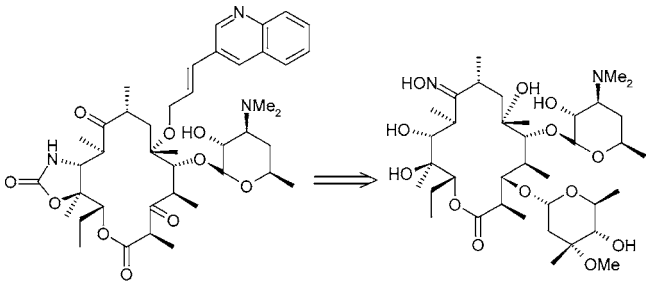
Organic Process Research & Development **2005**, *9*, 2–8

Highlights from the Literature

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

Cethromycin (ABT-773)

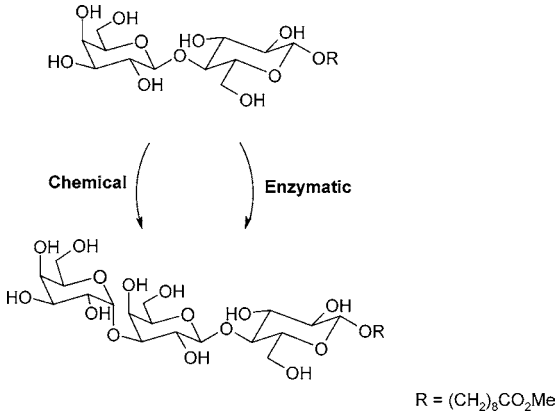
Erythromycin A has been used to treat bacterial infections of the upper and lower respiratory tract now for nearly 50 years. In pursuit of further medicines, ABT-773 was identified as a ketolide possessing superior potency against macrolide-resistant respiratory tract pathogens whilst maintaining enhanced gastric stability and broad spectrum activity. A recent communication by Plata and colleagues from Abbott Laboratories describes how the antibiotic cethromycin (ABT-773) (*Tetrahedron* **2004**, 10171) can be prepared using an effective protection strategy to enable regioselective C6-*O*-alkylation and subsequent stereoselective modification of the erythromycin nucleus. The group outline how ABT-773 could be prepared in 10 steps, with 7 isolations from commercially available erythromycin A oxime.



ABT-773, Cethromycin *Erythromycin A Oxime*

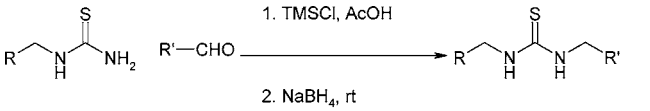
Enzymatic Processes

Yazbeck, Tao and colleagues from Pfizer have published a *Tetrahedron Asymmetry* report (*Tetrahedron Asymmetry* **2004**, 2757) outlining challenges in the development of efficient enzymatic processes in the pharmaceutical industry. These include the throughput of an enzymatic process, downstream processing issues, and competition from other methodologies.



The power of enzymatic synthesis is highlighted in a communication from Ratcliffe (Department of Research and Process Development, Synsorb), Palcic (University of Alberta) and co-workers (*Synthesis* **2004**, 2293). They report how the trisaccharide (see scheme) can be prepared on multigram scale using chemical or enzymatic synthesis methodology. Chemical conversion in 30% overall yield could be achieved in seven steps, or alternatively, a single-step enzymatic conversion of the lactoside using recombinant α(1→3)-galactosyltransferase with UDP-galactose or UDP-glucose/UDP-Glc epimerase gave the target trisaccharide in 85−90% yield.

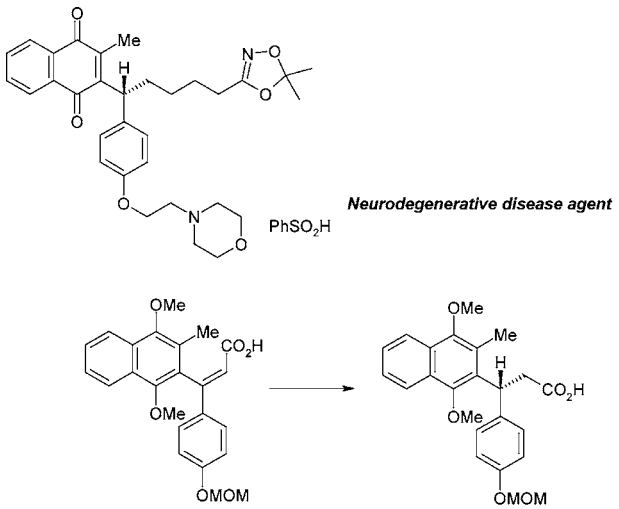
Unsymmetrical *N,N*′-Disubstituted Thiourea



Unsymmetrical N,N' disubstituted thiourea

A practical synthesis of unsymmetrical *N*,*N*′-disubstituted thioureas has been reported by Ciszewski and colleagues from Novartis (*Tetrahedron Lett.* **2004**, *45*, 8091) by the reductive alkylation of *N*-monosubstituted thioureas with aldehydes. *N*-Monosubstituted thioureas can in turn be synthesized by the reductive amination of thiourea with an appropriate aldehyde. The group have extended the methodology to carbamates.

Asymmetric Hydrogenation



Neurodegenerative disease agent

Asymmetric hydrogenation

An asymmetric hydrogenation as the key step towards the synthesis of a neurodegenerative disease agent (see

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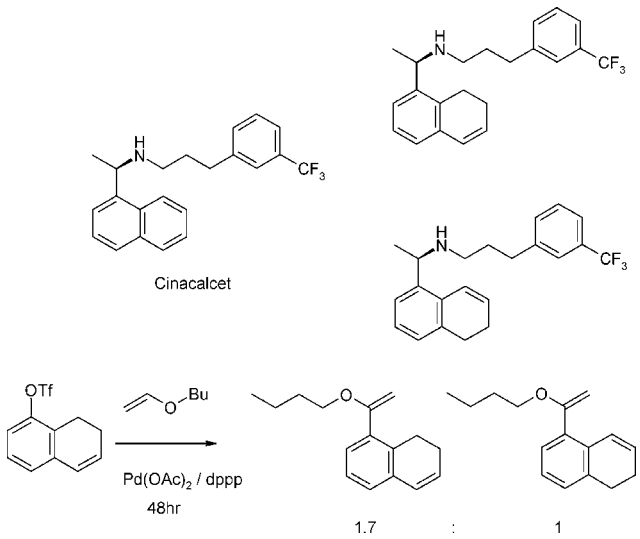
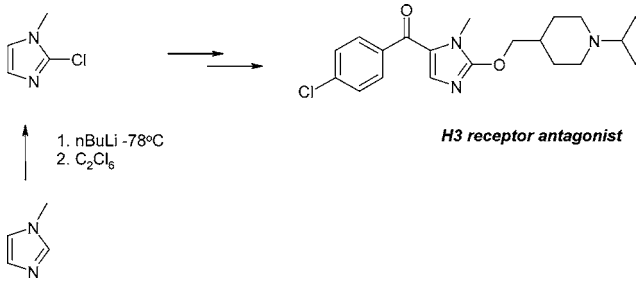
scheme above) has been disclosed by workers at Takeda Chemical Industries (*Tetrahedron Lett.* **2004**, *45*, 7757). This reaction in their synthetic route involved asymmetric hydrogenation of a hindered acrylic acid catalyzed by the Rh-JOSIPHOS system in the presence of a base to afford a chiral acid up to 93% ee. A variety of Rh catalysts and bases was screened in their development work and are reported.

Cinacalcet Congeners



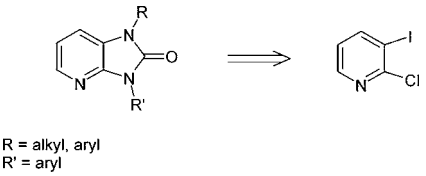
The appearance of low levels (<0.1%) of two new isomeric dihydronaphthalenes during late-phase manufacturing of Cinacalcet necessitated their synthesis which has been recently disclosed by Wang and colleagues from Amgen Inc (see scheme above) (*Tetrahedron Lett.* **2004**, *45*, 8355) starting from commercially available 5-hydroxytetralone in five linear steps. A key palladium-catalyzed double-bond migration was found to take place during a prolonged Heck coupling reaction scheme leading ultimately to the synthesis of both regioisomers from the same starting material.

H3 Receptor Antagonist



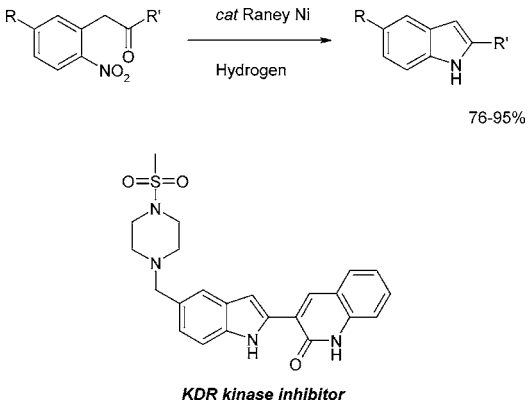
Starting from 1-methylimidazole, a concise, scalable, three-step synthesis of a histamine H3 receptor antagonist (see scheme above) has been reported by Mani and colleagues from Johnson and Johnson pharmaceutical research and development (*J. Org. Chem.* **2004**, *69*, 8115). The required 2-chloroimidazole was prepared in very good yield by halogen−metal exchange between the 2-lithio derivative and hexachloroethane, a readily available and inexpensive reagent. The group report that the byproduct, tetrachloroethylene, was quite stable to the workup conditions and could be removed by distillation (bp 121°C)

Disubstituted Imidazo[4,5-*b*]pyridine-2-ones



Kuethe and colleagues from Merck report (*J. Org. Chem.* **2004**, *69*, 7752) how regioselective palladium-catalyzed amination of 2-chloro-3-iodopyridine followed by a subsequent palladium-catalyzed amination leads to 2,3-diaminopyridines. Treatment with triphosgene leads to the unsymmetrical imidazo[4,5-*b*]pyridin-2-ones in just three synthetic steps, giving rise to pharmaceutically interesting molecules.

KDR Kinase Inhibitors



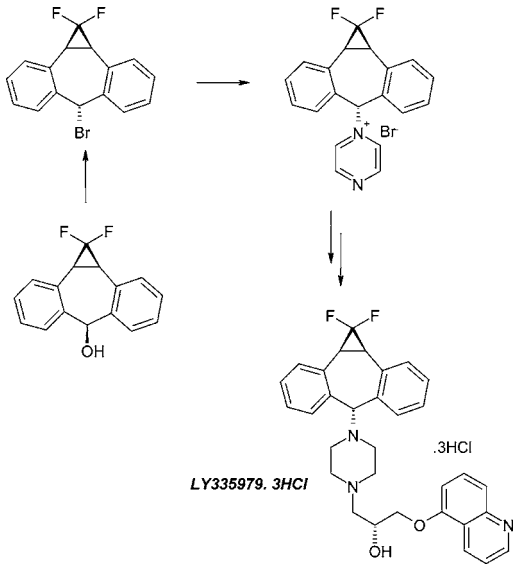
Wong and colleagues from Merck report (*J. Org. Chem.* **2004**, *69*, 7761) how reductive cyclization of an *o*-nitrobenzylcarbonyl compound using catalytic Raney nickel to give a 1*H*-indol-2-yl-1*H*-quinoline in excellent yield formed the key step of the synthesis en route to a KDR kinase inhibitor. The examination of the reductive cyclization reaction and optimization of conditions is described in their publication.

LY335979·3HCl

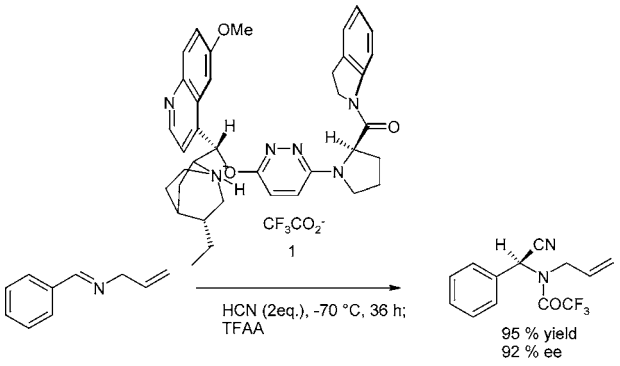
Barnett, Huff, and co-workers from Eli Lilly report (*J. Org. Chem.* **2004**, *69*, 7653) how studies of the displacement chemistry of 1,1-difluorocyclopropyldibenzosuberanyl alcohol (see scheme next page) and its activated bromide derivative have led to an improved approach towards the synthesis of the multidrug resistance modulator LY335979·3HCl. A multikilogram-scale process description is reported in the paper.

New Chiral Catalyst for the Enantioselective Strecker Reaction

The chiral ammonium salt **1** has been demonstrated by J. Huang and E. J. Corey (*Org. Lett.* **2004**, *6*, 5027) to be an



effective catalyst for the highly enantioselective Strecker reaction of *N*-allylbenzaldimines with hydrogen cyanide. During the study allyl was found to be a preferable protecting group compared to the traditional benzyl group. Dichloromethane was also found to be better than toluene, which is the traditional solvent for the Strecker reaction. In the aromatic series high ee's and yields were demonstrated. The method has been until now limited to the synthesis of aromatic α-amino acids.

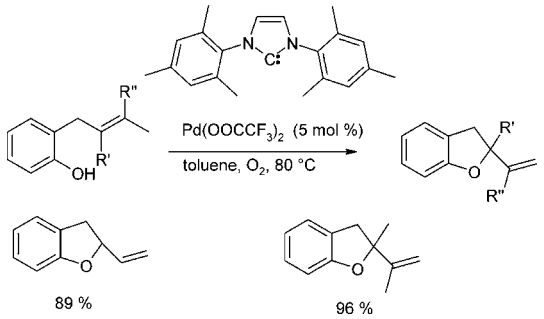


Palladium−Carbene Catalysts for Aerobic, Intramolecular Wacker-Type Cyclisation Reactions

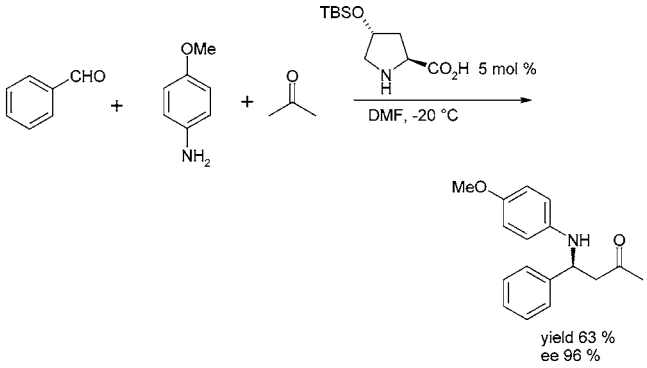
K. Muñiz has reported (*Adv. Synth. Catal*. **2004**, *346*, 1425) that a catalyst derived from in situ complexation of N-heterocyclic carbenes and palladium bistrifluoroacetate promotes efficiently the intramolecular Wacker-type cyclisation under aerobic conditions to form dihydrobenzofuran derivatives from 2-allyl phenols. Catalysts from Pd sources bearing chloride gave mixtures of the desired five- and six-membered derivative. The formation of the six-membered ring was completely suppressed by the use of palladium trifluoroacetate.

4-Siloxyproline, a New Soluble Asymmetric Catalyst

trans-4-*tert*-Butyldimethylsiloxy-L-proline (**1**) has been found by Hayashi, Y. et al. (*Adv. Synth. Catal*. **2004**, *346*, 1435) to display a higher catalytic activity than L-proline due to higher solubility which widens the substrate scope in

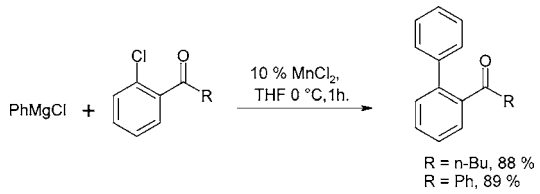


α-aminoxylation of carbonyl compounds as well as *O*-nitroso aldol/Michael and -Mannich reactions. In the case of the α-aminoxylation of ketones the yield obtained with proline was less than 5% in comparison to good yields with **1**.



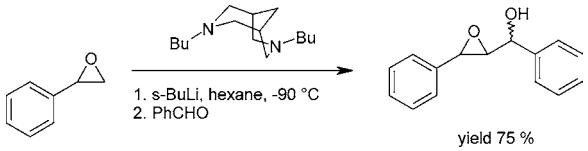
Cross-Coupling Reaction between *o*-Chloroaryl Ketones and Organonomanganese Reagents

Cahiez, G. et al. (*Org. Lett*. **2004**, *6*, 4395) have found that alkyl- and arylmanganese reagents react with *o*-chloro- or *o*-bromoaryl ketones to give the substituted ketones in high yields. The cross-coupling reaction is performed under mild conditions (−60 to 40 °C, 30 min to 4 h) and shows high chemoselectivity.



Substituted Epoxides by Lithiation of Terminal Epoxides

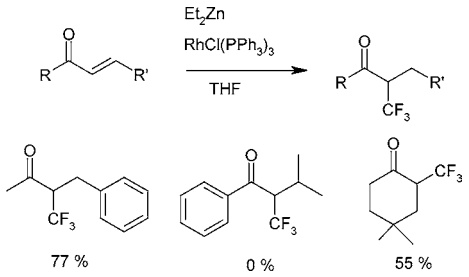
Hodgson, D. M. et al. have found (*Org. Lett*. **2004**, *6*, 4187) that diamine-ligand-assisted direct hydrogen−lithium exchange allows the generation of nonstabilized oxiranyllithium species which can be trapped by carbonyl-based electrophiles as aldehydes.



Rhodium-Catalyzed Novel Trifluoromethylation at the α-Position of α,β-Unsaturated Ketones

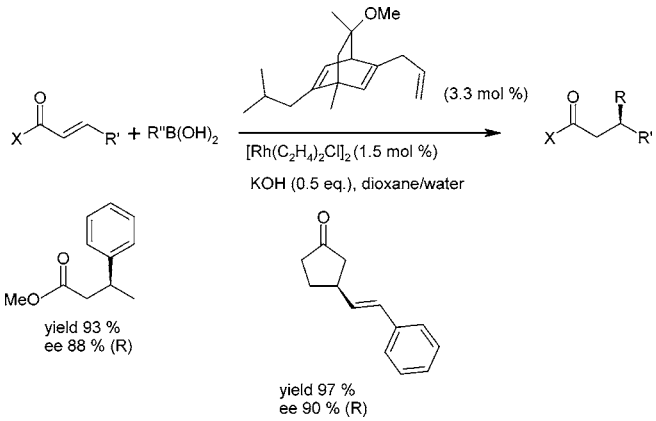
Sato, K. et al. (*Org. Lett*. **2004**, *6*, 4359) have found that treatment of α,β-unsaturated ketones with CF_3I in the

presence of Et_2Zn and $RhCl(PPh_3)_3$ gives novel α-trifluoromethylation products in varying yields.



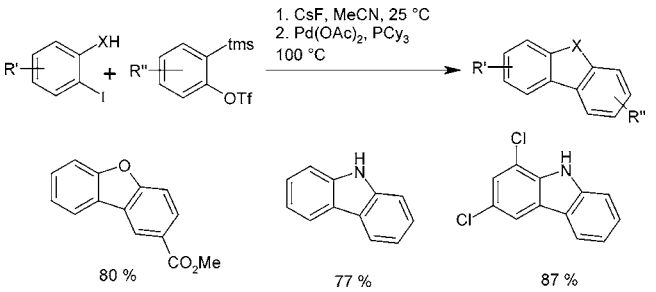
Chiral Dienes as Ligands for Rh(I) in Conjugate Additions of Boronic Acids to a Wide Range of Acceptors

Carreira, E. M. et al. (*Org. Lett*. **2004**, *6*, 3873) have found that some newly found substituted [2,2,2]-dienes display high selectivities as ligands in Rh(I)-catalysed conjugate additions to substrates not previously examined with diene ligands.



Synthesis of Carbazoles and Dibenzofurans via Cross-Coupling of *o*-Iodoanilines or *o*-Iodophenoles with Silylaryltriflates

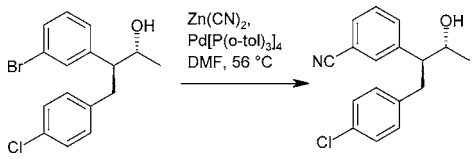
Larock, R. C. et al. (*Org. Lett*. **2004**, *6*, 3739) have found that treatment of *o*-iodoanilines or *o*-iodophenoles with silylaryl triflates in the presence of CsF affords the N- or O-arylated products which are subsequently cyclized under Pd-catalysis to the corresponding heterocycles.



Causes and Effects of High Cyanide Levels in the Pd-Catalyzed Cyanation Reaction

The Merck process group (Marcantonio, K. M. et al. *Org. Lett*. **2004**, *6*, 3723) have investigated the effect of some common laboratory practices to the well-known sensitive palladium-catalyzed cyanation reaction.

The group found that residual NaOH, NaCl (from previous steps), DMA from DMF (due to degradation of DMF) were found to increase the level of soluble cyanide which deactivates the catalyst. The group found that the problem could be overcome through higher loading, but a more practical method was found to be the slow addition of the reaction to the catalyst to prevent swamping of the catalyst with cyanide.



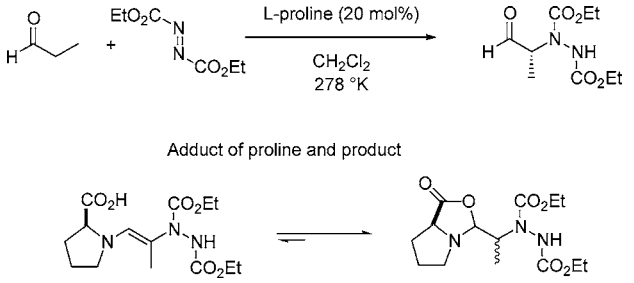
Complete Replacement of H_2 by D_2 via Pd/C-Catalyzed H/D Exchange Reaction

Sajiki, H. et al. (*Org. Lett*. **2004**, *6*, 3521) have found a general in situ D_2 gas generation method using 10% Pd/C-catalyzed H_2-D_2 exchange reaction in a H_2-D_2O system. H_2 gas sealed in a reaction flask with D_2O was efficiently converted into nearly pure D_2 gas, which can be used for reductive deuteration of substrates.

In Situ Catalyst Improvement in the Proline-Mediated α-Amination of Aldehydes

A group at Imperial College, London (UK) headed by Donna Blackmond has been examining kinetic data on proline-catalysed reactions, using calorimetry and have already reported on α-aminoxylation (Matthew, S. P. et al. *Angew. Chem. Int. Ed.* **2004**, *43*, 3317). New work on α-amination is described in which a considerable rate enhancement is observed if the product itself is mixed with proline and added to the reactants, when compared to the reaction with proline alone. This suggests that a proline-product adduct, possible in the oxazolidinone form, is a better catalyst than proline itself, and this has implications in the design of new catalysts (Iwamura, H. et al. *J. Am. Chem. Soc*. **2004**, *126*, 11770).

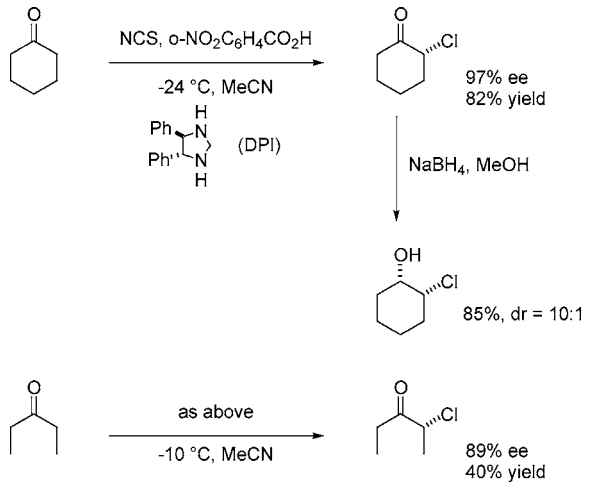
The rate enhancement was observed on the addition of either enantiomer of the product. The reaction also exhibits asymmetric amplification similar to that for the aminoxylation reaction. This nonlinear effect is consistent with a lower quality proline being kinetically resolved in the autoinductive process.



Enantioselective α-Chlorination of Ketones

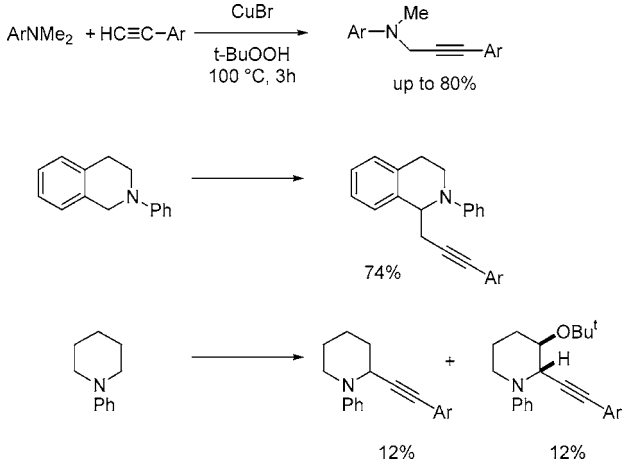
In past issues of Highlights from the Literature we have reported on the enantioselective chlorination of aldehydes, but the corresponding reaction of the less reactive ketones has been a harder "nut" to crack. A recent report from the group of Jørgensen in Denmark (Marigo, M. et al. *Angew.*

Chem., Int. Ed. **2004**, *43*, 5507) indicates that addition of additives such as benzoic acid derivatives is key to the success, when NCS chlorination is attempted with an asymmetric organocatalyst present and MeCN as solvent.



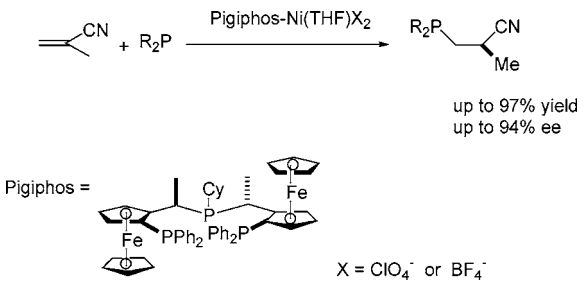
CuBr-Catalysed C−C Bond Formation Adjacent to Nitrogen: Formation of Propargylamines

Propargylamines are of great interest at present in the pharmaceutical industry, and there are many synthetic routes, some of them enantioselective. Now the group of Li in Montreal has reported that tertiary amines with a dimethyl group can couple with acetylenes under oxidative conditions forming a new carbon−carbon bond (Li, Z. et al. *J. Am. Chem. Soc.* **2004**, *126*, 11810). Less satisfactory results are obtained at present with amines other than aryldimethylamines.



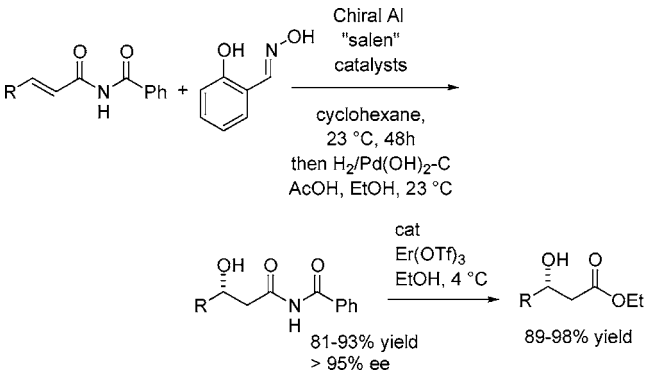
Nickel-Catalysed Highly Enantioselective Hydrophosphination of Methacrylonitrile

Chiral phosphines are widely used as ligands in asymmetric catalysis, but they can be expensive and are often prepared using resolution processes. It has now been found by the group of Togni at ETH, Zurich, that addition of a P−H bond across an olefinic bond can be achieved enantioselectively, using a nickel catalyst and the trisphosphine Pigiphos as ligand. (Sadow, A. D. et al. *J. Am. Chem. Soc.* **2004**, *126*, 14704). This catalyst had previously been used in asymmetric hydroamination (Fadini, L. et al. *Chem. Commun.* **2003**, 30). The catalyst works best as the perchlorate salt which may have safety implications for scale up (the BF_4 salt gave lower enantioselectivities at room temperature but 84% ee at lower temperature). Although the Pigiphos ligand is sterically demanding, best results are surprisingly obtained with bulky phosphine ligands.



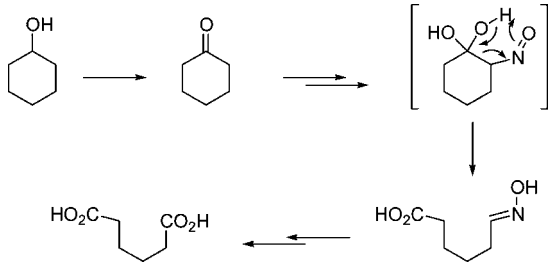
Enantioselective Hydration of Double Bonds

Whilst the enantioselective conjugate addition of weakly acidic nucleophiles (HN_3, HCN, $CH_2(CN)_2$, etc.) to α,β-unsaturated derivatives has been well studied, oxygen nucleophiles have rarely been successful. A recent report from the group of Jacobsen at Harvard focuses on oxime nucleophiles, with the cheap and readily available salicylaldoxime the reagent of choice (Vanderval, C. D. et al. *J. Am. Chem. Soc.* **2004**, *126*, 14724). The imide functionality required for achieving high enantioselectivity can be converted to other β-hydroxyderivatives.



Sodium Nitrite Oxidations

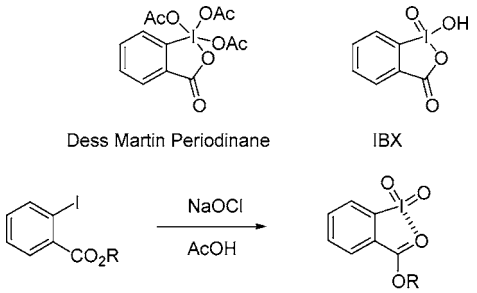
Recently, sodium nitrite in acetic anhydride as solvent was used as an effective reagent for oxidation of alcohols to carbonyl compounds (Bundgar, B. P. et al. *J. Chem. Soc., Perkin Trans. I* **2000**, 3559). It has now been found that cyclohexanols can be oxidized by sodium nitrite and oxygen in TFA with cleavage of the cyclohexane ring. It is suggested that, once the initial oxidation of alcohol to ketone has been completed, α-nitrosation takes place followed by cleavage of the ring (Masumura, Y. et al. *Tetrahedron Lett.* **2004**, *45*, 8221).



Soluble and Stable Periodinane Oxidising Reagents

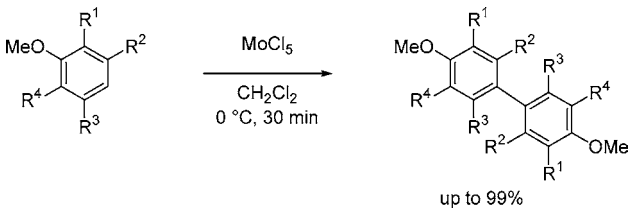
Dess−Martin periodinane and IBX reagents are widely used in synthesis, but there have been questions raised re their safety on large scale. In addition, IBX has very limited solubility in organic solvents, partly because of an extended series of intermolecular secondary bonding interactions that lead to three-dimensional polymeric chains. IBX esters have now been prepared by oxidation of *o*-iodobenzoic acid esters with hypochlorite. A wide variety of esters can be easily prepared, the ester group being altered to change solubility (Zhdankin, V. V. et al. *Chem. Commun.* **2004**, 106).

A variety of alcohols can be effectively oxidized in high yield using the IBX esters. Mild conditions and a catalyst such as TFA, BF_3-etherate, or even KBr can be used. Although the title of the article claims that the reagents are stable, there is no thermal hazard data to support this statement. Until a full hazard assessment has been undertaken to assess shock sensitivity etc., these reagents should be handled with extreme caution. Hopefully, once these studies have been completed, a useful replacement for IBX and Dess−Martin reagents will be available for larger-scale work. The simplicity of the preparation and the ability to change ester group to affect solubility and stability are attractive features. The reagents are reported to be soluble in MeCN, $CHCl_3$, CH_2Cl_2, and benzene! Isn't it time universities stopped exposing their students to highly toxic solvents such as benzene, which is hardly ever used in industry except as a raw material?



Oxidative Coupling of Alkylated Anisoles Using $MoCl_5$

Despite the Lewis acid character of $MoCl_5$, it can be used for the oxidative coupling of alkylated anisoles without loss of the alkyl groups such as *tert*-butyl (Mirk, D. et al. *Syn. Lett.* **2004**, 1970).

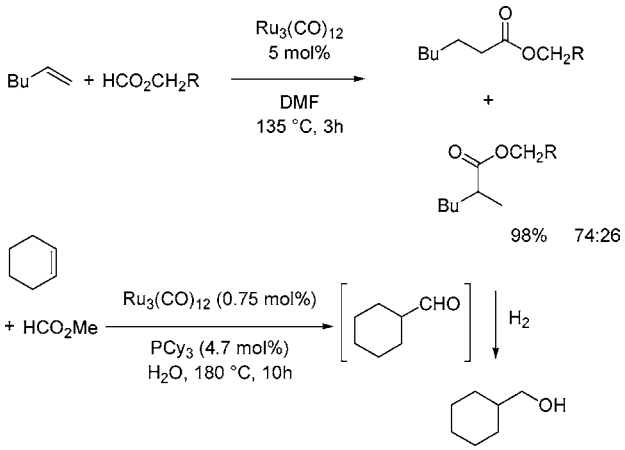


With para-substituted anisoles, ortho coupling takes place.

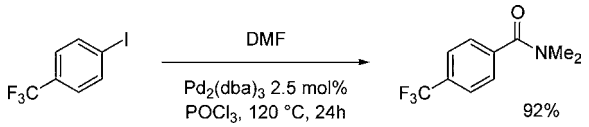
Carbonylation without Carbon Monoxide

Carbonylation reactions using organometallic catalysts were discovered more than 60 years ago and have occupied a central role in organometallic chemistry in both academia and industry. However, carbon monoxide is a toxic greenhouse gas, and there may be advantages to alternative strategies. These are briefly reviewed in a recent article (Morimoto, T. et al. *Angew. Chem., Int. Ed.* **2004**, *43*, 5580).

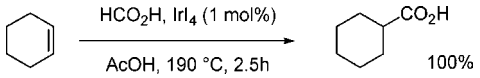
For batch processes use of liquid formates rather than gaseous CO may also be more convenient.



Formamides can also participate in similar processes and, of course, can participate in Heck-type processes with aryl halides.



At high temperatures, formic acid can also add to olefins using iridium catalysts.



Compared with the reactions of carbon monoxide, the reactions with formic acid and its derivatives require more severe conditions such as higher temperatures, longer reaction times. or additional reagents. It should also be noted that formic acid and formates are also made from CO; as a result the overall environmental advantage may be minimal.

Ethylene Tetramerisation

The conventional method of producing 1-hexene and 1-octene by oligomerisation of ethylene leads to a wide spectrum of linear α-olefins, and separation and purification increase the cost. Whilst a selective trimerisation of ethylene to 1-hexene has been achieved using a variety of catalyst systems, the tetramerisation to 1-octene has not previously been achieved. A recent paper (Bollmann, A. et al. *J. Am. Chem. Soc.* **2004**, *126*, 14712) reports that an aluminoxane-activated chromium/$(R^2)_2PNR^1$ system can yield 1-octene in selectivities up to 70%. The R^1 group has little influence on overall selectivity but affects catalyst productivity and electivity of byproduct 1-hexene. Yields and selectivity varied with R^2 group with isopropyl being the best. Catalyst

productivities of over 500,000 g/g Cr/h could be achieved after optimization.

Removal of Tin Residues

Tributyltin hydride-mediated reactions are very useful in organic synthesis, but removal of tin residues can be problematic. It is now reported (Harrowven, D. C. et al. *Chem. Commun.* **2004**, 1968) that using a mixture of KF and silica as the stationary phase in column chromatography leads to reduction of tin from stoichiometric levels down to 30 ppm. A mixture of 10% finely ground KF and 90% w/w silica gave much better results than previously suggested methods or the use of aqueous KF followed by silica chromatography. The tin waste is then conveniently in solid form rather than in solvent or aqueous waste. Perhaps this method could be adapted to larger-scale reactions.

Crystal Engineering in Development of Cocrystals

Poor aqueous solubility is a growing problem in the pharmaceutical industry and has an impact on the productivity of research and development. It has been suggested that modern methods of drug discovery (in vitro testing rather than in vivo, combinatorial chemistry, etc.) have generated molecular targets for which the most potent lead compounds are inherently poorly soluble. For amines and carboxylic acids, salt forms can provide a solution to the solubility issue. For other functional groups this option is not possible.

Cocrystals, however, where a small molecule interacts with the API to give a stable form, may offer advantages of increased solubility and stability. This area of research is discussed in a feature article (Almarsson, Ö. et al. *Chem. Commun.* **2004**, 1889).

Biotransformations in Low-Boiling Hydrofluoro Carbon Solvents

The scope of biotransformations can be considerably extended by the use of organic solvents. It has now been reported (Saul, S. et al. *Angew. Chem. Int. Ed.* **2004**, *43*, 5519) that the use of low-boiling hydrofluoro carbon solvents (HFCs) can lead to improved rates of reaction and yield when compared to similar reactions in organic solvents such as THF, MTBE. or hexane. HFCs used were CH_2F_2 (under pressure), $CF_2H{-}CF_2H$, CF_3CHFCF_3, the latter two being nontoxic and used in the pharmaceutical industry in metered-dose inhalers. HFCs are relatively hydrophobic, allowing enzymes to retain their essential active-site water, yet are polar enough to dissolve many organic molecules.

Various lipase-catalysed kinetic resolutions and desymmetrisations work well (48% yield, 99% ee) in HFCs.

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