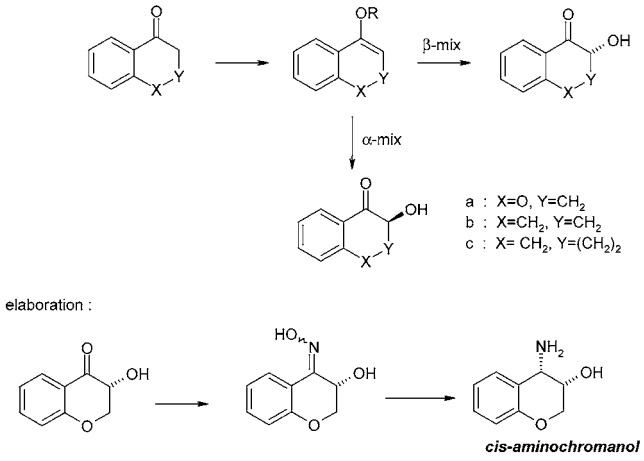
Organic Process Research & Development **2004**, *8*, 2–9

Highlights from the Literature

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

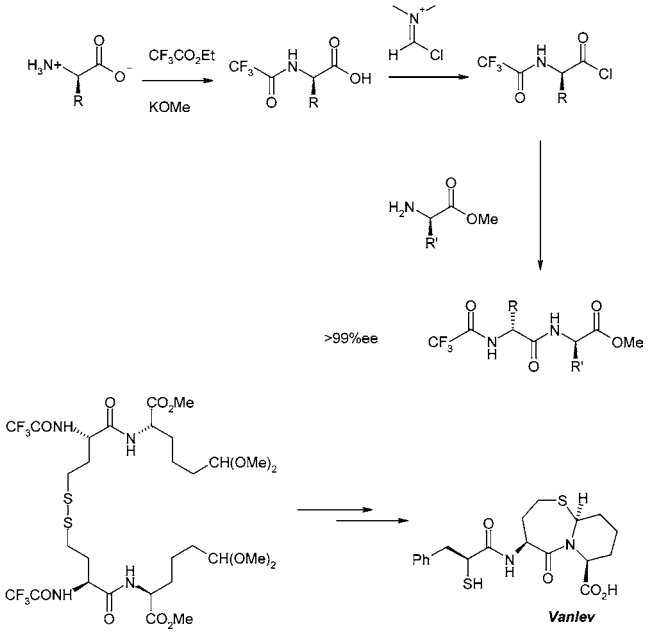
Sharpless Asymmetric Dihydroxylation for the Synthesis of α-Hydroxychromanone

The Sharpless asymmetric dihydroxylation reaction of enol ethers derived from their corresponding cyclic ketones has been used by Marcune and co-workers at Merck to give α-hydroxyketones with high enantioselectivity (*J. Org. Chem*. **2003**, *68*, 8088). The enantiomeric excess was found to be proportional to the length of the unbranched enol ether chain with a maximum ee for the pentyl enol ether. Branching of the enol ether chain (especially at the C-1 carbon) resulted in decreased selectivity. An efficient, scalable synthesis of α-hydroxychromanone in >90% ee was demonstrated using this method and provided the group with a chiral precursor to *cis*-aminochromanol.

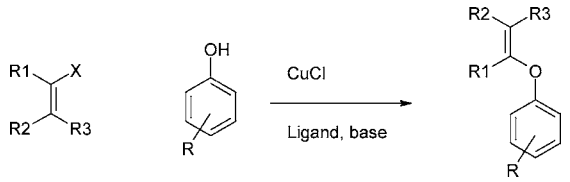


Use of *N*-Trifluoroacetyl Protecting Groups

The use of protected amino acid chlorides for peptide coupling reactions has long been avoided due to the extensive racemization that commonly occurs during either the acid chloride formation or the coupling reaction itself. Delaney and colleagues from Bristol-Myers Squibb (Tetrahedron 2003, 9019) describe a method which allows *N*-trifluoroacetyl-protected amino acid chlorides to be generated in high purity and with high retention of stereochemical integrity. Control of temperature is the predominant factor in controlling racemization, and rapid formation of acid chlorides under low temperature (−10 °C) can be conveniently achieved using a Vilsmeier reagent. Stereochemical integrity is further maintained when coupling of *N*-trifluoroacetyl acid chlorides is carried out with amino acid esters under Schotten−Baumann conditions using specific controls on pH, temperature, and agitation. In particular the group have used the basis of this methodology to prepare the late-stage intermediate en route to Vanlev (>100 kg input scale).

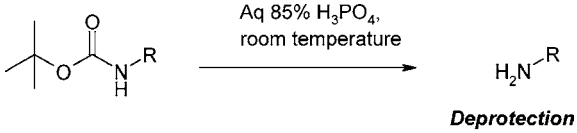


Vinyl Aryl Ethers



A general procedure for vinyl aryl ether bond formation by direct coupling of vinyl halides and phenols under mild Ullmann-type reaction conditions has been developed by Wan and co-workers at Eli Lilly (*Tetrahedron Lett.* **2003**, 8257). Using copper chloride as the catalyst and cesium carbonate as the base, vinyl bromides or iodides were reacted with phenols in refluxing toluene to produce vinyl aryl ethers in good to excellent yields.

Deprotection of *N*-BOC Groups



Aqueous phosphoric acid (85 wt %) has been found to be an efficient and mild reagent for the deprotection of *N*-BOC groups by Li and colleagues at Pfizer (*Tetrahedron Lett.* **2003**, 8113). Acid sensitive functionalities including benzyl and methyl esters, TBDMS ether, CBZ, and isopropylidene groups were found to be compatible with the

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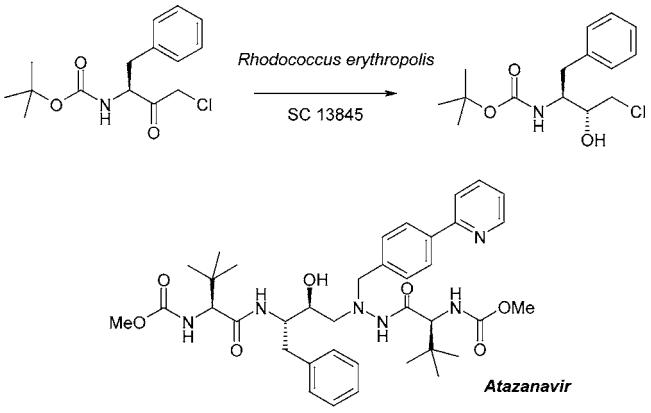
reaction conditions. The reactions are high yielding, and the workup is simple.

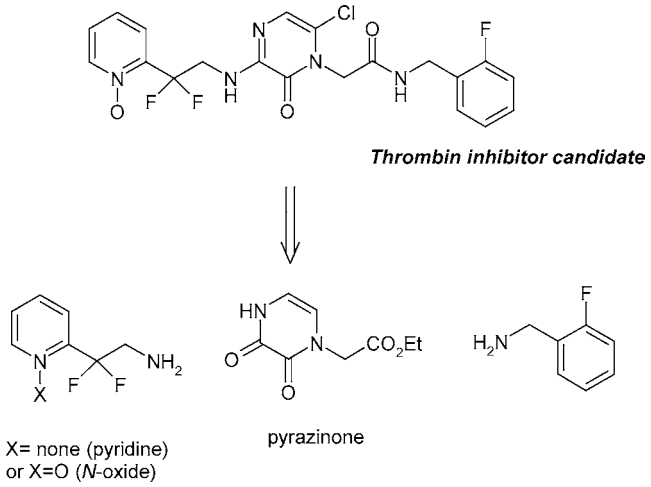
Microbial Reduction

The chiral intermediate (1*S*,2*R*)-[3-chloro-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid-1,1-dimethylethyl ester (see scheme below) has been prepared as part of the total synthesis of the HIV protease inhibitor Atazanavir by workers at Bristol-Myers Squibb (*Tetrahedron Asymmetry* **2003**, 3105). The diastereoselective reduction of (1*S*)-[3-chloro-2-oxo-1-(phenylmethyl)propyl] carbamic acid-1,1-dimethyl-ethyl ester was carried out using microbial cultures among which *Rhodococcus*, *Brevibacterium*, and *Hansenula* strains reduced the ketone to secondary alcohol. Three strains of *Rhodococcus* gave >90% yield. A diastereomeric purity of >98% and enantiomeric excess of >99% were obtained for the alcohol.

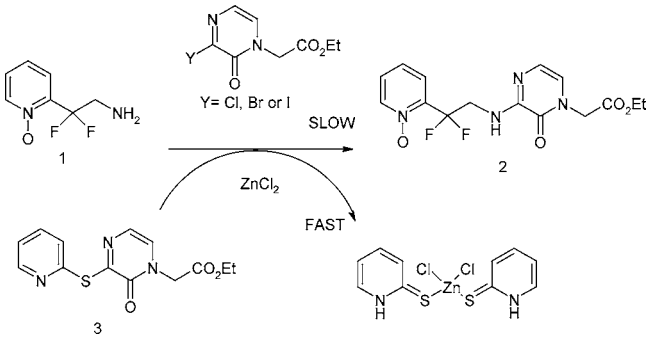


Synthesis

A six-step preparation of a thrombin inhibitor drug candidate from pyrazinone in 47% overall yield is described by Chung, Cvetovich, and co-workers (*J. Org. Chem*. **2003**, *68*, 8838).

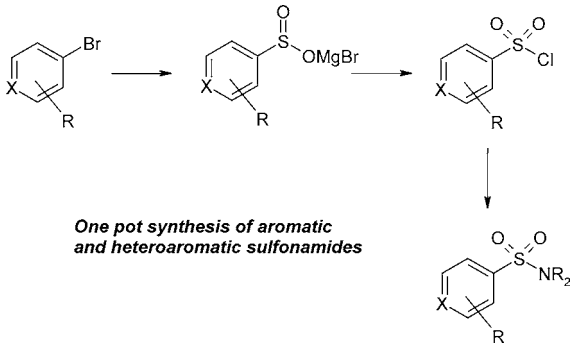


The problem of low reactivity between weak amine nucleophile **1** and poor electrophile 3-bromopyrazinone was overcome with the use of pyridinylthioimidate **3** in the presence of $ZnCl_2$ to afford adduct **2** in high yield. Several zinc complexes were characterized by solution- and solid-state NMR and X-ray crystallographic analyses and provided insight into the reaction mechanism. Preparation of pyridine *N*-oxide amine **1** was accomplished via a selective oxidation of the corresponding pyridinylamine. This chromatography-free synthesis was used successfully to prepare multikilogram quantities of the drug with reproducibility and high purity.



Preparation of Aromatic and Heteroaromatic Sulfonamides

A series of arene and heteroarene sulfonamides have been synthesized (*J. Org. Chem.* **2003**, *68*, 8274) by Barrett and co-workers in one vessel from aryl and heteroaryl bromides via conversion into the corresponding Grignard reagents using either magnesium or isopropylmagnesium chloride and subsequent reaction with sulfur dioxide, sulfuryl chloride, and an amine. This provides a useful method into this important class of medicinally important motifs without recourse to potent electrophiles.

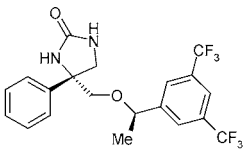


Practical Synthesis of Potent NK1 Antagonists

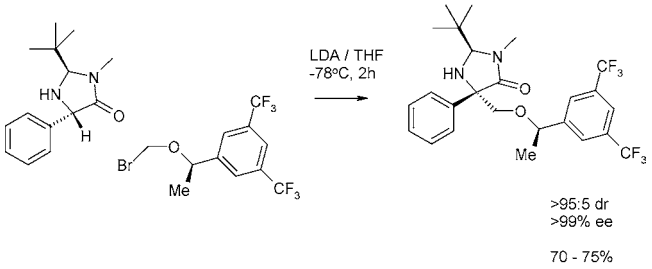
A highly efficient and practical synthesis of 4,4-disubstituted-2-imidazolidinones utilizing a "self-reproduction of the center of chirality" strategy is described by Shih and co-workers at Schering-Plough (*Org. Lett.* **2003**, 4249). This chemistry represents an elegant approach for the preparation of a quaternary chiral centre (see scheme on the following page) and has been utilized in the synthesis of the potent NK1 antagonist Sch425078.

Hydrogenation versus Transfer Hydrogenation of Ketones: Two Established Ruthenium Systems Catalyze Both

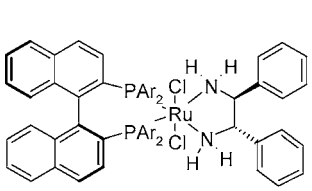
The groups of Rautenstrauch, V. at Firmenich SA and Morris, R. H. at the University of Toronto (*Chem. Eur. J.* **2003**, *9*, 4954) have jointly studied two different ruthenium-based catalytic systems, which were actually found to catalyze both enantioselective hydrogenation and enantioselective transfer hydrogenation of ketones. The first precatalyst



Sch 425078

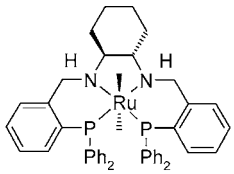


is the standard ketone hydrogenation catalyst [$Ru(Cl)_2$((*S*)-tolbinap){(*S*,*S*)-dpen}] (**1**), the other is the ketone transfer hydrogenation catalyst [$Ru(Cl)_2$((*S*,*S*)-$cyP_2(NH)_2$)] (**2**). The authors report that each of the catalysts was better in one of the methods than in the other and that the catalysts were complementary. The hydrogenation precatalyst **1** was as previously reported an excellent catalyst in the enantioselective hydrogenation of acetophenone after activation with *i*-PrOK in 2-propanol under standard conditions. The catalyst works at a loading of up to s:c 10^6 giving an ee of 78−83% of the product. The amount of *i*-PrOK is not critical for the enantiomeric excess. Under transfer hydrogenation conditions with activation with *i*-PrOK the amount of activator is crucial for the enantiomeric excess of the product (4−62%). The speed of reaction is, however, also dependent on the amount of *i*-PrOK. The reaction is fastest at high levels of activator, but this lowers the enantiomeric excess. The amount of catalyst for the transfer hydrogenation is also much higher s:c $<10^4$. With the second precatalyst **2** the authors found that only under transfer hydrogenation conditions was a high ee obtained (up to 98%). The hydrogenation gave only 20−25% ee. *i*-PrOK is again needed for the activation, and the optimum amount for the transfer hydrogenation is 0.5−1.0 equiv. The ee is again about constant with different amounts of activator in the hydrogenation. This interesting new experience that catalysts for hydrogenation or transfer hydrogenation are actually useful in both methods clearly shows that checking other catalyst systems in cross-tests will be worthwhile, even with those catalysts that previously gave unsatisfactory enantioselectivities.



Ar= 4-methyl phenyl

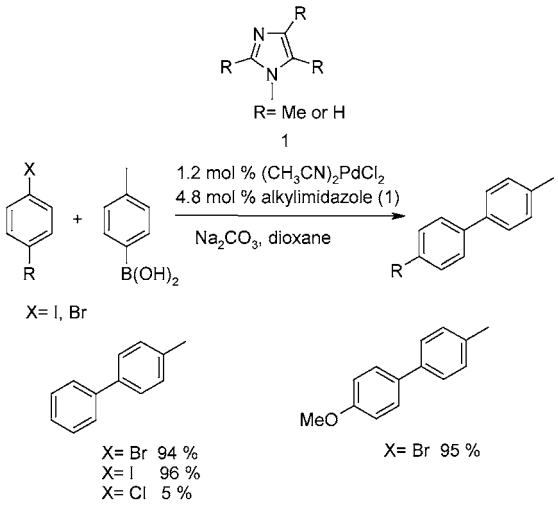
1



2

Novel Palladium Imidazole Catalysts for Suzuki Cross-Coupling Reactions

Mathews, C. J. et al. (*J. Mol. Cat. A: Chem.* **2003**, *206*, 77) have studied novel palladium imidazole catalytic systems for the Suzuki cross-coupling reaction. The commercially available and inexpensive imidazoles (**1**) were found to form with $PdCl_2$ or $(CH_3CN)_2PdCl_2$ an efficient catalytic system with high activity for bromo- or iodoarenes in dioxane, toluene, or water as solvent for the cross-coupling with aryl boronic acids. In all cases studied the yield was good to excellent. Different functionalities were well tolerated under the reaction conditions. For chlorobenzene no product was obtained although a good yield was obtained with activated 4-chloroacetophenone. Extensive catalyst decomposition was, however, observed in all catalytic systems, which is shown in the relatively low TON h^{-1} obtained. The highest number obtained was 239 in dioxane. A significant advantage of these catalytic systems is the complete lack of *homo*-coupling, which can be significant with other Pd(II) catalytic systems.



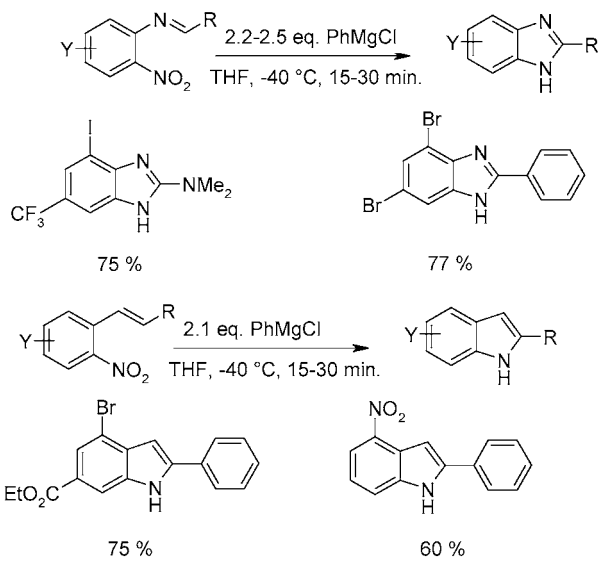
Mild Synthesis of Benzimidazoles and Indoles by the Reduction of Functionalized Nitroarenes with Phenylmagnesium Chloride

The group of Knochel, P. (*Chem. Eur. J.* **2003**, *9*, 5323) has found that treatment of phenylmagnesium chloride with various 2-amino-1-nitroaromatics or 2-nitrostilbenes under mild conditions affords polyfunctional benzimidazoles or indoles in satisfactory to good yields. The reaction is very rapid under mild conditions (THF, − 40 °C, 15−30 min) and is best explained by the involvement of functionalized nitrenes as intermediates. The method has a very broad functional group tolerence(CN, CO_2Et, CF_3, Br, Cl, OMe) in the synthesis of both benzimidazoles as well as indoles (see scheme on the following page).

A Mild and Versatile Pd-Catalyzed Cross-Coupling of Aryl Halides in Aqueous Surfactants

Various aqueous surfactants were found to be excellent media for the palladium-catalyzed Suzuki−Miyaura cross-coupling reaction under mild conditions (Arcadi, A. et al. *Eur. J. Org. Chem.* **2003**, 4080). Smooth cross-coupling of iodoanisole and different bromoarenes, including electron-rich derivatives, with arylboronic acids occurred at room temperature in high yields with either Pd/C or $Pd(PPh_3)_4$ as palladium source.

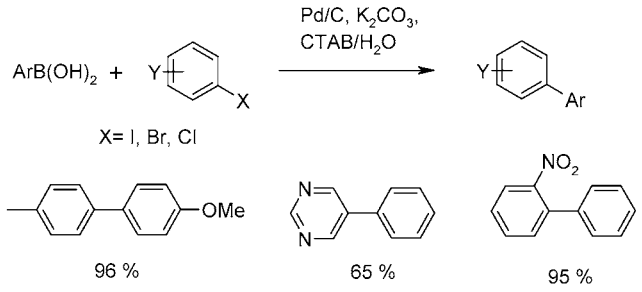
The authors found that the best surfactant for the reaction is cetyltrimethylammonium bromide (CTAB). The concen-



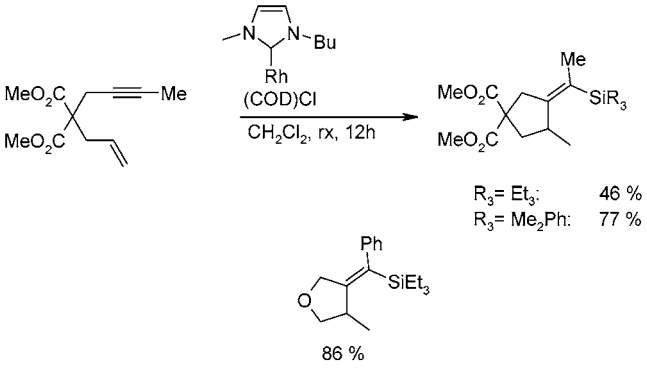
tration of the surfactant in water plays a pivotal role for the reaction outcome. The dehalogenation reaction, which is usually a drawback when the cross-coupling is done in water, was not observed in this case.

The aqueous surfactant/ Pd/C system was found to combine high activity under ambient conditions (air), easy separation, and recyclability.

For the less reactive aryl chlorides palladium acetate was found to be the best palladium source in the cross-coupling at 100 °C.



Use of Rhodium N-Heterocyclic Carbene Complexes in Catalytic Cyclization and Hydrosilylation of 1,6-Enynes

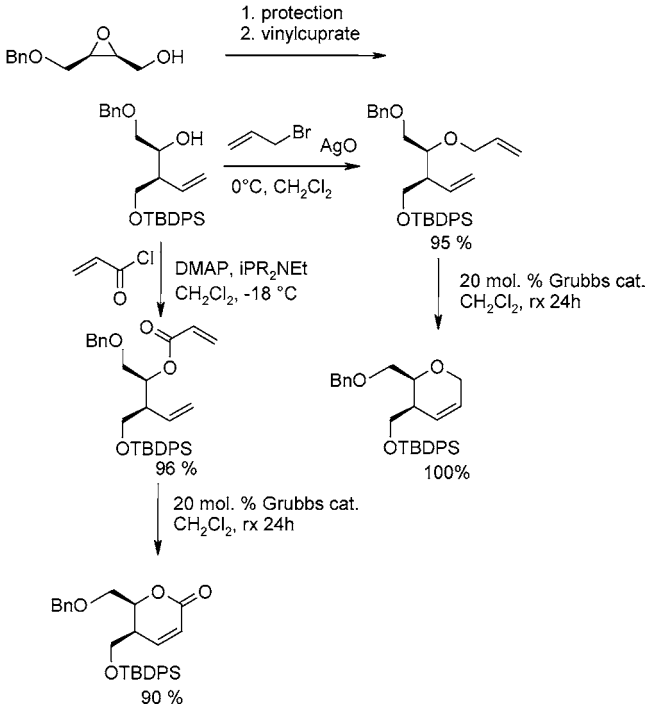


Chun, Y. K. et al. (*Eur. J. Org. Chem*. **2003**, 4341) have found that neutral rhodium complexes [RhCl(NHC)(cod)] (NHC = N-heterocyclic carbene) catalyse the hydrosilylation/ cyclization of 1,6-enynes and $HSiR_3$ to form 2-methyl-1-silylmethylidene-2-cyclopentanes in satisfactory yields. The best catalytic system was found to be **1**, and the best silane, HMe_2SiPh, giving yields as high as 89%. The catalytic system was stable enough to be recovered in 70% yield after the reaction. For the reaction 4 mol % of the catalyst is needed and 5 equiv of the silane.

Enantioselective Synthesis of Mono- and Disubstituted 3,6-Dihydro-2H-pyrans and 5,6-Dihydropyran-2-ones

Izzo, I. et al. (*Heterocycles* **2003**, *60*, 2057) have developed an efficient enantioselective synthesis of 3,6-dihydro-2H-pyrans and 5,6-dihydro-pyran-2-ones based on a ring-closing metathesis reaction using Grubbs' first-generation catalyst. Dihydro-2H-pyran and dihydropyran-2-one subunits are present in many biologically active natural products, and they are useful building blocks for the synthesis of oxygen heterocycles.

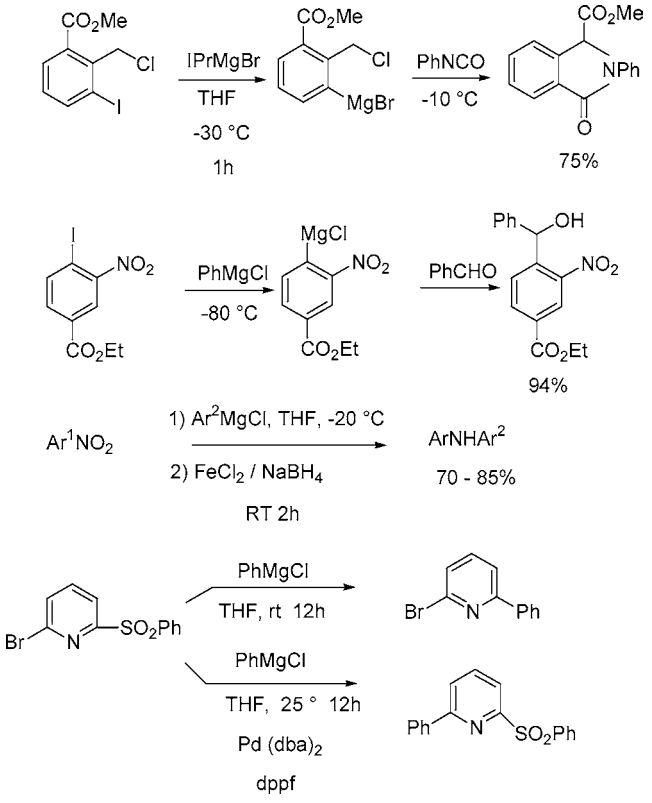
The intermediates for the ring-closing metathesis reaction are easily synthesized in both enantiomeric forms through stereospecific oxirane ring opening with lithium divinylcuprate of the commercially available epoxides followed by straightforward functional groups transformation.



Highly Functionalised Organomagnesium Reagents

More than 100 years after their discovery, Grignard reagents continue to be a source of interest in academia, whereas in industry, despite potential hazards associated with their use, the Grignard reagent is widely used on large scale. In previous issues of these highlights, we have commented on the value of generating Grignard reagents by halogen−magnesium exchange, both from a selectivity and a safety viewpoint, rather than by conventional reaction of magnesium metal. A recent review from the group of Knochel at Munich (Knochel, P. et al. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302) shows recent developments in this area and describes how Grignard reagents can be used in cross-coupling and amination reactions.

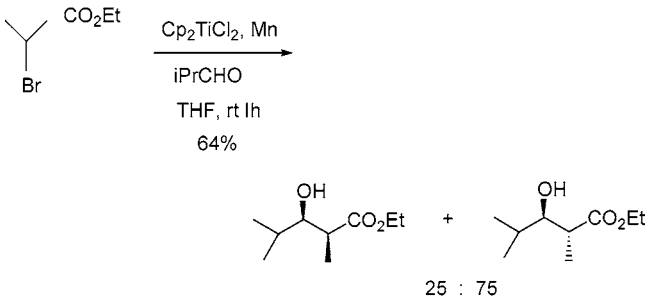
The halogen−metal exchange process allows Grignard reagents to be prepared with functional groups which would normally be expected to react, and examples are shown in the scheme.



Titanocene (III)-Promoted Reformatsky Reactions

The Reformatsky reaction is an excellent method for the synthesis of β-hydroxyesters from aldehydes and α-haloesters, but the classic reaction using zinc dust as a reductant can sometimes cause problems, particularly on scale-up. Although there have been many attempts to circumvent the problems of long reaction times or byproduct formation, many use esoteric or expensive reagents.

A recent paper (Parrish, J. D. et al. *Org. Lett.* **2003**, *5*, 3615) suggests the use of Nugent's reagent, Cp_2TiCl or titanocene (III) chloride as a mild reductant. Excellent results were obtained with unbranched α-bromoesters and a variety of aldehydes, whereas branched α-bromoesters give a mixture of syn and anti products with the latter predominating. Initial calculations suggest that the anti product is more stable than the syn by 0.8 kcal/mol and that the reaction is under thermodynamic rather than kinetic control.

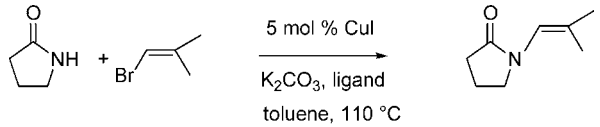


Copper-Catalysed Coupling of Amides and Carbamates to Vinyl Halides

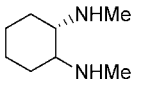
Transition metal-catalysed amination methods have been mentioned many times in these highlights (for reviews, see *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience, New York, 2002; Muci, A. R. et al. *Top. Curr. Chem*. **2002**, *219*, 131). Most of the work has focused on aromatic amination, with a recent trend being to move away from traditional palladium catalysts to cheaper copper (Klapars, A. et al. *J. Am. Chem. Soc*. **2002**, *124*, 7421). There have been a few examples of vinylation using Pd or Cu catalysis.

A recent report from the group of Buchwald at MIT (Jian, L. et al. *Org. Lett.* **2003**, *5*, 3667) shows that the choice of ligand for copper-catalysed reaction of amides and vinyl halides is important.

The reaction works in a number of solvents (THF, DMF, dioxane, toluene) and for a variety of substrates including cyclic and acyclic primary amides and carbamates. However, acyclic secondary amides do not work.



ligand	yield (%)
$Me_2NCH_2CH_2NMe_2$	0
$Me_2NCH_2CH_2NH_2$	31
$MeNHCH_2CH_2NHMe$	92



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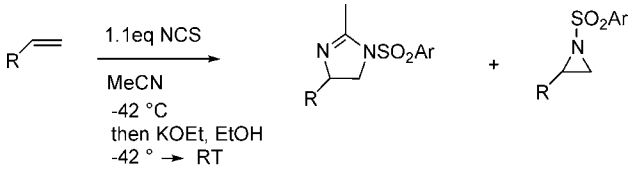
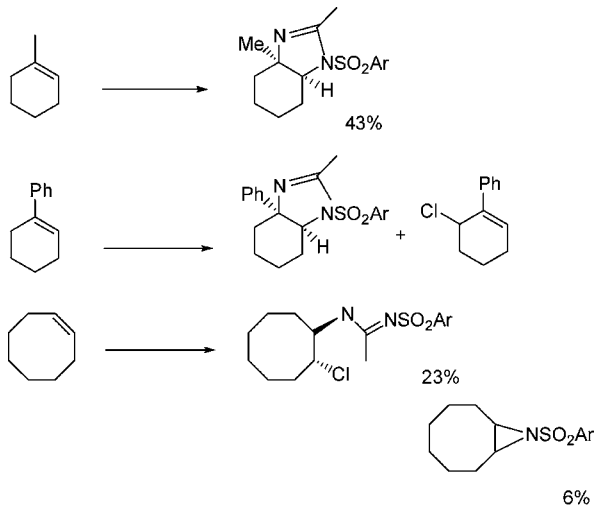
Electrophilic Diamination of Alkenes

Reaction of *N*-chlorosuccinimide with alkenes in the presence of acetonitrile leads to an electrophilic Ritter-type reaction in which the acetonitrile is incorporated into the molecule (Booker-Milburn, K. I. et al. *Org. Lett.* **2003**, *5*, 3313). A competing reaction is formation of an aziridines, which can be the major product in some cases.



R = Ph	60%	7%
R = 2-ClPh	44%	0%
R = 4-MePh	24%	23%
R = 2,4,6 trimethylPh	0%	49%

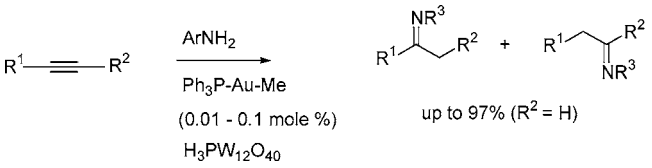
Cyclic olefins give moderate yields of imidazolines, with some aziridine byproducts. Occasionally, allylic chlorination can be a problem, and with cyclooctene, an amidine was formed. The amidines can normally be cyclised to imidazolines using potassium ethoxide as base.



Gold-Catalysed Intramolecular Amination of Alkynes

The condensation between carbonyl compounds and amines is the standard way to make imines but there is another way—addition of amines to alkynes. However, many methods use mercury as catalyst. A recent publication, however, describes the search for alternative catalysts and finds that Ph_3PAuMe is the best, provided that an acidic promoter is used—molybdenum and tungsten heteropolyacids are particularly useful (Mizushima, E. et al. *Org. Lett.* **2003**, *5*, 3349). Triflic acid and dodecylbenzenesulphonic acid are also powerful promoters, but methanesulphonic acid is surprisingly inferior. TONs are at present only at the 9000 level when aromatic amines with electron-withdrawing groups are used as substrates.

The reaction is selective when monosubstituted alkynes are used, but mixtures of products are obtained when two different substituents are present. At present only aromatic amine addition has been investigated.



Cost Reduction in the Heck Reaction using "Homeopathic" Ligand-Free Palladium Catalysis

A group at the Dutch company DSM has been investigating ways to make the Heck reaction more cost-effective and more environmentally friendly. Early work concentrated on increasing the catalyst activity (van Strijdonck, G. P. F. et al. *Eur. J. Inorg. Chem.* **1999**, 1073) and on developing a halide-free Heck reaction based on use of aromatic anhydrides as arylating agents (Stephan, M. S. et al. *Angew. Chem., Int. Ed.* **1998**, *37*, 662; Goossen, L. J. et al. *Synlett* **2002**, 1721).

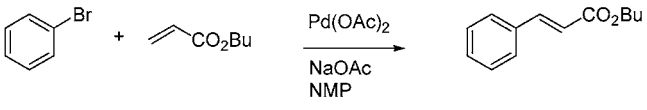
Although earlier work had shown that ligand-free palladium was successful, the disadvantage was that only iodides could be used as substrates. In most cases when, for example, bromides are used, a black precipitate (probably palladium metal) forms in the early stages of the reaction, and the reaction stops before full conversion. It is now suggested that for iodides, olefin insertion is the rate-determining step, whereas for bromides, oxidative addition of the substrate to palladium is probably rate-determining. This affects the catalyst in the resting state; whereas for iodides, the palladium is in the form of palladium (II) complexes, for bromides the resting state is probably a less stable Pd(O) complex, which can either enter the catalytic cycle or give rise to palladium black. The latter process appears to be self-catalysed and rapidly leads to deposition of all the palladium from the reaction mixture, and the reaction stops.

Since the Heck reaction is probably first order in palladium concentration and aggregation to form palladium black may be higher order, a simple solution to the problem would be to reduce the catalyst-to-substrate ratio. This concept has now been shown to work remarkably well (de Vries, A. H. M. et al. *Org. Lett.* **2003**, *5*, 3285). Whereas at higher palladium-to-substrate ratios, the reaction of bromobenzene with butylacrylate stops, when the ratio is in the range 0.01−0.1, acceptable rates of reaction are achieved. At concentrations of 0.00125%, however, the rate of reaction is lowered, although the catalyst functions well.

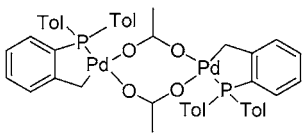
Using automated screening methods, a wide variety of substrates was screened and almost all gave high yields when 0.05 mol % palladium acetate was used as a catalyst. Substrates with electron-donating as well as electron-withdrawing groups in the aromatic halide all gave high yield and conversion with butyl acrylate in NMP at 135° for 1−15 h. Other olefins could also be used.

The ligand-free system was compared with the very active palladacycle (**1**) developed by Herrmann's group in Germany (Böhm, V. P. et al. *Chem. Eur. J.* **2001**, *7*, 4191). and the two catalysts gave very similar profiles. The DSM workers suggest that the active catalyst in these palladacycle reactions may, in fact, be ligand-free palladium.

This is a very important paper for process chemists, showing that a reduction in catalyst-to-substrate ratio can increase TOF, as well as being an extremely simple system of relatively low cost.



Mol% $Pd(OAc)_2$	Yield after 5½ hr
0.00125	below 10%
0.02	90%
0.08	98%
1.28	below 5%



Palladocycle (1)

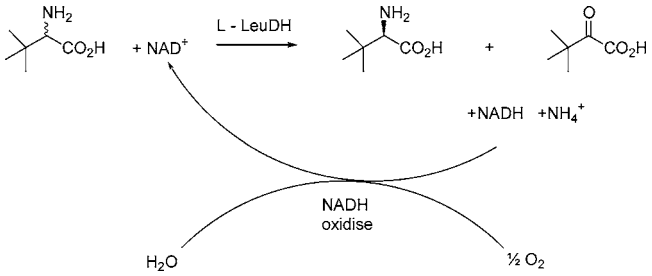
The "homeopathic" method shows the value of reducing Pd levels to an optimum. An earlier publication from Leadbeater at Kings College, London, had suggested that for certain Suzuki reactions, no metal was required at all (Leadbeater, N. E. et al. *Angew. Chem., Int. Ed.* **2003**, *42*, 1407).

Enzymatic Preparation of Enantiomerically Pure D-Tertiary Leucine

Owing to its bulky, hydrophobic *tert*-butyl side chain *tert*-leucine is used widely in the synthesis of biologically active compounds, and there have been many syntheses. A direct enzyme-catalysed route is used for the production of L-*tert*-leucine on an industrial scale, and it is based on the NADH-dependent reductive amination of the corresponding keto acid catalysed by leucine dehydrogenase (Bommarius, A. S. et al. *Chimia* **2001**, *55*, 50). In the process the NADH is efficiently regenerated using formate/formate-dehydrogenase.

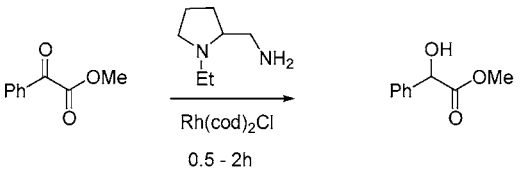
The D isomer, however, cannot be made via such a process since the corresponding D-specific enzyme is unknown. Although there have been reported enzymatic syntheses of D-*tert* leucine (for example, see Laumen, K. et al. *J. Mol. Catal. B: Enzymol.* **2002**, *19*, 55), prior derivatisation is required.

A recent report (Hummel, W. et al. *Org. Lett.* **2003**, *5*, 3549) describes the synthesis of D-*tert*-leucine by oxidation of the racemate using leucine dehydrogenase. The L-amino acid is oxidised completely owing to coupling of the primary reaction with a highly efficient irreversible NAD^+-generating step using NAD oxidase, a 99% ee product being produced. The unfavourable equilibrium of the dehydrogenase reaction is overcome by the coupling to the irreversible NAD^+ regeneration.



Enhancing the Enantioselectivity of Novel Homogeneous Organometallic Hydrogenation Catalysts

The need to develop new, more efficient asymmetric hydrogenation catalysts is widely acknowledged. A recent report from the group of Thomas, Raja, and Johnson at Cambridge, UK (Jones, M. D. et al. *Angew. Chem., Int. Ed.* **2003**, *42*, 4326) shows that the enantioselectivity of the homogeneous catalyst can be improved by heterogenising it at the inner walls of a mesoporous silica so that advantage is taken of the restricted space at the concave surface of the active centre. In all cases the heterogenised catalyst is superior to the analogous homogeneous version. The technique was demonstrated in two standard reactions, hydrogenation of α-phenylcinnamic acid and hydrogenation of methyl benzoylformate.



homogeneous	56% conv	69% ee
heterogeneous	100% conv	99% ee

Practical Heterogeneous Hydrogenation of Aromatic Ketones

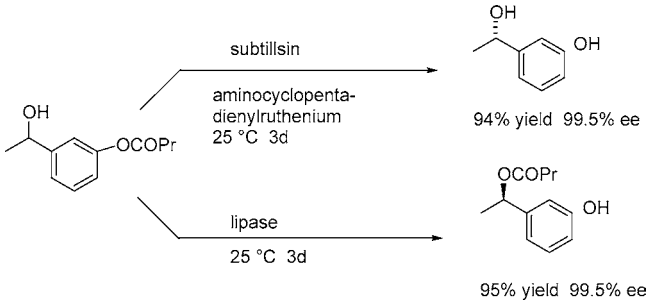
Although the performance of heterogenised versions of homogeneous catalysts is often inferior to the original, there are exceptions. A recent paper from the group of Lin at UNC Chapel Hill (Hu, A. et al. *J. Am. Chem. Soc.* **2003**, *125*, 11490) shows that novel chiral porous zirconium phosphonates based on the ruthenium BINAP−diphenylethylenediamine system developed by Noyori gives enantioselectivity superior to the parent system. The system can be recycled, and the table below shows results for the hydrogenation of acetonaphthone using the heterogeneous zirconcum−ruthenium system at 0.1% loading (700 psi H_2, 20 h).

run	1	2	3	4	5	6	7	8
ee	99	99	99.1	99	99	99.2	99.1	99
conversion	100	100	100	100	100	100	95	85

Dynamic Kinetic Resolution of Secondary Alcohols

Dynamic kinetic resolution (DKR) provides a useful methodology for converting racemic substrates to single-enantiomer products in high yield. Several groups have reported the use of enzyme−metal catalyst combinations, the metal acting to racemise the residual enantiomer to allow complete conversion to the desired product. All previous examples have used a lipase as the resolving agent. A complementary procedure, using subtilisin as the enzyme in the DKR of secondary alcohols, has recently been reported (Kim, M. J. et al. *J. Am. Chem. Soc.* **2003**, *125*, 11494).

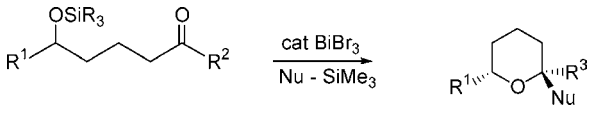
Owing to the low activity of the subtilisin in organic solvents, the enzyme was first treated with surfactant to enhance activity. Using THF as solvent and trifluoromethyl butyrate as the acyl donor, high enantioselectivity could be obtained with a wide variety of secondary alcohols, giving the opposite product to the lipase systems. This was shown by using the system below which requires no external donor.



Stereoselective Construction of Cyclic Ethers

Bismuth halides are relatively inexpensive and environmentally benign reagents and are often used as mild Lewis

acids in a variety of transformations (see Leonard, N. M. et al. *Tetrahedron* **2002**, *58*, 8373 and *Organo-Bismuth Chemistry*; Suzuki, H., Matano, Y., Eds.; Elsevier: New York, 2001). It has now been found that bismuth tribromide will catalyse the stereoselective intramolecular etherification of *δ*-trialkylsilyloxy aldehydes and ketones when trialkylsilyl nucleophiles are present (Evans, P. A. et al. *J. Am. Chem. Soc.* **2003**, *125*, 11456). Yields are in the range 70−95%, and selectivity for the shown isomer is greater than 19:1.



Creation and Use of a Highly Enantioselective Nitrilase Enzyme for Efficient Production of a Lipitor Intermediate

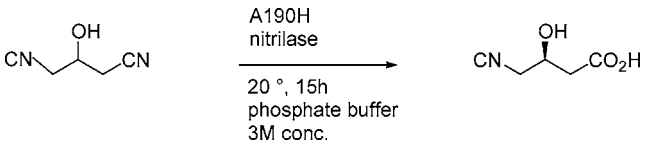
A key intermediate in the synthesis of the top-selling drug atorvastatin (Lipitor) is (*R*)-4-cyano-3-hydroxybutyric acid. One way to make this would be by enantioselective hydrolysis of one of the cyano groups in 4-cyano-3-hydroxy butyronitrile (hydroxyglutaronitrile), which being a meso compound should give high yields.

Enzymes are used for many industrial processes, but often their characteristics fall short of the desired properties for commercialisation. Shortcomings such as the following:

low specific activity
inadequate substrate scope
poor enantioselectivity at high conversion
intolerance to organic solvents

poor space−time−yield (low volumetric productivity) can all be problematic for large-scale work. However, with the advent of "directed evolution", many of these disadvantages can be "designed out". A recent paper from the Diversa Corporation (DeSantis, G. et al. *J. Am. Chem. Soc.* **2003**, *125*, 11476) describes the use of gene-site saturation mutagenisis to produce a highly active nitrilase.

By screening for nitrilase activity in the desired Lipitor transformation using genomic libraries collected from around the globe, 200 unique nitrilases were found. However, most of these enzymes suffered from the major disadvantage that enantiomeric excess decreased as the substrate concentration increased, a major drawback for commercialisation in a cost-competitive environment. Using directed evolution, a single amino acid variant nitrilase was produced, which is enantioselective at substrate concentrations up to 3 M. Some of the 330 amino acids in the most active natural nitrilase were changed to quickly produce 31584 clones which were screened. The most active mutants were further screened for concentration dependence. The resultant enzyme catalyses the selective hydrolysis of one nitrile group to give the product in 96% yield and 98.5% ee.



Will It Last Until Shutdown? Deciphering Catalyst Decay

For those involved in continuous processing with the use of fixed-bed catalysts, catalyst stability is a major issue, but research into this area receives much less attention than discovery of new catalysts. The cost of catalyst decay is not simply the cost of the replacement catalyst but also entails shutdown costs and lost production during the catalyst change, as well as environmental issues. A recent paper (Birtill, J. J. *Catal. Today* **2003**, *81*, 531) describes techniques used to decipher catalyst decay both in the lab and in the plant, using plant performance data and post-mortem characterisation.

From Maximum to Most Efficient Production Using a Continuous Oscillatory Baffled Reactor

A collaboration between the group of Professor Ni at Heriot-Watt University, Edinburgh, UK, and a team at James Robinson Ltd, Huddersfield, UK (a small speciality dyestuff and photographic chemicals manufacturer, part of the Yule Catto group), has resulted in a batch process for a key intermediate being converted to a continuous operation in an oscillatory baffled reactor. Instead of performing the process, which involves diazotisation, in a 16000-L batch reactor, a 270-L continuous reactor is used—it occupies only 60 M^2 factory space compared to 1200 M^2 for the batch process. Yield and product quality are identical, but productivity is increased. For more information see: http://www.ncl.ac.uk/pin/.

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