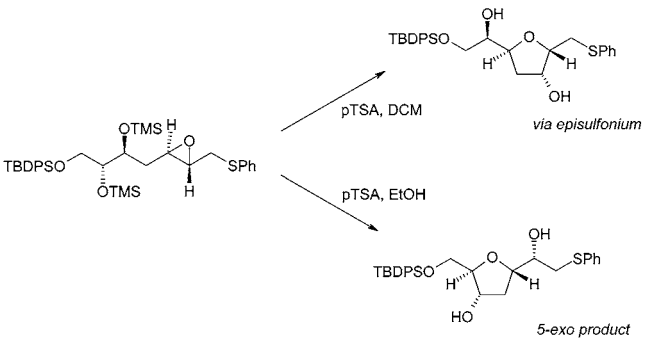



is also a reminder that DCM (usually used as a solvent) may react with substrates forming "dimeric" impurities.




### Regiochemical Control and Solvent Effects

Solvents can play a dramatic part in determining the outcome of reactions. Borhan and Sivakumar report (*Tetrahedron Lett*. **2003**, *44*, 5547) the regioselectivity of cyclization of a complex structure can be controlled by the appropriate choice of reaction conditions. Thus, while the 5-*exo* mode of cyclization is observed under protic conditions with polar solvents, the intermediacy of an episulfonium ion generated in nonpolar solvents leads to a regioisomeric THF product as shown in the scheme below.





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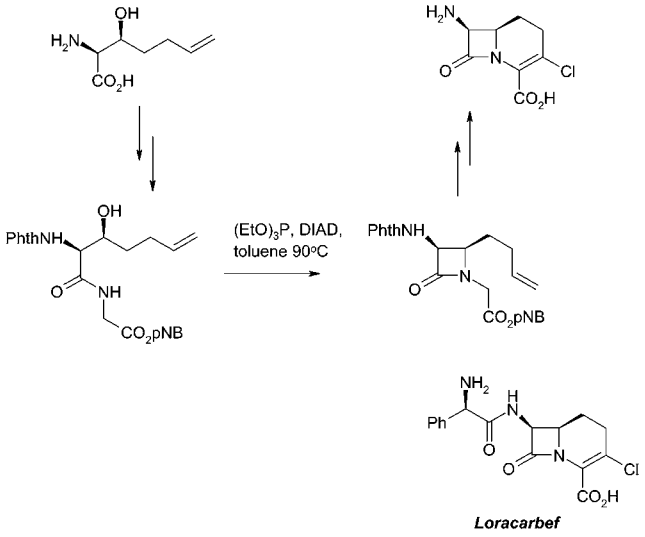
### Synthesis of the Carbacephem Antibiotic Loracarbef

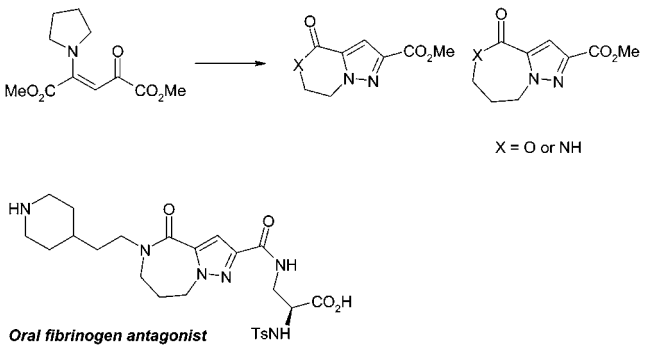
Zhang and colleagues at Lilly report how the nucleus of the carbacephem antibiotic loracarbef was synthesized from 2*S*,3*S*-2-amino-3-hydroxy-6-heptenoic acid (AHHA), which was derived from enzyme-catalyzed condensation of glycine and 4-pentenaldehyde (*Tetrahedron Lett*. **2003**, *44*, 5991). The bicyclic framework of this compound was established through sequential Mitsunobu reaction (using triethyl phosphite, DIAD in hot toluene) followed by a series of manipulations involving an aldol condensation. All synthetic steps are high-yielding, and no chromatographic separations were required.




*Loracarbef*

### Rapid Heterocycle Entry

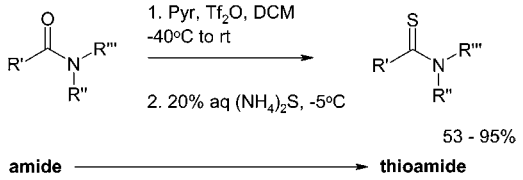
Cvetovich and co-workers at Merck report (*Tetrahedron Lett*. **2003**, *44*, 5867) how hydrazines condense with dimethyl 2-pyrrolidino-4-oxo-2-pentenedioate in the presence of aqueous HCl to form *N*-substituted pyrazole-3,5-dicarboxylates. More complex bicyclic derivatives, such as pyrazolo-oxazine pyrazolo-oxazepine, pyrazolo-pyrazine, and pyrazolo-diazepine were generated using 2-hydrazinoethanol, 3-hydrazinopropanol, 2-hydrazinoethylamine, and 3-hydrazinopropylamine. The condensations were performed in methanol at 25−50°C in the presence of a small amount of aqueous HCl. These core heterocycles form part of new pharmaceutical candidates, in particular, the oral fibrinogen antagonist shown.




*Oral fibrinogen antagonist*

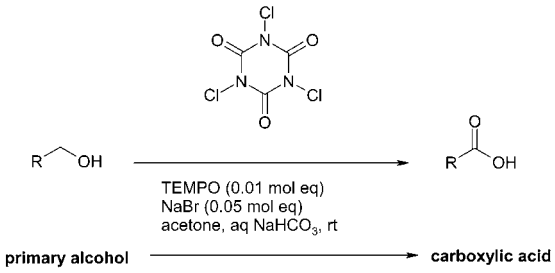
### Mild Method for the Conversion of Amides to Thioamides

Aqueous ammonium sulfide was found (Charette and Grenon, *J. Org. Chem*. **2003**, *68*, 5792) to be an ideal substitute for hydrogen sulfide for the thiolysis of activated amides. High yields of the corresponding thioamides were obtained for a broad range of substrates, using two different procedures that are both operationally simple and inexpensive, as well as amenable to large-scale preparation.



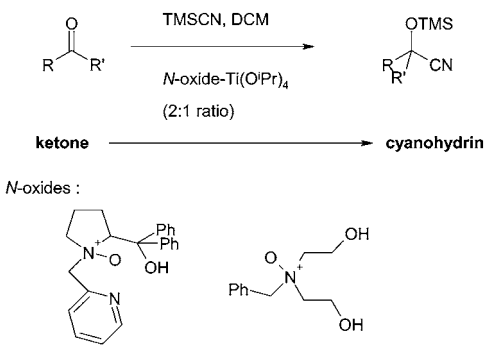

### Oxidation of Alcohols Using Trichloroisocyanuric Acid/ TEMPO Combination

Efficient oxidation of primary alcohols to the corresponding carboxylic acids can be carried out at room temperature and in acetone/water, using trichloroisocyanuric acid (TCCA) in the presence of catalytic TEMPO (Giacomelli, et al. *J. Org. Chem*. **2003**, *68*, 4999). The mild conditions of this procedure, absence of transition metals, nontoxic byproducts, and easy workup make this procedure attractive for laboratory and scale-up use. The group go on to describe a possible mechanism.



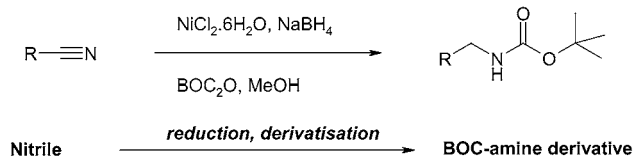

### Cyanosilylation of Ketones

Feng and co-workers describe (*Tetrahedron* **2003**, *59*, 5667) how a new family of bifunctional catalysts (*N*-oxides-Ti(O$^i$Pr)$_4$ (2:1)) containing a Lewis acid and a Lewis base was developed and how the catalysts have been applied to the catalytic cyanosilylation of ketones. The cyanosilylation products were obtained in 42−97% yield.



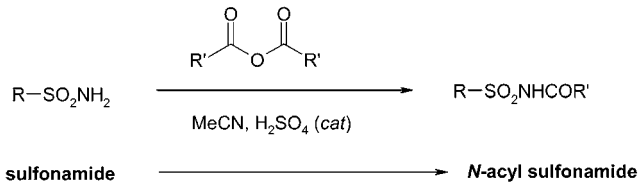
### Catalytic Reduction of Nitriles

Caddick and co-workers describe (*Tetrahedron* **2003**, *59*, 5417) a practical procedure for the conversion of nitriles to BOC amines. In their method, nickel boride reduction of nitriles has been demonstrated on a wide variety of substrates. It is noteworthy that the toxicity of this procedure is greatly reduced due to the *catalytic* nature of nickel(II) chloride used in combination with excess sodium borohydride. The protocol is marked by its resilience towards air and moisture.



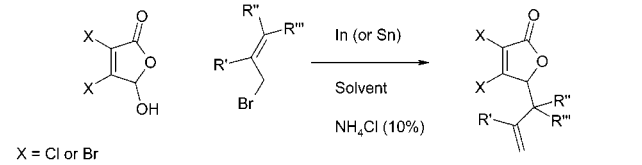

### Acid-Catalyzed Acylation of Sulfonamides

A highly efficient reaction between sterically and electronically diverse sulfonamides and carboxylic acid anhydrides to furnish monoacylated *N*-acylsulfonamides is described by Martin, Roschangar, and Eaddy at GSK (*Tetrahedron Lett*. **2003**, *44*, 5461). In their publication a typical procedure is described along with a number of examples.




### Metal-Mediated Allylation of Mucohalic Acids

Mucohalic acids have been used as aldehydes by Zhang and colleagues at Pfizer (*Tetrahedron Lett*. **2003**, *44*, 5579) in the indium- and tin-mediated Barbier-type allylation reaction to afford $\gamma$-allylic $\alpha$-$\beta$-unsaturated $\gamma$-butyrolactones in good to excellent yield. This structural motif is found in a variety of bioactive natural products.

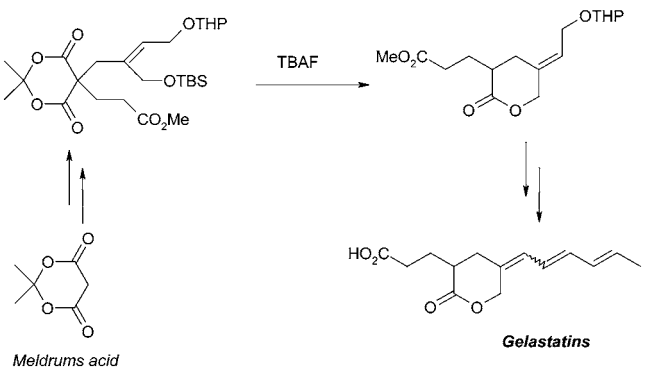


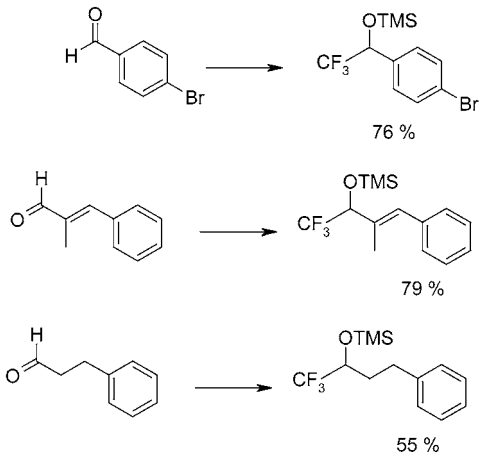

### Practical Total Synthesis of Gelastatins

The first and practical total synthesis of gelastatins (novel matrix metalloproteinase inhibitors possessing antitumor activity) was accomplished in nine steps starting from Meldrum's acid by Lee and co-workers (*Tetrahedron Lett*. **2003**, *44*, 5803). An interesting step in their synthesis is the TBAF-mediated deprotection, lactonisation, and decarboxylation (67% yield) shown in the scheme. This multistep reaction quickly constructs the necessary core for further synthetic manipulations and is an example where one reagent can be used to effect a sequence of steps in "one pot".

### TMS-Protected Trifluoromethyl Alcohols from $TMSCF_3$ and Aldehydes

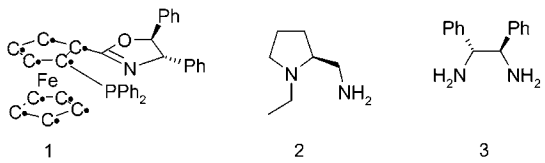
Surya Prakash, G. K. et al. (*J. Fluorine Chem*. **2003**, article in press) have described a new catalytic trifluoromethylation of aldehydes using trimethylamine *N*-oxide and trifluoromethyltrimethylsilane. Aromatic, aliphatic, and $\alpha$,$\beta$-unsaturated aldehydes provide good to excellent yields of the corresponding trifluoromethylated alcohols. The trimethylamine *N*-oxide is possible to recycle. The method is applicable to base-sensitive substrates.




### Potent New Heterogeneous Asymmetric Catalysts

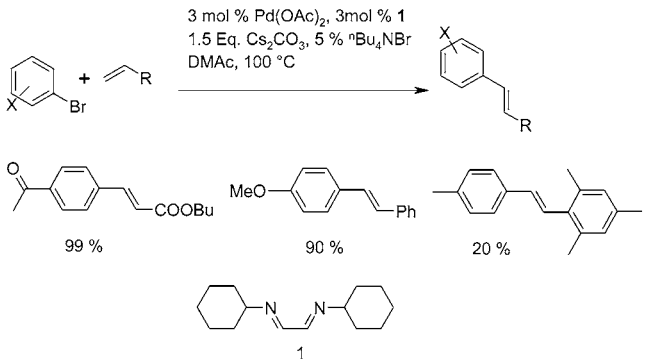
Rouzaud, J. et al. (*Helv. Chim. Acta*, **2003**, *86*, 1753) have developed a new set of air-stable $Rh^{I}$-based heterogeneous asymmetric hydrogenation catalysts. Individual members of this new family of catalysts all exhibit good enantioselectivities. The results show a marked increase in the enantiomeric excess once the catalyst is anchored onto the mesoporous silica using the triflate anion method. The best three ligands in the study giving the highest enantiomeric excess were **1**−**3**. It was found that prolonged storage of the heterogeneous catalyst under normal conditions did not alter the catalytic performance.




### Catalytic Activity of Pd(II) and Pd(II)/DAB-R Systems for the Heck Arylation of Olefins

Nolan, S. P. et al. (*J. Organomet. Chem*. **2003**, article in press) have studied the catalytic activity of Pd(II) and Pd(II)/DAB-R systems for the Heck arylation of olefins. The scope of the coupling process using Pd(II) sources and $\alpha$-diimine

as ligand in the presence of $Cs_2CO_3$ as base was tested using various substrates. The α-diimines represent a class of ligands of interest not only due to their σ-donating and low π-accepting abilities but also because they are easily synthesized by a one-step synthesis from the corresponding α-diketo compounds and various amines. Further ring-closure can afford various imidazolium salts, which are precursors of NHC ligands. The Pd(II) complexes are easily synthesized from $Pd(OAc)_2$ at room temperature. The $Pd(OAc)_2$/1,4-dicyclohexyldiazabutadiene (DAB-Cy, **1**) represent the highest activity with electron-neutral and electron-deficient aryl bromides in the coupling with electron-rich olefins. $Pd(acac)_2$ proved also to activate aryl bromides at higher temperature, with low catalyst loadings when the appropriate amount of $^nBu_4NBr$ was employed.

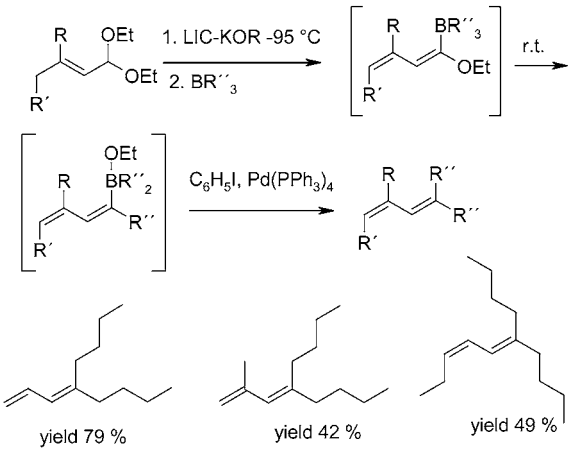



### Ionic Liquids as Media for Nucleophilic Fluorination

Murray, C. B. et al. (*J. Fluorine Chem.* **2003**, article in press) have published a first study on the use of ionic liquids as media for nucleophilic fluorinations of alkyl and alkoyl bromides and chlorides using alkali metal fluorides. The potential for using ionic liquids as butylmethylimidazolium hexafluorophosphate (BMIM)($PF_6$) as a recyclable solvent for nucleophilic fluorinations may be advantageous in comparison to polar aprotic solvents where the fluorination has to be performed at elevated temperatures, which limits the substrates to thermally stable ones. The authors found that the fluorination of benzyl and primary alkyl bromides can be performed with CsF at room temperature in medium to good yields. Potassium or calcium fluorides did not react. Although the reaction with CsF looks promising, the drawback with the chosen ionic liquid is the stability against the highly nucleophilic fluoride ion, which destroys the ionic liquid. Recycling of the solvent is limited to some extent. This could perhaps be overcome if another more stable ionic liquid not based on imidazolium salt were to be used.

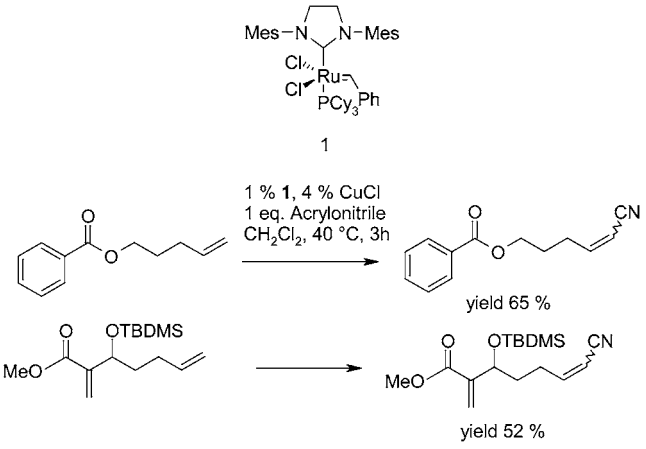
### Palladium-Catalyzed C−C Bond Formation with α,β-Unsaturated and α-Phenyl Acetals as Substrates in the Suzuki−Miyaura Reaction

Deagostino, A. et al. (*Eur. J. Org. Chem.* **2003**, 2612) have developed a one-pot procedure that, starting from α,β-unsaturated and α-phenyl acetals, gives 1,1-dialkylbuta-1,3-dienes and 1-methoxy-2-phenyl styrenes, respectively, when treated with LIC-KOR superbase and trialkylboranes in the presence of $PdL_4$−ArX. A cascade of quaternization reactions and 1,2-anionotropic rearrangements in the presence of an activated Pd π-complex may account for the formation of the 1,1-dialkyl-butadienes; in the absence of the conjugated system a standard Suzuki coupling takes place. 1,1-Dialkylbuta-1,3-dienes are not easily accessible with other methods. The yields reported are in the range 40−86%, depending on the structure of the alkyl chains in the trialkyl borane.




### Effective and Inexpensive Acrylonitrile Cross-Metathesis: The Utilization of Grubbs II Precatalyst in the Presence of Copper(I) Chloride

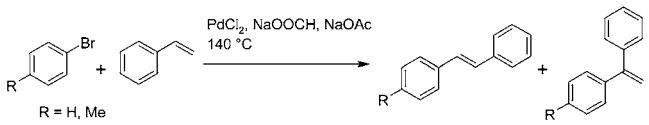
Rivard, M. and Blechert, S. (*Eur. J. Org. Chem.* **2003**, 2225) have found that the addition of Cu(I) chloride to the selective cross-metathesis reaction of acrylonitrile using Grubbs unmodified precatalyst **1** gives a significant increase in turnover of the catalyst. The added salt functions as a phosphane scavanger. It has been found that free phosphane has an inhibiting effect on the cross-metathesis reaction. The TON with 10% CuCl was 10-fold with 1 mol % of catalyst in comparison to the TON without CuCl. This protocol appears to be an attractive alternative to the other methods requiring modified precatalysts such as the molybdenum-based Schrock precatalysts, which exhibit a higher sensitivity to oxygen.




### Simple Method for Enhancement of the Ligand-Free Palladium Catalyst Activity in the Heck Reaction

Schmidt, A. F., and Smirnov, V. V. (*J. Mol. Catal. A: Chem.* **2003**, *203*, 75) have reported a simple catalytic

system, which is capable of catalyzing effectively the reaction of bromoarenes with styrene in air in the absence of any ligands. Quantitative yield of different products was achieved by using 0.04−1.6 mol % $PdCl_2$, 18% HCOONa, and a small excess of sodium acetate and a 6-fold excess of bromoarene. It was found that, during the reaction, formed colloidal palladium is the main reservoir of catalytically active homogeneous Pd(0) complexes.

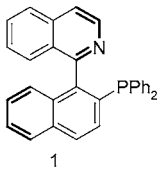



### The Use of Imidazolium Ionic Liquids for the Formation and Stabilization of $Ir^0$ and $Rh^0$ Nanoparticles: Efficient Catalysts for Hydrogenation of Arenes

Dupont, J. et al. (*Chem. Eur. J.* **2003**, *9*, 3263) have found that stable transition-metal nanoparticles are easily accessible through the reduction of $Ir^I$ or $Rh^{III}$ compounds dissolved in "dry" 1-*n*-butyl-3-methylimidazolium hexafluorophosphate ionic liquid by molecular hydrogen. The formation of the nanoparticles is straightforward. The isolated nanoparticles were found to be in the range of 2.0−2.5 nm in diameter according to TEM and XRD analysis. The isolated nanoparticles can be redispersed in the ionic liquid or in acetone or used in solventless conditions for liquid−liquid biphasic, homogeneous, or heterogeneous hydrogenation of arenes under mild reaction conditions (75 °C and 4 atm). The hydrogenation of arenes with functional groups, such as anisole, effect a concomitant hydrogenolysis of the C−O bond when the iridium nanoparticles are used under solventless conditions. Interestingly, in the reactions catalyzed by rhodium nanoparticles no hydrogenolysis products were observed in the hydrogenation of anisole. The recovered iridium nanoparticles can be reused several times without any significant loss in catalytic activity. Contrarily, the recovered rhodium nanoparticles show significant agglomeration into large particles with loss of catalytic activity.

### Synthesis of Enantiomerically Enriched Propargylamines by Copper-Catalyzed Addition of Alkynes to Enamines

The group of Knochel, P. (*Chem. Eur. J.* **2003**, *9*, 2797) has developed a new (*R*)-Quinap (**1**)/CuBr-catalyzed synthesis of enantiomerically enriched propargylamines by addition of alkynes to enamines. Various functionalized terminal alkynes add smoothly to N-protected enamines to afford the corresponding amines in good to high yields (66−99%). The best salt was CuBr giving the highest reaction rate, complete conversion, and the highest enantiomeric excess. The reaction is performed at room temperature, and the reaction times of 3−67 h were found, depending on substitution muster. For the enantioselectivity the best ligand was (*R*)-Quinap with an enantiomeric excess as high as 85%. Other ligands such as (*R*)-Binap or (*R*)-Pybox gave either no conversion or a low conversion with a low ee. The mild reaction conditions, the broad scope of the reaction, and the selective deprotection of the propargylamine products make this into a reaction of general interest.

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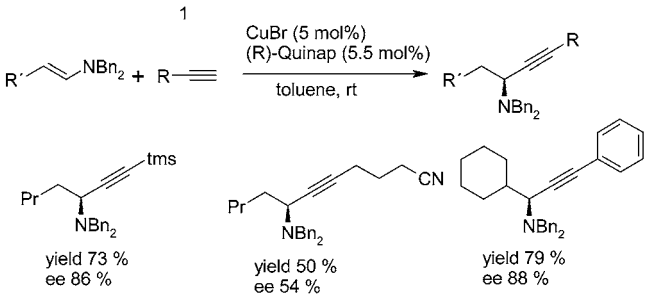
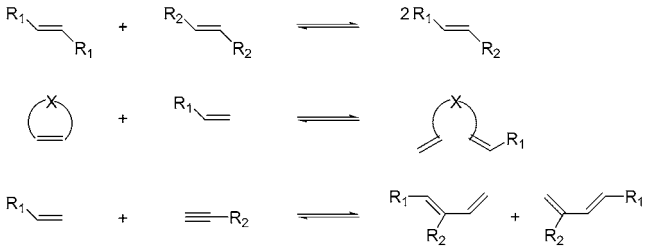


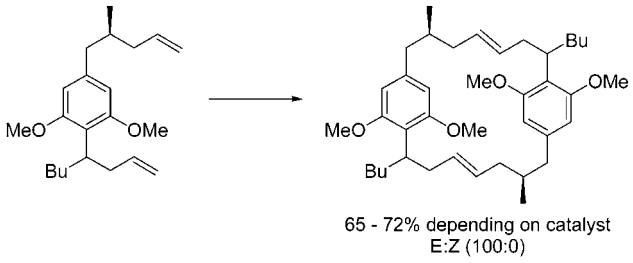

### Olefin Cross-Metathesis Review

A review of this important C−C bond-forming reaction has appeared from the group of Blechert in Berlin (Connon, S. J., et al. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900). The three types of reactions are shown below.



The process is catalytic, requiring 1−5 mol % of a metal carbene catalyst, and generally is high yielding under mild conditions with short reaction times. Gaseous ethylene is usually the only byproduct. It is no wonder that industrial chemists are interested in this area, which has already found application in bulk chemicals manufacture (Shell High Olefins process; Phillips Triolefin Process). With the availability of more active and robust second-generation catalysts based on ruthenium, which have a wide functional group tolerance, these reactions have wide synthetic potential, although E/Z selectivity can sometimes be an issue. Thus, complex materials such as sugars and nucleosides can be reacted.

The reversibility of the reaction is important, since it ensures the preferential formation of the most stable product, i.e., internal olefins at the expense of terminal olefins. This can be exploited in the synthesis of macrocycles.



### Large-Scale Manufacture of Peptides

I (T.L.) am always grateful when readers send me articles which are suitable for highlighting, particularly when they are in journals I do not regularly scan. For the next two papers I am indebted to Hilmar Weinmann of Schering, who is on the editorial advisory board of the journal.

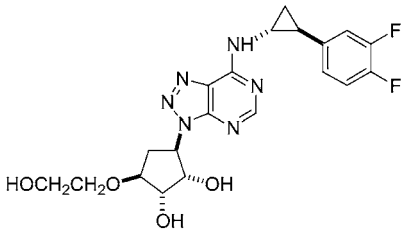
The first paper he mentions is on large-scale manufacture of peptides by chemical synthesis by Brian Bray of Trimeris (*Nature Rev., Drug Discovery* **2003**, *2*, July, 587). The 106-step synthesis of enfurvirtide is broken down into three smaller linear fragments which "converge" towards the final drug substance. Purification and validation issues are discussed as well as synthesis. FDA approved the drug to treat HIV infection in March 2003.

Several tonnes a year can be made by the process, which initially uses a solid-phase approach. There are only seven isolations in the whole 106-step process, which has an overall yield of ~30%.

### Facing Chirality in the 21st Century

The second paper is by Hans-Jürgen Federsel of AstraZeneca (*Chirality* **2003**, *15*, S128) on "Facing Chirality in the 21st Century" and is an overview of several projects at AZ. Included in the article is detail on the development of a synthesis of the molecule below in 29 steps on the pilot plant.

This is another example of how the structure of drug substances appears to be getting more complex, providing increased challenge for the chemists and engineers involved in process R&D and production, as well as increased business for the outsource providers who make the increasingly complex building blocks.

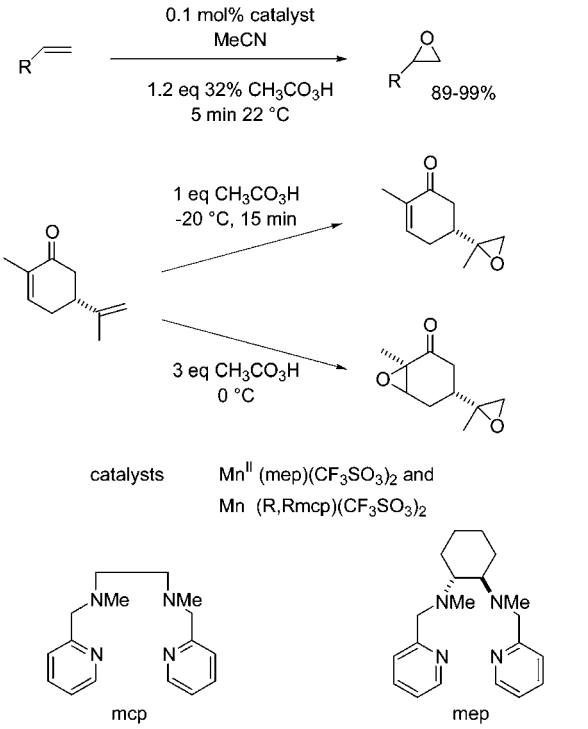



### Efficient Epoxidation of Electron-Deficient Olefins

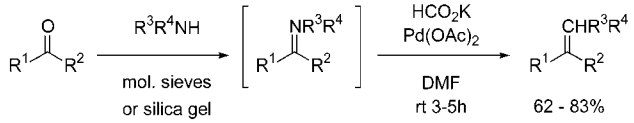
Catalytic epoxidation of terminal and electron-deficient olefins is still a challenging task, despite the development of new methods. Many of the latter are inefficient and difficult to scale or use expensive reagents or high catalyst loadings. It has now been found (Murphy, A. et al. *J. Am. Chem. Soc.* **2003**, *125*, 5250) that the manganese complexes of the simple amines below catalyse the epoxidation using peracetic acid. Hydrogen peroxide cannot be used because the catalyst system causes disproportionation of the reagent. For polyfunctional olefins, selectivity can be achieved by choice of temperature and stoichiometry.

### Reductive Amination

Reductive amination of carbonyl compounds is normally carried out with hydrogen or with hydride reagents. An alternative is to use potassium formate, which is soluble in

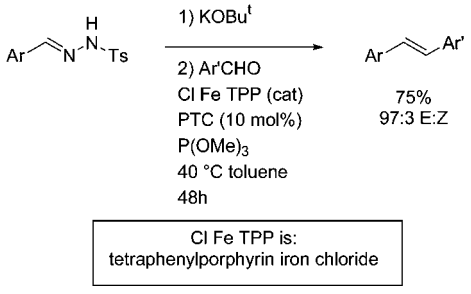



polar organic solvents and water, in the presence of palladium acetate catalyst (Basu, B. et al. *SynLett* **2003**, 555) Carbon−carbon double bonds may, however, also be reduced.




### A New Class of Wittig Reagents with E Selectivity

Phosphorus ylides bearing oxygen substituents have never been used in the Wittig reaction, presumably because they are difficult to prepare by phosphite alkylation, which gives the Arbuzov reaction. The group of Aggarwal at Bristol UK has now found that these ylides can be generated using diazoalkanes, and they react with aldehydes to give Wittig products. (Aggarwal, V. K. et al. *J. Am. Chem. Soc.* **2003**, *125*, 6034). A better protocol involves generating the diazo compound in situ, and reaction with the phosphite and Wittig olefination occur sequentially.




### Aqueous Organometallic Catalysis

Readers are no doubt well aware of the definitive work in the area of "Aqueous-Phase Organometallic Catalysis", edited by Cornils and Herrmann (Wiley VCH, 1998), which was reviewed in this journal. Cornils and Herrmann have

been involved in the large-scale applications of aqueous organometallic processes for bulk and fine chemical manufacture. Readers may not be aware of a second book on the subject by Ferenc Joó of the University of Debrecen, Hungary (Kluwer, Dordrecht, 2001, ISBN 1-4020-0195-9). Joó was involved in much of the early work in this fascinating area, and in contrast to the multiauthor-Cornils and Herrmann work, Joó has written the 300 pages himself. Of course, much of the focus is on hydrogenation and hydroformylation, but later chapters concentrate on C−C bond formation and oxidation processes.

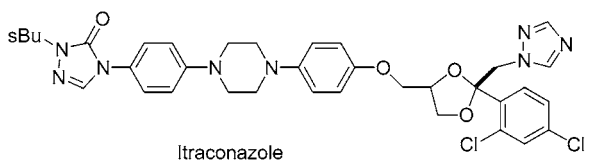
### High-Throughput pH Screening for Salts

Itraconazole is an example of an extremely water-insoluble drug that is marketed in an amorphous form (sporanex capsule) to achieve the desired oral bioavailability. The logical strategy to improve the absorption properties would be to prepare a salt form, but none have been patented, presumably because no crystalline or solid salts were obtained.

Given the p$K_a$ value of 3.7 for the piperazine unit of itraconazole, conventional wisdom would limit a salt screen to those strong acids having dissociation constants 2 units lower, i.e., 1.7 (Serajuddin, A. T. M. et al. In *Handbook of Pharmaceutical Salts*; Stahl, P.H., Wermuth, C.G., Eds.; Verlag: Zurich and Wiley VCH: Weinheim, 2002). Crystalline phases can, however, sometimes be "engineered" by selecting acid molecules on the basis of their structural complementarity, even though the p$K_a$ differences are inconsistent with salt formation in water. On this basis, a high-throughput screen was conducted to search for salts and for cocrystals of itraconazole with pharmaceutically acceptable salts. (Remenar, J. F., et al. *J. Am. Chem. Soc*. **2003**, *125*, 8456). Stable cocrystals, consisting of hydrogen-bonded trimers of two molecules of itraconazole with one molecule of a dicarboxylic acid such as fumaric acid, succinic acid, L-malic acid, or tartaric acid(s) were found. The crystal structure reveals a specific interaction between the dicarboxylic acid and the triazole group of itraconazole in the solid state. Cocrystals could not be made with maleic, malonic, glutaric, or adipic acids nor with monocarboxylic acids. The results suggest that geometry is more important than acid−base chemistry in directing crystallisation of certain drug molecules.

The salts achieve and sustain 4−20-fold higher concentrations compared to that achieved for crystalline itraconazole, and the malic acid salt rivals the commercial product containing amorphous drug substance.

Thus, studies limited to systems that follow the generally accepted rule of matching p$K_a$ values to ensure a strong salt pair in water may overlook opportunities for producing salt forms, which may be the preferred choice for formulation.



Itraconazole

### Nucleation of One Polymorph by Another

Lian Yu from Lilly has published a paper (Yu, L. *J. Am. Chem. Soc*. **2003**, *125*, 6380) in which he has shown that seeds of one polymorph can nucleate another polymorph of higher or lower thermodynamic stability without polymorph conversion, i.e. the nucleating polymorph remains. In the cases examined by melt crystallisation (D-mannitol and D-sorbitol) the late nucleating polymorph dominated the end product. This effect arises from heterogeneous nucleation between polymorphs and faster growth rate of the new polymorph and gives an alternative explanation for concomitant polymorphs (for a review, see Bernstein, J. et al. *Angew. Chem., Int. Ed.* **1999**, *38*, 3441).

### Disappearing Polymorphs

One of the best documented examples of disappearing polymorphism is that of 1,2,3,5 tetra-*O*-acetyl $\beta$-D-ribofuranose which, following its first preparation in 1947 (polymorph A mp 58 °C) subsequently disappeared, having been "replaced" by the more stable polymorph B (mp 82 °C). In the 1950s, attempts to obtain polymorph A in Europe, Australia, and the United States were all unsuccessful.

In 1981 polymorph A "reappeared" in Budapest, and strict precautions to preserve the polymorph were taken. The X-ray crystal structure of polymorph A has been determined at low temperature by a group from the Hungarian Academy of Sciences in Budapest (Bombicz, P., et al. *Angew. Chem., Int. Ed.* **2003**, *42*, 1957), and this shows the shortest intermolecular H−H distance (1.949 Å) ever observed in an organic crystal.

The crystals of polymorph A were obtained by careful recrystallisation from ethanol. To prevent any contamination by form B, the lab was repainted, and all furniture and equipment rigorously cleaned. All lab coats and clothing were washed after working with form B, and new glassware was always used when working with form A. Only when such strict precautions were taken, could form A be produced and studied. Crystals of A once produced were stored in sealed ampules.

Interestingly, the change from form A to form B could not be initiated by grinding or by heating. The phase change only occurs after seeding with minute amounts of form B. Thus, the system appears to be monotropic.

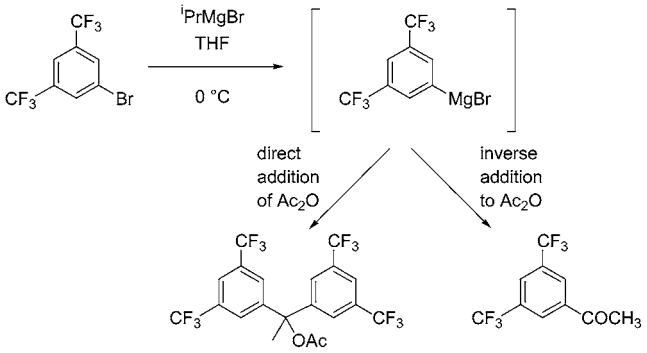
Unusually, the unit cell volume for the less stable form A is *lower* than that for stable form B at the same temperature. Usually it is the other way around, i.e. the more tightly packed polymorph has the lower free energy.

### Hazards of Trifluoromethyl Grignard Reagents and Related Compounds

The hazards of preparing and reacting aromatic Grignard reagents when perfluoroalkyl groups are present is well-known—the same applies to the corresponding lithium derivatives. For example 4-trifluoromethylphenylmagnesium bromide detonated, resulting in the destruction of a factory and loss of life.

A safe procedure for generating these Grignards is to use Knochel's halogen−magnesium exchange (THF, 0 °C, 1.1

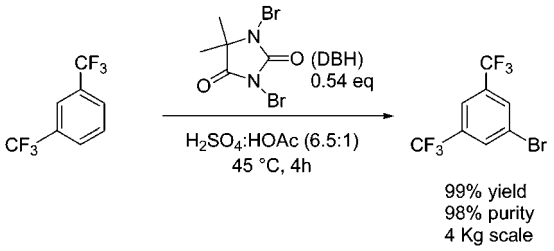
equiv of $^{i}$PrMgBr, 30 min) rather than direct reaction with magnesium, which can be slow and unpredictable (Abarbri, M. et al. *Tetrahedron Lett*. **1999**, *40*, 7449). A recent paper from the Merck Process R & D group (Leazer, J. L. et al. *J. Org. Chem*. **2003**, *68*, 3695), used this method to prepare the Grignard and react it with an excess of acetic anhydride to give the corresponding acetophenone.




The reason for the difference in safety, depending on whether the Grignard was prepared from Mg metal or by exchange, was evaluated by calorimetric methods. It was established that exothermic activity in the resultant Grignard only occurs when excess magnesium is present. These Grignards are considerably more stable in THF than in ether, but when loss of contact with solvent occurs, detonation will occur.

By carefully controlling these factors, scale-up of trifluoromethylphenyl Grignards can be achieved safely. An earlier report (Ashby, E. C. et al. *J. Org. Chem*. **1990**, *390*, 275) had indicated that other trihalomethylbenzenes are unstable in the presence of magnesium above −40 °C.

For the preparation of the starting bromo compound, the literature methods using NBS and DBH in concentrated sulphuric acid or TFA were found to be irreproducible, owing to inadequate mixing of the biphasic reaction mixture. To circumvent this, a cosolvent such as acetic acid was used.




## Green Solvents for Catalysis

Issue 2 of *Green Chemistry* (**2003**) volume 5 contains a number of interesting articles on the subject of new solvents. For example "Catalysis for Fine Chemicals: Who Nneeds (Will Use) New Solvents" by H.-U. Blaser and M. Studer of Solvias (*Green Chem*. **2003**, *5*, 112) analyzes, using case studies, the need for new solvents and concludes that supercritical $CO_2$, ionic liquids, fluorous media, or even water will be used ONLY under special circumstances and that much more information on scope and limitations is required (e.g., ecological, economical, as well as chemical).

In the same journal there is also a review article entitled "Green Chemistry Synthesis in Microreactors" from the excellent group at University of Hull, (Haswell, S. et al. *Green Chem*. **2003**, *5*, 240).

## BASF's Smart Ionic Liquid

BASF uses an ionic liquid in the manufacture of alkoxyphenyl phosphines, but not as a solvent. The acid scavenger *N*-methylimidazole forms a hydrochloride which has a melting point of only 75 °C and remains liquid in the process. It separates out as a liquid phase, making it easy to remove and recycle (*Chem. Eng. News* **2003**, Mar 31, 9).

## Recent Trends and Problems in Green Chemistry

One of the pioneers in green chemistry education, Albert Matlack (author of the book *Introduction to Green Chemistry*; Marcel Dekker, 2001), has written a concise summary of recent developments in the area (Matlack, A. *Green Chem.* **2003**, *5*, G7). He comments, however, that not all syntheses are as green as authors say they are—for example, a caprolactam synthesis from the silylenol ether of cyclohexanone is claimed to be environmentally benign, even though it uses TMS azide in methylene chloride!

## Pfizer Wins 2003 UK Process Award for Green Chemical Technology

The award was for the process for the production of the active ingredient in Viagra, sildenafil citrate, at several sites including Sandwich (UK) and Ringaskiddy (Ireland). The process produces a mere 9 kg of organic waste per kg of drug substance compared to the industry norm of 25−100 kg. This was achieved by designing a convergent, rather than linear, synthesis and minimising the number of extractions in the process. For details of the process see Dunn, P. et al. *Org. Process Res. Dev.* **2000**, *4*, 17). The awards, from the Crystal Faraday Partnership (www.crystalfaraday.org), were presented at the Institute of Chemical Engineers' Annual dinner. The award for a SME went to Thomas Swan and Co. for the world's first multireaction supercritical flow reactor.

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