Organic Process Research & Development **2011,** *15,* 22–30

Green Chemistry Highlights

Green Chemistry Articles of Interest to the Pharmaceutical Industry

1. Introduction

The American Chemical Society's (ACS) Green Chemistry Institute (GCI) Pharmaceutical Roundtable (PR) was developed in 2005 to encourage the integration of green chemistry and green engineering into the pharmaceutical industry.

The Roundtable currently has 15 member companies as compared to three in 2005. The membership scope has also broadened to include contract research/manufacturing organizations, generic pharmaceuticals, and related companies. Members currently include ACS GCI, AstraZeneca, Abbott Laboratories, Amgen, Boehringer-Ingelheim, Codexis, Dr. Reddy's, DSM Pharmaceutical Products, Eli Lilly and Company, GlaxoSmithKline, Johnson & Johnson, Lonza, Merck & Co., Inc., Novartis, Pfizer, Inc., and Roche.

One of the strategic priorities of the Roundtable is to inform and influence the research agenda. Two of the first steps to achieve this objective were to publish a paper outlining key green chemistry research areas from a pharmaceutical perspective (*Green Chem.* **2007**, *9*, 411−420) and to establish annual ACS GCIPR research grants. This document follows on from the Green Chemistry paper and is largely based on the key research areas though new sections have been added. The review period covers the first 6 months of 2010.

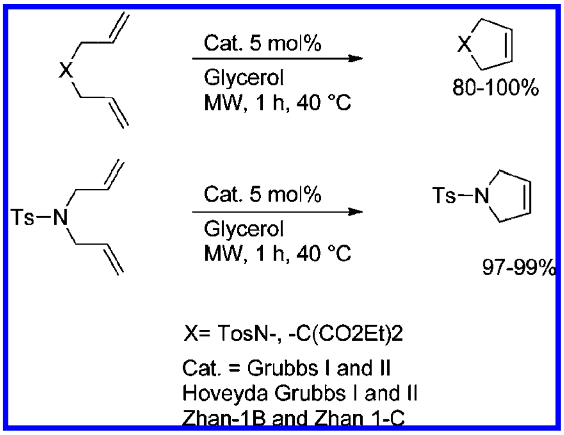
These articles of interest represent the opinions of the authors and do not necessarily represent the views of the member companies. Some articles are included because, whilst not currently being regarded as green, the chemistry has the potential to improve the current state of the art if developed further. The inclusion of an article in this document does not give any indication of safety or operability. Anyone wishing to use any reaction or reagent must consult and follow their internal chemical safety and hazard procedures.

2. Solvents

2-Methyltetrahydrofuran is often promoted as a greener ethereal solvent due to its ease of recovery, the fact it can be used for both reaction and workup, and the fact that it can be synthesised from renewable feed stocks such as corn starch. Milton et al. have reported a number of Grignard reactions and palladium catalysed cross coupling reactions, in some cases using very concentrated (5 M) solutions of Grignard reagents (note Grignard reactions are very energetic so detailed process safety studies should be performed before running such procedures at large scale) (*Green Chem.* **2010**, *12*, 381−383).

Gu and Jérôme have provided an overview on the use of glycerol as a green solvent. The review covers the physical properties of glycerol as well as its implications towards solvent/product separation. The performance of glycerol in chemical reactions is highlighted with specific examples on enhanced reaction selectivity (*Green Chem.* **2010**, *12*, 1127−2238).

Bakhrou et al. have illustrated the usefulness of glycerol as solvent in ring-closing metathesis reactions under microwave irradiation conditions. The intrinsic characteristics of glycerol such as high boiling point, low vapour pressure, high dielectric constant, and a polarity similar to organic solvents such as DMSO and DMF make it a good solvent to be used under microwave irradiation. Ring-closing metathesis of *N*,*N*-diallyltosylamine and diallylmalonate was achieved in high yield (*Tetrahedron Lett.* **2010**, *51*, 3935−3937).



3. Amide Formation

A review of boron catalysed direct amidation reactions has been published by Charville et al. from the University of Durham (*Chem. Commun.* **2010**, *46*, 1813−1823). The review summarises some of the key direct amidation papers from the past 15 years and outlines some of the limited mechanistic information for this reaction to date.

4. Oxidations

David Lathbury was an invited editor for a special feature section on oxidation chemistry in the first issue of *Org. Process Res. Dev.* in 2010. As noted by the editor, the number of contributions was disappointing, with only seven papers published. One article from this issue of interest to green chemists is by Alsters et al. The authors describe a "dark" singlet oxygen (DSO) reaction of *β*-citronellol, a key step in the manufacture of the fragrance additive, rose oxide. To avoid the use of photooxidation in the presence of a sensitizer, the group developed a nonphotolytic catalytic disproportionation of hydrogen peroxide to singlet oxygen using sodium molybdate. To achieve safe processing conditions, ethylene glycol was employed as solvent at 55 °C with slow addition of hydrogen peroxide. These conditions minimized hydrogen peroxide accumulation and also allowed easy catalyst recycling and

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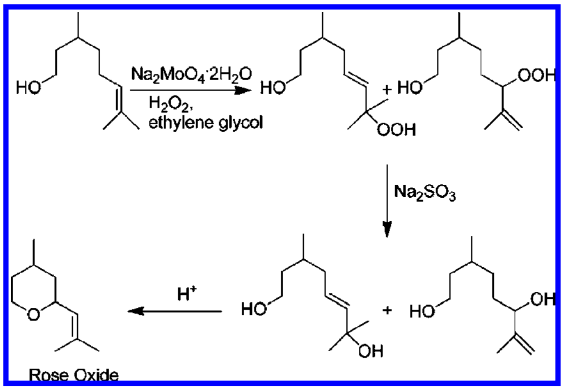
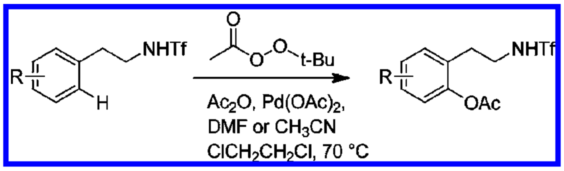
product isolation by extraction with MTBE (*Org. Process Res. Dev.* **2010**, *14*, 259−262).

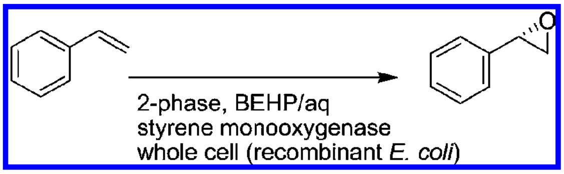


While oxygen is the ideal green oxidant since water is the only byproduct generated, its use is limited in the pharmaceutical industry due to safety concerns and process limitations. Johnson and Yates at Lilly have collaborated with Stahl at the University of Wisconsin to develop a high-pressure continuous flow tube reactor that offers a safe and scalable approach to the palladium-catalyzed aerobic oxidation of alcohols. To ensure the oxygen/organic vapour phase remains below the explosivity range, 8% oxygen in nitrogen is employed. The flow-based process provides excellent gas−liquid mixing to ensure high mass transfer is achieved for efficient oxidations. A variety of aliphatic and aromatic alcohols were oxidized to the corresponding aldehydes and ketones on a 10−40 g scale using 5% $Pd(OAc)_2$ and 20% pyridine at 100 °C in a 400 mL tube reactor. This was subsequently scaled to a 7 L tube reactor using only 1% $Pd(OAc)_2$ in which 1 kg of 1-phenethyl alcohol was converted to acetophenone. The authors suggest the 7 L reactor can be scaled 100-fold without the need for major engineering redesign (*Green Chem.* **2010**, *12*, 1180−1186).

Vickers et al. report a mild ortho C−H acetoxylation of phenethyltriflamides using 10% $Pd(OAc)_2$, *tert*-butyl peroxyacetate as the stoichiometric oxidant, and either DMF or acetonitrile (6 equiv) as critical additives. A wide range of phenethyltriflamides were acetoxylated in good yields, including aromatic rings with electron-donating groups (2-Me, 3-Me, 4-Me, 4-MeO) and electron-withdrawing groups (4-acetyl, 2-CF_3, 2-Cl, 3-Cl, 4-NO_2), and could be extended to derivatives of tyrosine, phenylalanine, and ephedrine. The authors suggest the reaction takes place via a seven-membered palladacycle involving the triflamide. Although the reaction is carried out in the nongreen solvent 1,2-dichloroethane, this chemistry represents an important advance in the development of atom-economical and efficient site-specific oxidation of an unactivated C−H bond (*Org. Lett.* **2010**, *12*, 2511−2513).

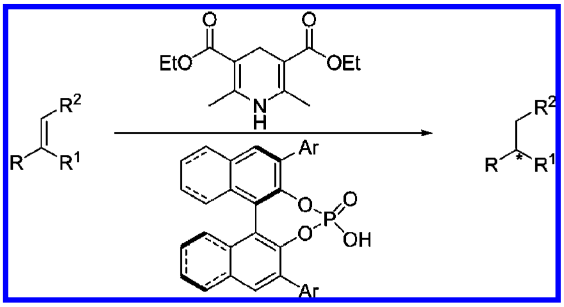


Kuhn et al. report a scalable biocatalytic whole-cell enantioselective epoxidation of styrene using styrene monooxygenase. Implementation of oxygenases at scale has been limited by a number of factors, including cofactor dependence, substrate and product toxicities, biocatalyst instability, and substrate uptake. In the current case, substrate and product toxicities were minimized by use of an organic solvent, bis-2-(ethylhexyl)-phthalate (BEHP), which provided a second phase with high substrate and product concentration. An exhaustive process intensification and optimization was undertaken to increase productivity. An in-depth environmental and economic comparison was carried out of the optimized biocatalytic process versus a number of alternative chemical processes including the Jacobsen-type salen catalyzed epoxidation and hydrolytic kinetic resolution of racemic styrene oxide. The BEHP solvent was identified as the highest environmental impact of the biocatalytic process due to its origin from fossil fuels and human toxicity. If this environmental concern could be addressed, the biocatalytic process would be environmentally superior to the chemical-based processes, of which the titanium silicate catalyzed process emerged as the chemical process with the best environmental profile. Interestingly, the biocatalytic process was more economical than any of the chemical-based processes (*Green Chem.* **2010**, *12*, 815−827).

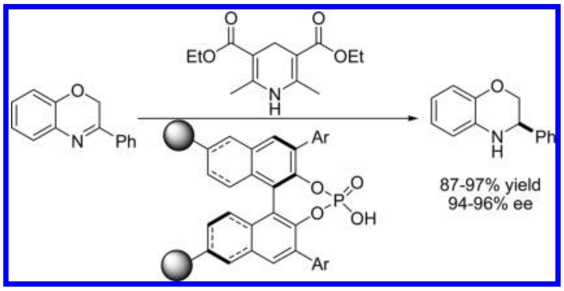


5. Asymmetric Hydrogenations

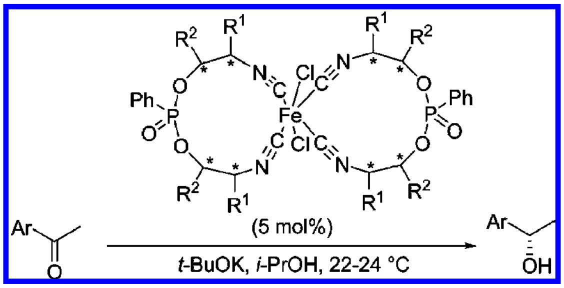
In the first half of year 2010, several review papers were published summarizing the advancement of asymmetric hydrogenations. He and Fan reviewed phosphine-free chiral metal catalysts, including *N*-heterocyclic carbene-based ligands and diamine-based ligands (*Org. Biomol. Chem.* **2010**, *8*, 2497−2504). Rueping and co-workers reviewed metal-free transfer hydrogenations (*Synlett* **2010**, 852−865). In this account, the authors introduced the development of asymmetric transfer hydrogenation using chiral BINOL-derived phosphoric acids as catalyst and Hantzsch dihydropyridines as the hydride source. A variety of substrates, including imines, indoles, pyridines, quinolines, and other heterocycles are reduced with good to excellent ee.



In a separate paper, Rueping and colleagues introduced the first success of immobilizing chiral BINOL phosphoric acids onto a polymer solid support (*Adv. Synth. Catal.* **2010**, *352*, 281−287). The polymer-supported catalyst was as effective as their homogeneous counterpart and catalyzed transfer hydrogenations of quinolines and benzoxazines with high selectivities. The authors demonstrated using the catalyst system in a “teabag" approach. The catalyst can be easily removed from the reaction mixture and be reused for 12 cycles without losing any reactivity and enantioselectivity.

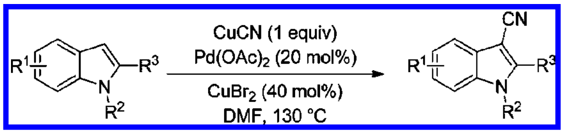


Naik et al. prepared a novel iron-bis(isonitrile) catalyst and applied it in asymmetric transfer hydrogenations of aromatic and heteroaromatic methylketones. Up to 91% ee was obtained (*Chem. Commun.* **2010**, *46*, 4475−4477).

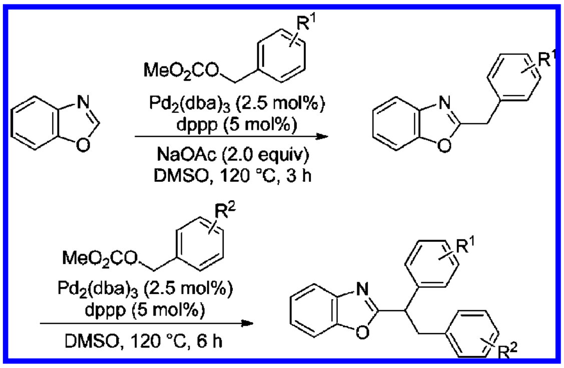


6. C−H Activation

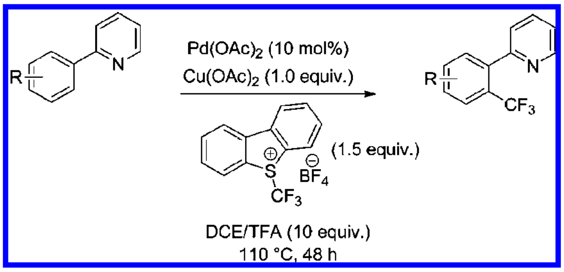
Methodology to activate C−H bonds was the focus of multiple publications during the first half of 2010. Some highlights of these citations include Reddy et al. who demonstrated conditions for the selective cyanation of indoles at the 3-position utilizing a Pd(OAc)$_2$ and CuBr$_2$ catalyst system in the presence of air at 130 °C (*Tetrahedron Lett.* **2010**, *51*, 3334−3336). Substitution was well tolerated including *N*-methyl, *N*-benzyl, and sterically hindered and electron deficient indoles where isolated yields ranged from 60% to 85%. The typical reaction time was under 24 h with the exception of the electron-deficient examples which required significantly more time. Overcyanation was not observed even in the presence of excess CuCN for extended reaction times. The methodology was limited to indoles however, as attempts to use these conditions for the cyanation of pyrroles and carbazoles were not successful.



The use of benzyl carbonates for sequential sp^2 and sp^3 C−H activation was published by Mukai et al. to generate substituted azoles (*Org. Lett.* **2010**, *12*, 1360−1363). Utilization of 2.0 equiv of NaOAc with 2.5 mol % of Pd$_2$(dba)$_3$ and 5 mol % of dppp in DMSO at 120 °C promoted the benzylation of azoles in good yields (56−92%) with the best yields achieved with electron-donating benzyl groups. Substitution of the azole was moderately tolerated with the best yield of 68% obtained with 5-phenyl azole. In a further investigation of the scope of the reaction, 1,3,4-oxadiazoles were subjected to the same conditions and good conversion was observed. Prior to the discovery of the optimal sp^2 conditions with NaOAc, small amounts of the double benzylation product resulting from the sp^3 C−H activation of the first benzyl group were observed. After a significant investigation into this finding, studies indicated that simply removing the NaOAc while keeping all other components of the reaction unchanged resulted in a clean addition of a second benzyl group via sp^3 activation. A screening of carbonates with 2-benzylbenzoxazole showed the desired transformation generated the benzylated diarylmethanes in up to 71% yield. Finally, an investigation into the same conversion with a cinnamyl carbonate resulted in a double allylation to form an azole-containing 1,5-hexadiene substitution pattern. This unusual transformation was only achieved in a moderate yield (57%), but plans to investigate this formation further are underway.

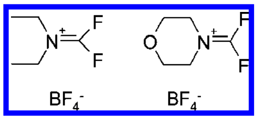


Based on the premise that an ArPd species generated from C−H activation could react with an electrophilic trifluoromethylating reagent to give ArCF$_3$, Wang et al. investigated the trifluoromethylation of arenes (*J. Am. Chem. Soc.* **2010**, *132*, 3648−3649). After a thorough screening of reaction conditions, the use of 10 equiv of TFA was found to be necessary and Cu(OAc)$_2$ was effective for enhancing the catalytic turnover in 1,2-dichloroethane. Electron-donating R groups provided the highest yields (up to 84%), but even electron-withdrawing groups provided moderate yields (at least 54%). While utilization of excess trifluoromethylation reagent, 10 equiv of TFA, 1,2-dichloroethane, and long reaction times are not optimal, the importance of introducing a trifluoromethyl group via C−H activation deserves further investigation.

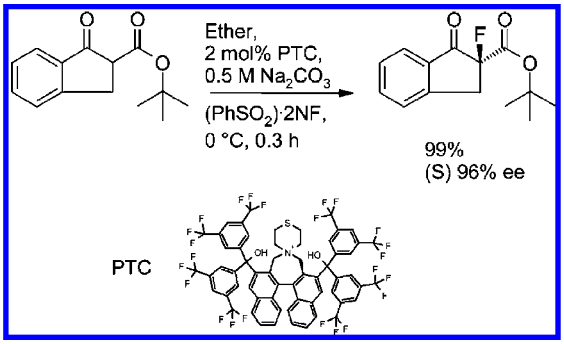


7. Greener Fluorination

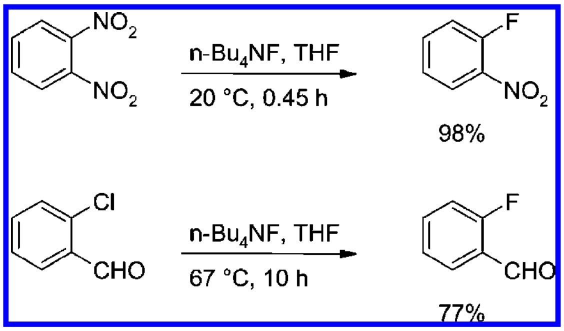
In AOI, V3, Issue 2, aminodifluorosulfinium salts were reported as versatile and safer alternatives to more traditional reagents like DAST. A full paper has now been published (*J. Org. Chem.* **2010**, *75*, 3401−3411) along with a commentary in Chemistry and Industry on these new reagents, which are now available as articles of commerce (*Chem. Ind. (London, U.K.)* **2010**, 17).



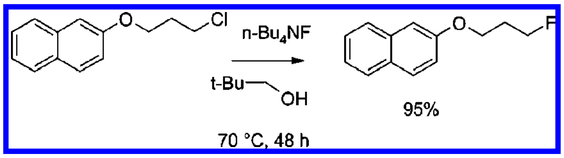
The efficient construction of chiral quaternary centres containing fluorine atoms remains a significant challenge. Wang et al. have reported the fluorination of β-keto esters under the control of a bifunctional phase transfer catalyst can give products in high yield and up to 99% ee chiral purity (*Chem. Commun.* **2010**, *46*, 321−323). Crucial to obtaining high ee was solvent choice and the presence of free hydroxyl groups on the PTC.



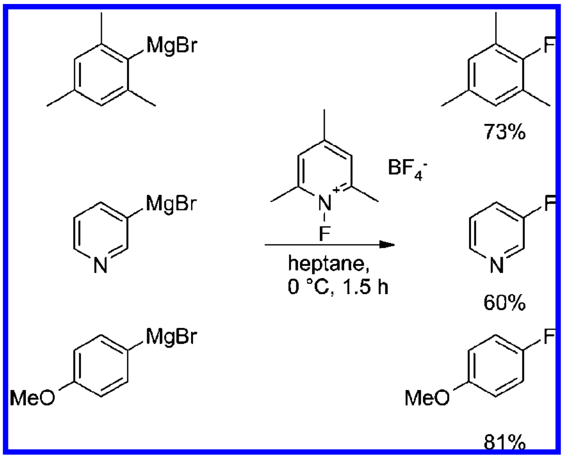
Hu et al. have described the application of anhydrous *n*-Bu_4NF as a fluorinating reagent to displace halogens and nitro groups in S_NAr chemistry with activated arenes (*Tetrahedron Lett.* **2010**, *51*, 432−434). The reactions take place under mild conditions with negligible side product formation.



n-Bu_4NF in *tert*-amyl alcohol has been reported by Kim et al. to give high yields of aliphatic fluorides from iodides, bromides, and chlorides (*Tetrahedron Lett.* **2010**, *51*, 432−434). The method is superior to *n*-Bu_4NF and CsF in MeCN, maximising conversion and yield by reducing side reactions such as hydrolysis and elimination.



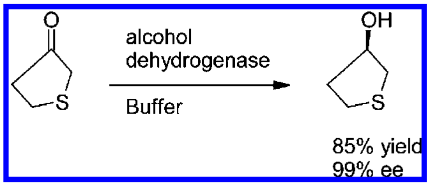
Anbarasan et al. have reported the efficient fluorination of aryl and heteroaryl Grignard reagents with various electrophilic fluorinating reagents at 0 °C, the best results being with F-TMP-BF_4 (*Angew. Chem., Int. Ed.* **2010**, *49*, 2219−2222). The choice of solvent, heptanes, or use of fluorinated ethers is crucial to achieving high selectivity and yield.



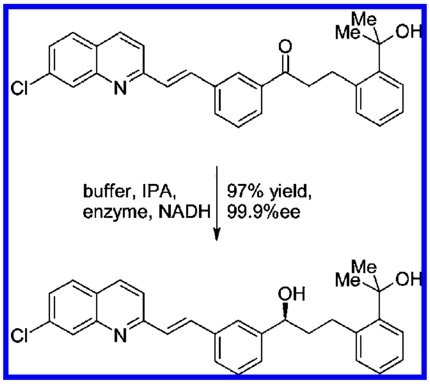
Finally, a comprehensive review article has been published by Grushin on the Pd, Rh, and Cu catalysed synthesis of aryl fluorides and trifluoromethyl arenes (*Acc. Chem. Res.* **2010**, *43*, 160−171).

8. Biocatalysis

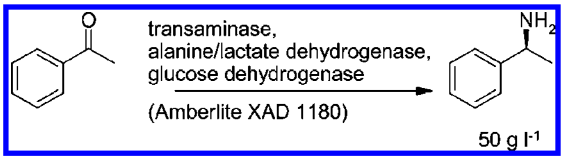
The increase in the number of applications of alcohol dehydrogenases used on scale continues unabated in 2010. Two important examples from opposite ends of the reactivity spectrum are reported here. Small chiral synthons can be difficult to prepare in high ee due to poor enantio-differentiation by many chiral catalysts. Pfizer has reported the efficient synthesis of a chiral alcohol intermediate to sulfopenem which can be run at 100 g L^{-1} and has been scaled up to 100 kg (*Org. Process Res. Dev.* **2010**, *14*, 188−192). The process is much greener than the multistep process previously used to make the synthon.



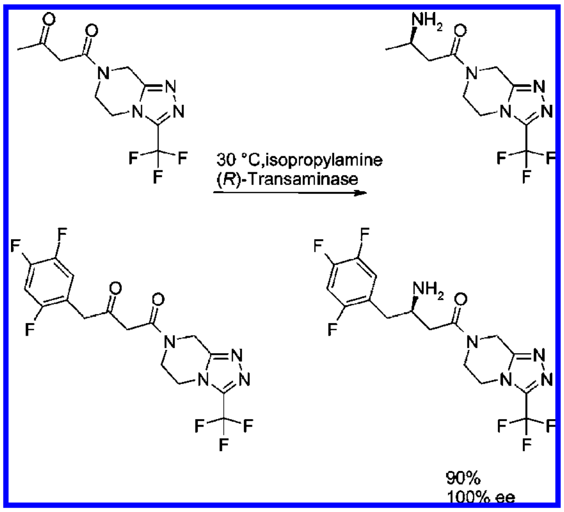
At the other end of the scale, large, very water-insoluble ketones are not attractive substrates for alcohol dehydrogenases. Liang et al. from Codexis have reported the evolution of an alcohol dehydrogenase to reduce the ketone intermediate to Montelukast (*Org. Process Res. Dev.* **2010**, *14*, 193−198). The technology was successfully proved on 170 kg batches. Isopropyl alcohol was used to recycle the cofactor. This process offers a much greener alternative to reduction with a stoichiometric boron reagent, (+)-DIP.



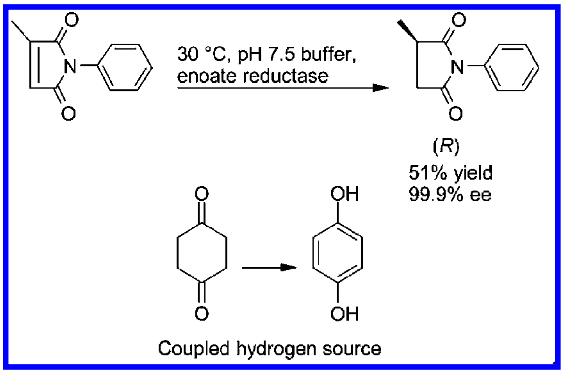
Truppo et al. have been investigating the efficiency of *ω*-transaminase reaction (*Org. Process Res. Dev.* **2010**, *14*, 234−237). Throughput can often be hindered by product inhibition of the enzyme. They reported that, for certain substrates, in situ product removal by ion exchange resins greatly increased throughput by a factor of 10. Product was isolated by removing the resin from the reaction mixture and simply eluting with aqueous base.



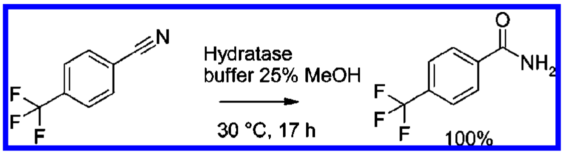
Keeping on the theme of *ω*-transaminases, Merck and Codexis have developed an (*R*)-selective transaminase for the synthesis of Januvia. This green process won a 2010 Presidential Green Challenge award. This is a stellar example of the power of modern molecular biology to rapidly develop efficient biocatalysts. Starting from a position of zero activity and a paucity of (*R*)-selective transaminases, a biocatalyst was evolved for the amination of the truncated Januvia ketone. This was then in turn evolved to efficiently turn over the API ketone (*Science* **2010**, *329*, 305−309).



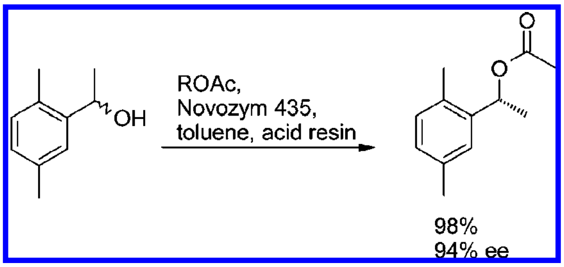
The reduction of activated alkenes to chiral products using flavoprotein oxidoreductases, e.g. Old Yellow Enzyme, is an attractive strategy since the substrates accepted are often complementary to those favored by asymmetric hydrogenation. Toogood et al. have published a comprehensive review on this enzyme class (*ChemCatChem* **2010**, *2*, 892−914). Developing efficient cofactor recycle is often a hindrance. Stueckle et al. have published an intriguing article on the use of simple organic molecules (e.g., 1,4-cyclohexanedione) as sacrificial hydrogen donors, thus avoiding dependence on nictotinamide cofactors and related coupled recycling systems (*Tetrahedron* **2010**, *66*, 663−667).



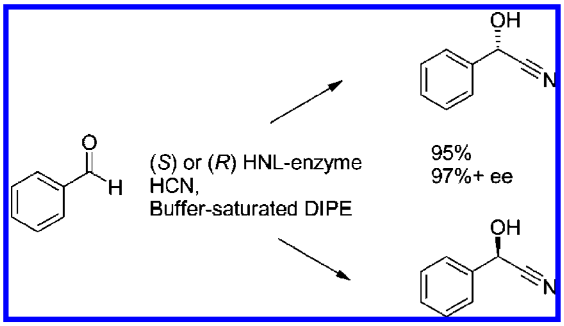
The application of nitrile hydratases that selectively hydrolyse nitriles to carboxamides has been hindered due to the poor solvent tolerance of this class of biocatalyst. Black et al. have identified a hydratase from *Rhodopseudomonas palustris* that can tolerate a range of cosolvents like DMSO and MeOH, thus greatly improving the efficiency of hydration of nitriles that are not soluble in pure water (*Tetrahedron Lett.* **2010**, *51*, 1639−1641).



The conversion of kinetic resolutions into dynamic kinetic resolutions (DKR) is a very attractive goal. With secondary alcohols, racemisation of the unwanted alcohol enantiomer is usually achieved with a ruthenium complex. This can add cost and issues with catalyst deactivation and postreaction metal removal. Cheng et al. have reported some DKR reactions where the metal has been replaced by a solid acidic resin (*Tetrahedron Lett.* **2010**, *51*, 2366−2369). These racemisation catalysts can give excellent yields and ee, but care needs to be taken that acid-catalysed transesterification does not erode the ee value of the product.



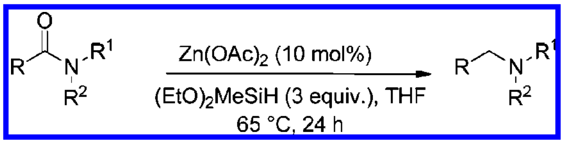
Cabirol et al. have reported an efficient synthesis of chiral cyanohydrins from benzaldehyde and hydroxynitrile lyase enzymes formulated as cross-linked enzyme aggregates (CLEAs). The reaction proceeded in organic solvent saturated with buffer. This facilitated downstream derivatisation and use of the chiral products. The CLEA catalysts could be recovered and reused (*Org. Process Res. Dev.* **2010**, *14*, 114−118).



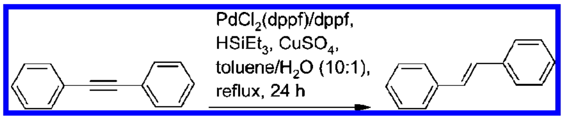
Laccase enzymes formulated as CLEAs, in combination with TEMPO, were shown to be active and reusable catalysts for the aerobic oxidation of aliphatic alcohols to aldehydes (*J. Mol. Catal. B* **2010**, *62*, 142−148).

9. Reductions

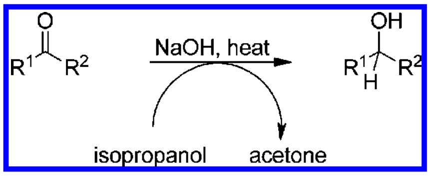
Das et al. have reported a highly chemoselective reduction of tertiary amides to the corresponding amines using silanes in the presence of zinc catalysts under mild conditions. The amide group is selectively reduced in the presence of ketone, alkene, hydrazine, ester, nitrile, and nitro groups. Yields are typically in the range 65−90% (*J. Am. Chem. Soc*. **2010**, *132*, 1770−1771). The authors published an addition recommending the use of methyldiethoxysilane following the observation that use of triethoxysilane with a Lewis acid may have resulted in the formation of silane, an extremely pyrophoric gas (*J. Am. Chem. Soc.* **2010**, *132*, 4971). Details may be found in the Supporting Information of the original communication.



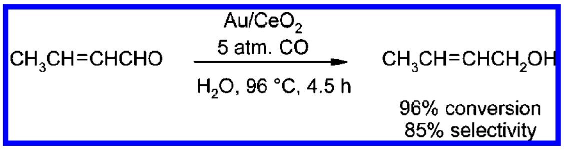
Silanes have also been employed by Luo et al. for the palladium catalysed stereoselective reduction of alkynes to the corresponding *trans*- or *cis*-alkenes (*Tetrahedron* **2010**, *66*, 1399−1403). The *trans*- product is formed in the presence of the $CuSO_4$ additive; the *cis*- adduct is obtained in the absence of the additive.



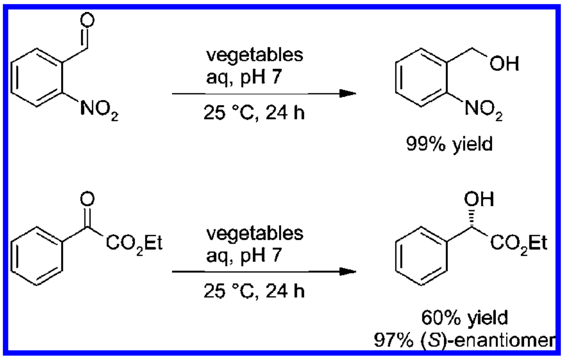
Zuidema et al. report a hydrogen transfer method for the reduction of ketones to secondary alcohols (*Synth. Commun.* **2010**, *40*, 1187−1191). Treatment of aliphatic and aromatic ketones with sodium hydroxide in boiling isopropyl alcohol for 24 h yielded the corresponding alcohols in 65−95% yield. Aldol products were not observed. Reaction times were significantly reduced under microwave conditions.



He et al. have developed an efficient ceria supported gold catalysed approach for the chemoselective reduction of α,β-unsaturated aldehydes using CO and water as the hydrogen source (*Chem. Commun.* **2010**, *46*, 1553−1555). The authors suggest this approach offers several advantages over conventional catalytic hydrogenation processes; high yields and chemoselectivity are achieved under mild conditions without the direct use of molecular hydrogen.



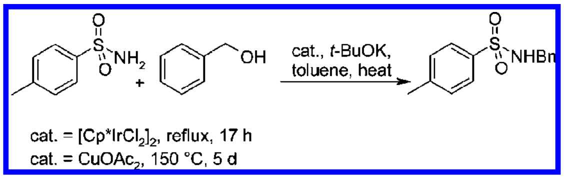
Finally, Suárez-Franco et al. present a highly sustainable bioreductive methodology for the conversion of aromatic aldehydes to the corresponding alcohols in excellent yields using homogenates of broccoli, cauliflower, beet, and spinach (*Biotechnol. Bioprocess Eng.* **2010**, *15*, 441−445). In addition, (*S*)-1-phenylethanol and (*S*)-ethyl mandelate were obtained in moderate yields from the corresponding ketones.



10. Alcohol Activation for Nucleophilic Displacement

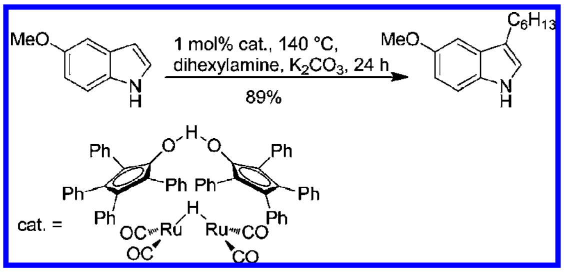
Two complementary reviews on the hydrogen autotransfer approach to alcohol activation have been published. The review by Dobereiner and Crabtree is focused on homogeneous catalysis and a range of bond forming reactions including oxidative additions leading to amides and esters. The mechanism is discussed (*Chem. Rev*. **2010**, *110*, 681−703). Guillena, Ramon, and Yus review approaches toward the alkylation of amines and cover heterogeneous and homogeneous catalyst systems as well as the use of amines as alkylating agents (*Chem. Rev.* **2010**, *110*, 1611−1641).

The challenges of heterogeneous versus homogeneous catalysis are highlighted by two papers on the alkylation of sulfonamides. Alkylation of 4-toluenesulfonamide can be achieved with benzyl alcohol in 92% yield, using potassium *tert*-butoxide in toluene. Zhu et al. use a homogeneous iridium catalyst $[Cp^*IrCl_2]Cl_2$ in a 17 h reflux (*Org. Lett.* **2010**, *12*, 1336−1339) whilst Martinez-Asencio et al. utilise copper acetate; however, the reaction requires 5 days at 150 °C to reach completion (*Tetrahedron Letters* **2010**, *51*, 325−327).

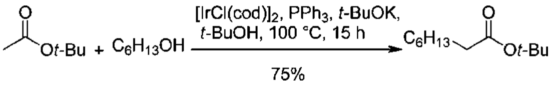


Saidi et al. report the alkylation of a range of arenesulfonamides with benzyl alcohol in the presence of $[\mathrm{Cp^*IrI_2}]\mathrm{Cl_2}$. With potassium carbonate in water at 115 °C, yields range between 25% and 74%. The authors also discuss the use of the catalyst for the alkylation of amines in water without the need for added base and present the first examples of application of the approach in an ionic liquid (*Org. Process Res. Dev.* **2010**, *14*, 1046−1049).

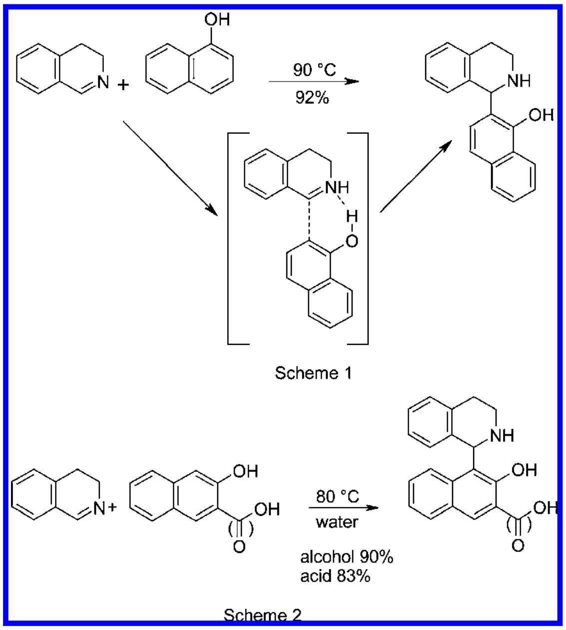
Amines have been used as the alkylating agent for the C-alkylation of indoles. Imm et al. use the Shvo catalyst, potassium carbonate (5 mol %), and 2−4 equiv of the amine in the absence of solvent. Isolated yields are >80% although the workup requires two chromatography stages (*Chem.—Eur. J.* **2010**, *16*, 2705−2709).



Iachi et al. have published an iridium catalysed α-alkylation of *tert*-butyl acetate with primary and benzylic alcohols. The reaction requires potassium *tert*-butoxide in *tert*-butanol as solvent and proceeds via condensation of the corresponding aldehyde generated in situ. The catalyst reduces the resulting α,*β*-unsaturated ester. Yields are typically >70% (*J. Am. Chem. Soc.* **2010**, *132*, 2536−2537).

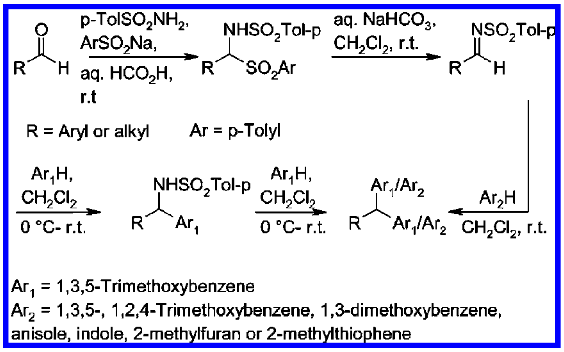


11. Friedel−Crafts Chemistry. Chao-Jun Li et al. describe a self-catalytic protocol for the preparation of 1-naphthoyl tetrahydroisoquinolines through an aza-Friedel−Crafts (aza-F−C) method run either neat or in/on water. Neat reactions of initial model substrates gave the highest yields and presented a regioselectivity indicative of a cyclic transition state enabling the self-catalysis from intrinsic functionality providing 100% atom economy (Scheme 1). Reactions were much less productive in typical organic solvents while water gave intermediate results. However, water proved invaluable in cases where electron-withdrawing substituents were present on the naphthols, pushing yields commonly into the 80−100% range. Neither 3-hydroxy-2-naphthoic acid nor 3-hydroxymethyl-2-naphthol would react neat, but they provided good yields of the expected products in degassed water (Scheme 2). Addition of 10 mol % of various acids had no effect on the output (*Tetrahedron* **2010**, *66*, 1045−1050).


Scheme 1

Scheme 2

Thirupathi and Kim present a high yielding procedure for the synthesis of triarylmethanes and bis-heteroarylarylmethanes utilizing inexpensive and relatively benign $\mathrm{FeCl_3 \cdot 6H_2O}$ as catalyst. The model reaction of the *N*-sulfonyl aldimines and 1,3,5-trimethoxybenzene did not occur with copper or rhodium iodides or in the absence of Fe(III) catalysts. Optimization studies indicated that $\mathrm{FeCl_3 \cdot 6H_2O}$ worked best and that catalyst at 2.5 mol % was preferable over higher loading. Subsequent F−C coupling with various aryl and heteroaryl compounds proceeded well, typically providing the trisubstituted methanes in 80+% yields and good selectivity. Results were typically best in dichloromethane although a comparative yield was achieved with acetonitrile in initial studies. Reactions were run comparing this method to various existing literature preparations of certain triaryl- or bis-heteroarylaryl methanes with similar outcomes (*J. Org. Chem.* **2010**, *15*, 5240−5249).

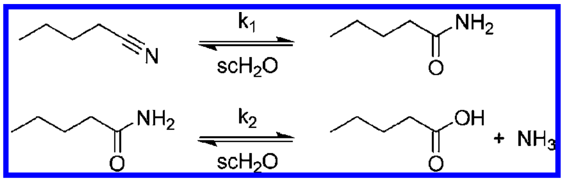


A fairly comprehensive review of recent advances in Friedel−Crafts alkylations has been compiled by Magnus Rueping and Boris Nachtsheim. The review focuses on developments in the past decade of catalytic protocols for the alkylation of arenes and heteroarenes avoiding the toxic aryl halides and stoichiometric Lewis acid methods common not long ago (*Beilstein J. Org. Chem.* **2010**, *6*, 6).

Marco Bandini, whose work has appeared in previous editions of this section, gives a positive review of a new book focussing on Friedel−Crafts acylations, in particular the catalytic and green methodologies developed recently. The book contains a comprehensive list of recent references of interest to any chemist contemplating use of F−C acylations (*J. Am. Chem. Soc.* **132**, *22*, 7822).

12. Chemistry in Water

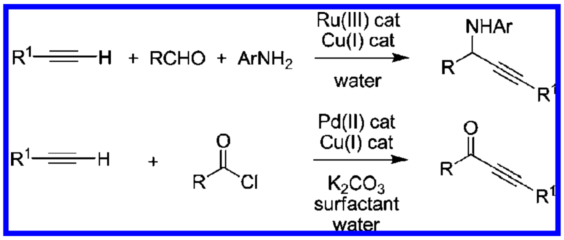
The hydrolysis of valeronitrile in supercritical water is described by Sarlea et al. (ChemSusChem **2010**, *3*, 85−90).



The kinetics of the hydrolysis of the nitrile to the amide and the acid at temperatures between 400 and 500 °C, 30 MPa pressure, and a residence time of 100 s are described in detail.

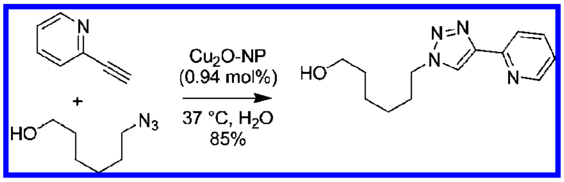
Some fundamental aspects and applications of supercritical water have recently been reviewed by Loppinet-Serani et al. (*J. Chem. Technol. Biotechnol.* **2010**, *85*, 583−589).

In a review by Chao-Jun Li an overview is given in the recent developments in the catalytic nucleophilic addition in water of terminal alkynes to aldehydes, imines, iminium ions, acid chlorides, etc. (*Acc. Chem. Rev.* **2010**, *43*, 581−590).



The addition reaction can be catalyzed by various readily available metal catalysts, such as copper, silver, gold, iron, palladium, ruthenium, and indium.

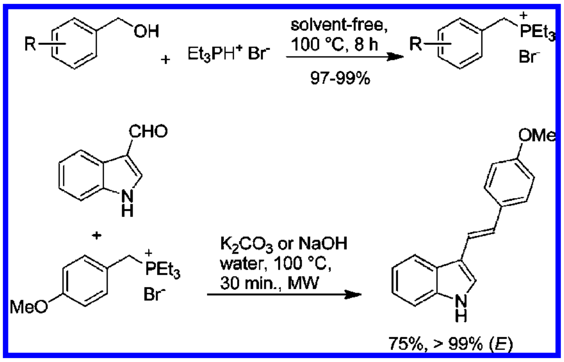
Azide−alkyne click reactions in water catalyzed by stabilized copper(I) oxide nanoparticles are described by Zhang et al. (*Adv. Synth. Catal.* **2010**, *352*, 1600−1604).



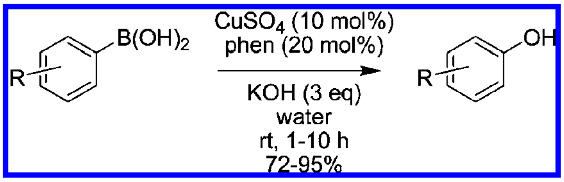
The 20 nm polyvinylpyrrolidone (PVP) coated Cu_2O nanoparticles, prepared in water from copper acetate by reduction with $NaBH_4$ in the presence of 40 kDa PVP, are used in 1 mol %.

The recently described Wittig reactions in water, as for example by McNulty and Das, have been improved with respect to the preparation of the phosphonium salts and reaction conditions (*Eur. J. Org. Chem.* **2009**, 4031−4035).

Traditional preparation of the triethylallyl and triethylbenzylphosphonium salts suffers from the odoriferous and lachrymator properties of Et_3P and allyl or benzyl halide and the easy oxidation to phosphine oxides. In a recent paper McNulty and co-workers describe the preparation of the phosphonium salts from benzylic or allylic alcohol and air-stable $Et_3P{\cdot}HBr$. In addition, the aqueous Wittig reaction is accelerated by microwave irradiation (*Chem.*—*Eur. J.* **2010**, *16*, 6756−6760).

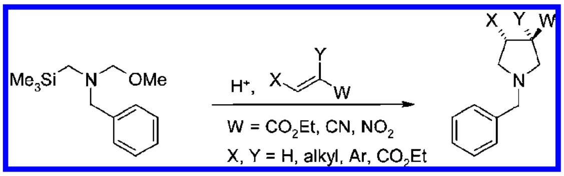


The oxidatative hydroxylation of arylboronic acids is described by Xu et al. The reaction proceeds at ambient temperature in basic water by air oxidation with $CuSO_4$ and 1,4-phenanthroline as a catalyst−ligand combination. The hydroxylation of arylboronic acids in water offers an alternative for the standard hydroxylation of arylhalides (*Org. Lett.* **2010**, *12*, 1964−1967).



13. Continuous Processing and Process Intensification

A US patent by BASF uses a continuous processing methodology for the synthesis of alkyleneimines from sulphuric acid monoesters of aminoalkanols in the presence of a base. The main characteristic of this two-stage process is the extreme operating conditions (up to 210 °C and 100 bar of pressure) applied to develop an efficient and safe process by making use of the continuous plug flow reactor characteristics of a high surface area, lower operating volumes, and greater process control (*US7683216 BB*). Pfizer scientists reported the use of flow conditions to carry out [3 + 2] dipolar cycloaddition reactions of an unstable azomethine ylide precursor with a range of electron-deficient alkenes in the presence of trifluoroacetic acid. This highlights the feasibility of using continuous processing methodology to handle highly reactive and hazardous intermediates while maintaining a lower inventory (Tetrahedron Lett. **2010**, *51*, 1026−1029).



Jensen et al. describe the synthesis of nitro-tetrazolates which involve high energy intermediates using micromixer methodology to minimise the operating volumes whilst ensuring efficient mixing and heat transfer. The authors have also carried out a detailed investigation into the various kinetic parameters influencing the formation of process components which is very important for understanding the robustness issues involved (*Ind. Eng. Chem. Res.* **2010**, *49*, 4132−4139). Hessel et al. published a review of various categories of reactions that benefit from processing within a 'Novel Operating Window' using micro- and milli-structured continuous reactors. A wide range of reactions are described which could be processed in an efficient manner compared to traditional batch processing (*Bioorg. Med. Chem.* **2010**, *18*, 3707−3719).

Ciriminna and Pagliaro published a review article on industrial oxidations employing TEMPO and its analogs for the conversion of alcohols to aldehydes, ketones, and carboxylic acids. Of most interest to the green chemistry community are the sections which review the use of TEMPO in continuous processes and as a supported catalyst. A number of examples were provided that demonstrated continuous processing offers increased throughput and product quality given the shorter reaction times that can be achieved by more rapid heat removal of highly exothermic oxidations. Use of a variety of supported catalysts was reviewed, including (1) SiliaCat TEMPO, which involves sol−gel encapsulation in a silica matrix and affords a support that is solvent independent and does not shrink or swell, (2) Merrifield resins functionalized with TEMPO, and (3) FibreCat Tempo in which TEMPO is adsorbed on a polypropylene polymer backbone (*Org. Process Res. Dev.* **2010**, *14*, 245−251).

14. General Green Chemistry

The Presidential Green Chemistry Challenge Award for greener synthetic pathways went to Dow and BASF for their zeolite catalysed epoxidation of propylene to give propylene oxide. The greener reaction conditions award went to Merck and Codexis for a new process to make sitagliptin via an evolved transaminase as discussed in section 8.

For those interested in some of the very large scale aspects of Green Chemistry as applied to biofuels or bulk chemicals, there is an excellent review published by Bozell and Peterson (*Green Chem.* **2010**, *12*, 539−554).

Nearly 20 years ago Roger Sheldon published a paper detailing typical waste levels for small molecule pharmaceuticals. Sa et al. from Pfizer has published a similar paper giving typical waste levels for large molecule pharmaceuticals (biologics) (*Green Chem.* **2010**, *12*, 755−766).

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