Organic Process Research & Development **2009,** *13,* 397–408

Green Chemistry Highlights

Green Chemistry Articles of Interest to the Pharmaceutical Industry

1. Introduction

The American Chemical Society Green Chemistry Institute Pharmaceutical Roundtable (ACS GCIPR) is a partnership between 12 current member companies and the ACS GCI. The mission of the ACS GCIPR is to encourage the integration of green chemistry and green engineering into the pharmaceutical industry. 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 GCI PR research grants. This document is the second annual issue to follow on from the *Green Chemistry* contribution and is largely based on the key research areas, although new sections have been added that reflect prevailing interests of the industry. The review period covers all of 2008.

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

Pfizer have published their one page solvent selection guide targeted at medicinal chemistry (*Green Chem*. **2008**, *10*, 31−36). Nine solvent properties are used to categorize the solvents based on worker safety assessment, process safety assessment, environmental assessment and a regulatory assessment but this information is then distilled into a simple 1 page summary. For each of the undesirable solvents a chemically or functionally equivalent greener alternative is given. This publication also gives details of Pfizer's Green Chemistry reagent selection guide.

It is often challenging to select the greenest solvent which is compatible with the reagents and reaction conditions used. To aid in this decision GSK has developed a solvent selection tool for organic reaction systems. The solvent selection methodology was developed earlier by Gani et al. (*Comput. Chem. Eng*. **2005**, *29*, 1661−1676) and has now been extended to handle multistep reaction systems (*Chin. J. Chem. Eng*. **2008**, *16*, 376−383).

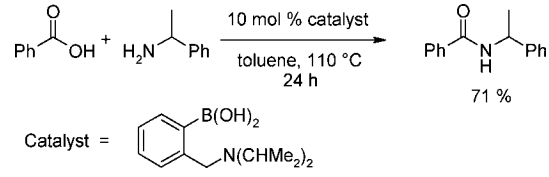
Ionic liquids have been claimed (mainly by their inventors) to be green solvents on the basis of their lack of volatility and flammability. However, others have pointed out the lifecycle concerns in their synthesis and the fact that some ionic liquids are toxic to the environment. A publication by Cho et al. reports the ecotoxicity of several ionic liquids with particular focus on the anion (*Green Chem.* **2008**, *10*, 67−72). The authors compare the ecotoxicity data of the ionic liquid with their equivalent alkali metal salts and with common organic solvents (MeOH, DMF, IPA). The authors concluded that heavily fluorinated anions such as SbF_6^- and PF_6^- were the most toxic. Some useful applications are now being reported in the field of enzymatic catalysis. Enzymatic reactions in ionic liquids were originally reported by Sheldon and recently Lye and co-workers have reported that the addition of 10% v/v of an ionic liquid to organic solvents can extend enzyme life and give more productive reactions (*J. Mol. Catal. B: Enzym*. **2008**, *55*, 19−29).

The Mitsui Chemical Company in Japan has revealed their new green synthesis of methanol which is based on the reaction of CO_2 with hydrogen. Methanol is traditionally made from carbon monoxide and hydrogen which in turn come from methane. The Mitsui process uses the sun's energy to make hydrogen via water photolysis and Mitsui claim that the new process will emit half of the CO_2 that it consumes (*Chem. Eng. News* **2008**, *86*, 13).

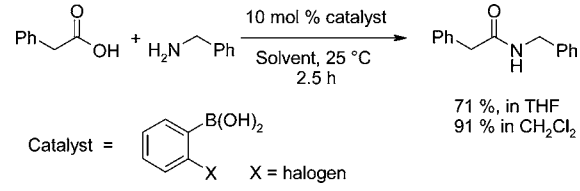
Organic carbonates, such as propylene carbonate, butylene carbonate and diethyl carbonate were used as solvents in Pd-catalysed asymmetric allylic substitution reactions. Schäffner et al. have illustrated that organic carbonates can replace less environmentally friendly solvents such as dichloromethane in this type of reaction without compromising the enantioselectivity of the reaction (*ChemSusChem* **2008**, *1*, 249−253).

3. Amide Formation

The use of catalysts to promote direct amide formation from acids and amines where the only byproduct is water has been growing in recent years since a key publication by Tang in 2005 (*Org. Synth.* **2005**, *81*, 262−267). During this period, Arnold et al. have published their work using a new bifunctional catalyst (*Green Chem. 2008*, **10**, 124−134). Although this catalyst looks less industrially relevant than the simple boric acid catalysed reactions reported by Tang, it is a more active catalyst than simple boric acid and can work at a lower reaction temperature (80 °C).



Al-Zoubi et al. have reported that even lower temperatures (room temperature) can be used if molecular sieves are added to absorb the water byproduct. The authors used 2-halophenylboronic acids as catalyst (*Angew. Chem., Int. Ed.* **2008**, *47*, 2876−2879).



Nordstrøm et al. from the Centre for Sustainable and Green Chemistry at Technical University of Denmark have reported the reaction of alcohols and amines catalysed by $Ru(COD)Cl_2$

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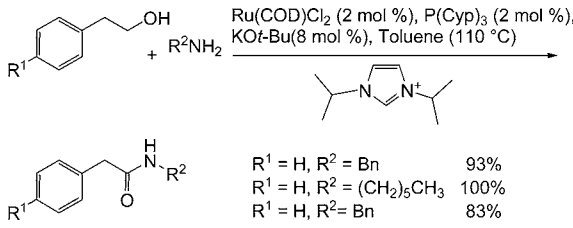
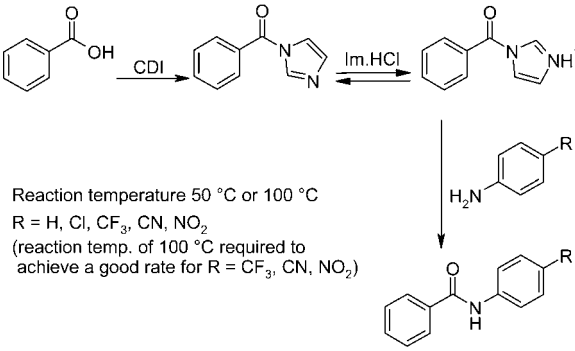
with a phosphine and imidazole-based ligand (*J. Am. Chem. Soc.* **2008**, *130*, 17672−17673).

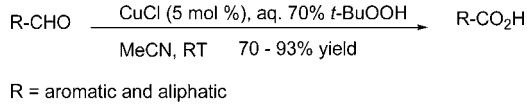


Carbonyl diimidazole is a very popular amide bond formation reagent used in the synthesis of a number of commercial pharmaceuticals (e.g., sildenafil citrate and sunitinib). One problem is that the intermediate imidazole is not reactive enough for weakly basic amines. Woodman et al. from the AstraZeneca process group have reported that the addition of imidazole hydrochloride speeds up the reaction by an order of magnitude. Rate constants in the presence and absence of imidazolide hydrochloride are given for several aniline derivatives as well as some heteroarenes. All of the data was collected in *N*-methylpyrrolidinone so it is not known if the rate enhancement is also observed in greener solvents (*Org. Process Res. Dev.* **2009**, *13*, 106−113).



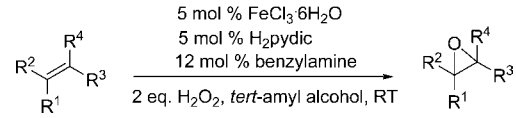
4. Oxidations

Mannama and Sekar at the Indian Institute of Technology, Madras, reported a process for oxidation of aldehydes to the corresponding carboxylic acids (*Tetrahedron Lett.* **2008**, *49*, 1083−1086). The oxidation can be performed highly efficiently at room temperature with 70% *tert*-butyl hydroperoxide (in water) in the presence of a catalytic amount of ligand-free CuCl in acetonitrile. This oxidation protocol works well under very mild conditions for various aldehydes, including aromatic and aliphatic aldehydes.

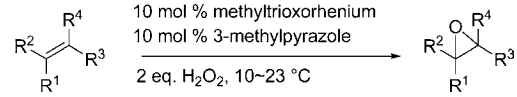


Epoxides play an important role in industry as intermediates for the production of fine chemicals as well as pharmaceuticals. Although a major method for producing epoxides in industry is dehydrochlorination of chlorohydrins, direct epoxidation of alkenes is more favorable than the two-step procedure, and extensive studies of direct epoxidation methods have continued.

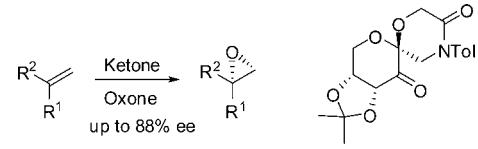
Bitterlich et al. developed inexpensive biomimetic iron catalysts for the environmentally benign epoxidation of olefins with hydrogen peroxide as a terminal oxidant. It was demonstrated that benzylamine is a preferred structural element for the coligand in this general epoxidation of aromatic and aliphatic olefins. The system showed good-to-excellent reactivity to mono-, di- and trisubstituted aromatic olefins, as well as to internal di- and trisubstituted and functionalized aliphatic olefins. It is noteworthy that inactive aliphatic olefins can be oxidized in up to 96% yield (*Eur. J. Org. Chem.* **2008**, 4867−4870).



Yamazaki explored an efficient catalytic system, methyltrioxorhenium/3-methylpyrazole, for epoxidation of alkenes with aqueous 35% H_2O_2 in excellent yields under organic solvent-free conditions. The use of 3-methylpyrazole is significant for achieving high yields of epoxides. Pyridine and pyrazole were inferior to 3-methylpyrazole as the additive for organic solvent-free epoxidation (*Tetrahedron* **2008**, *64*, 9253−9257).



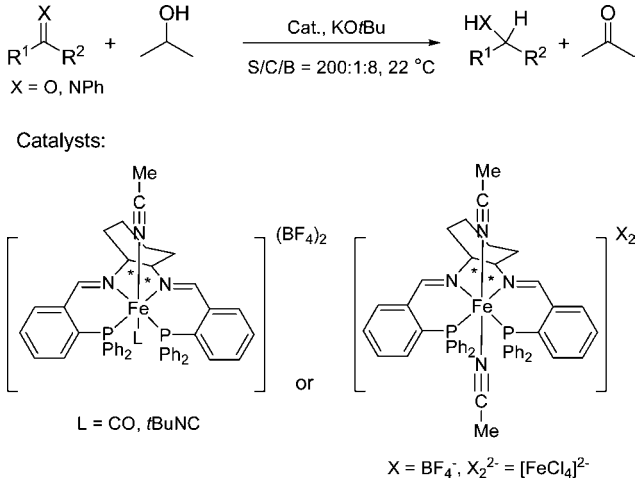
Shi et al. reported chiral ketone catalysts for asymmetric epoxidation of various 1,1-disubstituted terminal olefins. Up to 88% ee has been achieved with a lactam ketone, and a planar transition state is likely to be a major reaction pathway (*J. Org. Chem.* **2008**, *73*, 9539−9543).



Shi et al. have reviewed the literature on asymmetric epoxidation of olefins catalysed by chiral ketones and iminium salts (*Chem. Rev.* **2008**, *108*, 3958−3987).

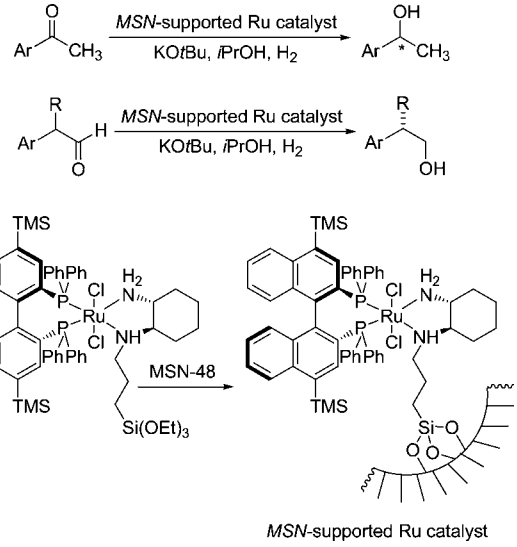
5. Asymmetric Hydrogenations

There were over 150 articles related to asymmetric hydrogenation published in 2008. A review article by Eberhardt et al. on this subject appeared in *Chem. Soc. Rev.* **2008**, *37*, 839−864. Wang et al. also published a review focusing on asymmetric transfer hydrogenation. Efforts in the development of selective, environmentally benign and reusable catalytic systems are highlighted (*Chem. Asian J.* **2008**, *3*, 1750−1770). The majority of the papers related to asymmetric hydrogenation focus on modifying catalysts and ligands. One paper that may eventually lead to "greener" reaction conditions was reported by Sui-Seng et al. who developed the first iron catalyst system for asymmetric hydrogenation at 50 °C and asymmetric transfer hydrogenation at room temperature. Low to modest ee (18−76%) was obtained in the transfer hydrogenation of acetophenone with isopropyl alcohol. Iron catalysts have the advantages of being more environmentally friendly and less expensive (*Angew. Chem., Int. Ed.* **2008**, *47*, 940−943).



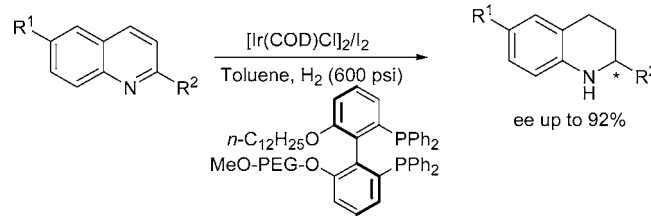
The practical applications of chiral catalysts in industrial processes are often hindered by their high cost as well as difficulty in removing trace amounts of toxic metals from the organic products. These concerns may be alleviated by using potentially "greener" recoverable solid-supported catalyst systems, which have been one of the focus areas of recent asymmetric hydrogenations.

Mihalcik and Lin prepared chiral $RuCl_2$−diphosphine-diamine complexes with a siloxy functionality which can be readily attached to a silica surface; i.e., mesoporous silica nanospheres (MSNs). Up to 99% ee was achieved in asymmetric hydrogenation of aromatic ketones to afford chiral secondary alcohols and racemic aryl aldehydes to give chiral primary alcohols (*Angew. Chem., Int. Ed.* **2008**, *47*, 6229−6232).



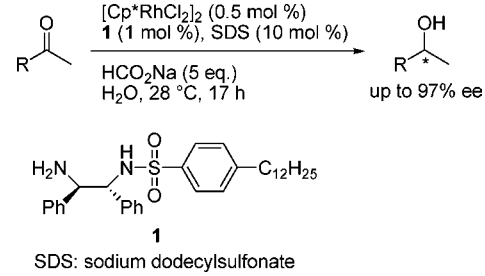
McDonald et al. reported rhodium and ruthenium catalysts complexed with a diphosphine ligand immobilized on silica to effect asymmetric hydrogenation of various enamides, β-keto-esters and aromatic ketones. The immobilized catalyst was reused for five recycles without losing selectivity and led to reduced solvent, ligand and metal waste (*Green Chem.* **2008**, *10*, 424−432).

Zhou and Wang developed a MeO-PEG-supported bisphosphine ligand that is synthesized from (*S*)-MeO-Biphep. The Ir complex of the ligand provided up to 92% ee in asymmetric hydrogenation of quinolines. The catalyst system is air-stable and can be recycled with minimal loss in activity and enantioselectivity (*J. Org. Chem.* **2008**, *73*, 5640−5642).

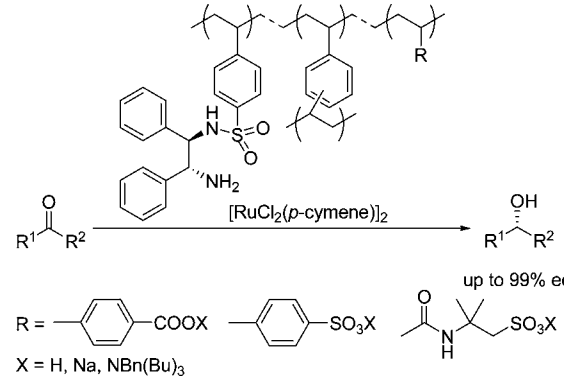


The generality of thesecatalyst immobilization strategies should allow the wider applications of many highly active and enantioselective heterogeneous catalysts for asymmetric hydrogenations, potentially on industrial scale in the future.

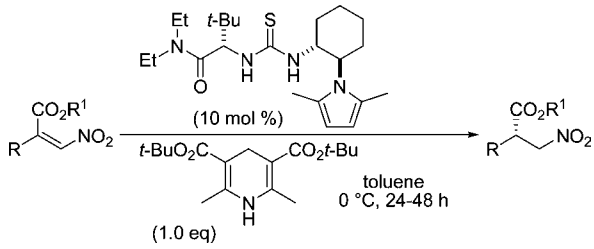
In several asymmetric transfer hydrogenations, water was used as solvent. Ahlford et al. developed a novel lipophilic rhodium catalyst to catalyse asymmetric transfer hydrogenation of alkyl and aryl ketones in aqueous media with good yields and enantioselectivities (*Green Chem.* **2008**, *10*, 832−835).



Arakawa et al. have successfully synthesized polymer-supported chiral 1,2-diamine monosulfonamides as ligands. By using the complex of this chiral ligand with $[RuCl_2(p\text{-cymene})]_2$, the enantioselective reduction of aromatic ketones was achieved in water to give optically active secondary alcohols with up to 99% ee. The catalyst was recycled several times without loss of catalytic activity (*Adv. Synth. Catal.* **2008**, *350*, 2295−2304).

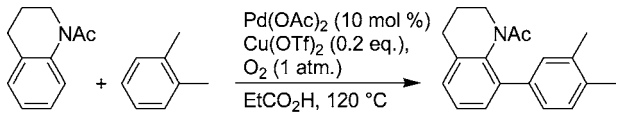


Organocatalytic asymmetric transfer hydrogenation of β-nitroacrylates was developed by Martin et al. to synthesize enantiopure β^2-amino acids. The highly enantioselective thiourea-catalysed conjugate reduction of β-nitroacrylates to their saturated analogues has a significantly broad scope. The reaction itself is tolerable to air, moisture and up-scaling and is metal-free (*J. Am. Chem. Soc.* **2008**, *130*, 13862−13863).



6. C−H Activation

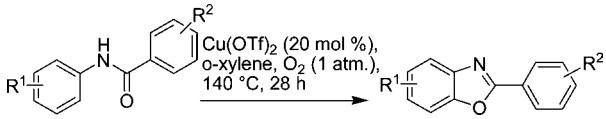
A review by Li et al. contains references to some current and early work on direct arylation of simple arenes (*Synlett* **2008**, 949−957). This chemistry requires the presence of a directing group (acetanilide) but allows for formation of biaryls without having to use aryl halides or organometals.



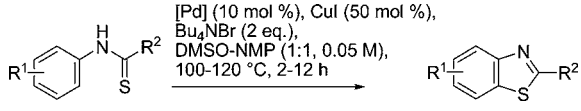
78%

Kakiuchi and Kochi present a review of transition-metal-catalysed carbon−carbon bond formation via carbon−hydrogen bond cleavage (*Synthesis* **2008**, 3013−3039). Their review surveys the literature dealing with catalytic C−C bond formation via cleavage of otherwise unreactive sp^2 and sp^3 C−H bonds up to 2007.

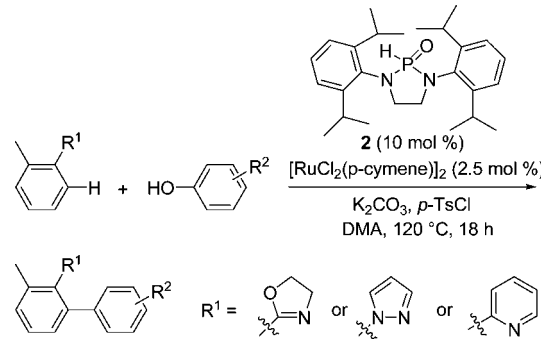
The novel synthesis of arylbenzoxazoles from benzamides with copper catalysis in the presence of an oxygen atmosphere was reported by Ueda and Nagasawa (*Angew. Chem., Int. Ed.* **2008**, *47*, 6411−6413). Yields of between 40 and 93% were achieved with a variety of R^1 and R^2 substituents. These conditions allow a potentially straightforward alternative to traditional reactions of aldehydes or carboxylic acids with 2-aminophenols.



A similar cyclization to generate benzothiazoles from thiobenzanilides with copper, palladium and tetrabutylammonium bromide was also investigated by Inamoto et al. (*Org. Lett.* **2008**, *10*, 5147−5150). Substitution was well tolerated, and yields of 44 to >99% are reported for $PdCl_2$, $PdCl_2$(cod) and $PdBr_2$. A 2-aminobenzothiazole was also generated via this methodology.

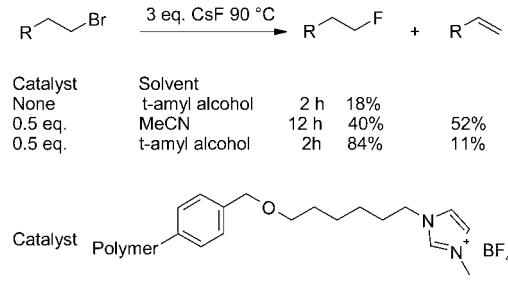


Ackermann and Mulzer developed ruthenium-catalysed coupling of arenes with phenols in the presence of 2.5 mol % of a ruthenium precursor and 20 mol % of the HASPO preligand **2** (*Org. Lett.* **2008**, **10**, 5043−5045). Oxazolines were arylated with phenols in the presence of potassium carbonate and *p*-toluensulfonyl chloride in DMA. A variety of electron-rich and electron-deficient phenols were examined, and yields of 47 to 91% were obtained. Other additives were screened, but *p*-toluenesulfonyl chloride proved to be the most effective. Pyrazolyl- and pyridyl-substituted arenes were also amenable to these reaction conditions. Additionally, the ligand **2** could be replaced with $MesCO_2H$ and DMA replaced with toluene to give similar yields for several examples. Overall, this work presents dehydrative arylation with inexpensive, readily available phenols.

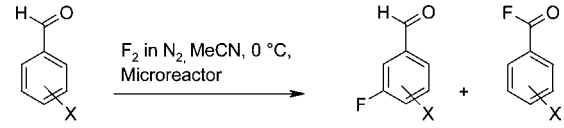


7. Greener Fluorination

Kim et al. have reported that the use of a polymer-supported ionic liquid catalyst and tertiary alcohol solvent greatly increase the reaction selectivity in S_N2 displacement by fluoride. The catalyst/solvent combination gives predominately substitution rather than elimination (*Tetrahedron* **2008**, *64*, 4209−4214).

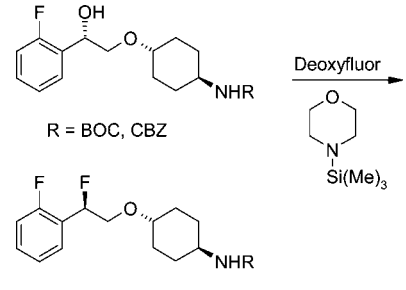


A group from Durham University describe the use of a microchannel flow reactor to synthesize fluorinated aromatics using F_2 in N_2 (*Org. Process Res. Dev.* **2008**, *12*, 339−344).



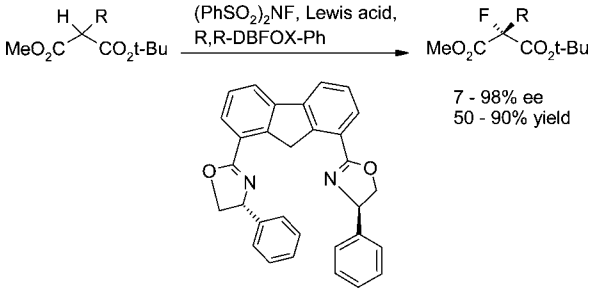
30 - 60%

Bio and co-workers from Amgen have described the in situ preparation of bis(dialkylamino) SF_2 reagents which greatly improve the selectivity (elimination is suppressed) and ee in the S_N2 conversion of chiral alcohols to fluorides via inversion of chiral alcohols (*Synthesis* **2008**, 891−896). Toluene can replace dichloromethane as the reaction solvent, and the reactions can be run at 0 °C rather than −70 °C.

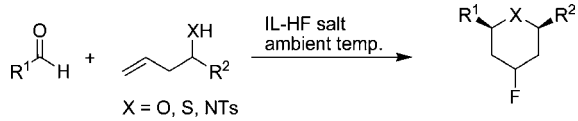


99% ee

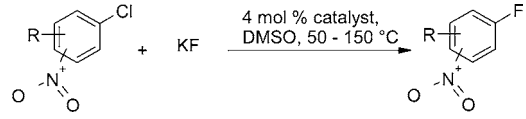
The fluorination of racemic dialkyl malonates to produce highly functionalized fluorinated synthons in high ee and yield has been reported (*Angew. Chem., Int. Ed.* **2008**, *47*, 164−168).



Kishi et al. reported a highly efficient Prins cyclization of homoallylic alcohols, thiols and amines with various aldehydes in an ionic liquid HF salt ($Et_4NF \cdot 5HF$) that afforded the corresponding 4-fluorinated heterocycles in good to quantitative yields. Amines need to be protected as tosylates. The reaction proceeds at ambient temperature and employs no organic solvent, and the reaction medium can be reused up to five times (*Chem. Commun.* **2008**, 3876−3878).



The Halex process to prepare aryl fluorides from aryl chlorides traditionally involves a large excess of inorganic fluoride and temperatures >250 °C. Lacour et al. have reported some novel P=N=P catalysts that enable reactions to proceed at 50−150 °C with a small excess of fluoride (*Adv. Synth. Catal.* **2008**, *350*, 2677−2682).

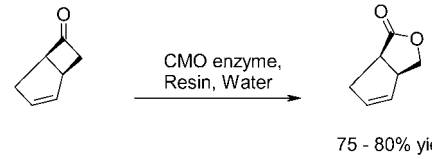


Ma and Cahard have published a recent review on the synthesis of fluorinated materials which contains a comprehensive survey of the latest catalytic routes to form chiral carbon−fluorine bonds as well as trifluoromethylation and perfluoromethylation chemistry (*Chem. Rev.* **2008**, *108*, 6119−6146).

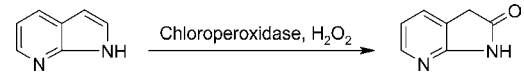
8. Biocatalysis

Oxidations. Carboxylic acids are one of the most important intermediates in organic chemistry. Ongoing process development for the preparation of carboxylic acids by oxidation under mild conditions is essential for green and sustainable chemistry. Ohta et al. at Keio University, Japan, recently reported a clean and effective alcohol oxidizing system using three enzymes for the preparation of a variety of carboxylic acids (*Tetrahedron Lett.* **2008**, *49*, 1217−1219). Regeneration of NAD^+ by NADH oxidase with molecular oxygen enabled oxidation of alcohols to carboxylic acids in good yield under mild conditions (25 °C, 1 atm).

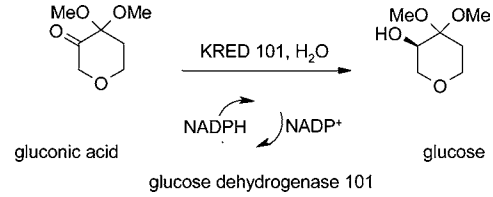
Hilker et al. have reported the scale-up of a Baeyer−Villiger oxidation to 25 g L^{-1} using in situ substrate dosing and product removal (*Nat. Protoc.* **2008**, *3*, 546−554). In the past, the synthetic utility of cyclohexanone monooxygenases has been severely limited by poor throughput and enzyme stability issues. A single regioisomer was reported.



Roberge et al. from Merck have found a highly stable form of chloroperoxidase. Preparation of the enzyme as a cross-linked aggregate enhanced hydrogen peroxide tolerance (*J. Mol. Catal. B: Enzym.* **2008**, *56*, 41−45). Concentrations of up to 1.2 M H_2O_2 could be tolerated. The greener oxidation of 7-azaindole to 7-azaoxindole in 90% yield is described.

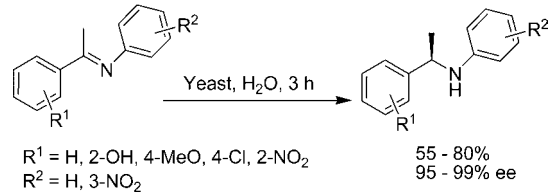


Reduction. The Merck group have also described the pilot-scale (80 kg) asymmetric synthesis of 4,4-dimethoxytetrahydro-2H-pyran-3-ol with a ketone reductase and in situ cofactor recycling using glucose dehydrogenase (*Org. Process. Res. Dev.* **2008**, *12*, 584−588). The product was produced in high yield (∼95%) and high ee (99%). Critical scale-up factors were agitation and pH control.

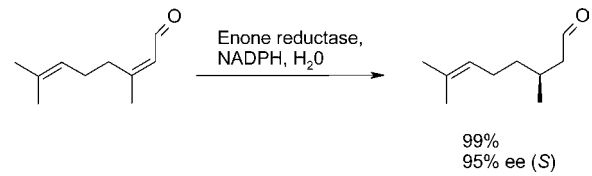


The same group have published on the stabilisation of alcohol dehydrogenase and glucose dehydrogenase enzymes by using ionic liquids as additives. Enzyme life can be extended to give more productive reactions when 10% v/v of certain ionic liquids are used instead of traditional solvents (*J. Mol. Catal. B: Enzym.* **2008**, *55*, 19−29). Examples such as reduction of *p*-bromoacetophenone are described.

The reduction of unactivated aryl imines in water by a yeast, *Candida parapsilosis*, to produce (*R*)-amines in high ee and good yield has been reported (*Tetrahedron: Asymmetry* **2008**, *19*, 93−96).



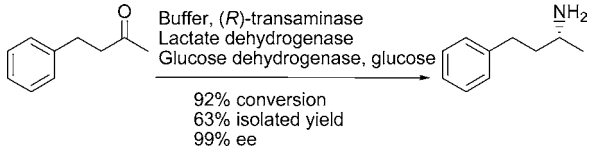
Hall et al. have published on the asymmetric bioreduction of activated C=C Bonds using *Zymomonas mobilis* NCR enoate reductase and "old yellow enzymes" (*Adv. Synth. Catal.* **2008**, *350*, 411−418). Prochiral activated double bonds are reduced to chiral alkenes in high ee. Adjacent carbonyl functions are not reduced. Examples of activating groups are aldehyde, ketone, amide, and nitro.



Fryszfowska et al. have reported on the highly enatioselective reduction of β,β-disubstituted nitroalkenes by the anerobic organism, *Clostridium sporogenes*, to give the corresponding nitroalkane in 35−86% yield and up to 97% ee. α,β-Substituted nitroalkenes were also reduced, but with lower ee and yield (*J. Org. Chem.* **2008**, *73*, 4295−4298).

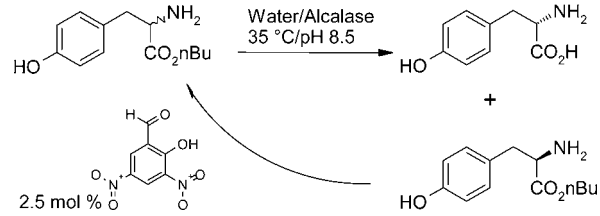
Transaminase. Over the past year there has been an upsurge of interest in the use of transaminase enzymes to prepare homochiral amines and amino acids. There have been four recent publications looking at increasing the process efficiency of such reactions.

Koszelewski et al. (*Adv. Synth. Catal.* **2008**, *350*, 2761−2766) have studied the synthesis of chiral amines from ketones using both (*S*)- and (*R*)-selective ω-transaminases and D- or L-alanine as the amine donor. The equilibrium was displaced using lactate dehydrogenase/NADH/glucose dehydrogenase to remove pyruvate. The effects of cosolvents and pyridoxal phosphate cofactor were examined. A range of ketones were examined, often giving the corresponding amines in high conversion and ee, the enantiomer selected by choice of (*R*)- or (*S*)-ω-transaminase. Free hydroxyl functionality on the ketone seems to inhibit the enzyme. A range of aryl−alkyl, alkyl−alkyl ketones and β-keto esters were examined.



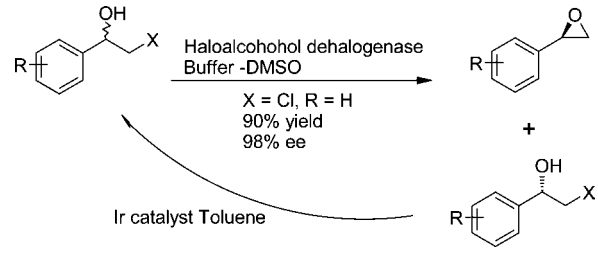
In similar work, Truppo et al. also describe a lactate dehydrogenase coupled system to remove pyruvate and also the use of isopropylamine as a donor, conceptually much simpler than the use of a three-enzyme system (*Org. Biomol. Chem.* **2009**, *7*, 395−398). A further variation reported by Koszelewski et al. (*Angew. Chem., Int. Ed.* **2008**, *47*, 9337−9340) is the use of alanine and an amino acid dehydrogenase to convert ammonia and pyruvate back to alanine. This represents a formal asymmetric reductive amination with ammonia. A range of ketones were converted to (*S*)-amines usually in high conversion and ee, even for small alkyl−alkyl ketones such as butanone. An example of transaminase technology being used to prepare a target molecule has been reported by Hanson et al. (*Org. Process Res. Dev.* **2008**, *12*, 1119−1129). The undesired (*S*)-enantiomer is oxidised by amino acid deaminase to the α-keto acid. This is then converted to the desired (*R*)-amino acid using D-transaminase and D-alanine as the amine donor. The reaction is run in water as a 'one pot' system giving the (*R*)-product in 85% yield and 96% ee. Due to solubility issues with the racemic amino acid, the reaction was also investigated using the α-keto acid as the starting material. Lactate dehydrogenase/formate dehydrogenase were found to be an effective solution to inhibition by the pyruvate byproduct. This was found to be much more efficient than using pyruvate decarboxylase to remove pyruvate.

Dynamic Kinetic Resolution/ Desymmetrisation. Schichl et al. (*Eur. J. Org. Chem.* **2008**, *20*, 3506- 3512) have reported an efficient synthesis of amino acids by resolution of racemic amino esters using cheap detergent proteases, for example, alcalase. The amino ester is racemised in situ by formation of a Schiff base between the amino ester and a salicylaldehyde derivative. The 3,5-dinitro compound was found to be most active and was used as the racemisation catalyst at 2.5 mol %. A range of amino acids was prepared.

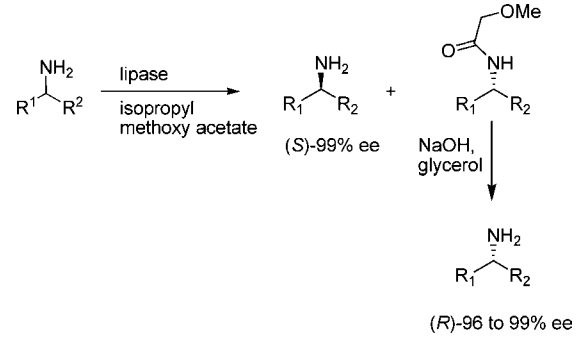


Small, highly functionalized molecules with quaternary chiral centres are valuable intermediates but often have lengthy syntheses involving resolution. Cortijos and Snape (*Tetrahedron: Asymmetry* **2008**, *19*, 1761−1763) have reported the desymmetrisation of a *meso*-diol using *Pseudomonas fluoroescens* lipase. The monoacetate is formed in high ee. Limiting the yield is the formation of the diacetate. The acylation complements hydrolysis of the diacetate which yields the (*R*)-mono ester in 92% ee.

Haak et al. (*J. Am. Chem. Soc.* **2008**, *130*, 13508−13509) have reported a dynamic kinetic resolution (DKR) of β-halo alcohols to give (*R*)-epoxides, the biocatalyst being a halo alcohol dehydrogenase, and the racemising catalyst, a novel iridacycle. The reaction is performed as a two-phase 'one-pot' system. Although it has to be added slowly over the course of the reaction, the iridacycle is unusual for an alcohol racemisation catalyst in that it will tolerate a biphasic reaction mixture. Activity was also seen with alkyl β-halo alcohols.



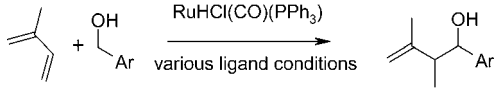
Amine Resolution. BASF have published improvements on the bioresolution of amines. The commercially available Novozym 435 has been identified as equivalent to the proprietary BASF catalyst, and isopropyl methoxyacetate was the optimum acyl donor. Improved procedures are also given for the hydrolysis of the acyl enantiomer (*Synthesis* **2008**, *14*, 2283−2287).



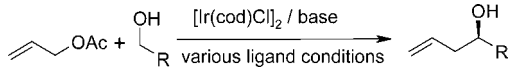
9. Reductions

There were no articles of interest to report on amide reduction during this review period.

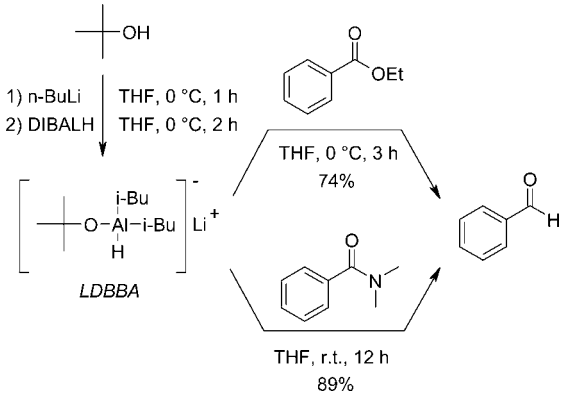
Krische and co-workers report a methodology for C−C bond formation using a carbonyl allylation reaction via transfer hydrogenation incorporating a ruthenium catalyst (*J. Am. Chem. Soc.* **2008**, *130*, 6338−6339). The allylation proceeds on either benzyl alcohols (via in situ oxidation, see section 10) or benzaldehyde substrates (using isopropyl alcohol as a terminal reductant) with acyclic 1,3-dienes directly. Reasonable yields are obtained with control of branch regioselectivity (61−93%). Isotopic labelling studies corroborate a mechanism involving hydrogen donation from the reactant alcohol or isopropyl alcohol.



In a related vein, the same group have demonstrated direct iridium-catalysed carbonyl allylation of either benzyl alcohols or benzaldehydes using allyl acetate as an alternative to preformed allyl metal reagents (*J. Am. Chem. Soc.* **2008**, *130*, 6340−6341). The examples shown proceeded with good yields (55−80%) and enantioselectivity (>90% ee).

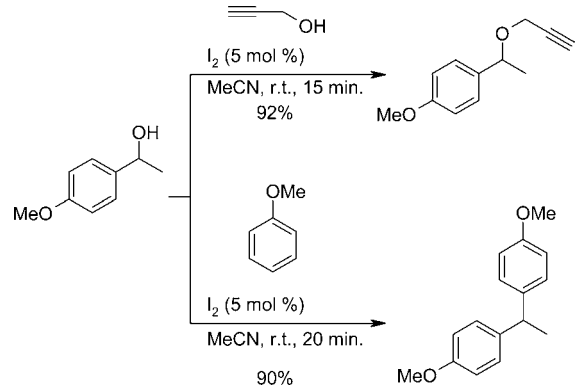


The group of An report the partial reduction of tertiary amides into aldehydes using a new class of reducing agents; metal diisobutyl-*tert*-butoxyaluminium hydrides. The group has previously reported on the partial reduction of esters to aldehydes in high yields. Methyl, ethyl and isopropyl esters were all partially reduced by lithium diisobutyl-*tert*-butoxyaluminium hydride (LDBBA) under mild conditions (0 °C, THF), thereby offering a practical alternative to the commonly used very low temperature DIBALH reductions (*Tetrahedron Lett.* **2008**, *48*, 5061−5064). In their recent report, the group reduce various *N*,*N*-dimethyl aromatic amides possessing both electron-withdrawing and electron-donating groups to aldehydes, in addition to a simple aliphatic amide and a heterocyclic amide (*Bull. Korean Chem. Soc.* **2008**, *29*, 1407−1408). Over-reduction to benzyl alcohol is not discussed in either approach.



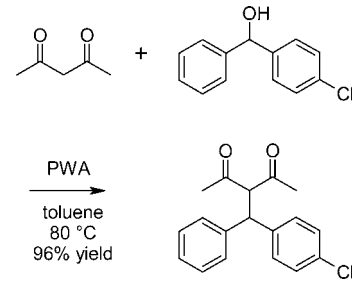
10. Alcohol Activation for Nucleophilic Displacement

Two emerging catalyst classes for alcohol substitution are molecular iodine and gold salts. The former has been used as an environmentally benign reagent for various organic functional group conversions for many years, but it is only recently that researchers have successfully applied it to nucleophilic substitution reactions of alcohols. Sun and Wang report the iodine-catalysed benzylation of arenes with benzyl alcohols, an approach that avoids the use of heavy metals commonly required for such transformations (*Tetrahedron Lett.* **2008**, *49*, 4929−4932). Srihari et al. report similar catalysis of substituted benzyl alcohols with C- and O-nucleophiles in acetonitrile with the benefits of short reaction times and operationally simple protocols (*Synlett* **2008**, *7*, 1045−1049).



Finally, the group of Chan has applied molecular iodine catalysis to the allylic alkylation of both aryl and alkyl thiols with allylic alcohols under conditions that are both air and moisture tolerant. Although the majority of reactions use 1,4-dioxane, the reactions also work in a range of pilot-plant suitable solvents such as toluene, THF and water (*Synlett* **2008**, *14*, 2204−2208). The same group have also reported that gold salts were successfully applied to the allylic alkylation of both aromatic and heteroaromatic compounds with allylic alcohol under mild reaction conditions. While the use of methylene chloride as solvent allows the greatest yields, THF is proven to be a suitable replacement (*Org. Biomol. Chem.* **2008**, *6*, 2426−2433). On a related theme, Muzart has compiled the first review of gold-catalysed alcohol chemistries, including both inter- and intramolecular C−C and C−heteroatom bond-forming reactions involving C−OH bond cleavage (*Tetrahedron* **2008**, *64*, 5815−5849).

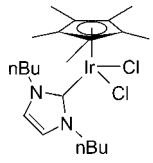
Wang et al. report a phosphotungstic acid (PWA)-catalysed direct benzylation of β-dicarbonyl compounds with a variety of benzyl alcohols (*Eur. J. Org. Chem.* **2008**, 4999−5004). Catalyst loading of 0.6 mol % in a range of useful solvents exemplified this powerful protocol for carbon−carbon bond-forming reactions which provide monoalkylated dicarbonyl compounds in high yields with great efficiency. Overall, the protocol provides a clean and efficient alternative to existing catalytic systems.



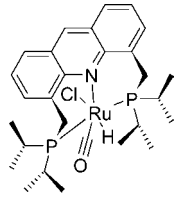
In an earlier paper the same authors report a PWA-catalysed C−N bond formation protocol via nucleophilic substitution reactions of benzylic and simple aliphatic alcohols with sulfonamides, benzamides and 4-nitroaniline (*Eur. J. Org. Chem.*

2008, 4367−4371). Again, low catalyst loadings are employed, and the recyclable nature of the catalyst is demonstrated.

A number of examples of the hydrogen borrowing approach towards activation of primary and secondary alcohols have been published in the synthesis of amines. Peris et al. describe the use of iridium catalyst (**3**) and silver triflate in a base-free alkylation of primary amines with primary and secondary alcohols. Anilines are monoalkylated, whereas primary amines (benzylamine, hexylamine and cyclohexylamine) show variable amounts of mono- and bis-alkylation. The catalyst system has also been applied to the synthesis of benzyl ethers (*Chem.−Eur. J.* **2008**, *14*, 11474−11479). Gunanathan and Milstein have applied ruthenium catalyst (**4**) to the preparation of primary amines from primary alcohols and ammonia. The reaction is run in toluene under 7.5 atm pressure, and yields are generally >70% (*Angew. Chem., Int. Ed.* **2008**, *47*, 8661−8664).

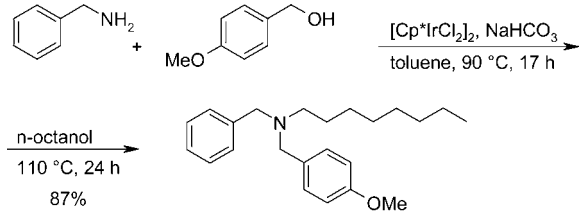


(3)



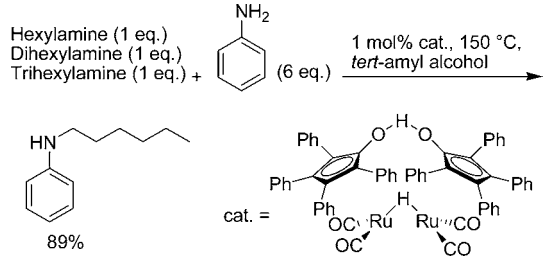
(4)

Fujita, Enoki and Yamaguchi use bis(pentamethylcyclopentadienyl)iridium dichloride with sodium bicarbonate as base in the alkylation of amines (aryl, primary or secondary). Alkylation of secondary amines requires more forcing conditions allowing selective monoalkylation of primary amines. The methodology allows sequential alkylation to provide differentially substituted tertiary amines (*Tetrahedron* **2008**, *64*, 1943−1954).



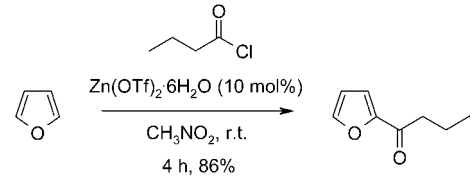
Cp* = pentamethylcyclopentadienyl

In a related reaction, Hollmann et al. have shown the Shvo catalyst to be effective in the alkylation of aniline using amines as the substrate. All three alkyl chains of a tertiary amine are transferred to afford monoalkylated anilines with ammonia as the byproduct. The first stage of the proposed mechanism is dehydrogenation of the amine to the imine (*Chem. Commun.* **2008**, 3199−3201). The same group have also used pyrrolidine and piperidine to alkylate anilines, affording the tertiary amine in modest (25−68%) yields (*Tetrahedron Lett.* **2008**, *49*, 5742−5745).



11. Friedel−Crafts Chemistry

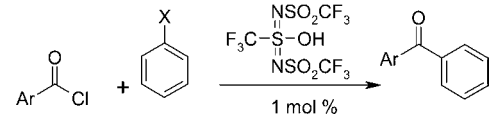
He et al. report the successful use of $Zn(OTf)_2 \cdot 6H_2O$ as a water-tolerant Lewis acid for the acylation of electron-rich heteroaromatics and anisole with acid chlorides and anhydrides. Whilst unactivated systems were not investigated, this work describes a mild catalytic system suitable for large-scale application that does not require drying at high temperature under vacuum before use (*Synth. Commun.* **2008**, *38*, 255−264).



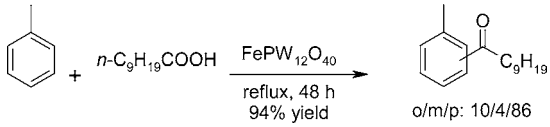
Poulsen and Jørgensen present a review of catalytic asymmetric Friedel−Crafts alkylation reactions. Three catalyst classes are addressed (copper complexes, other metal complexes and organocatalysts) with regards to promoting the alkylation of aromatic and heteroaromatic compounds by activated alkenes, carbonyl compounds and imines. As the majority of nucleophiles reported are electron-rich compounds such as indole, the authors highlight the need to expand these powerful reactions to include less activated simple benzene derivatives (*Chem. Rev.* **2008**, *108*, 2903−2915).

A procedure for the F−C acylation of aromatic compounds directly with various carboxylic acids in the presence of P_2O_5/SiO_2 is described by Zarei et al. (*Tetrahedron Lett.* **2008**, *49*, 6715−6719). The catalyst is reportedly easy to prepare and may be removed from the reaction mixture by filtration. Aryl ketones from both electron-rich and electron-poor aromatic compounds were prepared cleanly in 1−5 h, many run neat at reflux while some required boiling 1,2-dichloroethane−unacceptable from a green chemistry perspective−but solvent-free cases are useful and other solvents may prove possible.

Garlyauskayte and co-workers (*Tetrahedron Lett.* **2008**, *50*, 446−447) report that a novel super acid has demonstrated remarkable catalytic ability in the electrophilic acylation of aromatic substrates utilizing aroyl chlorides. Bis(trifluoromethylsulfonylimino)trifluoromethanesulfonic acid was employed, typically at 1 mol %, on a range of aroyl chlorides acylating chloro-, fluoro-, and unelaborated benzene with favorable results. Calculations of deprotonation enthalpies for this acid catalyst reveal gas-phase acidity on the order of 21 pK_a units greater than that of trifluoromethanesulfonic acid and approximately equal to that of $HSbF_6$.

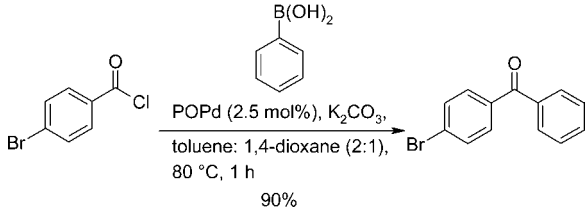


Shimizu et al. have investigated polyvalent metal salts of phosphotungstic acid (PWA) as effective heterogeneous catalysts for Friedel−Crafts acylation of aromatics with carboxylic acids (*Catal. Commun.* **2008**, 980−983). Iron(III) salts show high yields and the highest turnover number (2500) reported to date and can be reused without loss of activity.



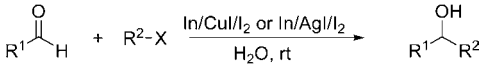
Firouzabadi and Jafari present a review of cesium and aluminum salts of phosphotungstic acid as eco-friendly and efficient heterogeneous catalysts in organic synthesis (*Curr. Org. Chem.* **2008**, *12*, 233−256). The application of these catalysts in Friedel−Crafts acylation and alkylation of aromatic compounds is discussed. Fries, Claisen and pinacol rearrangements; esterification; amidation; ether formation; protection of thiols, alcohols and amines; conversion of aldehydes to their acylals; ring-opening of epoxides; selective protection of one hydroxy group in diols; preparation of β-hydroxythioethers and regioselective bromination of aromatic compounds are also discussed.

A palladium phosphinous acid-catalysed cross-coupling alternative approach to Friedel−Crafts acylation products has been reported by Wolf and co-workers. Aromatic and aliphatic acyl chlorides were coupled with arylboronic acids to yield ketones in a procedure that avoids the harsh reaction conditions, untunable regiocontrol and low substrate scope that can accompany Friedel−Crafts acylations. The use of 1,4-dioxane as cosolvent would, however, require substitution during scale-up (*Tetrahedron Lett.* **2008**, *49*, 5773−5776).

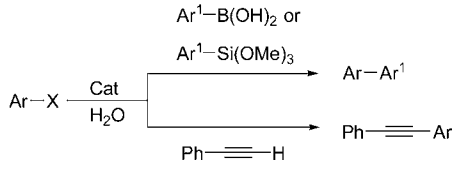


12. Chemistry in Water

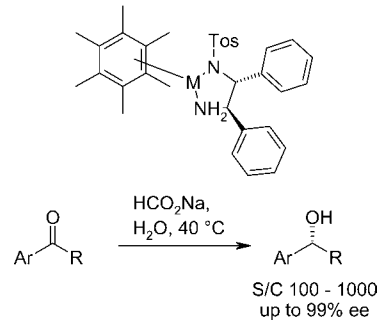
An efficient method has been developed for the Barbier−Grignard-type alkylation reaction of aldehydes using unactivated alkyl halides in water in the presence of an In/CuI/I_2 or In/AgI/I_2 system (*J. Org. Chem.* **2008**, *73*, 3922−3924). The reactions proceeded more efficiently in water than in organic solvent.



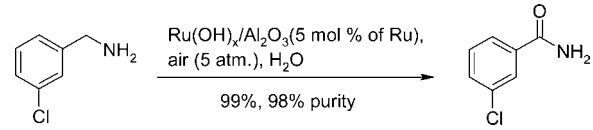
Inés et al. have prepared a PCN−palladium pincer complex containing a phosphinamino group used in Hiyama, copper-free Sonogashira and Suzuki cross-coupling reactions in water. The research favorably compared the use of this catalyst in water against typical conditions in organic media (*Organometallics* **2008**, *27*, 2833−2839).



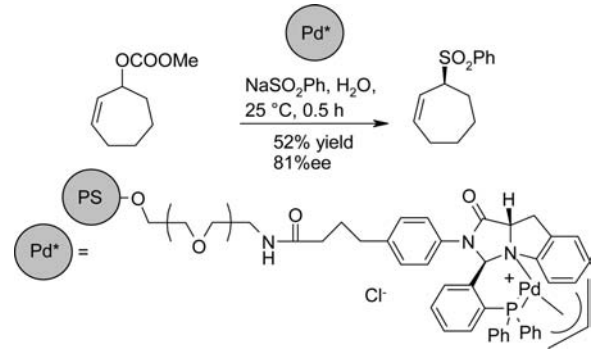
Wu et al. recently reported asymmetric transfer hydrogenation of ketones by formate in water with Rh-TsDPEN and Ir-TsDPEN catalysts (*Chem.−Eur. J.* **2008**, *14*, 2209−2222).



The oxygenation of primary amines to amides remains a significant challenge to synthetic chemists. Kim et al. report a catalytic approach using oxygen from air in water under supported ruthenium catalysis - a development that offers the advantages of avoiding toxic byproduct formation and easy catalyst separation and recycling (*Angew. Chem., Int. Ed.* **2008**, *47*, 9249−9251).

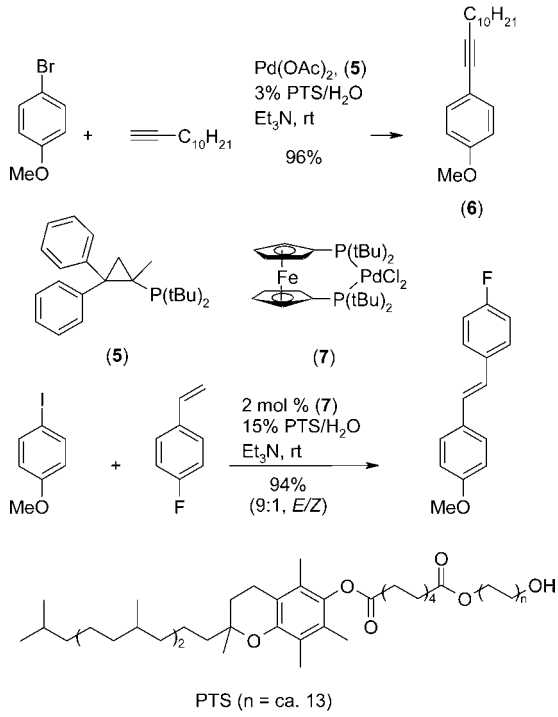


Uozumi and Suzuka describe a π-allylic substitution of allyl esters with sodium arylsulfinate in water catalysed by an amphiphilic polystyrene−poly(ethylene glycol) (PS−PEG) resin-supported phosphine−palladium complex to give allyl sulfones in good to high yields (*Synthesis* **2008**, *12*, 1960−1964). Catalytic asymmetric allylic substitution of cycloalkenyl esters also took place in water using a PS−PEG resin-supported chiral imidazoindole-phosphine−palladium complex to give cycloalkenyl sulfones with up to 81% ee.



Lipshutz et al. have published studies on palladium-catalysed chemistry in water using the nonionic amphiphile PTS, based on vitamin E (commercially available as an aqueous solution). Reactions occur in nanometer micelles formed by the PTS. Copper-free Sonogashira couplings can be achieved in good yield at ambient temperature for a range of substrates using X-Phos as ligand. Electron-rich substrates are successfully coupled using ligand **5**; 96% yield of **6** in 10 h, cf. three days with X-Phos (*Org. Lett.* **2008**, *10*, 3793−3796). The same approach has been applied to Heck couplings of aryl iodides, and one bromide, with acrylates and styrenes using catalyst **7**, the first examples of the reaction solely in water at ambient temperature. Efficient mixing is essential (*Org. Lett.* **2008**, *10*, 1329−1332). The same group have applied the approach to ring-closing metathesis reactions in water at ambient temper-

ature using a second-generation Grubbs catalyst. The reactions are facilitated by polyoxyethanyl α-tocopheryl sebacate (*Adv. Synth. Catal*. **2008**, *350*, 953−956).



13. Continuous Processing and Process Intensification

Balini et al. report that 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine supported on polystyrene (PS-BEMP) is an efficient catalyst for the addition of nitroalkanes (1−1.5 equiv) to α,*β*-unsaturated carbonyl compounds (1.0 equiv) in the absence of a reaction medium (*Adv. Synth. Catal*. **2008**, *350*, 1218−1224). To optimize the catalyst's reuse and improve the environmental efficacy of solvent-free conditions, a solvent-free cyclic continuous-flow reactor has been set up.

Yoshida and co-workers (*Angew. Chem., Int. Ed*. **2008**, *47*, 7833−7836) successfully utilized the characteristics of a micro reactor, such as efficient mixing, good temperature control and short residence times, to accurately control the reactions involving highly reactive aryl lithium species. Numerous examples of high-yielding reactions involving aryllithium compounds with alkoxycarbonyl groups in a micro reactor are reported which cannot be achieved using conventional batch processing methodology.

Barthe et al. (*Chem. Eng. Technol*. **2008**, *31*, 1146−1154) describe the details of the reactor designing requirements for a Corning micro glass reactor to meet the requirements suggested by Lonza, based on an organometallic process. The key criteria in designing this reactor were accurate control of the reaction temperature and concentration distribution within the reactor which was critical in determining the process selectivity. A multiple injection microstructure where a reactor layer channel sandwiched between two layers of heat transfer fluid ensured good distribution and efficient heat dissipation. A detailed investigation into the application of such a reactor system is published as a second part by Roberge et al. (*Chem. Eng. Technol.* **2008**, *31*, 1155−1161).

Another interesting publication was based on the development of a nondispersive fibre reactor for two-phase reactions by Massingill, Jr. et al. (*Org. Process Res. Dev*. **2008**, *12*, 771−777). Continuous processing of biphasic reactions using nonstirred reactors is of interest from two angles: (1) attaining the mass transfer efficiency across the two phases and also (2) from the viewpoint of efficient downstream processing involving phase separation. This publication discusses use of a fibre reactor for achieving both of these operations using the same reactor. An etherification reaction, a dehydrochlorination reaction, a transesterification reaction and vegetable oil neutralization are showed as examples for this approach.

A special issue of [*Org. Process Res. Dev.* **2008**, *12* (5)] devoted to continuous processing mainly in line with the needs of pharmaceutical chemical processing was published. The works therein include studies based on a new Corning individual glass microstructure reactor, oxidation, halogen exchange reactions and also publications on continuous downstream processing.

14. Super Critical Fluid Chromatography Separations

Zhao et al. from Abbot Laboratories have published their analysis of polysaccharide stationary phases in the chiral resolution of proline derivatives (*J. Chromatogr., A* **2008**, *1189*, 245−253). In each case SFC outperformed HPLC. The article describes the improved selectivity, robustness and shorter run times of SFC compared to those of HPLC.

Abbott et al. from the Laboratory of Proteomics and Analytical Technologies have published their analysis of SFC as a tool for analyzing biomolecules (*J. Sep. Sci*. **2008**, *31*, 1223−1230) in cases where undesirable additives were required for resolution in HPLC. Preferred, or no, additive was required for analysis using SFC. Again, SFC outperformed HPLC, providing better resolution and shorter run times.

15. General Green Chemistry

The 2008 academic award in the Presidential Green Chemistry Challenge was awarded to Professors Robert Maleczka and Mitch Smith for their work on Green Borylation Reactions. For a recent reference from the Maleczka and Smith laboratories concerning the application of iridium-catalysed borylation to thiophene derivatives, see Chotana et al. (*Tetrahedron* **2008**, *64*, 6103−6114). Professors Maleczka and Smith were also awarded a Pharmaceutical Roundtable Research Grant in 2007.

Carlos Martinez et al. from Pfizer have published their enzymatic synthesis of pregabalin which forms the basis of the commercial process (*Org. Process Res. Dev*. **2008**, *12*, 392−398). The *E*-factor for the enzymatic process was 17 which compared favorably with the *E*-factor of the previous classical resolution process which was 86. The authors give a detailed breakdown of material usage for the two processes.

Henderson et al. from GSK have reported a very systematic and detailed environmental, health, safety and life-cycle assessment of two processes to make 7-aminocephalosporanic acid

(7-ACA), one a traditional chemical process and the second a process involving two enzymatic reactions (*Ind. Biotechnol*. **2008**, *4*, 180−192). It was found that the chemical process used 60% more energy and 16% more mass (excluding water), has double the greenhouse gas impact and about 30% higher photochemical ozone-creation potential.

Liand Trost have published a perspective called "Green chemistry for chemical synthesis" (*Proc. Natl. Acad. Sci. U.S.A.* **2008**, *105*, 13197−13202). The perspective gives a good coverage of green chemistry advances from academic laboratories over the past 15 years. Another perspective is published by Sheldon, "E factors, green chemistry and catalysis: an odyssey" (*Chem. Commun*. **2008**, 3352−3365); in contrast to the Li and Trost perspective, this article covers many industrial processes.

Microwave reactions are often promoted as green, energy-efficient chemistry because of their short reaction times; however, Razzaq and Kappe have written a very balanced article in which they make a detailed comparison of the energy use of four reactions (Diels−Alder, hydrolysis, cyclocondensation and Suzuki reactions) using both microwave and conventional heating. Although the microwave approach uses less energy in some cases, sometimes the microwave approach uses more energy than conventional heating (*ChemSusChem* **2008**, *1*, 123−132).

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