Organic Process Research & Development

GREEN CHEMISTRY HIGHLIGHTS

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Green Chemistry Articles of Interest to the Pharmaceutical Industry

1. INTRODUCTION

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

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

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

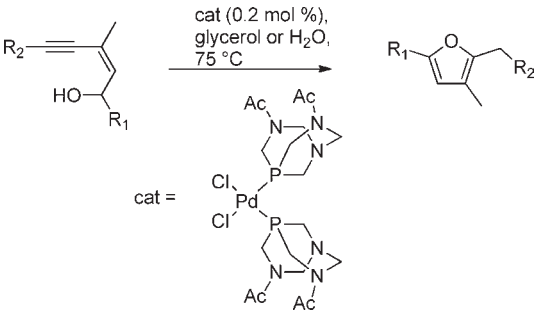
These articles of interest represent the opinions of the authors and do not necessarily represent the views of the member companies. Some articles are included because, whilst not currently being regarded as green, the chemistry has the potential to improve the current state of the art if developed further.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

2. SOLVENTS

Green replacements for polar aprotic solvents are eagerly sought and are currently missing from the Green Chemistry "tool box". Given a choice between DMF, DMAc, and NMP some companies recommend *N*-methylpyrrolidinone (NMP) on the basis that, although this solvent carries the same reprotoxicity hazards as DMF and DMAc, it is less volatile, and hence the risk of exposure is reduced. Lammens et al. have reported a new synthesis of NMP from biomass using methanol as the source of the *N*-methyl group (*Green Chem.* **2010**, *12*, 1430−1436). Organic carbonates have many similar properties to polar aprotic solvents, although in general they have reduced toxicity and are usually immiscible with water. Schaffner et al. have reviewed the use of organic carbonates as solvents in synthesis and catalysis; the review also covers their preparation and properties (*Chem. Rev.* **2010**, *110*, 4554−4581).

Raymond et al. from Rowan University have detailed the lifecycle impact of three pharmaceutical processes from BMS, Pfizer and Novartis. In this article SimaPro 7.1 software is used to calculate the emissions during the manufacture of the solvents and their process use. Ecosolvent is used to estimate emissions due to waste stream incineration. The article also gives a very useful table listing detailed lifecycle assessment for the production of 1 kg of a selection of common organic solvents. The authors conclude that in each of the processes the pharmaceutical process itself is only responsible for a small percentage of the emissions. It is the manufacture of the solvents and their incineration which cause the majority of the emissions (*Green Chem.* **2010**, *12*, 1826−1834).

Glycerol is more often being used as a solvent for organic synthesis and is considered to be biodegradable, inexpensive, nontoxic, highly polar and immiscible with hydrocarbons. Glycerol is also able to form strong hydrogen bonds and to dissolve inorganic compounds. Francos and Cardierno have made a comparison between the use of water and glycerol as solvent in the metal-catalyzed cyclo-isomerization of (*Z*)-2-en-4-yn-1-ols into furans. Although reactions proceeded faster in water, it was much more effective to recycle the catalyst in glycerol without significant loss of activity (*Green Chem.* **2010**, *12*, 1552−1555).



3. AMIDE FORMATION

N-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC) is a widely used reagent in medicinal chemistry, early scale-up for peptide coupling and other amide bond-forming reactions. Traditionally the reagent is used in combination with 1-hydroxybenzotriazole which suppresses racemization. However, 1-hydroxybenzotriazole explodes violently near its melting point and was the cause of a large explosion at the Lacamas plant in Oregon, United States, in May, 2005. Lorenz et al. from the Chemical Development group at Boehringer-Ingelheim have studied replacing 1-hydroxybenzotriazole with either *N*-hydroxysuccinimide or a variety of substituted hydroxypyridines (all of which have a much greater level of thermal stability and are not explosive). The final method selected for scale-up into the pilot plant used 2-hydroxypyridine and EDC as reagents and 2-MeTHF as solvent; amide (**1**) was obtained in 81% yield and 96% ee. The product was essentially racemic if

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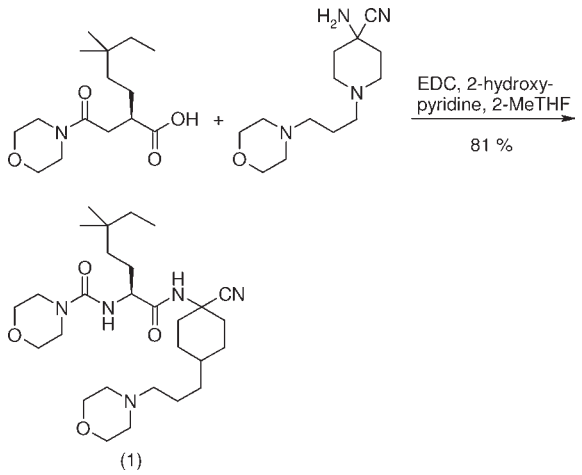
N-hydroxysuccinimide was used in conjunction with EDC. (*J. Org. Chem.* **2010**, *75*, 1155−1161)

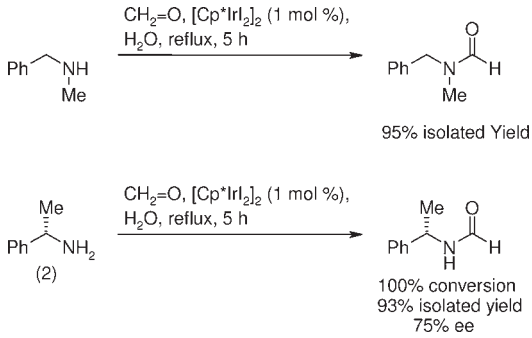


(1)

Chaudhari et al. have reported the use of sulfated tungstate as a solid acid catalyst for amide synthesis. If benzoic acid was reacted with benzylamine in the presence of sulfated tungstate catalyst (18 wt %) for 12 h in boiling toluene, an 81% yield of the desired amide was observed. An 8% yield was obtained in the absence of catalyst. The catalyst could be simply filtered off and reused several times (*Green Chem.* **2010**, *12*, 1707−1710).

Marcelli has published a theoretical paper giving some mechanistic insights into direct amide formation catalyzed by boronic acids. Density functional theory was used to calculate and propose the lowest energy catalytic cycle (*Angew. Chem., Int. Ed.* **2010**, *49*, 6840−6843).

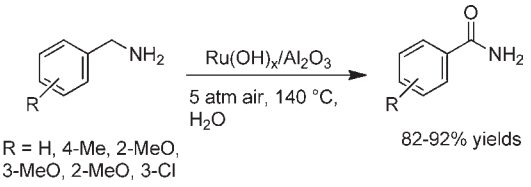
Formamides are a useful class of compounds which have been used as low-molecular weight protecting groups and as reagents for Vilsmeier formylation. Saidi et al. have reported the iridium-catalyzed formylation of amines with formaldehyde. Both primary and secondary amines can be used, and the reaction proceeds in boiling water. One downside of this technology is that some of the stereochemistry is lost; if enantiomerically pure (*S*)-1-phenethylamine (**2**) is used, a product with 75% ee is obtained (*Tetrahedron Lett.* **2010**, *51*, 5804−5806).



4. OXIDATIONS

Roger Sheldon has reviewed oxidations in water. For water-insoluble substrates, the two primary approaches include: the use of phase transfer reagents to transfer the oxidant to the organic phase, such as reactions involving H_2O_2 or hypochlorite, and use of water-soluble catalysts to carry out the oxidation in the aqueous phase, typically used for oxidations with molecular oxygen. Also highlighted are the use of the more environmentally benign metals in catalytic quantities, such as iron, copper, and manganese, as well as organo-catalysts, to replace the stoichiometric metal conditions used historically; and immobilization techniques, including reusable metal nanoparticles, which are finding wider use. (Green Oxidation in Water. In *Handbook of Green Chemistry*; Anastas P. T., Ed.; Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, 2010; pp 75−103.)

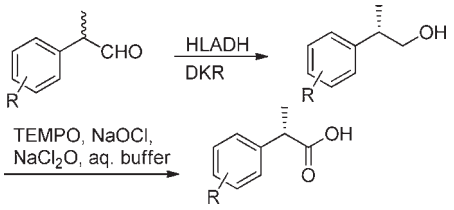
Mizuno et al. reviewed recent research in their laboratories on the use of polyoxometalates covalently immobilized to silica via cationic imidazolium linkers. Tungstate and vanadate catalysts were used for epoxidations (0.8% catalyst load) and for sufide to sulfoxide oxidations (0.005% catalyst load). Ruthenium hydroxide on alumina was developed to carry out a number of oxidations, including conversion of alcohols to aldehydes, amines to nitriles, nitriles to amides, and benzylic oxidations (see related article in section 10). The authors reviewed the oxidative synthesis of nitriles from alcohols and ammonia in THF using air (6 atm), a method which has good substrate scope. Oxidation of primary amines to amides was also described, although this oxidation requires 140 °C and 5 atm air which will limit usefulness on substrates with sensitive functional groups (*Top. Catal.*, **2010**, *53*, 876−893).



R = H, 4-Me, 2-MeO, 3-MeO, 2-MeO, 3-Cl

Subramanian reviewed work on gas-expanded liquids (CO_2 dissolved in a solvent) at the University Of Kansas Centre for Environmentally Beneficial Catalysis. These solvent systems have the advantage of providing significant gas expansion near ambient temperature with modest pressures (50 − 60 bar) and provide a range of polarity based on composition and pressure. The author discussed a number of examples of green oxidations in gas-expanded liquids. Use of molecular oxygen in CO_2-expanded solvents has several advantages, including increased solubility of oxygen and a wider range of conditions within a nonflammable envelope. Use of H_2O_2 in CO_2 leads to formation of peroxycarbonic acid, which can be used for olefin epoxidations in CO_2-expanded MeCN/water as a homogeneous system, providing >85% yields. The group has recently developed a stable ozone-CO_2 system which cleaves double bonds at 0 °C and 44 bar (*Coord. Chem. Rev.* **2010**, *254*, 1843−1853).

The profens continue to be targets for development of cheaper and greener routes. Galletti et al. describe an approach in which racemic aldehydes are reduced to the corresponding alcohols using a dynamic kinetic resolution with horse liver alcohol dehydrogenase, and then oxidized to the carboxylic acid using catalytic TEMPO and NaClO (both 2 - 6 mol %), and 2 - 4 equiv of $NaClO_2$ in buffered acetonitrile (*Synlett*, **2010**, 2644−2648).



Zotova et al. reported the development of catalytic oxidations of alcohols to aldehyde and ketones using the commercially available X-cube™ reactor under flow conditions. The reactions were carried out in toluene at 90 °C, with either 5 bar oxygen or 15 bar air, and

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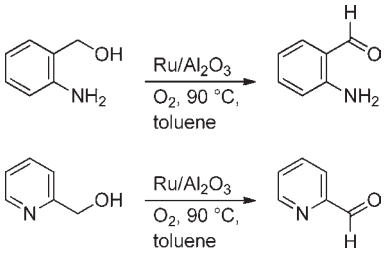
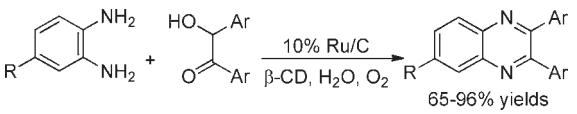
5% Ru/Al_2O_3 as the heterogeneous catalyst. Kinetic studies revealed both the carbonyl product and water byproduct inhibited the reaction. The reaction rate was accelerated by employing a desiccant cartridge to remove water. Higher pressures of oxygen were required to overcome product inhibition. Challenging substrates such as pyridyl alcohols and aniline alcohols were cleanly converted to the corresponding aldehydes (*Green Chem.* **2010**, *12*, 2157−2163).

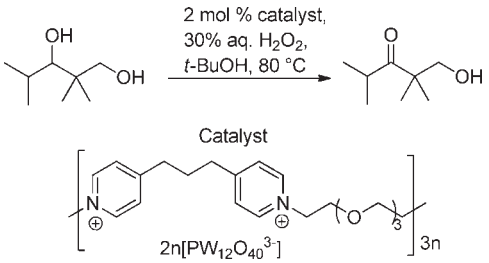


Keeping with the theme of oxidations under flow conditions, Sedelmeier et al. reported the use of flow chemistry for oxidation of alcohols and aldehydes to carboxylic acids using $KMnO_4$, and the Nef reaction of nitroalkanes to ketones and carboxylic acids. A limitation of flow chemistry has been the inability to handle slurries, but in the reported study ultrasound pulses were used to convey slurries of the MnO_2 byproduct through the system without plugging (*Org. Lett.* **2010**, *12*, 3618−3621).

Akkilagunta et al. described the use of cyclodextrins to enable aerobic alcohol oxidations in water under neutral conditions using Ru/C as the heterogeneous catalyst. NMR studies indicated the cyclodextrins formed inclusion complexes with the alcohol substrates, facilitating the oxidation that did not occur in the absence of the cyclodextrin. The catalyst could be recycled 5 times with minimal loss of activity. The authors demonstrated the value of the methodology for the one-pot synthesis of quinoxalines by oxidation of benzoins in the presence of *o*-phenylenediamines (*Synlett* **2010**, 2571−2574).



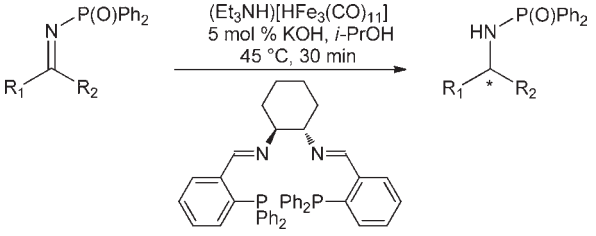
Yamada et al. reported a phosphotungstate catalyst complexed within a polymer matrix for the oxidation of hindered alcohols in excellent yields using H_2O_2 in *t*-BuOH at 80 °C. Secondary alcohols react faster than primary, as exemplified by the oxidation of a secondary alcohol in the presence of a primary alcohol. The heterogeneous catalyst could be recycled 5 times with no loss of activity (*Org. Lett.* **2010**, *12*, 4540−4543).



5. ASYMMETRIC HYDROGENATION

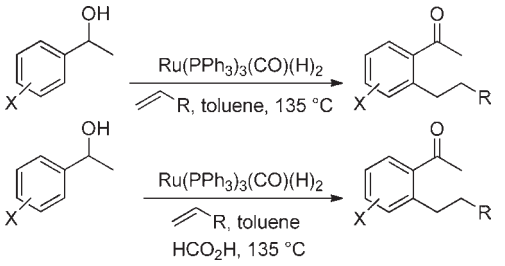
Three reviews on asymmetric hydrogenation have been published. Castillon and co-workers review the asymmetric hydrogenation and transfer hydrogenation of imines using iridium, palladium, ruthenium, or rhodium catalysts in combination with various ligands. A wide range of catalysts, ligands, and substrates are discussed (*ChemCatChem* **2010**, *2*, 1346−1371). Dieguez and colleagues published a review highlighting the asymmetric hydrogenation of minimally functionalized terminal olefins to produce chiral hydrocarbons, which is considered a sustainable approach to chiral hydrocarbons because of its atom economy and operational simplicity (*Chem.—Eur. J.* **2010**, *16*, 14232−14240). A review by Palmer and Zanotti-Gerosa covers homogeneous asymmetric hydrogenation of traditionally difficult functional groups such as weakly functionalized carbon−carbon and carbon−nitrogen double bonds. This review also introduces a few examples of asymmetric hydrogenation on large-scale in the pharmaceutical and chemical industry (*Curr. Opin. Drug Discov.* **2010**, *13*, 698−716).

The search for economical and environmentally friendly catalysts that are effective for a wide range of substrates continues. Beller et al. reported an efficient iron-based catalytic system that promotes asymmetric transfer hydrogenation of N-(diphenylphosphinyl) ketimines. A variety of aromatic, heteroaromatic, and cyclic ketimines were hydrogenated with up to 98% yield and 98% ee (*Angew. Chem. Int. Ed.* **2010**, *49*, 8121−8125).



6. C−H ACTIVATION

Watson et al. have described the first example of tandem oxidation/arene C−H activation of benzyl alcohols with alkenes to generate ketones using $Ru(PPh_3)_3(CO)(H_2)$ in toluene at 135 °C. Conditions were optimized utilizing 2.3 to 5 equiv of the alkene where R was *t*-butyl to achieve isolated yields of between 76 and 98%. Dialkylated products were isolated when X was H or *p*-methoxy. To expand the scope of the reaction, the possibility of direct one-pot conversion to the corresponding benzyl alcohol was investigated. The addition of 5 equiv of formic acid to the reaction once the C−H activation reaction was complete resulted in formation of benzyl alcohols in moderate to good yields (43 - 87%). Finally, a variety of alkenes were screened for both reactions to determine the scope. The results of the C−H activation were in agreement with previous work by Murai utilizing Wilkinson's catalyst with the subsequent conversion to the benzyl alcohol demonstrated for most substrates (*Org. Lett.* **2010**, *12*, 3856−3859).



An improved method for the synthesis of oxindoles utilizing catalytic copper was described by Klein et al. via a double

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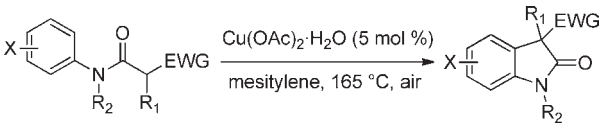
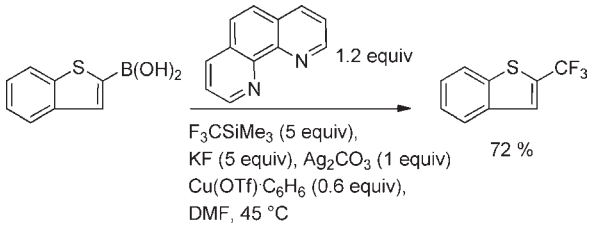
C−H activation process. Previous methodology for this transformation required stoichiometric or excess amounts of copper reagents and excess base for acceptable conversions. Optimized catalytic conditions were described that utilize $Cu(OAc)_2 \cdot H_2O$ (5 mol %) in the presence of air with boiling toluene to gave good conversion with long reaction times. However, increasing the temperature by boiling in mesitylene (165 °C) resulted in high yields in only 1.5 h. R^1 group functionalization was well tolerated (Me, vinyl and phenyl) and electron donating and electron withdrawing X groups were not problematic with yields near 80% with the exception of 4-CO_2Et (53%). For EWGs it was possible to utilize Et, *i*-Pr and *t*-Bu esters all near 90% yield and similarly the cyano group at this position resulted in 89% yield. When phenyl was used in place of the electron withdrawing groups none of the desired conversion was observed (*Org. Lett.* **2010**, *12*, 3446−3449).



7. GREENER FLUORINATION

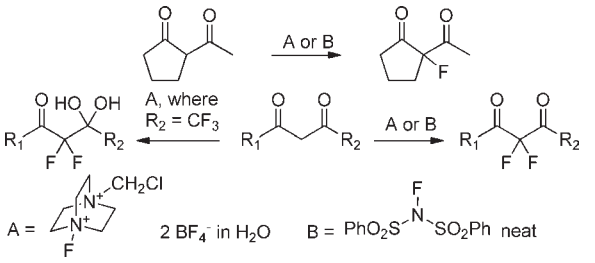
Trifluoromethyl-substituted aryl groups are commonly found in pharmaceuticals and agrochemicals. Traditional chemistry techniques used to manufacture this particular moiety leave much to be desired in terms of green reagents and environmental performance. Recently, a cohort of papers has appeared focusing on the use of metal-catalyzed reactions to form the key aryl-CF_3 bond.

Chu and Qing have reported oxidative cross-coupling using aryl boronic acids as the substrates. The combination of Cu(I) and 1,10- phenanthroline was the optimal catalyst reported. A range of aryl and heteroaryl boronic acids were successfully converted to the corresponding Aryl-CF_3 compounds. The use of DMF, high Cu loading and stoichiometric Ag_2CO_3 somewhat detract from the greenness of this procedure, but greener reagents and a more active catalyst could probably be found (*Org. Lett.* **2010**, *12*, 5060−5063).



Progress so far in this emerging area has been summarized by Lundgren and Stradiotto (*Angew. Chem., Int. Ed.* **2010**, *49*, 9322−9324).

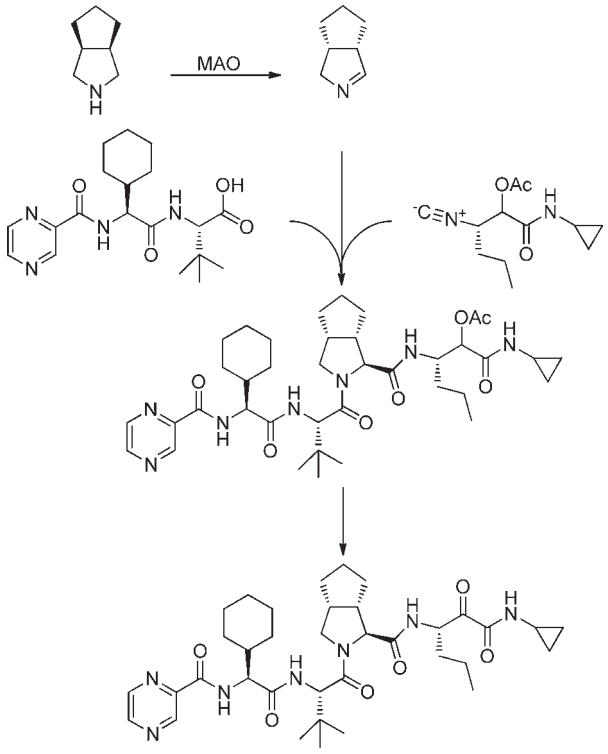
Stavber and Stavber describe the fluorination of active carbonyl compounds in water or under solvent free conditions using Selectfluor or Accufluor as the F^+ source. Reaction products depended on the nature of the ketone substituents. Products were isolated usually in high yield, 70−95% (*Adv. Synth. Catal.* **2010**, *352*, 2838−2846).



Finally, an up-to-date and wide-ranging review article on recent advances in catalytic enantioselective fluorination reactions has been published by Lectard et al. (*Adv. Synth. Catal.* **2010**, *352*, 2708−2732).

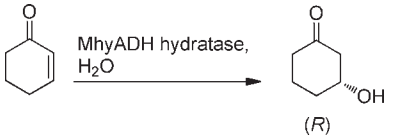
8. BIOCATALYSIS

Znabet et al. have reported a very convergent and efficient synthesis of the HCV NS3 protease inhibitor, telaprevir (*Chem. Commun.* **2010**, *46*, 7918−7920). The strategy involves the desymmetrization of a commercially available meso amine using a monoamine oxidase, MAO, and a three component Ugi-type coupling as the pivotal bond-forming reaction, followed by an oxidation to give the API (see for example Kohloer et al. in *Angew. Chem., Int. Ed.* **2010**, *49*, 2182−2184). The new sequence is 11 steps (7 in the longest linear sequence), compared with 24 steps in the original sequence. The new approach avoids a lot of protection and deprotection.

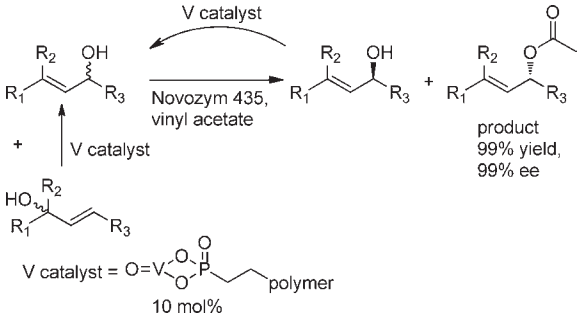


Jin et al. have reported an unusual Michael hydratase activity from *Acaligenes denitrificans* DSMZ14773. It is believed to be part of a pathway degrading cyclohexanol. The enzyme adds water to

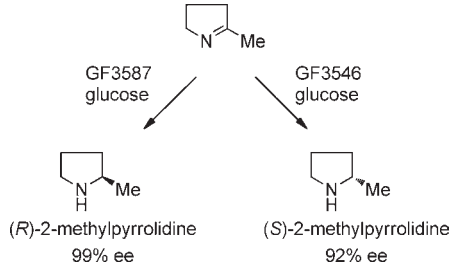
α,β-unsaturated ketones and is (*R*)-selective. Whilst still at a very early stage of development, this class of biocatalyst could provide a useful expansion to the range of enzyme-catalyzed reactions available to the synthetic chemist (*Chem. Commun.* **2010**, *46*, 8588−8590).



Akai et al. have developed a highly efficient molecular migration followed by a dynamic kinetic resolution to turn mixtures of allyl alcohols into single enantiomers. The migration of the hydroxyl group to the least substituted carbon is catalyzed by an oxovanadium catalyst. In the presence of a lipase and vinyl acetate, an (*R*)-selective resolution and in situ racemization catalyzed by the same vanadium catalyst result in high yields of the corresponding (*R*)-esters in good ee (98% yield, 99% ee). This effectively converts a pair of racemic structural isomers into a single enantiomeric compound in high ee (*Org. Lett.* **2010**, *12*, 4900−4903).



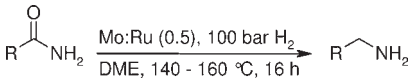
A pair of novel stereo complementary imine reductases has been identified from *Streptomyces* spp. GF3587 and 3546. Conversions of up to 92% were seen in the presence of glucose (*Org. Biomol. Chem.* **2010**, *8*, 4533−4535).



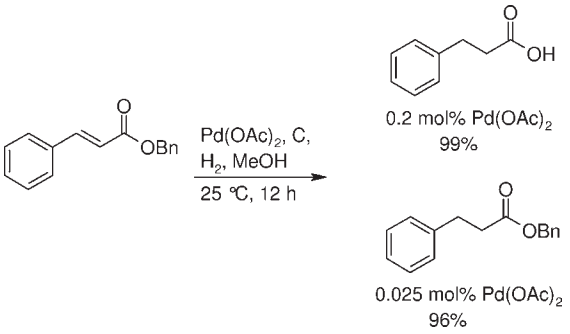
Finally for this section, two books were published in 2010 that contain several chapters featuring detailed case studies of the use of biocatalysis/biotechnology to prepare complex chiral pharmaceutical agents on manufacturing scale (*Asymmetric Catalysis on Industrial Scale: Challenges, Approaches and Solutions*, 2nd ed.; Blaser, H.-U., Federsel, H.-J., Eds.; Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, 2010 and *Green Chemistry in the Pharmaceutical Industry*; Dunn, P. J., Wells, A. S., Williams, M. T., Eds.; Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, 2010).

9. REDUCTIONS

Beamson et al. have published comprehensive research towards the hydrogenation of amides using Ru/Mo catalysis. The active catalyst, consisting of Mo:Ru at about 0.5 ratio, was prepared in situ and found to give the best results reducing amides to amines with the reactivity of primary > tertiary ≫ secondary; whereas Ru alone gave no amine product. Indications of a bimetallic, heterogeneous active catalyst are presented, along with an imine intermediate pathway mechanism that fits observed results. The catalyst could be recovered and reused. The reaction conditions are harsh but comparable to those reported by Nunez Magro et al. (*Chem. Commun.* **2007**, 3154−3156) and much milder than traditional copper chromite-based catalysts (typically 200 bar H_2, 250 °C). Primary amides are reduced under optimized conditions to mostly the primary amine with some alcohol formation, but no secondary amine. Aromatic rings did not survive the reduction conditions, and additional water pushed selectivity towards the alcohol product (*Adv. Synth. Catal.* **2010**, *352*, 869−883).

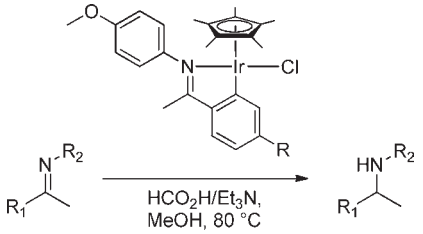


Felpin and Fouquet revealed a protocol utilizing $Pd(OAc)_2$ and charcoal as a surrogate for Pd(0) in hydrogenation reactions. A stock solution of $Pd(OAc)_2$ in THF was used directly with 90% charcoal/$Pd(OAc)_2$ loading. Charcoal has no effect on reductions but sequesters Pd to very low residual levels. The accuracy and ease of measuring the catalyst in this fashion as well as the nonpyrophoric nature of the Pd metal precursor were stressed vs handling pyrophoric Pd/C. Reductions of alkene and alkyne functionality typically proceeded with low catalyst loading at 25 °C to provide very good yields. Debenzylation was also achieved easily and cleanly, and the catalyst loading could be tuned to allow alkene reduction without affecting debenzylation (*Chem.—Eur. J.* **2010**, *16*, 12440−12445).

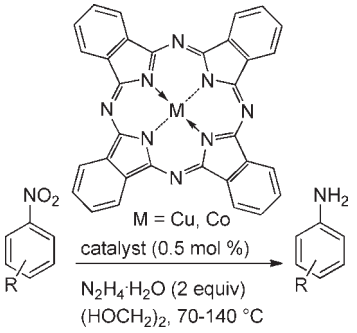


Iridium(III) catalysts have been developed by Wang et al. that display remarkable efficacy enabling reductive aminations via transfer hydrogenation with formic acid/triethylamine. The cyclometalated iridium complexes specifically reduced a wide variety of imine substrates with little, if any, undesirable side reductions. Very high yields (most >90%) were typically achieved within 5 h, and amino acids and alcohols are suitable amine sources. Ammonium formate and ammonia both afforded primary amines. The catalyst where R = CN was most effective in trifluoroethanol, while that with R = OMe

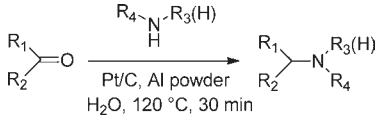
performed better in methanol (*Angew. Chem., Int. Ed.* **2010**, *49*, 7548−7552).



A new method for the chemoselective reduction of substituted nitrobenzenes with hydrazine hydrate utilizing cobalt or copper phthalocyanines was described by Sharma et al. The best general reaction conditions were established using hydrazine hydrate as hydrogen source in ethylene glycol. Nitrobenzenes with halogen, methyl, hydroxyl, ether, acid, aldehyde, ester, amide, nitrile, aniline, ketone, lactone, and heterocyclic substituents were all reduced with nearly perfect selectivity and conversion by GC/MS. *m*-Nitrostyrene suffered some olefin reduction, but the cobalt phthalocyanine afforded much better selectivity than its copper analogue. Reduction of dinitrobenzenes provided nearly complete conversion selectively to the corresponding nitroanilines. A mechanistic study suggests the reduction proceeds through the nitrosobenzene rather than the azobenzene pathway (*Adv. Synth. Catal.* **2010**, *352*, 1834−1840).

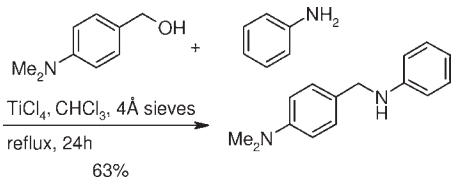


A procedure for direct reductive amination in water, which serves also as the hydrogen source, was related by Simion, et al. The imine is formed in water initially, followed by reduction with catalytic Pt(0)/C. Hydrogen is provided by the action of aluminium powder on water at 120 °C, with most reactions complete in 30 min. Overall yields were very good, ranging from about 70% to quantitative. Reaction of cyclohexanone with pyrrole or pyridine provided the completely reduced products although not in as high a yield as reaction with either pyrrolidine or piperidine. The use of benzaldehyde provides the benzylamines as well as relatively small amounts of benzyl alcohol (*Lett. Org. Chem.* **2010**, *7*, 388−391).

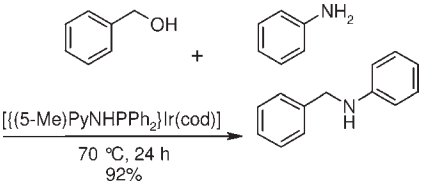


10. ALCOHOL ACTIVATION FOR NUCLEOPHILIC DISPLACEMENT

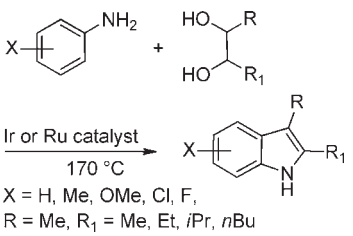
Tsai et al. report that $TiCl_4$-activated selective nucleophilic substitution reactions of *tert*-butyl alcohol and benzyl alcohols containing electron-donating substituents can be carried out with various oxygen, nitrogen and carbon nucleophiles in moderate yields. A wide variety of nucleophiles were explored, and the reaction is catalytic (10−30 mol %) in $TiCl_4$, although the use of chloroform at reflux is not ideal in the long term (*Tetrahedron* **2010**, *66*, 6869−6872).



Michlik and Kempe report a highly active iridium catalyst based on anionic P,N-ligands for the selective monoalkylation of anilines with primary alcohols, under mild reaction conditions. Nearly quantitative conversion was observed at 70 °C with a catalyst loading as low as 0.05 mol % iridium (*Chem.—Eur. J.*, **2010**, *16*, 13193−13198).



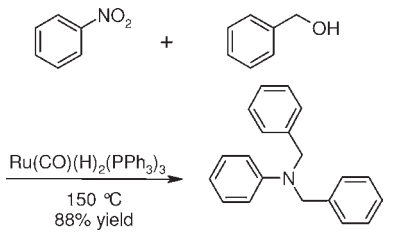
Continuing with the theme of N-alkylation of anilines with alcohols, Tursky et al. describe a method for the synthesis of 2,3-disubstituted indoles. Anilines and 1,2-diols are condensed under neat conditions with catalytic amounts of either $[Cp^*IrCl_2]_2$/MsOH or $RuCl_3 \cdot xH_2O$/phosphines at 170 °C. Yields are typically 50−70%. Unsymmetrical diols favor the isomer with the larger substituent at C-2; e.g. the iridium catalyst system affords a 7:1 mixture (R_1 at C-2:C-3) where X = H, R = Me, and R_1 = *n*Bu in 65% yield (*Org. Biomol. Chem.* **2010**, *8*, 5576−5582).



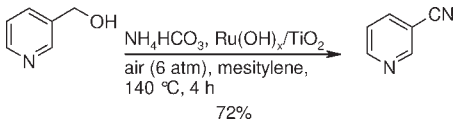
In a novel twist to the hydrogen-borrowing strategy for C−N bond formation, Feng et al. have developed a selective ruthenium-catalyzed tertiary amine formation reaction using primary alcohols and nitroarenes as starting materials. The in situ reduction of the nitroarene avoids handling the potentially toxic aniline. The ruthenium catalyst plays a key role in which the alcohol oxidation, nitro reduction and imine reduction are accomplished in a cascade. The reaction proceeds well for a

dx.doi.org/10.1021/op200128q |*Org. Process Res. Dev.* 2011, 15, 748–756

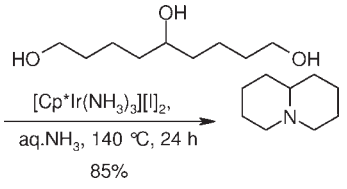
range of different substrates, and a tentative mechanism is proposed (*Org. Lett.* **2010**, *12*, 4888−4891).



K. Yamaguchi et al. report the use of ruthenium hydroxide on titanium dioxide as a heterogeneous catalyst for the alkylation of ammonia, its surrogates (e.g., urea) and amines with a range of alcohols. Secondary alcohols were converted to secondary amines, primary and benzylic alcohols afforded tertiary amines, while unsymmetrical tertiary amines could be obtained by alkylation of secondary amines. Reactions were run in mesitylene at 130−140 °C, yields were generally greater than 80%, and the catalyst could be recovered by filtration and reused. Some mechanistic studies were conducted. The catalyst could also be used in the oxidative conversion of allylic and benzylic alcohols to nitriles (*Chem.—Eur. J.* **2010**, *16*, 7199− 7207).

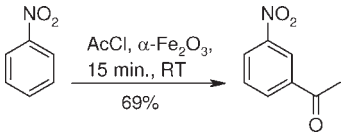


Kawahara et al. describe the multialkylation of aqueous ammonia with alcohols catalyzed by water-soluble and air-stable $[Cp^*Ir(NH_3)_3][I]_2$ catalyst. A variety of tertiary and secondary amines can be synthesized by the alkylation of aqueous ammonia with primary and secondary alcohols. The catalyst can be recycled by a facile procedure, maintaining high activity. A one-pot synthesis of quinolizidine, starting from 1,5,9-nonanetriol, was also demonstrated (*J. Am. Chem. Soc.* **2010**, *132*, 15108−15111).



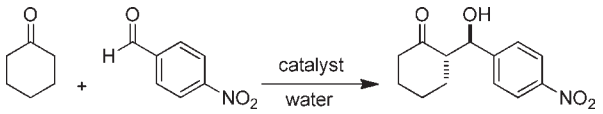
11. FRIEDEL−CRAFTS CHEMISTRY

Sharghi et al. describe the catalytic Friedel−Crafts acylation and benzoylation of a range of aromatic compounds using activated hematite (α-Fe_2O_3) as catalyst. The most active form of the catalyst was obtained by sonication followed by heating the solid at 200 °C for 72 h. Greater than 90% conversion was obtained with 5 mol % catalyst under solvent-free conditions at ambient temperature. Reactions were usually complete within 1 h and generally afforded >98% para-substitution of functionalized arenes; notably, acylation of nitrobenzene was achieved in 69% yield after 15 min. The presence of chloride ion is important with no reaction observed when acetic anhydride was used. The catalyst could be recovered by addition of hydrogen peroxide and filtration and was reused 10 times with only a moderate loss of activity (*Adv. Synth. Catal.* **2010**, *352*, 3031−3044).



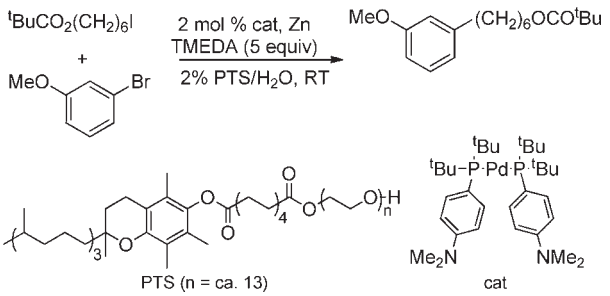
12. CHEMISTRY IN WATER

Mase and Barbas have given a review of organocatalysis in, on and by water. As an example, in various asymmetric aldol reactions catalyzed by different proline-derived organocatalysts the organic solvent, e.g. DMSO, can be replaced by water. With a catalyst loading of 10 mol % only limited erosion of the ee occurred.

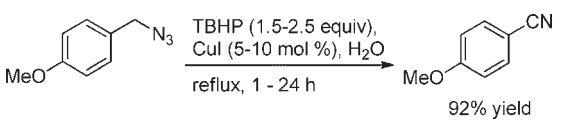


Organocatalytic Mannich, Michael, cycloaddition and multicomponent reactions in water are also discussed (*Org. Biomol. Chem.* **2010**, *8*, 4043−4050).

The zinc-mediated palladium-catalyzed cross-coupling in water with aryl bromides is described by Krasovskiy et al. Instead of reaction under standard Negishi coupling conditions with organozinc halides in organic solvents, in water RZnI can be generated in situ from metallic zinc and alkyl iodides. The amphiphile PTS (2%) is considered to form the actual catalytic micellar "microreactors", while TMEDA is necessary as diamine activator of the zinc surface. The aqueous cross-coupling tolerates various functional groups, such as aledehydes, ketones, esters and amides (*J. Am. Chem Soc.* **2010**, *131*, 15592−15593).



The oxidative conversion of primary azides to nitriles under aqueous conditions with *tert*-butyl hydroperoxide (TBHP) and 5−10 mol % copper iodide catalyst has been described by Lamani and Prabhu.

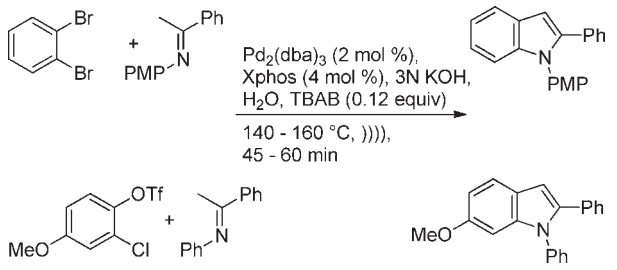


Remarkably, the conversion only proceeds with TBHP and not with other oxidants, e.g., NMO, TEMPO or H_2O_2. Excellent yields up to 92% are obtained with CuI as catalyst. Substantial nitrile hydrolysis has been observed with other Cu(I) or Cu(II)

dx.doi.org/10.1021/op200128q |*Org. Process Res. Dev.* 2011, 15, 748–756

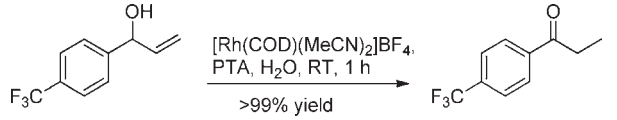
catalysts under the aqueous reflux conditions (*Angew. Chem., Int. Ed.* **2010**, *49*, 6622−6625).

Substituted indoles can be prepared by microwave-assisted palladium-catalyzed C−C/C−N bond-forming reaction "on water" from imines and *o*-dihaloarenes, as described by Barluenga et al. The regioselectivity of indole formation with substituents on the benzene ring can be controlled by using *o*-chlorosulfonates (triflate or nonaflate) or *o*-chlorobromides or iodides.

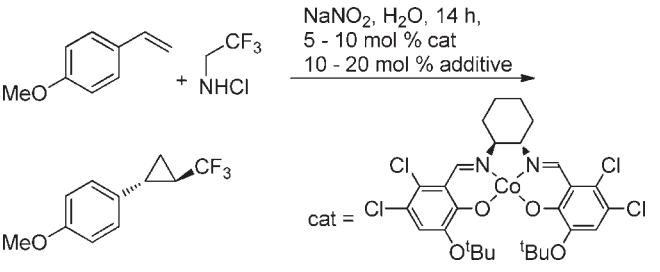


While this reaction in organic solvents only proceeds with LiO*t*Bu or NaO*t*Bu as base, the "on water" reaction can be achieved with NaOH or KOH. Less sulfonate hydrolysis is observed in the latter case (*Chem.—Eur. J.* **2010**, *16*, 11707−11711).

A very mild isomerization of allylic alcohols to ketones in water has been described by Ahlsten et al. Catalyzed by 2 mol % of the cationic rhodium complex $[Rh(COD)(MeCN)_2]BF_4$ in combination with 4 mol % phosphatriazaadamantane (PTA), the reaction in general proceeds at room temperature in less than 1 h (*Green Chem.* **2010**, *12*, 1628−1633).



In a series of papers Morandi and Carreira describe the iron-catalyzed cyclopropanation of alkenes and alkynes under aqueous conditions with in situ generated trifluoromethyl diazomethane (*Angew. Chem., Int. Ed.* **2010**, *49*, 938−941 and *Angew. Chem., Int. Ed.* **2010**, *49*, 4294−4296). The asymmetric equivalent of the cyclopropanation reaction has been described in their most recent paper. Enantioselectivities up to 90% have been obtained using 5−10 mol % of a chiral cobalt catalyst and 10 mol % *N*-methylimidazole or 20 mol % of Ph_3As as additive (*Angew. Chem., Int. Ed.* **2011**, *50*, 1101−1104).



13. CONTINUOUS PROCESSING AND PROCESS INTENSIFICATION

Hydroformylation of higher alkenes using immobilized rhodium catalysts in a continuous mode coupled with nanofiltration technique was investigated by Janssen et al. The reactor consists of a gas saturation−reaction loop wherein the reaction occurs and a membrane filtration loop wherein the catalyst is filtered from the product stream and recycled. Such a concept can be extended to pharmaceutical processing for enabling shorter synthetic routes using reactive gases, e.g., CO, whilst maintaining a lower material inventory and also avoiding many moving parts associated with overhead stirring in the batch processing mode. Understanding the cost associated with obtaining such immobilized catalyst in bulk and the complexity in building such a multistaged reactor system on larger scale will be important (*Angew. Chem. Int. Ed.* **2010**, *49*, 7738−7741).

An article on the use of continuous processing for selective palladium catalyzed aerobic oxidation of alcohols was published by Ye et al. In this manuscript, the authors reported how they overcame gas−liquid mass transfer challenges by using high liquid and gas linear flow velocities in tubular reactors with high length-to-diameter ratio and also demonstrated the applicability of the concept on reasonably large scales (*Green Chem.* **2010**, *12*, 1180−1186).

A book chapter highlighting developments in the application of continuous processing in pharmaceutical industry with numerous examples has been published (Proctor, L.; Dunn, P. J.; Hawkins, J. M.; Wells, A. S.; Williams, M. T. Continuous Processing in the Pharmaceutical Industry. In *Green Chemistry in the Pharmaceutical Industry*; Dunn, P. J., Wells, A. S., Williams, M. T., Eds.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2010; pp 221−242.)

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