Organic Process Research & Development **2010,** *14,* 770–780

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 13 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, Boehringer-Ingelheim, Codexis, Dr. Reddy's, DSM Pharmaceutical Products, Eli Lilly and Company, GlaxoSmithKline, Johnson & Johnson, Merck & Co., Inc., Novartis, Pfizer, Inc., and Roche. Schering Plough and Wyeth, both members in 2009, are now affiliated with Merck & Co., Inc. and Pfizer respectively, as a function of the merger and acquisition activity during the year.

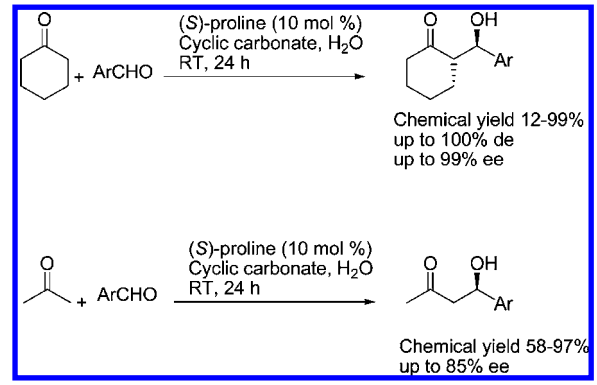
One of the strategic priorities of the Roundtable is to inform and influence the research agenda. Two of the first steps to achieve this objective are to publish a paper outlining key green chemistry research areas from a pharmaceutical perspective (*Green Chem.* **2007**, *9*, 411−420) and to establish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

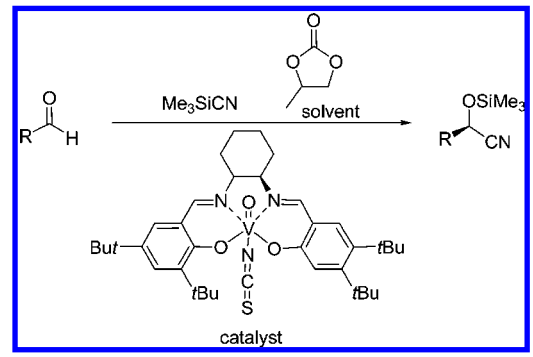
2. Solvents

Akien and Poliakoff (*Green Chem.* **2009**, *11*, 1083−1100) have published a review which tabulates the use of gas-expanded liquids in around 30 different chemical reactions. Perhaps not surprisingly the most common reaction reported in a gas-expanded liquid is hydrogenation. A gas-expanded liquid is a liquid, the volume of which is increased when pressurised with a condensable gas as such as CO_2. Some solvents such as THF can dissolve very large quantities of CO_2 and expand enormously; other solvents such as water can only dissolve a relatively small quantity of CO_2. The use of gas-expanded liquids greatly reduces the issues associated with the high pressures generated by supercritical fluids.

Cyclic carbonates, such as propylene and ethylene carbonate, gain more and more interest as green solvents. Both solvents can be prepared by the 100% atom efficient reaction between carbon dioxide and ethylene or propylene; in addition they have low toxicity and low flammability, although one issue that limits their use amongst process chemists is their relatively high viscosity. North et al. have demonstrated the use of propylene and ethylene carbonate in (*S*)-proline-catalysed asymmetric aldol reactions. Especially ethylene carbonate proves to be an efficient replacement for the often used polar solvents such as DMF or DMSO. High yields, high diastereo- and enantioselectivities were obtained in the reaction between cyclohexanone or acetone with a variety of aromatic aldehydes. The amount of water added is a critical factor towards yield and stereoselectivity (*ChemSusChem.* **2009**, *2*, 862−865).



North et al. have also demonstrated the use of propylene carbonate in the asymmetric cyanohydrin synthesis using VO(salen)NCS as a catalyst. A range of aromatic as well as aliphatic aldehydes were converted to the corresponding cyanohydrins which were obtained in high enantioselectivity and high yield (*Tetrahedron Lett.* **2009**, *50*, 4452−4454).



3. Oxidations

Supported Catalysts. Research on supported catalysts, particularly gold, has generated the most publications in the area of greener oxidations during the second half of 2009.

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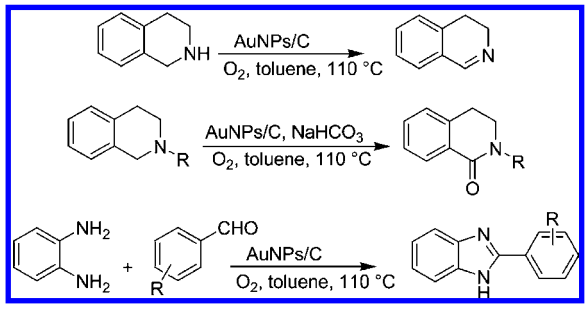
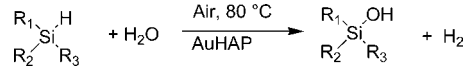
Supported catalysts offer significant green chemistry opportunities, including the following:

catalyst recycle
avoiding workup to remove metal contaminants
efficiency and process intensification
flow chemistry
terminal oxidation by oxygen or hydrogen peroxide

Immobilized Gold. Gajan et al. describe the preparation of gold nanoparticles supported on hydrophobic silica that provide excellent reactivity for the liquid-phase epoxidation of styrene (*J. Am. Chem. Soc.* **2009**, *131*, 14667−14669). Bawaked et al. have prepared gold catalysts supported on graphite, titanium dioxide, and silica for the aerobic epoxidation of cyclohexene under solvent-free conditions. Addition of catalytic quantities of hydroperoxide initiator was required for reactivity. Gold on graphite was the most reactive and selective catalyst system (*Green Chem.* **2009**, *11*, 1037−1044). Oliveira et al. describe the use of silica-supported gold nanoparticles for the aerobic oxidation of alcohols to carboxylic acids with subsequent esterification to methyl esters (*Green Chem.* **2009**, *11*, 1366−1370). So et al. report the use of graphite-supported gold nanoparticles for aerobic oxidation of amines to imines and amides, and for the oxidative coupling of *o*-phenylenediamines with benzaldehydes. On the basis of kinetic isotope effects and Hammett correlations, the authors propose the rate-determining step is C−H bond cleavage at the benzylic position (*Chem. Asian J.* **2009**, *4*, 1551−1561).



Mitsudome et al. report the first catalytic and highly selective conversion of aliphatic silanes to silanols in water using hydroxyapatite-supported gold nanoparticles under an air atmosphere (*Chem Commun.* **2009**, 5302−5304).



Immobilized Noble Metals. Mori et al. report the aerobic oxidation of primary and secondary alcohols to aldehydes and ketones, respectively, using 5 mol % of 10% ruthenium on carbon in toluene as solvent with no other additives (*Chem. Commun.* **2009**, 5159−5161).

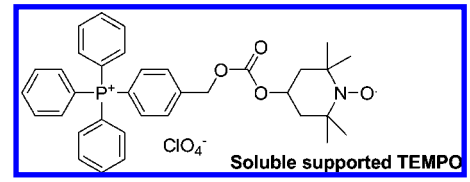
Palladium nanoparticles dispersed on an organoclay matrix were used for the aerobic oxidation of benzyl alcohol to benzaldehyde under base-free and solvent-free conditions. The catalyst was reused three times with minimal loss of activity (*Green Chem.* **2009**, *11*, 1499−1502).

Selective aerobic oxidation of styrene to benzaldehyde in water has been achieved by Feng et al. using a water-soluble catalyst system involving Pd(II) complexed with covalently bound 2,2′-dipyridylamine on PEG2000. Under optimized conditions, benzaldehyde was obtained in 85% yield with 13% acetophenone. The catalyst remained active for eight cycles (*Green Chem.* **2009**, *11*, 1446−1452).

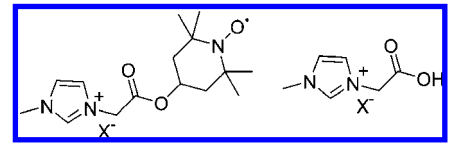
Immobilized Titanium. Guidotti et al. describe the use of silica-supported titanocene for the epoxidation of alkenes using hydrogen peroxide in acetonitrile. Slow addition of hydrogen peroxide provides the epoxide with good selectivity, minimizing the formation of allylic oxidation byproducts (*Green Chem.* **2009**, *11*, 1421−1427).

Immobilized Cu−Al. Kantam et al. have reported the use of copper-aluminium hydrotalcite in conjunction with *rac*-BINOL and K_2CO_3 to oxidize a wide range of alcohols to aldehydes and ketones under aerobic conditions in yields ranging from 60−100%. The composite catalyst could be filtered and reused for five cycles with no loss of activity (*Adv. Synth. Catal.* **2009**, *351*, 2633−2637).

Supported Organocatalysts. Roy et al. have designed tetraarylphosphonium salts (TAP) as soluble supports for oxidation catalysts. Three catalysts have been designed that incorporate an oxidant to mimic the low-molecular weight counterpart: a sulfoxide to mimic DMSO for Swern-type oxidations, a TEMPO analogue, and an iodobenzene analogue. The oxidative catalysts can be precipitated, filtered, and reused for four cycles (*J. Org. Chem.* **2009**, *74*, 8510−8515).

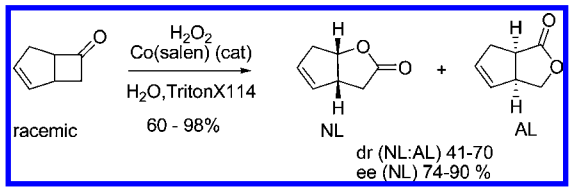


Miao et al. have designed a supported organocatalytic system involving a TEMPO-functionalized imidazolium salt (5%), a carboxylic acid substituted imidazolium salt (10%), and sodium nitrite (5%), for the aerobic oxidation in water of a wide range of alcohols. The authors have shown the catalysts can be recycled four times without loss of activity (*Adv. Synth. Catal.* **2009**, *351*, 2209−2216).



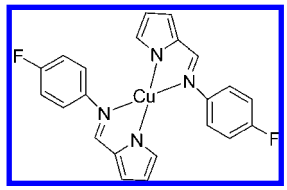
Resins. The regioselective epoxidation of carvone has been carried out using H_2O_2 and a basic resin, Amberlite IRA-900, in methanol (*Ind. Eng. Chem. Res.* **2009**, *48*, 10217−10221).

Greener Oxidation Conditions. *Oxidation in Water.* Two publications by the groups of Scarso and Strukul describe enantio- and diastereoselective Baeyer−Villager oxidations in water using H_2O_2 as the oxidant. Cyclobutanones were oxidized to butyrolactones in ee up to 90% using a chiral cobalt-salen catalyst in a micellar environment. No reaction occurred in the absence of a surfactant (*Green Chem.* **2009**, *11*, 1517−1520).



Similarly, enantioselective Baeyer−Villager oxidations of cyclic 4-, 5-, and 6-membered cyclic ketones were conducted in water using Pt(II) complexes with di- and monophosphine ligands. Again, addition of a surfactant was critical for the reaction to proceed. Enantioselectivities up to 92% ee were obtained with *meso*-cyclohexanones, among the highest observed to date for chemocatalytic Baeyer−Villager oxidations, although the yield was sacrificed to obtain the highest ee (*Chem.—Eur. J.* **2009**, *15*, 7930−7939).

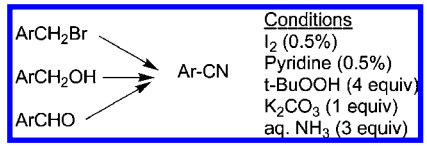
Figiel et al. describe the aerobic oxidation of a range of benzylic alcohols to aldehydes in water using TEMPO along with copper−imino complexes, affording 99% conversion after 2 h at 80 °C with one atmosphere of O_2, 1% $CuSO_4$, and 2% of the ligand (*Adv. Synth. Catal.* **2009**, *351*, 2625−2632).



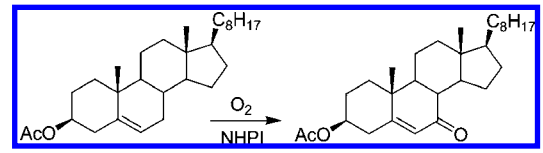
Oxidation of secondary aliphatic and aromatic alcohols was achieved in water using $PhI(OAc)_2$ activated by Et_4NBr. The reactions afford high yields in a few hours at room temperature. Little to no reaction occurred with this system in organic solvents (*Tetrahedron Lett.* **2009**, *50*, 3227−3229).

Solvent-Free Conditions. Methyl-substituted aromatics are oxidized to the corresponding carboxylic acid using aqueous *tert*-BuOOH under microwave conditions with no other reagents, solvents, or catalysts. Other alkyl-substituted aromatics are cleanly converted to ketones under these conditions. Use of 1−2 mol % of an ionic liquid improved the conversions dramatically, presumably due to increased heating efficiency (*Green Chem.* **2009**, *11*, 1857−1861).

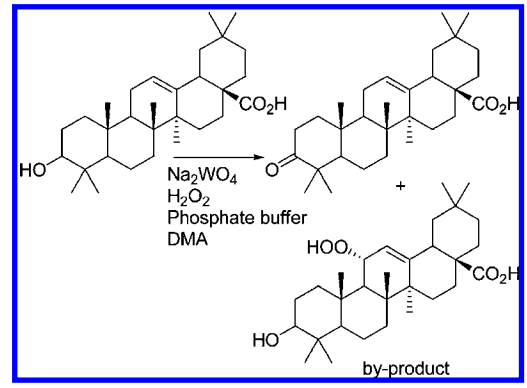
Zhang et al. describe the use of iodine-pyridine-*tert*-BuOOH for the oxidation of benzylic systems to ketones and primary amines to nitriles under solvent-free conditions at 80 °C. In the presence of aqueous ammonia and the same catalytic conditions, bromides, alcohols, and aldehydes are also oxidized to nitriles (*Green Chem.* **2009**, *11*, 1973−1978).



Other Green Oxidation Conditions. Allylic oxidation of cholesteryl acetate is a key step in the synthesis of vitamin D. The current industrial process generates an allylic bromide intermediate using molecular bromine. Yao et al. describe a greener oxidation to produce the enone using O_2 and catalytic amounts of *N*-hydroxyphthalimide (5%) along with 0.5% each of $Co(OAc)_2$ and $Mn(OAc)_2$ to enhance reactivity (*Green Chem.* **2009**, *11*, 2013−2017).



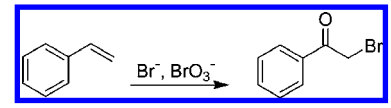
Hida et al. report the development of a pilot-plant process (22 kg) for the oxidation of a secondary alcohol (oleanolic acid) to a ketone using Na_2WO_4 and H_2O_2 under neutral conditions. Statistical experimental design was used to optimize yield and minimize formation of a hydroperoxide and other overoxidation byproducts. Calorimetry studies are described in depth, providing insight into how oxidation reactions can be safety scaled (*Org. Process Res. Dev.* **2009**, *14*, 289−294).



Oxidative Halogenations. Employing halide ion with in situ oxidation to a halogenating agent is a sustainable alternative to conventional halogenations using either molecular halogens or reagents derived from molecular halogens. Podgorsek et al. have reviewed recent research in the area of oxidative halogenations using oxygen or H_2O_2 as oxidant (*Angew. Chem.* **2009**, *48*, 8424−8450).

Kikushima et al. report the use of 5% NH_4VO_3 as catalyst for the bromination of arenes, alkenes, and alkynes using Bu_4NBr and *p*-TsOH in acetonitrile with oxygen as the terminal oxidant (*Chem. Asian J.* **2009**, *4*, 1213−1216).

Firouzabadi et al. describe the iodination and bromination of arenes using NaI and NaBr, respectively, in water with oxone as the terminal oxidant. Iodolactonization and iodoetherification reactions were also successful using this system (*Can. J. Chem.* **2009**, *87*, 1675−1681). The bromide/bromate system has been used to convert a wide range of alkenes to α-bromoketones in aqueous acidic media (*Tetrahedron Lett.* **2009**, *50*, 2529−2532).

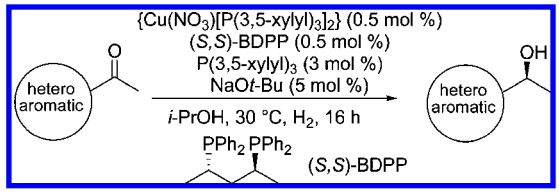


Oxidative chlorination and bromination using electrochemical oxidation in the presence of catalytic Pd affords aromatic halogenation in good yields in the solvents DMF or DMA (*J. Am. Chem. Soc.* **2009**, *131*, 11310−11311).

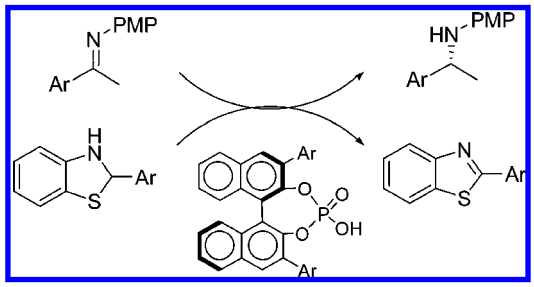
4. Asymmetric Hydrogenations

There have been increasing research activities in searching for more economical or environmentally friendly catalyst

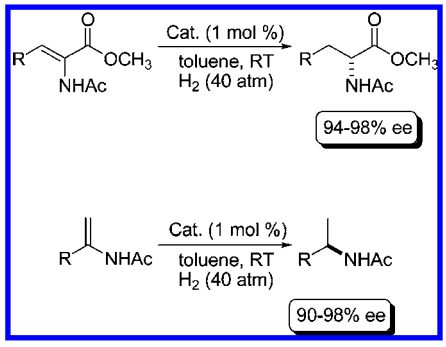
systems by using less expensive metals or organocatalysis. Shimizu et al. reported asymmetric hydrogenations using a catalytic system that combines copper(I) and chiral diphosphine ligands. In the asymmetric hydrogenation of enones or heteroaromatic ketones, good to high enantioselectivity was obtained (mostly ~90% ee or higher) (*Synlett* **2009**, *19*, 3143−3146).



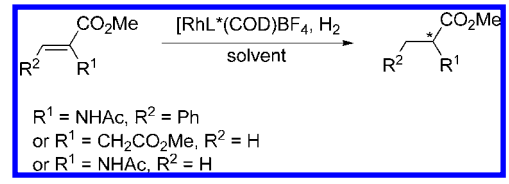
Zhu and Akiyama reported asymmetric transfer hydrogenation using a chiral phosphoric acid as the catalyst and benzothiazoline as the hydrogen source. The asymmetric hydrogenation of imines gave excellent ee (95−98%) and good yield (84−96%) (*Org. Lett.* **2009**, *11*, 4180−4183).



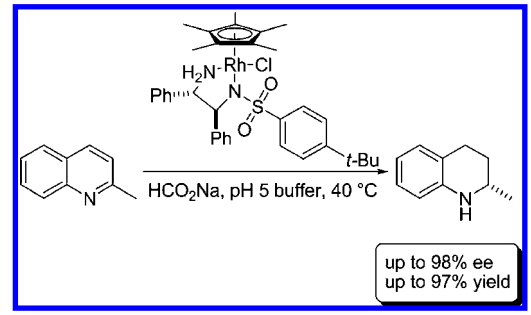
The solid-supported catalytic system is another area that has received continuous attention. Shi et al. developed a self-supporting immobilization strategy, which allows heterogeneous asymmetric hydrogenation under continuous-flow mode. The self-assembled metal−organic frameworks were constructed by mixing multitopic MonoPhos-based ligands and $[Rh(COD)_2]BF_4$. The resulting self-supported catalysts showed excellent catalytic performance for the asymmetric hydrogenation of a number of α-dehydroamino acids and 2-aryl enamides. The catalysts are easily recycled without significant loss in enantioselectivity. A drop in the catalyst reactivity during recycling can be minimized by the employment of a continuous-flow system, which produced products with >99% conversion and 96−97% ee for a total of 144 h (*Chem.—Eur. J.* **2009**, *15*, 9855−9867).



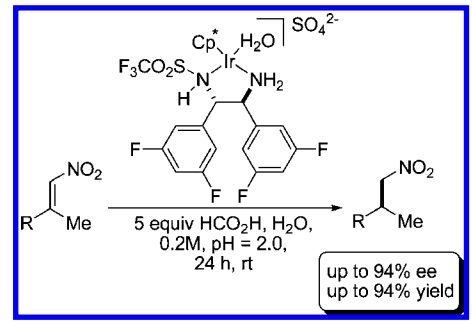
Schaffner et al. investigated alternative "green solvents" for asymmetric hydrogenations. Asymmetric hydrogenations of methyl α-acetylaminocinnamate, dimethyl itaconate, and methyl 2-acetamidoacrylate in organic carbonates such as propylene carbonate (PC) and butylene carbonate (BC) gave similar or better results than using standard solvents such as MeOH, THF, and CH_2Cl_2. These carbonate solvents are generally considered as "green solvents" because of their environmentally friendly synthesis, as well as their high biodegradability and nontoxicity (*Chirality* **2009**, *21*, 857−861).



The use of water as a reaction medium has been under intense investigation due to its potential economic and ecological gains. Wang et al. have developed the first organometallic asymmetric transfer hydrogenation (ATH) protocol for the asymmetric reduction of quinoline derivatives in water. The reactions were carried out in air, and excellent enantioselectivities and good yields were observed under buffered conditions for a broad range of substrates (*Angew. Chem., Int. Ed.* **2009**, *48*, 6524−6528).



Soltani et al. reported a mild catalytic asymmetric transfer hydrogenation of β,β-disubstituted nitroalkenes in water. The iridium catalyst developed is readily prepared and air stable. Formic acid is utilized as an inexpensive, safe, and readily available reductant. The reaction provides good enantioselectivities and yields of chiral nitroalkanes (*Org. Lett.* **2009**, *11*, 4196−4198).

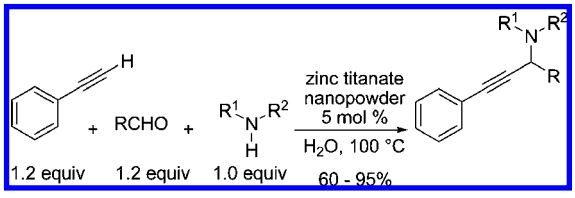


5. C−H Activation

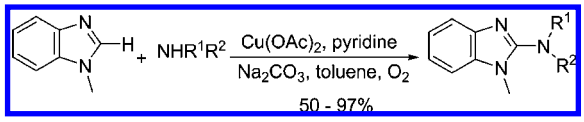
Activation of C−H bonds continues to be well represented in the literature, and multiple groups have published a variety of functional transformations. In addition to the work highlighted in the following paragraphs, multiple

reviews on the subject were published in the second half of 2009. Among these reviews is coverage by Zhou et al. of two recent methodologies for meta-selective arene functionalization (*Angew. Chem., Int. Ed.* **2009**, *48*, 7126−7128). McGlacken and Bateman present aryl−aryl bond formations with a variety of metals published from 2006 to October of 2008 (*Chem. Soc. Rev.* **2009**, *38*, 2447−2464). Chen et al. provide a thorough account of palladium-catalyzed formation of C−C bonds via C−H activation (*Angew. Chem., Int. Ed.* **2009**, *48*, 5094−5115). Ackermann et al. review the arylation of arenes by C−H bond cleavage since the middle of 2006 (*Angew. Chem., Int. Ed.* **2009**, *48*, 9792−9826).

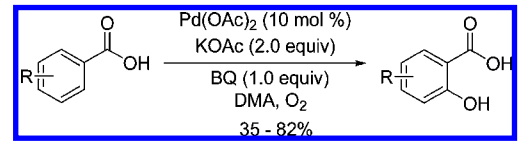
Mukhopadhyay and Rana report the three-component couplings of an aldehyde, amine, and alkyne (A3-couplings) in water at 100 °C with nanopowder zinc titanate (*Catal. Commun.* **2009**, *11*, 285−289). Yields of up to 95% were possible in the three-component couplings with several functionalized aldehydes and cyclic secondary amines. It was possible to run the reaction under a nitrogen atmosphere, and the catalyst was successfully recycled and resubjected to the reaction conditions up to 10 times without a significant decrease in reaction yield. Different grades of zinc titanate were investigated, and the nanopowder generated higher yields than commercial grade zinc titanate.



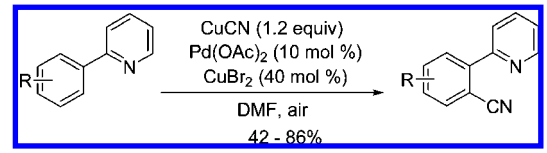
Wang and Schreiber discuss the use of oxidative copper couplings to functionalize benzimidazoles to generate 2-amidobenzimidazoles (*Org. Lett.* **2009**, *11*, 5178−5180). Optimal reaction conditions utilized 0.2 equiv of $Cu(OAc)_2$, 20 equivof pyridine, and 2 equiv of Na_2CO_3 in toluene with atmospheric oxygen. Good yields are reported for most examples with dimerization of the benzimidazole minimized by utilization of excess nucleophile (5 equiv). These conditions were also effective for the activation of the C−H bond of oxazoles, thiazoles, and fluorinated aromatic rings.



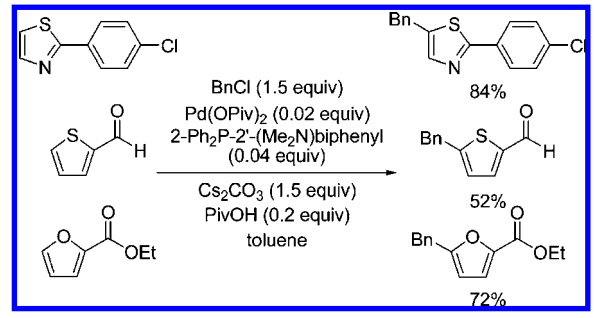
Ortho hydroxylation of substituted benzoic acids with $Pd(OAc)_2$ was reported by Zhang and Yu (*J. Am. Chem. Soc.* **2009**, *131*, 14654−14655). The optimized conditions utilized an oxygen atmosphere and the addition of benzoquinone, but the reaction did proceed in the absence of benzoquinone with oxygen or in the presence of benzoquinone with an air atmosphere. Electron-rich arenes were hydroxylated in very good yield, and electron-withdrawing groups were also well tolerated. In many cases lower yields could be increased by raising the oxygen pressure to 5 atm.



Jia et al. have described the palladium-catalyzed ortho cyanation of substituted arylpyridines with CuCN in the presence of air (*Org. Lett.* **2009**, *11*, 4716−4719). When the reaction was performed with a nitrogen atmosphere, conversion was significantly lower. The electron-withdrawing nature of the nitrile hindered activation of a second ortho C−H, and the monoaddition product predominated. A variety of functional groups were utilized, and as expected. electron-rich substrates showed increased reactivity. Methyl substitution at the meta position resulted in good regioselectivity to generate the less hindered ortho-substituted product driven by steric effects.



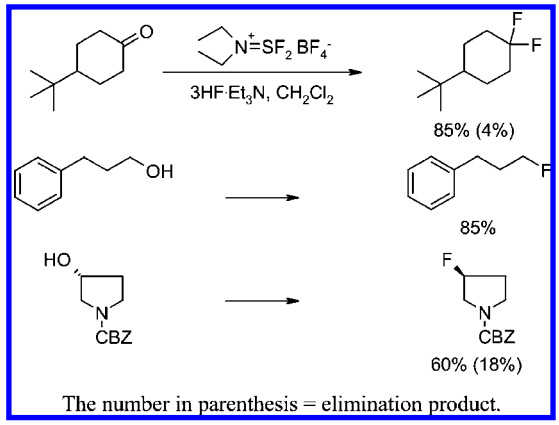
Palladium-catalyzed benzylation of heteroarenes that are incompatible with previous benzylation methods have been published by Lapointe and Fagnou (*Org. Lett.* **2009**, *11*, 4160−4163). After an extensive screen of benzyl leaving groups, chlorides were found to generate the highest yields of desired products with $Pd(OPiv)_2$, PivOH, 2-Ph_2P-2′-(Me_2N)biphenyl, and Cs_2CO_3 in toluene. In addition to the examples shown, functionality on the arene was well tolerated, and examples with indolizines, imidazopyrimidine, 1,2,3-triazoles, and oxazoles were also benzylated in good yield. Examples with substituted benzyl chlorides (4-fluoro, 4-nitro, 2-chloro, and 3-chloro) were also demonstrated.



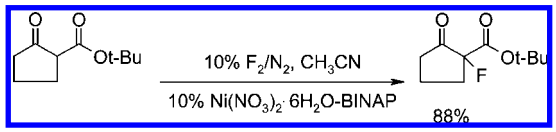
6. Greener Fluorination

Beaulieu et al. have reported the synthesis of aminodifluorosulfinium salts as crystalline, stable fluorinating reagents (*Org. Lett.* **2009**, *11*, 5050−5053). These salts show much higher thermal stability and are easier to handle than comparable molecular fluorinating agents such as DAST and Deoxo-Fluor. When activated by 3HF·Et_3N, the salts will convert alcohols to fluorides, ketones to *gem*-difluorides, and acids to acid fluorides. The aminodifluorosulfinium salts are also more

selective than traditional reagents, giving more selective reactions with lower amounts of elimination. The promoter, $3HF \cdot Et_3N$ is pH neutral and can be used in standard borosilicate glassware.

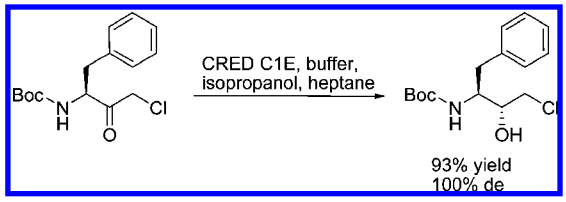


Chambers et al. have reported the direct fluorination of β-ketoesters in acetonitrile using 10% fluorine in nitrogen. The reaction is catalysed by Ni−phosphine complexes. Unfortunately, in the presence of chiral phosphines, no enantiocontrol of the formed carbon−fluorine bond was detected (*J. Fluorine Chem.* **2009**, *130*, 792−798).

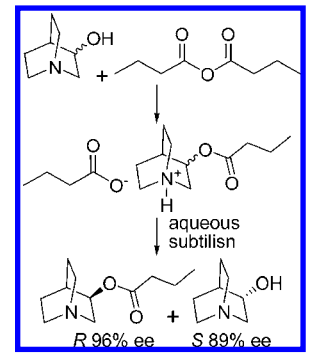


7. Biocatalysis

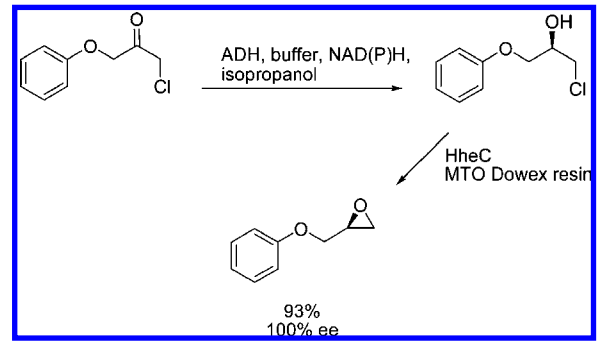
Alanvert et al. have reported the very efficient synthesis of α-chloroalcohols from α-chloroketones to produce intermediates useful in the synthesis of HIV protease inhibitors. A NAD-dependent alcohol dehydrogenase using isopropanol to recycle the cofactor in a biphasic reaction mixture gave products in high yields, purity, and perfect diastereomeric excess (*Tetrahedron: Asymmetry* **2009**, *20*, 2462−2466).



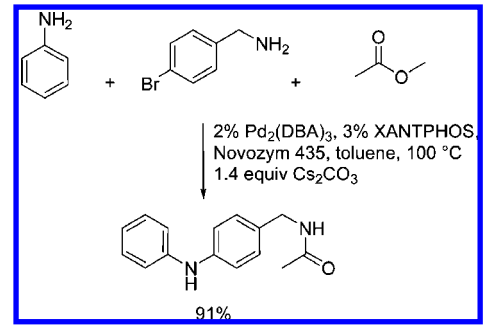
The same group (ALMAC) have also disclosed a very efficient bioresolution of secondary alcohols containing the tertiary amine functionality. If after reaction with an acyl donor a mobile protic ionic liquid is formed, this mixture can be directly treated with an enzyme such as subtilisin and resolved without workup or the need to add additional organic solvent. The enzyme is dosed as an aqueous solution which supplies the required water (*Tetrahedron: Asymmetry* **2009**, *20*, 2112−2116).



Schrittwieser et al. have examined the tandem enzyme process to prepare enantiopure epoxides. Reduction of α-chloroketones via alcohol dehydrogenase is followed by ring closure with halohydrin dehalogenase to form the epoxide. The dehalogenase reactions can be low yielding due to unfavorable equilibria. This publication describes the use of hydroxide-loaded ion-exchange resins to drive the equilibrium in the desired direction (*Tetrahedron: Asymmetry* **2009**, *20*, 483−488). Products are produced in high yield (≥90%) and in high ee. The enantiomer preference was determined by choice of *S*- or *R*-selective alcohol dehydrogenase.

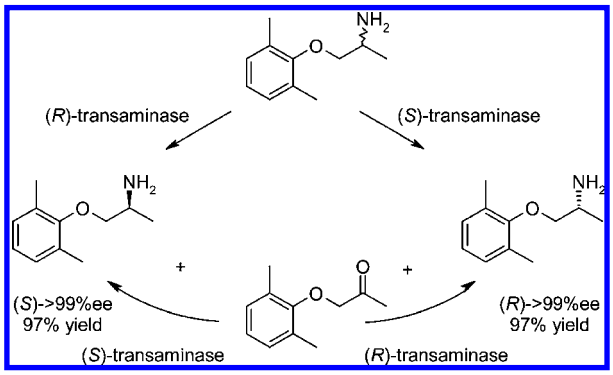


Combining reactions in cascade-type processes is attractive as an approach to greener multistep synthesis. Caiazzo et al. have reported a number of palladium-catalysed carbon−carbon and carbon−heteroatom reactions that have been performed in 'one pot' mode alongside *Candida Antarctica B* lipase reactions (*Org. Biomol. Chem.* **2009**, *7*, 2926−2932).

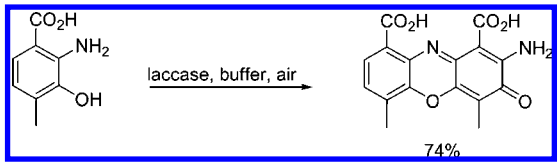


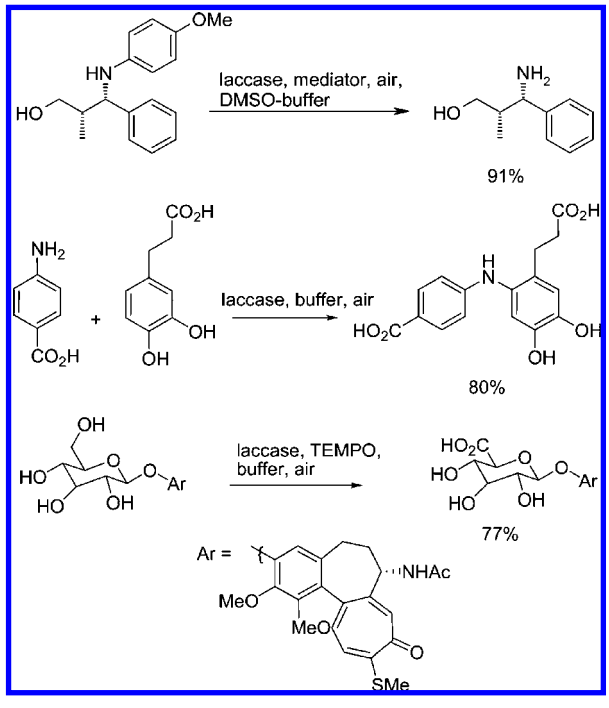
Koszelewski et al. have described an efficient use of *S*- and *R*-selective ω-transaminases to deracemise a racemic amine to produce either enantiopure (*S*)- or (*R*)-mexiletine in high yield. The process works by running first a kinetic resolution with an ω-transaminase of the opposite selectivity to produce a mixture of chiral amine and ketone and then converting the ketone to the amine with an ω-transaminase of the required selectivity.

The amine donor/acceptor, alanine−pyruvate cycle is driven in the required direction by amino acid oxidase or amino acid dehydrogenase (*Org. Lett.* **2009**, *11*, 4810−4812).



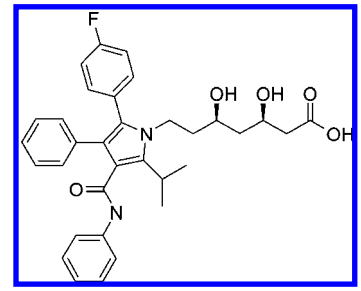
Laccases in the presence of oxygen and, if required, a redox mediator (redox cocatalyst) will perform many oxidations often associated with toxic heavy metals and hypervalent iodine reagents. Witayakran and Ragauskas have published an up- to-date review on the application of laccase technology to organic synthesis (*Adv. Synth. Catal.* **2009**, *351*, 1187−1209).





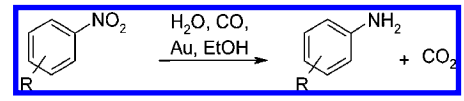
Continuing with the theme of oxidation, Leak et al. have reviewed the application, scope, and limitations of three enzyme classes utilised for greener oxidation. The classes covered are the nonheme iron monooxygenases, haloperoxidases, and Baeyer−Villiger monooxygenases (*Biocatal. Biotransform.* **2009**, *27*, 1−26).

Biocatalysis has developed into a pivotal technology for the large-scale synthesis of chiral 1,3-diol intermediates used in statins. Patel has published a review of the opportunities offered by different enzyme classes (hydrolase, aldolase, alcohol dehydrogenase, halohydrin dehalogenase, and nitrilase) in the synthesis of atorvastatin (Lipitor) (*J. Mol. Catal. B: Enzym.* **2009**, *61*, 123−128).

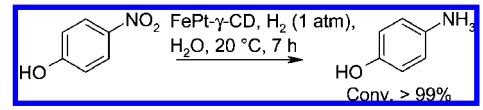


8. Reductions

He et al. describe a TiO_2-supported nanogold-catalyzed chemoselective methodology for reduction of nitro compounds utilizing water as the hydrogen source under a carbon monoxide atmosphere. The solvents of choice are ethanol or neat water, providing essentially quantitative yields for the variety of substrates tested. Nitrobenzene is reduced quantitatively to aniline in 3 h at 25 °C under 1 atm of CO or 1 h at 5 atm. Nitroaryl compounds bearing electron-acceptor or -donor substituents are reduced with excellent conversion and selectivity. Dinitro-substituted aryl compounds are selectively reduced to nitro anilines. Des-halogenation of aryl substrates is negligible, and the procedure works as well for nonactivated aliphatic compounds. Reactions using hydrogen gas with this Au catalyst provide very little reduction, indicating a transient Au−H active species evolved by the CO reduction of water (*Angew. Chem., Int. Ed.* **2009**, *48*, 9538−9541).

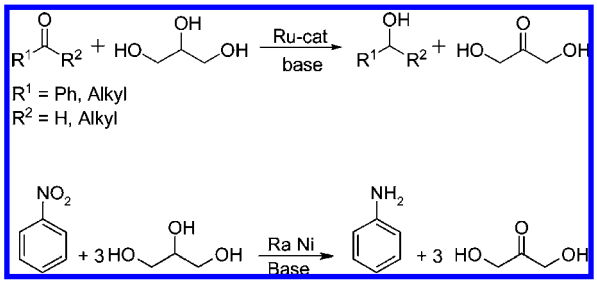


Mori et al. have modified an FePt nanoparticle catalyst with cyclodextrin, allowing colloidal aqueous hydrogenations. Reduction of allyl alcohol in water to *n*-propanol is essentially complete in 4 h under 1 atm pressure of hydrogen at 20 °C. 4-Nitrophenol is quantitatively reduced to 4-aminophenol in 7 h under the same conditions. The catalyst demonstrates a 10:1 bias toward the reduction of allyl alcohol versus 3-cyclohexene-1-methanol, presumably due to steric effects and inhibition by the molecular recognition properties imposed by the γ-CD surface. The catalyst is recovered magnetically and shows very good retention of activity (*Green Chem.* **2009**, *11*, 1337−1342).



Wolfson et al. relate research wherein glycerol is used as solvent and hydrogen donor for a variety of catalytic transfer hydrogenations encompassing carbonyl, alkene, and nitro reductions. Glycerol is noted for its nontoxic and biodegradable nature and its manufacture from renewable resources. It facilitates the dissolution of inorganic salts, acids, bases, enzymes, and even transition metal complexes. Glycerol is immiscible with hy-

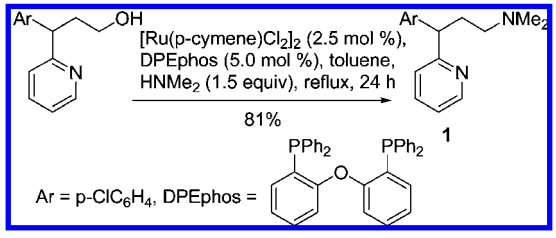
drophobic solvents which allow product recovery by a simple extraction. Various homo- and heterogeneous catalysts were screened for activity against different reduction targets. Ru(*p*-cumene)Cl_2 dimer with KOH was effective in the reduction of benzaldehyde, providing a quantitative yield in 24 h. Cyclohexene was completely reduced in 9 hours using 5 wt % Pd/C; however, styrene required only 5 h for the reduction. Nitrobenzene with Raney Ni and NaOH gave a 43% yield in 24 h. All reductions were performed at 70 °C and produced dihydroxyacetone as a byproduct (*Tetrahedron Lett.* **2009**, *50*, 5951−5953).



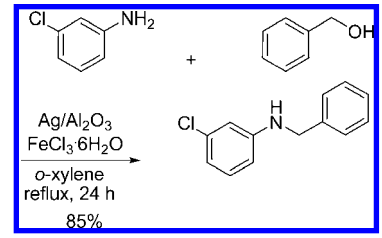
9. Alcohol Activation for Nucleophilic Displacement

Zaitsev et al. show that either a ruthenium(IV) catalyst $[Ru(Cp^*)(\eta^3\text{-}C_3H_5)(CH_3CN)_2](PF_6)_2$ or a combination of $[Ru(Cp^*)(CH_3CN)_3](PF_6)_2$ and camphorsulfonic acid is an excellent catalyst for the allylation of thiols using allyl alcohols at room temperature (*Chem.—Eur. J.* **2009**, *15*, 6468−6477). Thought to proceed via a π-allyl ruthenium species, the reaction is very high yielding and complete in minutes. Some control over the linear to branched ratio of the products arising from secondary allyl alcohols can be achieved, although the linear product predominates with time. (Cp* = pentamethylcyclopentadienyl).

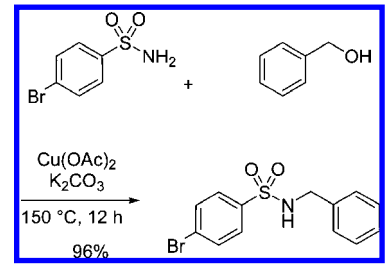
Hanti et al. discuss the *N*-alkylation of amines and sulfonamides with alcohols using the hydrogen-borrowing approach (*J. Am. Chem. Soc.* **2009**, *131*, 1766−1774). The reactions are catalysed by a homogeneous ruthenium catalyst and bidentate phosphine ligand (dppf or DPEphos) in toluene at reflux. Primary and secondary amines can be prepared, and reaction of diols with primary amines affords N-heterocycles; alkylation of primary sulfonamides and use of secondary alcohols require more forcing conditions (boiling xylene). The methodology has been applied to the syntheses of a number of pharmaceuticals including chlorpheniramine (**1**).



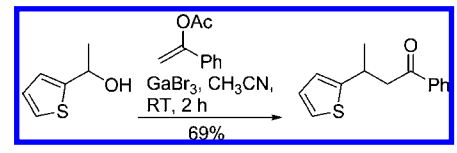
Two examples of the hydrogen-borrowing approach towards activation of benzyl alcohols using heterogeneous nonplatinum group metals have been published for the synthesis of amines. Likhar et al. describe the use of copper−aluminium hydrotalcite for the alkylation of various anilines and amines with primary and secondary benzyl alcohols. The catalyst system shows excellent selectivity with good to high yields. In addition, the catalyst can be easily recycled (*Eur. J. Org. Chem.* **2009**, 5383−5389). Shimizu et al. have applied an alumina-supported subnanometre-sized silver catalyst in the presence of a Lewis acid cocatalyst to the benzylation of anilines with primary and secondary benzyl alcohols. Several Lewis acids were screened, with $FeCl_3 \cdot 6H_2O$ the most effective. The reaction is run in *o*-xylene at reflux, and yields are generally greater than 70% (*ChemCatChem* **2009**, *1*, 497−503).



In an extension to the hydrogen-borrowing methodology, Shi et al. report the $Cu(OAc)_2$-catalysed *N*-alkylation of sulfonamides with benzylic alcohols. Although the reaction conditions are harsh (150 °C, sealed-tube), it is early days in the development of this chemistry, and avoiding the use of sulfonyl chlorides offers a clear advantage over current methods. Yields are typically >90% (*Angew. Chem., Int. Ed.* **2009**, *48*, 5912−5915 and *Adv. Synth. Catal.* **2009**, *351*, 2949−2958).

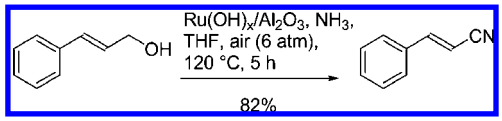


Nishimoto et al. achieve α-alkylation of carbonyl compounds by direct addition of alcohols to enol acetates (*Angew. Chem., Int. Ed.* **2009**, *48*, 9131−9134). A range of enol acetates are alkylated with predominantly allylic, benzylic, or propargylic alcohols in the presence of indium(III) iodide, gallium(III) bromide, or iron(III) bromide. Aldehyde-derived enol acetates are also alkylated. Most of the examples are run in 1,2-dichloroethane, although acetonitrile has been used as an alternative solvent. Yields are reasonable.



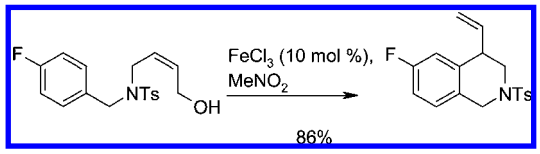
Oishi et al. describe an oxidative synthesis of nitriles from primary alcohols and ammonia (*Angew. Chem., Int. Ed.* **2009**, *48*, 6286−6288). Allylic and benzylic alcohols are treated with

a solution of ammonia in THF in an autoclave at 120−130 °C under 6 atm air in the presence of ruthenium hydroxide on alumina. Yields are good, and the double bond of unsaturated nitriles is unaffected by the reaction conditions. Primary amides are obtained by the addition of water after 5 h and continuing the reaction under argon.



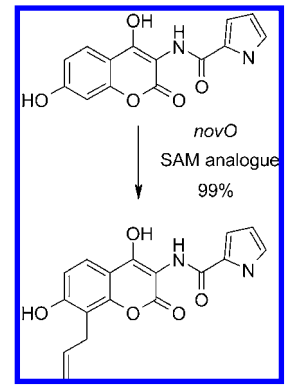
10. Friedel−Crafts Chemistry

Development of mild and efficient catalytic alkylations of electron-poor arenes is an ongoing challenge that the group of Bandini (*Adv. Synth. Catal.* **2009**, *351*, 2521−2524) has successfully tackled through the application of $FeCl_3$ catalysis with activated alcohol electrophiles. Despite the use of Schlenk tubes which could limit the ease of scale-up, a range of intramolecular allylic, benzylic and propargylic alcohols undergo alkylation onto electron-deficient arenes. Halogens and cyano and ester arene substituents are all tolerated, and the configuration of the carbon−carbon bond does not significantly influence the chemical output of the reaction. Whilst currently limited to intramolecular alcohols, the findings still represent a significant advance in terms of environmentally benign catalysis of Friedel−Crafts alkylation of these challenging substrates.



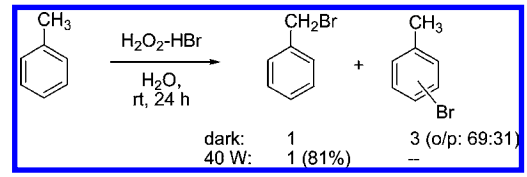
On a related theme, Arata (*Green Chem.* **2009**, *11*, 1719−1728) has published a review of recent studies on solid superacid catalysis, which highlights their potential in developing greener processes. Significant focus is placed on sulfated zirconia catalysis of Friedel−Crafts acylations. Test reactions of acid anhydrides with toluene show comparable or improved reactivity relative to $AlCl_3$-mediated conditions. These results also contrast with other well-known solid acid catalysts, such as silica−alumina and zeolites, which are inactive under the conditions.

Gruber-Khadjawi (*Angew. Chem., Int. Ed.* **2009**, *48*, 9546−9548) and co-workers report novel examples of biocatalytic Friedel−Crafts alkylation of coumarins. In nature methyl groups are selectively introduced into reactive aromatic rings by methyltransferases (Mtases) in combination with (*S*)-adenosyl-(L)-methionine (SAM) cofactors. In these studies, SAM analogues were synthesised and employed to access methyl, allyl, propargyl, and benzylated arenes with excellent regioselectivity. Whilst the reaction scale reported is limited and there are some stringent structure requirements, the results may serve as the start of a new biocatalytic approach to arene alkylation.

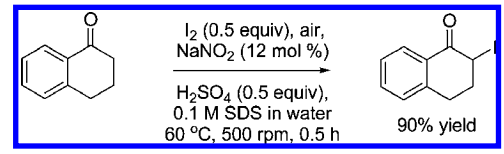


11. Chemistry in Water

Electrophilic and radical bromination 'on water' of benzylic and α-keto positions using the H_2O_2−HBr system has been described by Podgoršek et al. (*Tetrahedron* **2009**, *65*, 4429−4439). This system is especially attractive because of mild reaction conditions, inexpensive reagents, and environmental impact as compared to those of other bromination methods. Irradiation with a 40 W standard incandescent light bulb exclusively results in benzylic bromination, while the dark reaction preferentially gives electrophilic bromination. In the paper the H_2O_2−HBr system is compared with bromination by NBS. In general a comparable reactivity is observed for aromatic ring bromination. H_2O_2−HBr is more reactive for benzyl and ketone bromination, while NBS is preferred for aromatic ring bromination of activated tetralones and oxidative bromination of styrene.



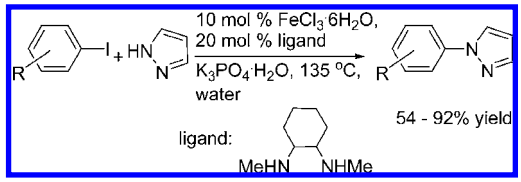
Atom-efficient iodination of ketones with molecular iodine in water under aerobic oxidative conditions has been described by Stavber et al. (*Green Chem.* **2009**, *11*, 1262−1267).



With air as the terminal oxidant, sodium nitrite (5−12 mol %) as a catalyst, and H_2SO_4 as an activator in a 0.1 M aqueous SDS solution, high yields have been obtained for various ketones, using only 0.5 equiv of I_2 (for a review on other iodination methods see: Stavber et al. (*Synthesis* **2008**, 1487−1513).

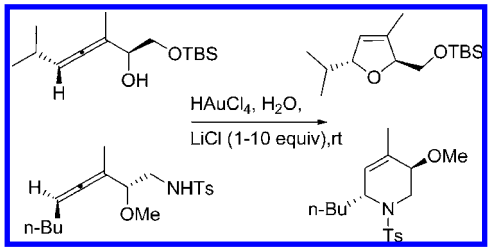
Lee et al. report that the iron(III)-catalyzed *N*-arylation of pyrazoles can be performed under aqueous conditions (*Tetrahedron Lett.* **2009**, *50*, 5868−5871). Reactions of various aryliodides with pyrazole and 10 mol % $FeCl_3$(diamine)$_2$ complex in water at 135 °C (sealed tube) give good coupling yields. It should be noted that the nature of the iron catalyst is under discussion and that trace amounts of copper impurities

may be the actual catalyst (see Buchwald, S.L. Bolm, C. *Angew. Chem.* **2009**, *48*, 5586−5587).



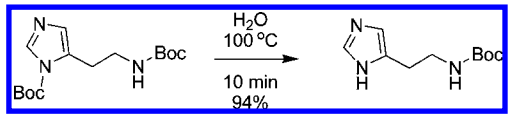
Also *N*-arylation of other *N*-heterocycles is described, albeit generally resulting in lower yields.

A sustainable method for gold-catalyzed cycloisomerization of hydroxyl- and amine-substituted allenes has been published by Winter and Krause (*Green Chem.* **2009**, *11*, 1309−1312).



Chloroauric acid ($HAuCl_4$) was chosen as catalyst for the cycloisomerization for solubility and stability reasons. LiCl was added to prevent the Au catalyst from precipitating at the end of the reaction when all substrate is consumed. In this way the amount of catalyst can be reduced from 5 to 1 mol %, and the catalyst can be reused. For insoluble substrates 5 vol % of THF was added to reach full conversion.

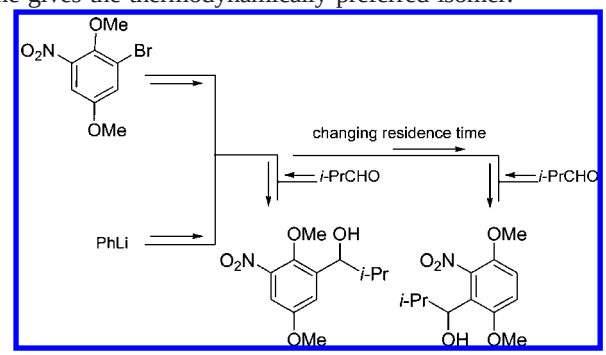
The selective deprotection of *N*-Boc groups in boiling water has been described by Wang et al. (*Chem. Commun.* **2009**, 5144−5146). At higher temperatures water acts as dual acid/base, omitting the use of additional deprotection agents. Especially nitrogen heterocycles and anilines can be readily deprotected in reaction times as short as 5−10 min for triazoles, imidazoles, and pyrazoles and up to several hours for substituted anilines. Nitrogen heterocycles and amides can be selectively Boc deprotected in boiling water in the presence of Boc-protected aliphatic amines.



A review paper with recent advances of organocatalytic reactions in water has been published by Raj and Singh (*Chem. Commun.* **2009**, 6687−6703). Various asymmetric aldol, Michael, Mannich, and Hantzsch reactions and cycloadditions described by Sing and co-workers as well as other groups are summarized in this paper.

12. Continuous Processing and Process Intensification

Nagaki et al. (*Angew. Chem., Int. Ed.* **2009**, *48*, 8063−8065) used the concept of flash chemistry in a microreactor system to generate and react highly unstable nitro-substituted aryl lithium compounds with a wide range of electrophiles. The authors also demonstrated, by changing the residence time of the lithiated species generated, that they could alter the selectivity between the product isomers. A short residence time favors the kinetically favored isomer, where a longer residence time gives the thermodynamically preferred isomer.



Bogdan et al. (*Angew. Chem., Int. Ed.* **2009**, *48*, 8547−8550) reported a continuous-flow synthesis of ibuprofen in three steps without intermediate purification and finally ending with the crude product solution. Although the authors have demonstrated the process at a small scale, and with final chromatographic purification, the concept illustrates tuning each step so that the reaction contents can be carried forward. An efficient downstream purification step in the end could significantly reduce the waste formation, processing costs, and reagent use. Challenges remain in designing processes involving more steps and also in managing the dilution factors.

A special issue of (*Chem. Eng. Technol.* **2009**, *32* (11)) entitled "Novel Process Windows" mainly focuses on the use of flow chemistry for process intensification.

13. General Green Chemistry

A book *Green Chemistry in the Pharmaceutical Industry* has been published by Wiley-VCH (editors Dunn, Wells, and Williams) and contains articles from several companies; AstraZeneca, BMS, Dr Reddy's, GSK, Merck, Nicholas Piramal, Pfizer, DSM, and Takeda as well as articles from leading academics. The book provides an excellent overview of Green Chemistry.

The best protecting group is no protecting group at all, but if a protecting group is to be used, it should have as low a molecular weight as possible. With a molecular weight of 29 the formyl group compares favorably with other protecting groups for amines (cf. Cbz group molecular weight 135). However, this protection is almost never used, as the method of forming the protecting group and cleavage back to amine and formamide are relatively poor. Deutsch et al. (*Tetrahedron* **2009**, *65*, 10365−10369) provide a new way to prepare formamides from methyl formate. If this is combined with Sheldon's methodology to remove formyl groups using enzymatic chemistry (*J. Mol. Catal. B: Enzym.* **2008**, *54*, 67−71), the formyl group may become a more practical proposition.

Ma et al. have published a detailed environmental assessment of the chemistry to make an atorvastatin intermediate. This assessment includes *E* factors calculated with and without water (*Green Chem.* **2010**, *12*, 81−86). Cue and Zhang have published a review entitled "Green Process Chemistry in the Pharmaceutical Industry" (*Green Chem. Lett. Rev.* **2009**, *2*, 193−211).

Kang has published "A Commentary: An Industrial Perspective on Green Chemistry" (*Tetrahedron* **2010**, *66*, 1029−1030). This edition of *Tetrahedron* was a special edition which contained 20 articles on Green Chemistry.

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