Green Chemistry Highlights

Green Chemistry Articles of Interest to the Pharmaceutical Industry

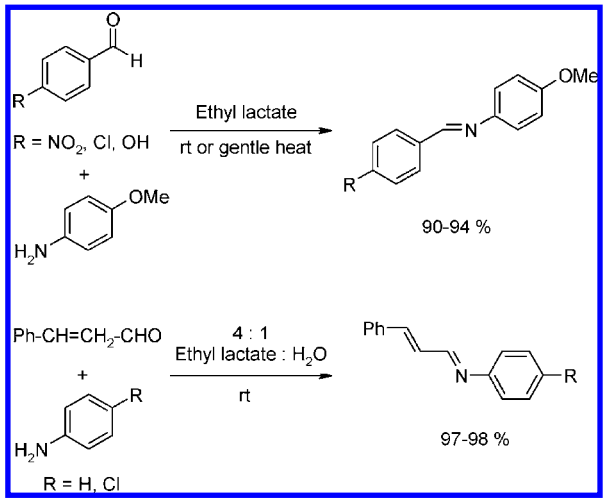
1. Introduction

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. Today, members include the ACS GCI plus 12 pharmaceutical-related companies including AstraZeneca, Boehringer Ingelheim, Codexis, DSM Pharmaceutical Products, Eli Lilly and Company, GlaxoSmithKline, Johnson & Johnson, Merck & Co., Inc., Novartis, Pfizer, Schering Plough, and Wyeth. 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, although the solvent section has been expanded and biocatalysis added. The "Greener Mitsunobu" focus area has been combined with the "Alcohol Activation for Nucleophilic Substitution" area. The review period covers the first 6 months of 2009.

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.

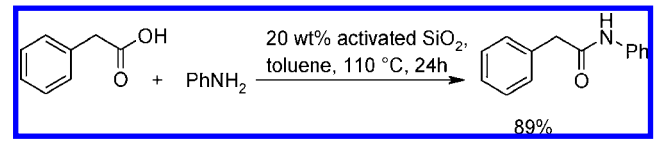
2. Solvents

Ethyl lactate is often thought of as a green solvent due to its low toxicity (it is approved by the FDA as a food additive), is derived from renewable sources, and is biodegradable. Bennett et al. report the preparation of a variety of aryl aldimines using either ethyl lactate as solvent or ethyl lactate "tuned" with up to 30% water. The workup of ethyl lactate reactions can often be a problem due to its high boiling point (154 °C) and solubility in water, but for these preparations this is not a problem as the preparations are designed as "direct drop" processes where the desired aldimine is simply filtered off, washed, and dried (*Green Chem.* **2009**, *11*, 166−168).



3. Amide Formation

Comerford et al. have published a paper (*Chem. Commun.* **2009**, 2562−2564) which described the use of activated silica to catalyse amide formation. The silica used is standard K60 flash chromatography silica which has been activated by heating to 700 °C. Twelve amide-forming reactions are reported including the one given in the scheme below.



The authors use a variety of Green Chemistry measures, E factor, atom economy etc., to compare the SiO_2 methodology with other common amide-forming reagents.

4. Oxidations

During the first half of 2009, 45 articles were published containing the keywords "green oxidation." The majority of these articles focused on improved oxidation methods that avoided use of stoichiometric metal oxidants or oxidants that minimized waste. Nearly 150 publications contained the keywords "catalytic oxidation," but only a few of these were of interest to the organic chemistry community.

Three reviews and one monograph on oxidations were published in the first half of 2009. (1) "Sustainability in Catalytic Oxidation: An Alternative Approach or a Structural Evolution" is the title of the review article of Teles and Cavani. The authors review developments in green catalytic oxidations, primarily focused on the oxidation of alkanes, including use of alternative reagents, design of new catalysts with improved selectivity, novel reactions, and advances in reactor technologies. Examples are provided which demonstrate that better sustainability is often linked to improved economics. The industrial processes for propene oxide production and processes being developed for the synthesis of adipic acid are described (*ChemSusChem* **2009**, *2*, 508−534).

(2) Hermans et al. review opportunities and challenges in selective oxidation catalysis. They stress the importance of designing sustainable oxidation processes for feedstocks that in the future will be derived from renewable sources. Oxidation

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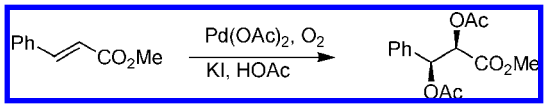
activation methodologies are discussed, including chemo- and biocatalysis, thermal, photocatalysis, and electrocatalysis. An interesting discussion on the advantages and limitations of photooxidation is presented, with the authors' belief that photocatalysis will play an increasingly important role in the future (*Top. Catal.* **2009**, *52*, 1162−1174).

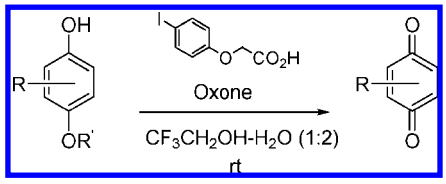
(3) Matienko, Mosolova and Zaikov reviewed the oxidation of hydrocarbons, primarily arylalkanes, using molecular oxygen and transition metals (*Russ. Chem. Rev.* **2009**, *78*, 227−247).

(4) Mizuno authored a monograph entitled "Modern Heterogeneous Oxidation Catalysis." Catalyst classes reviewed include metal oxides, polyoxometalates and zeolites. The book includes a collection of 7 chapters in a section entitled "Recent Achievements and Challenges for a Greener Chemical Industry."

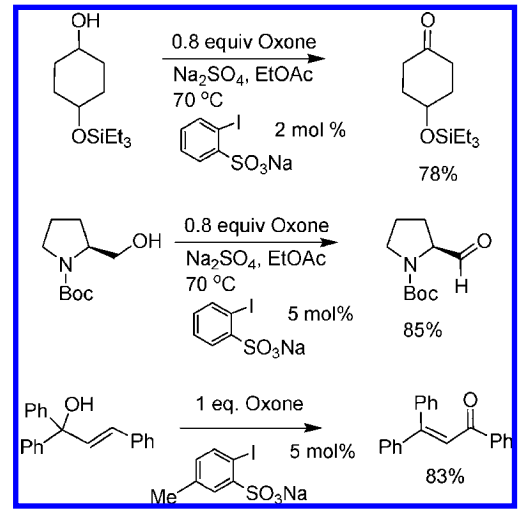
Wang, Jiang, and Chen describe the diacetoxylation of alkenes using catalytic palladium and molecular oxygen. The process avoids the use of stoichiometric oxidants such as $PhI(OAc)_2$ and also avoids toxic metals generally associated with dihydroxylation chemistry, such as osmium. The process is highly diastereoselective, which the authors propose is due to a cis-acetoxylpalladation step in the catalytic cycle (*J. Am. Chem. Soc.* **2009**, *131*, 3846−3847).



2-Iodoxybenzoic acid (IBX), which is readily prepared from 2-iodobenzoic acid and Oxone, is a popular stoichiometric oxidant for the oxidation of alcohols to ketones. Two alternative methods were recently reported. 4-Iodophenoxyacetic acid, in conjunction with Oxone, has been developed by Yakura et al. as a superior system for the oxidation of *p*-alkoxyphenols to *p*-benzoquinones. Used at the 20 mol % level, this reagent afforded the quinones in 78 − 99% yields in trifluoroethanol−water (1:2) as solvent. In contrast, 2-iodobenzoic acid resulted in complex reaction mixtures with yields <40% (*Chem. Pharm. Bull.* **2009**, *57*, 252−256).

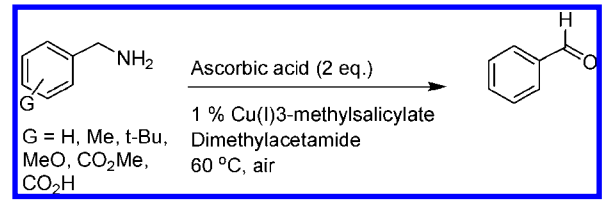


Uyanik, Akakura, and Ishihara have disclosed 2-iodoxybenzenesulfonic acid (IBS) as a more active catalyst for the selective oxidation of alcohols to aldehydes, ketones and carboxylic acids using Oxone. Typically 1 to 5 mol % of the sulfonic acid is used in conjunction with 0.6 to 0.8 equiv of Oxone. The reaction is carried out in nonaqueous solvents including acetonitrile, ethyl acetate and nitromethane. The byproduct from Oxone can be simply removed by filtration. The power of this catalytic method is shown in the oxidation of alcohols containing acid-sensitive functional groups such as silyl ethers and ketals, in the oxidation of alcohols to aldehydes, and in the oxidative rearrangement of tertiary allylic alcohols to enones (*J. Am. Chem. Soc.* **2009**, *131*, 251−262; *Org. Lett.* **2009**, *11*, 3470−3473).

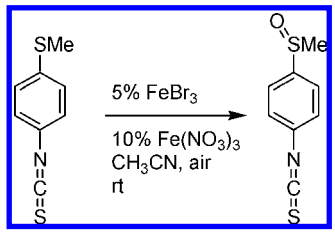


Shibuya et al. developed a versatile one-pot oxidation of primary alcohols to carboxylic acids using an oxidation system consisting of $NaClO_2$ and a catalytic amount of the azaadamantane *N*-oxide, 1-Me-AZADO. This system avoids the generation of NaOCl, which causes overoxidation of many classes of substrates, by its consumption by the hydroxylamine which is formed upon alcohol oxidation with the *N*-oxide. This results in a milder and more selective oxidation system which is demonstrated in the high yielding oxidation of the electron-rich 1-(3,4-dimethoxyphenyl)-2-ethanol (*Chem. Commun.* **2009**, 1739−1741).

Traditional oxidation of amines typically involves stoichiometric use of metallic reagents that have poor substrate compatibility and generate large quantities of toxic waste. As an alternative, Srogl and Voltrova reported an aerobic oxidation of amines to carbonyl compounds based on catalytic copper (1 mol %) with stoichiometric ascorbic acid as oxidative mediator and oxygen as the terminal oxidant. Good yields were obtained in the oxidation of both electron-rich and electron-poor benzylic amines to the corresponding benzaldehydes (*Org. Lett.* **2009**, *11*, 843−845).

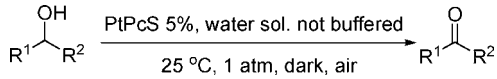


While a number of sulfide to sulfoxide oxidations are known, Kinen, Rossi, and Rossi have developed a mild oxidation system that affords clean oxidations of labile substrates. The authors use as catalyst either $FeBr_3$ or its complex with β-cyclodextrin or as its DMSO complex, ferric nitrate (10 mol %) as the oxidation promoter, and air as the terminal oxidant. Acetonitrile is the preferred solvent. Using these conditions, 4-(methylthio)phenylisothiocynanate is oxidized to the corresponding sulfoxide in high yield (*Green Chem.* **2009**, *11*, 223−228).



In recent years several groups have reported the use of supported gold catalysts for the oxidation of alcohols to aldehydes and ketones. These protocols, however, have suffered from the required use of organic solvents and strong bases to afford high yields. Ni et al. have now identified an oxidation system carried out under neutral conditions with H_2O_2 in water. Using gold supported on TiO_2 as catalyst, unactivated alcohols are converted to the corresponding carbonyl products in good yields. Control experiments demonstrated the high activity of the catalyst is a function of both the high dispersion of gold on the support as well as a synergistic effect with TiO_2 (*Green Chem.* **2009**, *11*, 756−759).

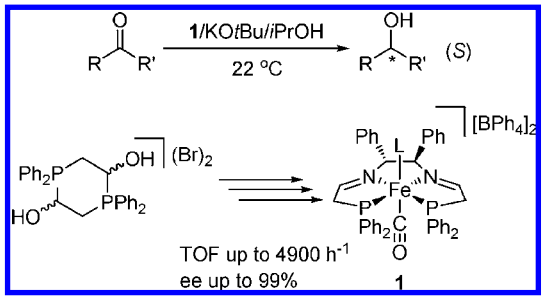
A catalytic aerobic oxidation of allylic alcohols to the corresponding aldehyde or ketone has been developed by Tonucci et al. using a water-soluble platinum tetrasulfophthalocyanine catalyst. The reactions take place in water at room temperature using ambient air as the oxidant. The reactions, however, are quite slow, requiring 2 weeks to reach 70 − 90% conversion using a catalyst concentration of 5 mM (*Green Chem.* **2009**, *11*, 816−820).



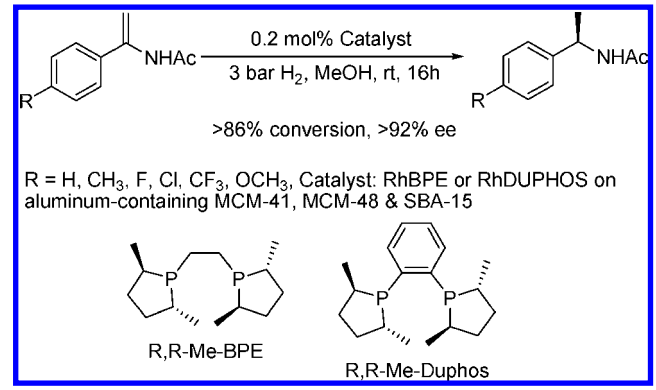
5. Asymmetric Hydrogenations

A review paper is published in *Chem. Soc. Rev.* **2009**, *38*, 2282−2291, introducing the applications of greener iron catalysts in asymmetric hydrogenation and transfer hydrogenation of ketones. Iron catalysts are much less expensive and more environmentally friendly than palladium and ruthenium catalysts.

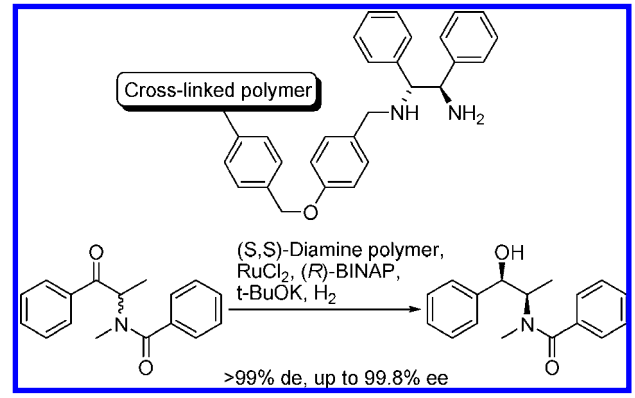
As an improvement to their work in 2008, Mikhailine et al. have discovered a new iron catalyst (**1**) for the asymmetric transfer hydrogenation of ketones. This catalyst has significantly higher activity and selectivity (*J. Am. Chem. Soc.* **2009**, *131*, 1394−1395).



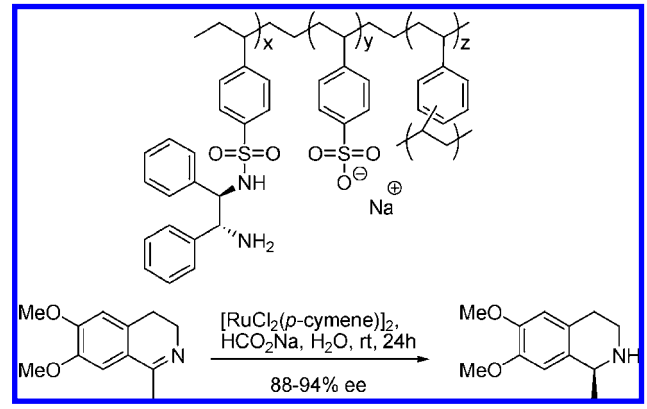
Crosman and Hoelderich reported heterogeneous chiral catalysts of immobilized rhodium diphosphine complexes on aluminium-containing MCM-41, MCM-48, and SBA-15 type materials. The immobilized catalysts showed high activities and excellent chemo- and enantioselectivities in the hydrogenation of α-arylenamides. The catalysts could be reused at least four times without any activity loss, obtaining TON larger than 2000 (*J. Catal.* **2009**, *265*, 229−237).



Chiwara et al. successfully prepared various types of polymer-immobilized catalysts of chiral diamine-ruthenium-BINAP-t-BuOK system. Asymmetric hydrogenation using these catalysts yields *syn*-*β*-amide alcohol exclusively with nearly perfect enantioselectivities. The polymer-immobilized catalysts could be reused several times without loss of activity (*J. Org. Chem.* **2009**, *74*, 1391−1393).



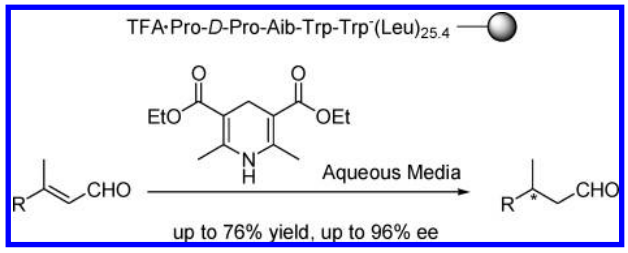
As an extension of their work in 2008, Haraguchi et al. developed the catalytic asymmetric transfer hydrogenation of imines with the use of a polymer-immobilized chiral ruthenium catalyst both in organic solvent and in water. The corresponding amines were obtained in good yields with good enantioselectivities (*Org. Biomol. Chem.* **2009**, *7*, 69−75).



Two groups have explored magnetically separable catalysts in asymmetric hydrogenation and transfer hydrogenation.

Panella et al. prepared the catalyst of chirally modified Pt supported on Fe_3O_4 nanoparticles dispersed in a silica matrix, and applied it for the enantioselective hydrogenation of various activated ketones. The novel catalyst can be easily separated from the reaction solution by applying an external magnetic field and recycled several times with almost complete retention of activity and enantioselectivity (*J. Catal.* **2009**, *261*, 88−93). Li et al. reported a magnetically recoverable ruthenium catalyst, which combines the merits of mesoporous silicas and magnetic nanoparticles. This heterogeneous catalyst afforded high catalytic activities and enantioselectivities in the asymmetric transfer hydrogenation of imines and aromatic ketones. This catalyst can be easily recovered and reused at least nine times without noticeable loss of ee values (*J. Mol. Catal. A: Chem.* **2009**, *298*, 31−35).

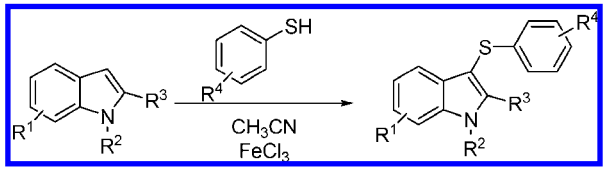
Akagawa et al. developed a resin-supported N-terminal prolyl peptide having a β-turn motif and a polyleucine tether for the organocatalytic asymmetric transfer hydrogenation under aqueous condition (*Tetrahedron: Asymmetry* **2009**, *20*, 461−466).



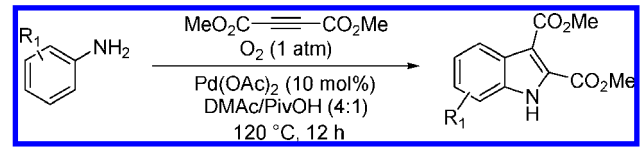
6. C−H Activation

Tetrahedron 65(16) recognizes the Tetrahedron Young Investigator's Award for 2008 that was awarded to Professor Justin Du Bois at the Tetrahedron Symposium in July 2008. In addition to an article by Du Bois highlighting his work with Rh-catalyzed intramolecular C−H aminations, several additional C−H activation papers covering a range of functionality follow.

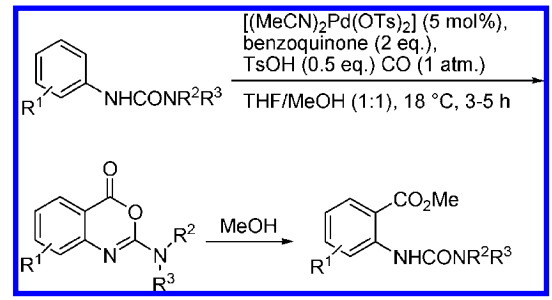
Yadav et al. describe the formation of 3-arylthioindoles by the reaction of thiols with indoles in refluxing acetonitrile with 20 mol % anhydrous $FeCl_3$ (*Synthesis* **2009**, 1520−1524). Reaction times range from 6 to 7 h and yields range from 80 to 92% with a wide range of functionality at various positions on the indole and thiol. It is also worth noting that benzyl thiol and mercaptobenzothiazole also work well under these conditions. Reaction is only observed at the 3 position of the indole in all cases.



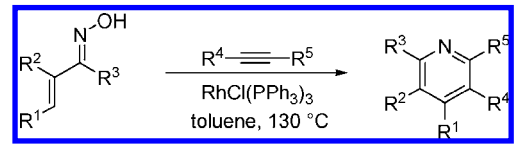
The formation of indoles from anilines and alkynes was investigated by Shi et al. (*Angew. Chem., Int. Ed.* **2009**, *48*, 4572−4576). The reactions work best in a 4:1 mixture of DMAc and pivaloyl alcohol with 10 mol % $Pd(Ac)_2$ under 1 atm of oxygen at 120 °C without any ligand or base. These conditions were amenable to a variety of functional groups and substitution on the aniline ring. Yields range from >95% for alkyl substitutions to 38% for 4-aminophenol. Other substituted alkynes were investigated with slightly lower yields compared with dimethyl butynedioate.



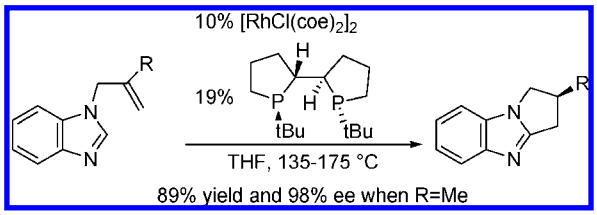
While many C−H activations require high temperatures, Houlden et al. report on the room temperature ortho-carbonylation of aniline derivatives (*Angew. Chem., Int. Ed.* **2009**, *48*, 1830−1833). After room temperature activation and carbonylation, reaction conditions can be utilized to isolate cyclic imidates or methanol solvolysis can be used to generate methyl anthranilates. Substitution on the aromatic ring was well tolerated but electron withdrawing groups benefited from higher reaction temperatures. Yields ranged from 90% for an unsubstituted aryl ring to 5% for the *p*-CF_3 group (increased to 30% at 50 °C). Starting from *N*-aryl urea derivatives, quinazalones can also be generated in one step in 80% yield utilizing this methodology.



Parthasarathy and Cheng report on the rhodium-catalyzed gram-scale synthesis of substituted pyridines from oximes and alkynes (*Synthesis* **2009**, 1400−1402). The oximes were available in one step by reaction of the appropriate ketone with hydroxylamine and then reacted with commercially available alkynes. Reactions were conducted in Schlenk glassware on 2 g scale and the best yield (84%) was observed when R^1, R^2, R^3 = Me and R^5, R^6 = Ph.

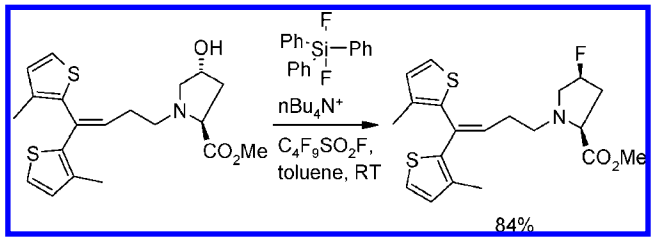


The intramolecular cyclization of substituted imidazoles with high enantioselectivity was investigated by Tsai et al. (*Chem. Commun.* **2009**, 3910−3912). This methodology was a chiral follow-up to previous work conducted by their group investigating the achiral cyclization. An extensive ligand screen resulted in the identification of TangPhos as the ligand of choice. The reaction conditions were tolerant of aryl functionality when R was a substituted aryl group. Electron-rich and electron-poor substitution on the benzimidazole both required higher temperatures and showed slightly lower enantioselectivity.

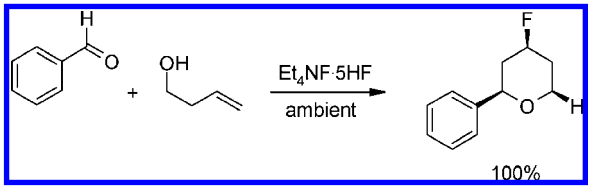


7. Greener Fluorination

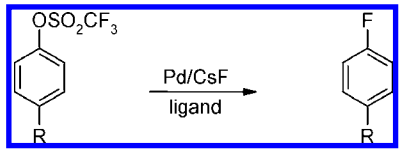
Factors that can severely limit the yields of fluorides obtained from the direct fluorination of primary and secondary alcohols are the formation of byproducts resulting from elimination, and in the case of chiral secondary alcohols, epimerization at the chiral centre. Whilst not practically atom-efficient, Zhao et al. (*Synlett* **2009**, 779−782) have reported that a combination of perfluorobutanesulphonyl fluoride and tetrabutylammonium triphenyldifluorosilicate, under mild conditions, could significantly decrease these undesired side reactions. The alcohol is converted to the perfluorobutanesulphonate ester in situ.



Kishi et al. (*Eur. J. Org. Chem.* **2009**, 103−109) have published on the Prins and related reactions of aldehydes and homoallylic alcohols. These reactions give 4-fluorotetrahydopyrans with high degrees of cis selectivity, except for benzaldehydes with strongly electron-withdrawing groups. Ionic liquid-HF salts such as $Et_4NF \cdot 5HF$ acted as the reaction medium, catalyst and source of fluoride ion.



Watson et al. have published a communication (*Science* **2009**, *325*, 1661−1664) describing the successful reductive elimination of an aryl fluoride from a Pd complex. This was further elaborated into a process to prepare aryl fluorides from the corresponding triflates and CsF under Pd catalysis avoiding harsh oxidants and stoichiometric metals. Although in some cases unexpected regio-isomers were detected, the results are promising for the development of this technology as a route to multifunctionalised aryl fluorides from triflates or bromides.



Tetraalkyl ammonium fluorides are widely employed both as base catalysts and as convenient sources of fluoride for the synthesis of fluorinated molecules. Solid/polymer-supported versions of these reagents often have operational advantages such as being less hygroscopic and easier to recover and recycle. Fringuelli and co-workers (*Curr. Org. Syn.* **2009**, *6*, 203−218) have published a review on the use of these materials in a range of reactions.

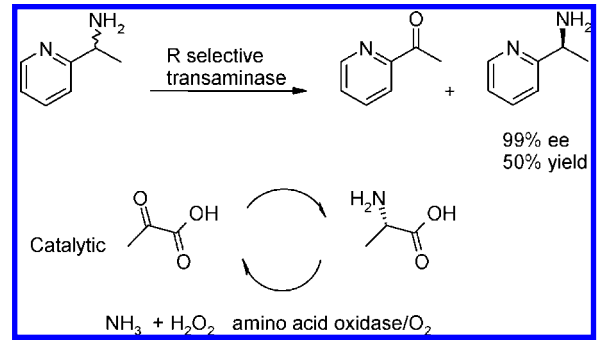
The safe and reliable use of various fluorination methods including nucleophilic fluorination (DAST), trifluoromethylation (Ruppert's reagent) and electrophilic fluorination (Selectfluor) in a continuous-flow microreactor is reported by the Ley group (*Tetrahedron* **2009**, *65*, 6111−6625).

Special attention was given to the use of in-line scavenging procedures in order to obtain clean products without the need for further purification. Working under pressure and being able to superheat solvents gave good increases in reaction rate.

Finally, a comprehensive review (*Curr. Org. Chem.* **2009**, *13*, 47−70) of halogenations under solvent free conditions has been published, including the construction of a wide variety of carbon−fluorine bonds.

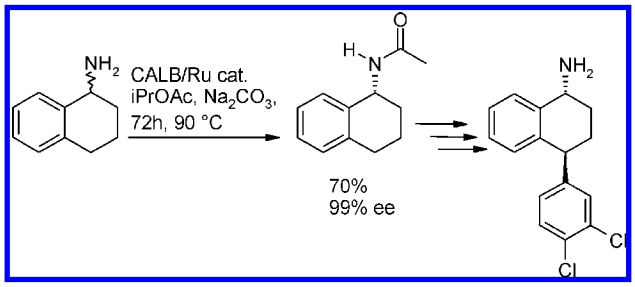
8. Biocatalysis

Truppo et al. have described a process for the resolution of amines using a transaminase in combination with an amino acid oxidase and a catalytic amount of pyruvate as the amine acceptor. This overcomes the inherent limitation in productivity of such systems due to inhibition of ω-transaminase at higher pyruvate concentrations. A range of benzylamines were resolved with excellent ee (99%$^+$) and conversion (50%). The amine enantiomer could be selected via *S*- or *R*-selective transaminase (*Chem. Commun.* **2009**, 2127−2129).

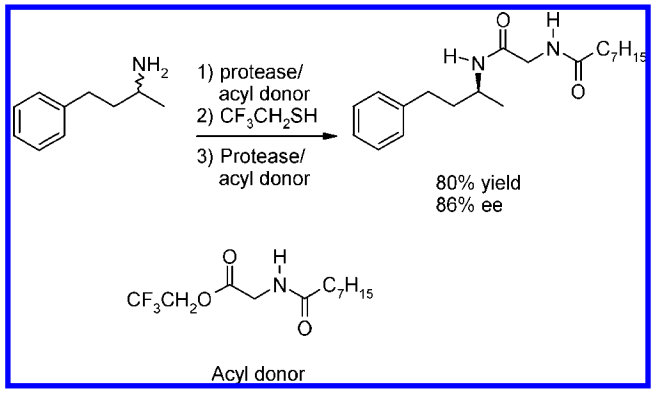


A chemoenzymic approach to chiral amines has been published by the Backvall group (*Chem.—Eur. J.* **2009**, *15*, 3403−3410). Racemisation with a Shvo-type Ru catalyst in conjunction with kinetic resolution by acylation with donors, for example isopropyl acetate/bibenzylcarbonate and Novozym 435, gave the corresponding *R*-amides/carbamates in high yield and high purity. Carbamates could be deprotected under mild hydrogenolysis. This dynamic kinetic resolution was applied to a range of structural classes of amines giving yields of 60−95%, and ee of 90−99%. The

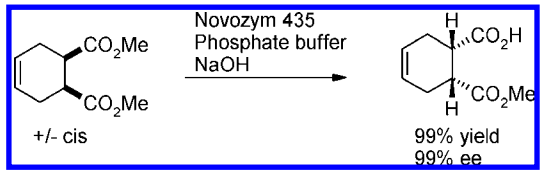
developed methodology was applied to a synthesis of norsertraline.



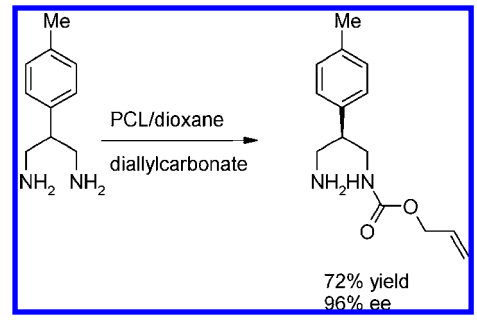
A drawback of the above methodology to generate chiral amines/amides is that the enantiomer of the product is governed by the enantioselectivity of the enzyme catalyst; usually Novozym 435 or other variants of the *Candida antarctica B* lipase, which, as with most other lipases, yields *R*-stereoisomers. Blidi (*J. Org. Chem.* **2009**, *74*, 2901−2903) has developed an amine DKR using *S*-selective alkaline proteases with glycine analogues as acyl donors. Unusually for this class of reaction, racemisation of the undesired amine enantiomer was performed with a thio radical in a 'one pot' process but sequential to the enzyme kinetic resolution followed by a second resolution. Whilst not yet offering the very high ee found with *C. antartica B* lipase, this work shows that *S* amines (78−94% ee) may be accessible via DKR, and demonstrates an alternative to metal catalysed racemisation of the undesired amine enantiomer.



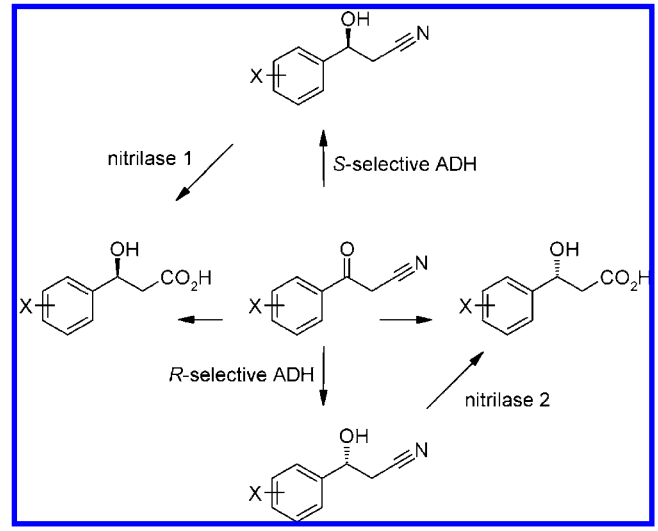
One of the most productive routes to chiral synthons is via enzymic desymmetrisation of simple meso compounds. Goswami and Kissick, from Bristol-Myers Squibb, (*Org. Process Res. Dev.* **2009**, *13*, 483−488) have described an efficient process catalysed by *C. antarctica B* lipase to prepare a chiral monoester from the corresponding meso compound. The enantiomer obtained is the opposite of that obtained from a pig liver esterase hydrolysis.



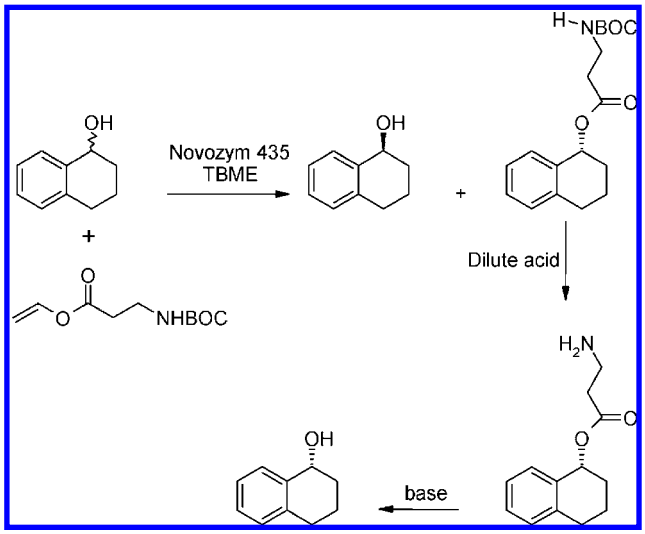
In a similar theme, the desymmetrisation of 2- substituted 1,3-diamines has been described (*J. Org. Chem.* **2009**, *74*, 2571−2574) using *Pseudomonas cepacia* lipase and diallycarbonate as the acyl donor. 2-Aryl-substituted compounds generally gave the best ee values.



Enantiopure β-hydroxy acids and nitriles are useful synthons and Ankati et al. (*J. Org. Chem.* **2009**, *74*, 1658−1662) have shown that they can be efficiently prepared via reduction with an alcohol dehydrogenase, followed by hydrolysis of the nitrile function with a nitrilase. By correct choice of dehydrogenase, both enantiomers are accessible. Aryl and alkyl examples are reported; with aryl compounds giving ee in the range 95−99%. The application of a nitrilase to perform the hydrolysis reduces side reactions and maintains chiral integrity. The β-hydroxy acids can be prepared in a 'one pot' process by sequential addition of the two enzymes.



In the enzyme-catalysed resolution of racemic alcohols, a factor detracting from operability at scale and green credentials is the need to efficiently separate the alcohol and ester enantiomers. This becomes unattractive if chromatography has to be employed. A number of technical solutions exist to overcome this separation issue. Brossat et al. (*Org. Process Res. Dev.* **2009**, *13*, 706−709) have described a simple ester tag that enables the ester enantiomer to be extracted into dilute aqueous acid; hence a simple and straightforward separation is achieved. The *R* enantiomer can be recovered via simple base hydrolysis of the ester.



A factor which often limits the productivity and economic viability of enzyme processes employing supported enzymes is loss of activity. Wiemann et al. (*Org. Process Res. Dev.* **2009**, *13*, 617−620) describe a simple procedure for coating commercially available enzyme resins, for example Novozym 435 with a silicon polymer. This procedure gives an active catalyst that is much more robust to mechanical abrasion and with reduced enzyme leakage.

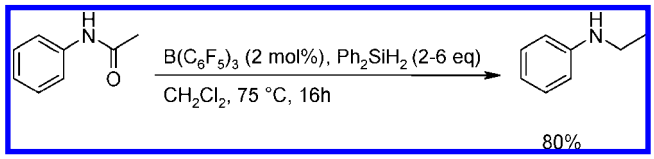
Review Articles of Interest. Matsuda et al. have reviewed recent progress in the development of biocatalysts for asymmetric oxidation and reduction (*Tetrahedron: Asymmetry* **2009**, *20*, 513−557).

Kayser (*Tetrahedron* **2009**, *65*, 947−974) has published a review on 'designer' recombinant microorganisms. The focus is on oxidation, especially advances in the use and application of Baeyer−Villigerases.

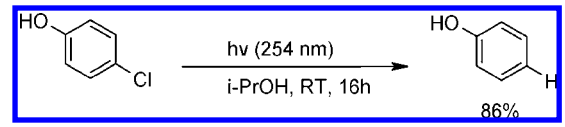
Höhne and Bornscheuer have provided a concise and up-to date review of biocatalytic routes to prepare chiral amines (*ChemCatChem* **2009**, *1*, 42−51).

9. Reductions

Tan and Zhang have extended the concept of organocatalysis using Lewis acidic $B(C_6F_5)_3$ in metal-free catalytic hydrogenation reactions from imine and nitrile reductions to include various new groups, such as amides, carbonyls, enamines and enol esters. Diphenylsilane gave hydrogenation products, rather than hydrosilylation, under the mild conditions and while the authors found dichloromethane was a good solvent, toluene and acetonitrile were suitable for certain substrates (*Tetrahedron Lett.* **2009**, *50*, 4912−4915).



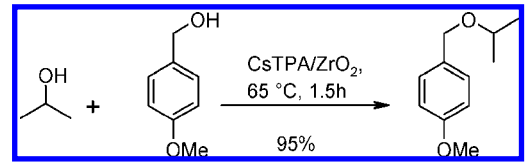
An unusual approach to aryl chloride and fluoride hydrodehalogenation is reported by Dichiarante et al. that avoids the use of metal catalysts or hydrides. A series of electron rich aryl halides are reduced at room temperature, including phenols, methyl ethers and anilines, via irradiation in neat isopropanol (*Green Chem.* **2009**, *11*, 942−945). Hypophosphorous acid in either acetone/water or acetonitrile/water was also found to be a complementary system in many cases.



While a possible drawback of using photochemistry is the large consumption of energy by the UV lamps, a related paper by the same group attempts to tackle this criticism. By comparing a series of carbon−carbon bond forming reactions under thermal and photochemical activation using a simplified life-cycle analysis tool (EATOS) the authors observed that many photochemical reactions are not currently satisfactory from an environmental viewpoint. However, they conclude that changes identified by the life-cycle analysis could rectify this judgment - a finding that adds weight to the argument that all newly reported "environmental" processes would benefit from this simple evaluation to support their claims (*Green Chem.* **2009**, *11*, 239−249).

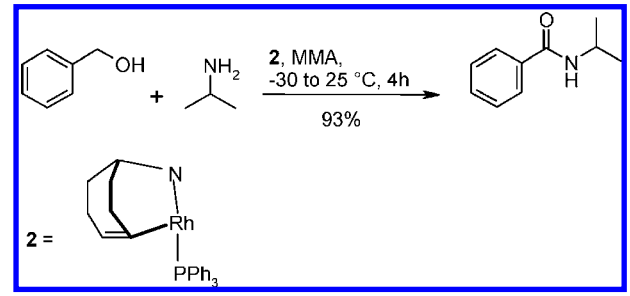
10. Alcohol Activation for Nucleophilic Displacement

In a paper that may prove of interest in the pursuit of greener ether solvents, Rao et al. report the preparation and use of zirconia supported cesium exchanged 12-tungstophosphoric acid catalysts for the synthesis of a wide range of unsymmetrical ethers from primary and secondary alcohols (*Catal. Commun.* **2009**, *10*, 1394−1397). The catalyst is reusable without any loss in catalytic activity and the only reaction byproduct is water.

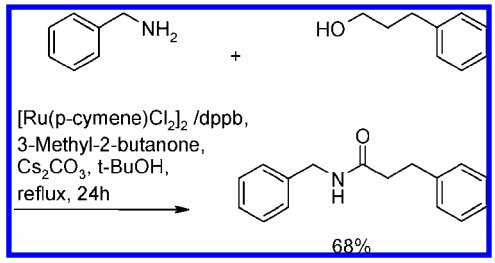


A number of examples of the hydrogen borrowing approach towards activation of primary and secondary alcohols have been published and the area has recently been reviewed by Nixon et al. (*Dalton Trans.* **2009**, 753−762).

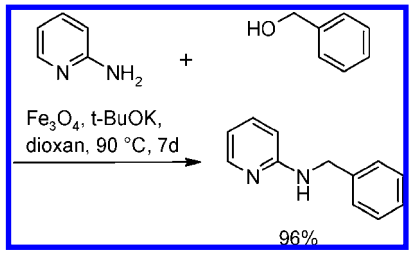
Zweifel et al. describe the use of the highly active catalyst **(2)** for the coupling of primary alcohols with water, methanol or amines in the presence of either cyclohexanone or methyl methacrylate as hydrogen acceptor to give carboxylic acids, esters and amides (*Angew. Chem., Int. Ed.* **2009**, *48*, 559−563). Reported yields are high, reaction conditions very mild and typical catalyst loading 0.1 mol %.



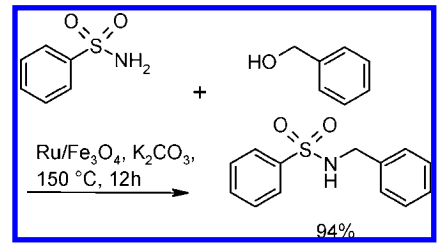
In a similar vein, Watson et al. report the synthesis of secondary amides from primary alcohols and amines using a catalyst comprised of commercially available [Ru(p-cymene)Cl_2]$_2$ and bis(diphenylphosphino)butane (dppb) in the presence of 3-methyl-2-butanone as hydrogen acceptor (*Org Lett.* **2009**, *11*, 2667−2670). Interestingly, a single example of a tertiary morpholine amide is also reported. Catalyst loading is 2.5 mol % and reported yields are good although reaction does require 24 h at reflux.



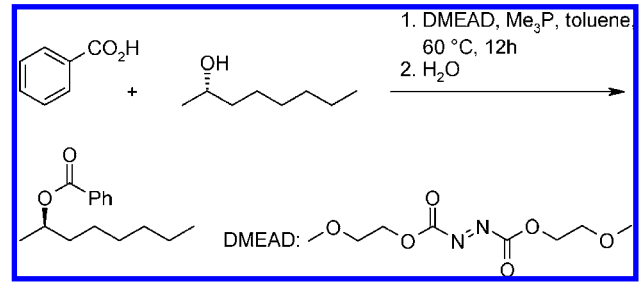
Alternative metals to iridium, rhodium and ruthenium catalysts are gaining increasing attention in the field of hydrogen borrowing and recent publications have explored the use of heterogeneous catalysts. Shimizu et al. report the preparation and use of alumina supported silver subnanoclusters for the direct C−C cross-coupling of primary and secondary alcohols (*Angew. Chem., Int. Ed.* **2009**, *48*, 3982−3986). The reaction is carried out in toluene at 115 °C in the presence of 20 mol % Cs_2CO_3 and 4 mol % Ag catalyst. Yields are typically >70% and the catalyst can be recycled. Kim et al. have applied a recyclable gold nanoparticle catalyst for the aerobic alcohol oxidation and C−C bond forming reaction between primary alcohols and ketones (*Tetrahedron* **2009**, *65*, 1461−1466). The reaction is carried out in toluene at 25 °C in the presence of 3 equiv of Cs_2CO_3 and 1 mol % Au catalyst. This catalyst is also described as a stand alone method for the oxidation of primary and secondary alcohols. In a first of its kind, Martínez et al. report the use of unmodified magnetite in the selective N-monoalkylation of aromatic amines with benzylic alcohols (*Org. Biomol. Chem.* **2009**, *7*, 2176−2181). The reaction is carried out at 90 °C in the presence of 2 equivalents of ^{t}BuOK and 20 mol % Fe_3O_4 catalyst and works best with poorly nucleophilic amines. In such cases yields are typically >80% and, although the reaction is in dioxan and takes 7 days, this does represent an interesting application of a cheap and readily available catalyst.



Continuing the C−N bond forming theme, Shi et al. describe the use of a magnetite-supported Ru catalyst for the efficient N-alkylation of sulfonamides with benzylic alcohols (*J. Am. Chem. Soc.* **2009**, *131*, 1775−1779). The reaction is carried out neat at 150 °C in the presence of 2 mol % K_2CO_3 and 0.4 mol % Ru catalyst. Yields are typically >80% and, due to its magnetic property, the catalyst can be easily recycled.

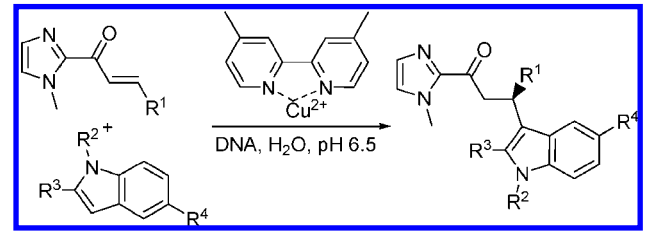


Kumara Swamy et al. have published a comprehensive review of the Mitsunobu and Related Reactions (*Chem. Rev.* **2009**, *109*, 2551−2651). The review contains 1855 references and includes modified protocols in section 9. The authors acknowledge the need for greener methods. Hagiya et al. present di-2-methoxyethyl azodicarboxylate (DMEAD) as a replacement for DEAD/DIAD in Mitsunobu protocols (*Tetrahedron* **2009**, *65*, 6109−6114). The resulting hydrazine is water-soluble and easily recovered for reoxidation. Use of trimethylphosphine allows separation of both byproduct through aqueous extraction, although the pyrophoric nature of trimethylphosphine presents handling and safety issues.



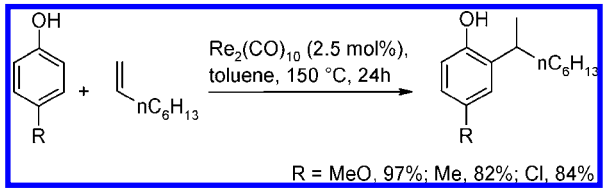
11. Friedel−Crafts Chemistry

Boersma et al. claim the first catalytic asymmetric Friedel−Crafts alkylation reaction with olefins using water as the solvent and mediated by a DNA-based catalyst. A hybrid catalyst generated by noncovalent binding of a transition metal complex to DNA allows transfer of chirality from the double helix DNA structure to the catalyzed reaction. Various alkylations were performed with low loading of catalyst derived from a cheap, natural source of DNA along with a simple Cu(II) complex in good yields (60 − 87%) and ee (69 − 82) (*Angew. Chem., Int. Ed.* **2009**, *48*, 3346−3348).



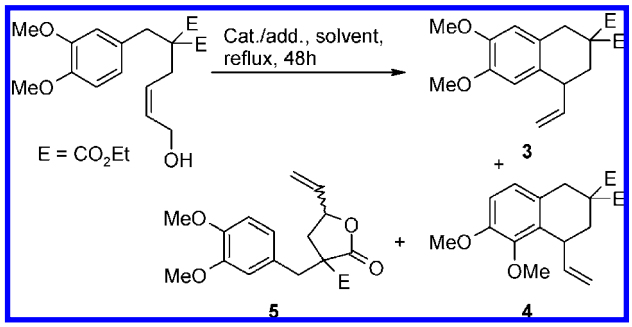
A communication from Kuninobu et al. reveals regioselective hydroarylation of terminal olefins with various phenolic compounds utilizing catalytic $Re_2(CO)_{10}$. Forma-

tion of primarily monosubstituted phenols with good regioselectivity is a highlight uncommon in typical FC reaction systems for these compounds (*J. Am. Chem. Soc.* **2009**, *131*, 9914−9915).

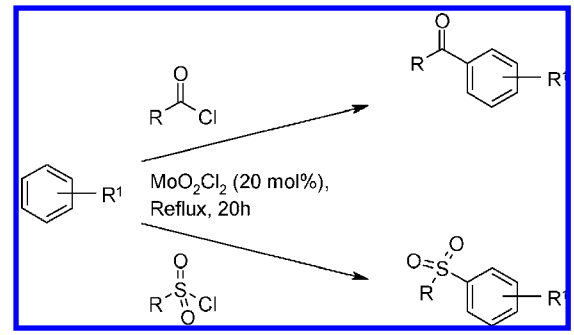


Alternatively, couplings with *gem*-disubstituted olefins preferentially formed *para*-substituted compounds.

Bandini and Tragni present a review summarizing recent advances in the direct use of π-activated alcohols for the regio- and stereospecific elaboration of various arenes via Friedel−Crafts protocols. Activation mechanisms and catalysts are discussed in relation to benzylic, propargylic, and allylic alcohols, as well as many specific catalysts and chemistries (*Org. Biomol. Chem.* **2009**, *7*, 1501−1507). The same group elucidate a particular case of intramolecular Friedel−Crafts allylic alkylation of arenes via direct activation of tethered allylic alcohols with AgOTf as an additive to various catalysts and by itself. Au, Ir, Mo, Pt, and Ru catalysts were employed providing varying mixtures and yields of **3**, **4**, and **5**. Silver and Au/Ag demonstrated specific formation of **3** (desired product), with the highest yield (89%) arising from the use of AgOTf alone. Interestingly, the Ir catalyst's selectivity for **3** over **5** was practically reversed by the inclusion of $AgSbF_6$ in place of AgOTf. None of the solvents used (dioxane for mixed systems and dichloroethane for Ag alone) is ideal for green chemistry, but substitutes may be available (*Adv. Synth. Catal.* **2009**, *351*, 319−324).



Use of MoO_2Cl_2 as a catalyst for Friedel−Crafts acylation and sulfonylation is detailed by de Noronha et al. Model reactions utilizing acyl and sulfonyl chlorides show good yields and regioselectivity. Solvent effects were studied in the acylation of anisole with *p*-toluoyl chloride. The neat mixture provided 85% yield, while in bromobenzene, which is inert under the reaction conditions, 82% was returned, each exclusively *para*-addition. Acetonitrile and dichloromethane did not perform as well with lower yields and slightly less selectivity. Variable yields were obtained, approaching 90% in the best cases (*Tetrahedron Lett.* **2009**, *50*, 1407−1410).

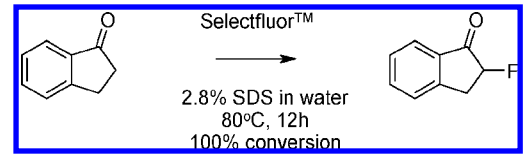


12. Chemistry in Water

A review paper giving an overview of the recent advances in the area of asymmetric synthesis in water with amino acids and their derivatives as effective chiral catalysts or essential components (chiral ligands) of chiral catalysts has been published by Paradowska et al. (*Angew. Chem., Int. Ed.* **2009**, *48*, 4288−4297). Metal-assisted asymmetric reactions in water are shown for Diels−Alder reactions, Michael reactions and aldol reactions, as well as organocatalytic aldol and Michael reactions in water.

In (*Chem. Rev.* **2009**, *109*, 725−748) Chanda and Fokin review various organic transformations that benefit from being performed "on water" under conditions as defined by Narayan et al. (*Angew. Chem., Int. Ed.* **2005**, *44*, 3275−3279) that involve stirring insoluble reactant(s) in aqueous emulsions or suspensions without addition of any organic cosolvent. Reactions that benefit from this protocol, independent of whether they occur "in" or "on" water, are presented and compared with the reaction rate and selectivity in other solvents. Among the reactions that benefit from being performed "on water" are: (hetero) Diels−Alder reactions, 1,3-dipolar cycloadditions, cycloaddition of azo-dicarboxylates, Claisen rearrangements, Passerini and Ugi reactions, nucleophilic substitution and ring-opening reactions, transition-metal catalyzed transformations, metal-free carbon−carbon bond forming reactions, bromination reactions, and oxidation and reduction reactions. In the final section theoretical studies based on energy calculations and other explanations such as cohesive energy density and hydrophobic aggregation are presented.

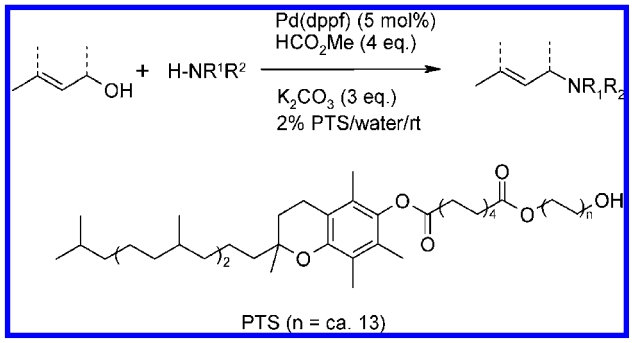
A micellar system was developed by Stabver et al. for the direct regioselective α-fluorination of a variety of cyclic and acyclic ketones in water with Selectfluor (F-TEDA-BF_4) as the fluorination reagent. Inexpensive sodium dodecyl sulfate (SDS) was found to be a good promoter for the fluorination of hydrophobic substrates without prior activation or use of acid catalysts.



Also the use of MeOH and MeCN as cosolvents has been described (*Synlett* **2009**, 589−594).

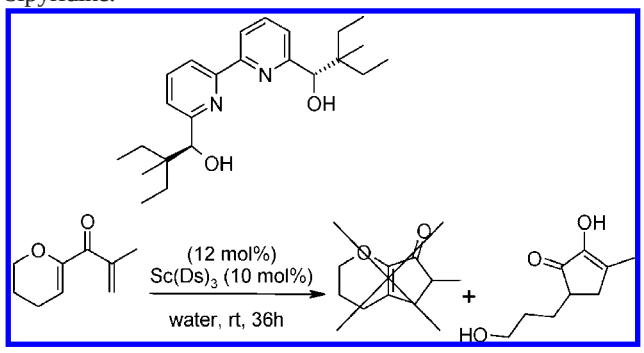
Lipshutz et al. have further elaborated the palladium-catalyzed chemistry in water using the nonionic amphiphile PTS. The regiocontrolled aminations of allylic alcohols in

nanometer micelles formed by the PTS in aqueous solution is described in (*Org. Lett.* **2009**, *11*, 2377−2379).



HCO_2Me (4 equiv) and K_2CO_3 are essential for the fast and high yield formation of allylic amines, most likely via the *in situ* formation of the allylic formate ester. Linear allylic amines are formed preferably over sterically more hindered branched products.

A remarkable Nazarov-type reaction in water of 2-alkoxy-1,4-pentanedien-3-ones, catalyzed by scandium dodecylsulfate ($Sc(DS)_3$), has been published by Kokubo and Kobayashi (*Chem. Asian J.* **2009**, *4*, 526−528). Compared to the conventional Nazarov reaction in organic solvents, in water the 2-alkoxy-2-cyclopentenone Nazarov products are trapped and instead result in the formation of cyclopentane-1,2-diones. In addition, an enantioselective Nazorov-type reaction has been demonstrated, albeit with moderate ee, by addition of a chiral bipyridine.



13. Continuous Processing and Process Intensification

A review on microstructured reactors (MSR) highlighting various reactor engineering parameters that affect the reactor performance has been published in (*Ind. Eng. Chem. Res.* **2009**, *48*, 6465). An analysis of the application of such MSRs for various multiphase reaction scenarios has been carried out and compared to the performance of conventional continuous reactors. One of the main features of the article is highlighting the importance of reactor configuration and other parameters for achieving desired mixing efficiencies for different multiphase reactions. This can be of interest to pharmaceutical processing in designing reactors for handling high energy and/or hazardous reactions.

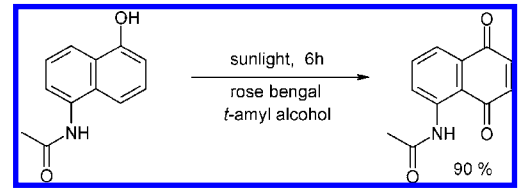
Continuous hydrogenation of a pharmaceutical intermediate using a Continuous Stirred Tank Reactor (CSTR) was reported by van Alsten et al. (*Org. Process Res. Dev.* **2009**, *13*, 629−633) for the reduction of a dinitro compound. Such unconventional hydrogenation reactors in the pharmaceutical industry can be used to process hydrogenations which require accurate control of reaction duration and also for reactions involving hazardous components where a need for keeping lower operating volumes exist. Another interesting article published by Lutz et al. (*Org. Process Res. Dev.* **2009**, *13*, 607−616) reviews the role of continuous processing in biocatalytic processes. The initial part of the review analyzes various reactor configurations available along with different options that can be considered for retaining the biocatalysts. The later section of the review details various continuous biotransformation processes reported in the literature.

14. SFC Separations

Preparative supercritical fluid chromatography (Prep-SCF) is often regarded as a green alternative to classical preparative high performance liquid chromatography (Prep-HPLC). Prof. Dewulf and co-workers, in collaboration with Johnson & Johnson, performed an exergetic life cycle analysis on the enantiomeric separation of a pharmaceutical intermediate. Depending on the system boundaries one process is greener than the other. In the "*a*" (process level) and "b" (plant level) boundary, Prep-HPLC requires 26 to 29% more resources quantified in exergy than Prep-SCF. However, in the "g" boundary (industry level) Prep-SCF requires 34% more resources than Prep-HPLC due to the high cumulative exergy extracted from the environment (*Green Chem.* **2009**, *11*, 1007−1012).

15. General Green Chemistry

The concept of "green photochemistry" using natural sunlight is an interesting concept and of course 100 years ago was the main way of carrying out photochemical reactions. Haggiage et al. have shown that 5-acetamido-1-naphthol can be converted to the 1,4-naphthoquinone in 90% yield in a six hour reaction on a sunny day in Dublin, Ireland (*Green Chem.* **2009**, *11*, 318−321). 5-Amido-1,4-naphthoquinones show some antibiotic properties.



This years Greener Synthetic Pathways Presidential Green Chemistry Challenge award went to the Eastman Company for their work on applying the use of enzymes to making personal care products. Although this essentially involves the application of a literature enzymatic esterification method because of the very large volumes involved in personal care products there is the potential for substantial environmental savings. Initially Eastman has applied their technology (which involves using an immobilised enzyme and solvent free conditions) to the manufacture of retinyl ester and esters of idebenone but are looking to apply the technology to emollient esters which have a much higher volume. For information on the process see http://www.eastman.com/greenprocess. (There is a lit. ref. to this work Cosmetics Toiletries 2009, 124 7, 56−63).

A previous winner of the Greener Synthetic pathways award was the Merck synthesis of sitagliptin using asymmetric hydrogenation technology and further information on this synthesis has been published by Hansen et al. (*J. Am. Chem. Soc.* **2009**, *131*, 8798−8804).

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