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 17 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, Bristol-Myers Squibb, Codexis, Dr. Reddy's, DSM Pharmaceutical Products, Eli Lilly and Company, GlaxoSmithKline, Johnson & Johnson, Lonza, Merck & Co., Inc., Novartis, Pfizer, Inc., Roche, and Sanofi.

One of the strategic priorities of the Roundtable is to inform and influence the research agenda. Two of the first steps to achieve this objective were to publish a paper outlining key green chemistry research areas from a pharmaceutical perspective (*Green Chem.* **2007**, *9*, 411−420) and to establish annual ACS GCIPR research grants. This document follows on from the Green Chemistry paper and is largely based on the key research areas though new sections have been added. The review period covers the first 6 months of 2011.

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

Organometallic-catalysed reactions are nowadays very commonly used in pharmaceutical production. Bensaid et al. found a greener replacement for DMF or DMAc for direct Pd-catalysed coupling between aryl halides and heteroaromatics. The use of pentan-1-ol and 3-methylbutan-1-ol as solvents in such cross-coupling reactions resulted in the desired cross-coupled product in moderate to good yields (*Tetrahedron Lett.* **2011**, *52*, 1383−1387).

There is a lot of controversy on the greenness of ionic liquids. However, ionic liquids represent such a broad group of solvents that some of them might be sufficiently nontoxic and biodegradable. Maia provided an overview on recent applications of ionic liquids in organic synthesis and catalysis as well as some recent findings on the toxicity and biodegradability of ionic liquids (*Mini-Rev. Org. Chem.* **2011**, *8*, 178−185). In addition Petkovic et al. have provided a critical overview on the understanding of the toxicity and environmental impact of ionic liquids. A structured approach is followed that classifies most commonly encountered ionic liquids by the head of the cation. This comprehensive overview highlights that one has to be careful with the generalisation that ionic liquids are either 'green' or 'toxic' (*Chem. Soc. Rev.* **2011**, *40*, 1383−1403).

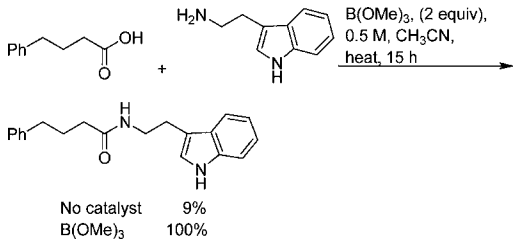
Henderson et al. from GSK have published a detailed article on the GSK solvent selection guide. The article provides both simple and complex guides to help chemists choose greener solvents in medicinal chemistry and process development (*Green Chem.* **2011**, *13*, 854−863). In particular GSK have now published their life cycle scores for the 110 solvents that are in the guide.

A perspective entitled "Searching for Green Solvents" outlines Professor Jessop's view of four grand challenges in the area of green solvent research (*Green Chem.* **2011**, *13*, 1391−1398). Solvents are plotted on Kamlet−Taft diagrams (polarity vs basicity). The article also concludes that academic research in the area of green solvents is not currently focussed on the applications that will make the largest environmental impact.

3. AMIDE FORMATION

Komura et al. have reported that mesoporous silica (MCM-41) is a very effective catalyst for the direct amidation of fatty acids (such as palmitic acid and octanoic acid) with long-chain amines such as *n*-hexylamine. Yields of 94% can be obtained in boiling toluene, and the authors report a comparison of this catalyst with other direct amidation catalysts which have been reported recently (*Green Chem.* **2011**, *13*, 828−831).

Direct amidation using boric acid or aryl boronic acids is well established, but Starkov and Sheppard have reported direct amidation using borate esters such as trimethyl borate (*Org. Biomol. Chem.* **2011**, *9*, 1320−1323). Unfortunately, for best results 1 or 2 equivalents of the borate are needed.



Allen and Williams have published a tutorial review highlighting recent literature advances on metal-catalysed approaches to amide bond formation (*Chem. Soc. Rev.* **2011**, *40*, 3405−3415). In particular, this review highlights the opportunities such reactions present to access target molecules via alternative routes due to the ability to start from substrates other than the amines and carboxylic acids utilized in the majority of classical amide bond-forming methods. With this in mind, the review is organized with respect to the starting materials employed for the amide bond formation, and places focus on esters, aldehydes, alcohols, nitriles, and oximes. In addition, sections are included on recent developments in aminocarbonylation and the industrially important cross-coupling of amides with aryl halides and derivatives.

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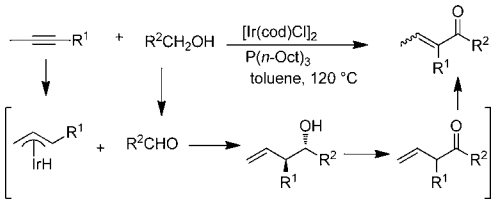
4. OXIDATIONS

Four reviews on green oxidations were published in the first half of 2011.

Hollmann et al. reviewed biocatalytic oxidations, providing an excellent overview and thoughtful assessment of scope and limitations. Many of these oxidations are whole-cell processes, due to the requirement for cofactors, although advances have been made in commercial availability of isolated oxidoreductases. Nonetheless, the authors argue that current methodologies for whole-cell catalysis are no more challenging than other experimental set-ups typically used by the organic chemist and should not be a barrier to use. Some of the transformations reviewed include alcohol oxidation, alcohol and amine resolution, aromatic hydroxylation, Baeyer–Villager oxidation, epoxidation, "ozonolysis", hydroxylation on nonactivated aliphatic C–H bonds, and heteroatom oxidation (*Green Chem.* **2011**, *13*, 226–265).

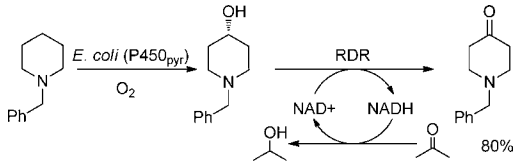
Zhou and Crabtree provide a concise but excellent overview of the current state of the art in C–H oxidations of alkanes catalyzed by the platinum group metals. The authors discuss three variants of oxidations with this class: (1) representing the majority of examples of relevance to organic synthesis are the oxides, primarily RuO_4 which is usually generated in situ from periodate oxidation of RuO_2 or $RuCl_3$; these oxidants offer no opportunity for ligand-assisted modifications to tune reactivity or selectivity; (2) coordination complexes, again primarily Ru but with representation from the other Pt group metals; and (3) the more rare organometallic catalysts with carbon donor ligands (*Chem. Soc. Rev.* **2011**, *40*, 1875–1884).

Suzuki reviewed oxidations catalyzed by iridium, generally focused on hydrogen transfer processes, covering 18 distinct reaction types. Of primary interest to the organic chemist are tandem reactions in which iridium oxidizes one component, and then serves as a catalyst to promote its reaction with another reagent, as the example below shows. Iridium is the metal of choice for the "hydrogen-borrowing" redox reactions that have been discovered and developed within the past 5 years (*Chem. Rev.* **2011**, *111*, 1825–1845).



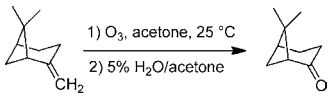
Tsukuda et al. reviewed aerobic oxidations using polymer-supported nanoclusters of gold (<2 nm). The review primarily focuses on the authors' work using poly(*N*-vinyl-2-pyrrolidone) as the polymeric backbone for oxidations which include alcohols to ketones in aqueous media, α-hydroxylation of benzylic ketones, N-formylation of amines using MeOH, oxygenation of alkenes, and intramolecular hydroalkoxylations and hydroaminations. Mechanistic studies suggest the gold clusters react with oxygen to form reactive superoxo- or peroxo-like species on the surface (*Chem. Asian J.* **2011**, *6*, 736–748).

Zhang et al. reported a tandem biocatalytic oxidation of methylene groups to ketones using a whole-cell monooxygenase-catalyzed regioselective hydroxylation followed by an alcohol dehydrogenase-catalyzed alcohol oxidation to provide ketone products in a single-pot transformation in 80–87% yields. Oxidation of *N*-benzylpiperidine was carried out in aqueous solution to provide *N*-benzyl-4-piperidone in 80% yield, an intermediate that requires three steps and 39% yield via a nonenzymatic route (*Chem. Commun.* **2011**, *47*, 3284–3286).



While bleach is an attractive green oxidant since it generates only NaCl and water as byproducts, NaOCl oxidations of alcohols using nitroxyl radicals such as TEMPO are often carried out in dichloromethane. Jannsen et al. investigated alternate solvents and catalysts for bleach oxidations, finding that ester solvents such as MeOAc and *i*-PrOAc gave equivalent or better results than dichloromethane. The cocatalysts NaBr (which generates the more reactive oxidant HOBr) and borax ($Na_2B_4O_7{\cdot}10H_2O$, unknown catalytic effect) were also studied, with the finding that the effectiveness of the cocatalyst depended on the nature of the alcohol substrate. The authors suggest simple screening of solvents and cocatalysts can quickly lead to optimized conditions that avoid dichloromethane (*Green Chem.* **2011**, *13*, 905–912).

Ozonolysis is a green oxidation process with high atom efficiency and producing oxygen as the only byproduct, but has had limited application due to the safety of handling the potentially explosive ozonide intermediates, the use of flammable solvents in the presence of oxygen, and the high exothermicity of the quenching step. Irfan et al. describe a continuous flow apparatus using the commercially available O-Cube that carries out the ozonolysis and quenching steps in flow mode. The small reactor volume and high heat transfer capability of the flow system minimize the risks of larger batch operations. The authors provide several examples, including ozonolysis of aromatic/aliphatic alkenes and alkynes, oxidation of an amine to a nitro group, and sulfide oxidation. Conversion of β-pinene to nopinone was conducted at ambient temperature at a flow rate of 1 mL/min using water/acetone as quench reagent vs the batch process reported in the literature that required reaction at −78 °C with a dimethyl sulfide quench (*Org. Lett.* **2011**, *13*, 984–987).



Nobis and Roberge from Lonza provide a perspective on scaling ozonolysis reactions using a gas–liquid loop continuous reactor and describe implementation at the 450 L scale for the conversion of ton quantities of a chrysanthemic ester to the corresponding aldehyde (*Chim. Oggi/Chem. Today* **2011**, *29*, 56–58). In back-to-back articles, Exner and co-workers from Dishman offer additional thoughts on scaling ozonolysis reactions in both batch and flow mode and review two case studies from Pfizer and Shionogi published within the past few years (*Chim. Oggi/Chem. Today* **2011**, *29*, 59–60, 62).

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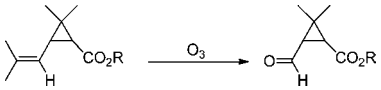
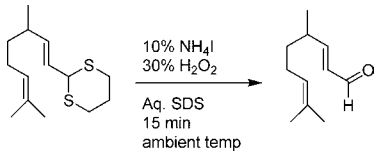
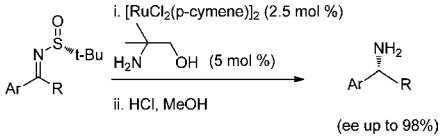


Traditional methods of cleaving dithioacetals employ heavy metals such as Hg or Ag. Greener methods employing hypervalent iodine reagents such as *o*-iodobenzoic acid (IBX) have been developed recently but still require stoichiometric quantities of the hypervalent iodine reagent and thus generate a substantial amount of waste. Ganguly and Mondal report cleavage of dithioacetals using catalytic iodonium ion generated from iodide and H_2O_2 using an aqueous micellar system employing the anion surfactant sodium dodecylsulfate (SDS). Yields of 80−100% were reported with dithioacetals containing a wide range of functional groups (*Synth. Commun.* **2011**, *41*, 2374−2384).

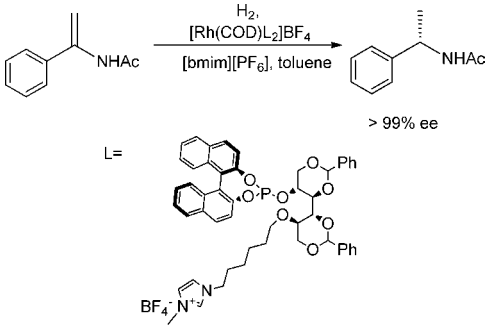


5. ASYMMETRIC HYDROGENATION

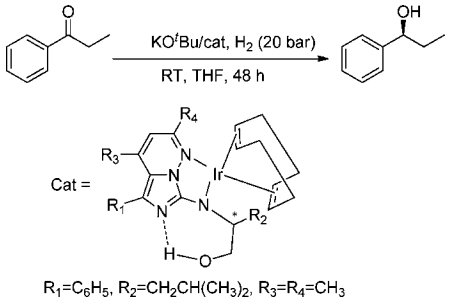
Guijarro et al. worked on ruthenium-catalyzed asymmetric transfer hydrogenation of *N*-(*tert*-butylsulfinyl) imines by using some achiral *β*-amino alcohols which have been shown as efficient ligands. The ruthenium complex prepared from $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %) and 2-amino-2-methyl-1-propanol (5 mol %) leads to *α*-branched, chiral primary amines with very high optical purities (up to 98% ee) by the diastereoselective reduction of the imines followed by removal of the sulfinyl group under mild acidic conditions (*Tetrahedron Lett.* **2011**, *25*, 789−791).



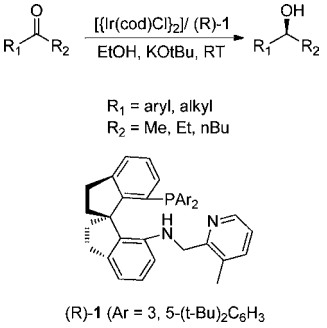
Functionalized olefins such as enamides, *α*-dehydroamino acid esters and dimethyl itaconate were asymmetrically hydrogenated using a rhodium catalyst bearing easily synthesized ionic phosphate ligands. Zhao et al. report high efficiency and excellent reusability of the catalyst in ionic liquid−toluene biphasic medium (*Tetrahedron: Asymmetry* **2011**, *22* , 769−774).



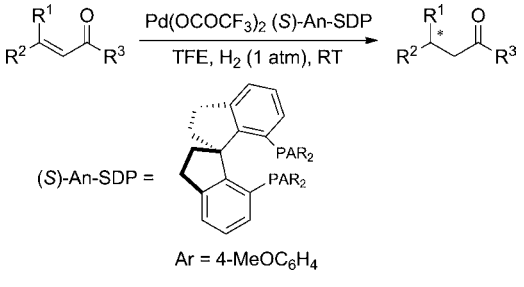
Carbonyl Reduction. A phosphorus-free catalytic system employing amido iridium catalyst for highly enantioselective hydrogenation of simple ketones is presented by Irrgang et al. The authors report the synthesis of the chiral ligand in one pot with inexpensive starting materials (*Angew. Chem., Int. Ed.* **2011**, *50*, 2183−2186).



New iridium catalysts with tridentate spiro ligands were designed by Xie et al. for the hydrogenation of simple ketones. The chiral alcohols were obtained in up to 99% ee, and the TON for the catalysts is as high as 4.5 million (*Angew. Chem., Int. Ed.* **2011**, *50*, 7329−7332).



Conjugate Reduction. Very few methods exist for the selective asymmetric hydrogenation of the C=C bond of linear *α*,*β*-unsaturated ketones (*Angew. Chem., Int. Ed.* **2008**, *47*, 10133−10136). A $Pd(OCOCF_3)_2$−(*S*)-An-SDP complex has been used by Wang et al. as catalyst under mild conditions for the reduction of *β*,*β*-disubstituted unsaturated ketones with good specificity and enantioselectivity (*Synlett* **2011**, *7*, 947−950).



6. C−H ACTIVATION

Multiple reviews covered various aspects of C−H activation in the first half of 2011, most of which will not be discussed here. Among these reviews, however, was a recent issue of *Chemical Society Reviews* covering a variety of aspects of C−H activation from stereoselectivity in the C−H activation reaction to enzymatic

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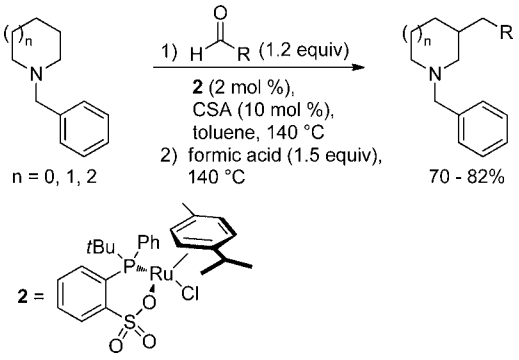
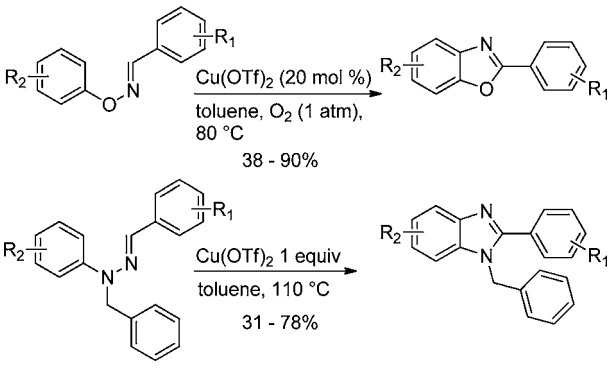
C−H activation (*Chem. Soc. Rev.* **2011**, *40*, 1847−2040). One additional review worth noting, authored by Fischmeister and Doucet, covered the recent use of green solvents in C−H activation reactions with palladium and ruthenium catalysts (*Green Chem.* **2011**, *13*, 741−753).

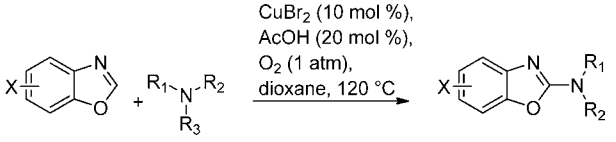
While several methods have been reported for C(2)-activation, Sundararaju et al. report on the ruthenium-catalyzed sp^3 activation of cyclic amines and subsequent C(3)-alkylation reaction with aldehydes (*J. Am. Chem. Soc.* **2011**, *133*, 10340−10343). Very good selectivity for the C(3) position was observed in toluene at 140 °C with 1.2 equivalents of aldehyde, 2 mol % of the ruthenium catalyst and 10 mol % CSA. Formic acid (1.5 equiv) was added at the end of the reaction to drive the dehydration/hydrogenation process to completion. While aromatic, heteroaromatic, and aliphatic aldehydes were all explored along with 5-, 6-, and 7-membered cyclic amines, the application of aliphatic aldehydes led to competitive mono- and dialkylated products. One drawback may be the formation of ruthenium catalyst **2** requiring a two-step synthesis from commercially available materials. Other commercially available ruthenium catalysts were explored, but incomplete conversion was observed. It is also worth noting that the benzylated amine precursors utilized for the C−H activations were generated from free amines and benzyl alcohol utilizing the same ruthenium catalyst **2**. This could potentially allow opportunities for telescoping both steps, although that aspect was not explored in this paper.



Guru et al. disclose the synthesis of benzimidazoles and benzoxazoles via a copper-mediated C−H activation followed by C−N or C−O bond formation respectively (*J. Org. Chem.* **2011**, *76*, 5295−5308). A total of 21 benzimidazoles and 25 benzoxazoles are reported with reasonable yields and good tolerance for functionality. For most examples the R_2 substituent was at the 4-position affording 5-substituted products, while cyclization of 3-methyl-*N*-benzyl bisarylhydrazone resulted in only a 2:1 ratio of products favoring the less sterically hindered product. Similar results were reported for the synthesis of benzoxazoles with good tolerance for functionality. The main drawback of these routes may be the synthesis of the starting *N*-benzyl bisarylhydrazones and bisaryloxime ethers, which highlight the challenges of delivering a completely green route. Additionally, the benzimidazole cases require a full equivalent of the copper triflate for reaction completion. Overall, these transformations provide a novel entry into the benzimidazole and benzoxazole ring systems from readily available aldehydes, boronic acids, and amines.

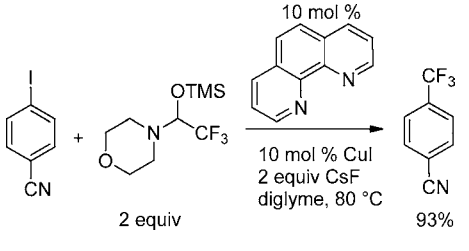


A new method for oxidative amination of benzoxazoles was described by Guo et al. utilizing tertiary amines. A screening of reaction conditions resulted in utilization of $CuBr_2$ (10 mol %) with acetic acid (20 mol %) and 1 atm of oxygen at 120 °C in dioxane generating an 89% yield for $R^1 = R^2 = R^3 =$ Et. Similarly a wide variety of alkyl amines resulted in yields between 54 and 92%. When three different R groups were used, the product favored abstraction of the least sterically hindered alkyl group and, in the presence of a monobenzyl substituted amine, benzyl group cleavage was favored. Additionally, the use of benzyl-protected morpholine or piperidine resulted in cleavage of the benzyl group to generate the corresponding piperidine and morpholine benzoxazoles. Finally, the scope of the X group substitution was investigated with good success for electron-donating groups but electron-withdrawing groups, e.g. nitro, resulted in very low conversion even with stoichiometric amounts of $CuBr_2$ (*Org. Lett.* **2011**, *13*, 522−525).



7. GREENER FLUORINATION

The attractive properties of the trifluoromethyl group, including high lipophilicity, strong electron-withdrawing ability and its characteristic size, makes this motif one of the most commonly found in pharmaceuticals and agrochemicals. The synthesis of trifluoromethylated aromatics is therefore of considerable interest. Kondo et al. have described a copper-catalyzed trifluoromethylation using trifluoroacetaldehyde (fluoral) hemiaminals as reaction partner, which were claimed to be readily accessible and stable (*Adv. Synth. Catal.* **2011**, *353*, 1247−1252). Starting from various aryl iodides the synthesis of trifluoromethylated aryl and heteroaryl compounds was achieved in good to excellent yields, although diglyme has proven to be the best solvent in all cases. In addition, review articles focussing either on the copper-catalyzed and -mediated aromatic trifluoromethylation or on the metal-catalyzed trifluoromethylation in general have been published by Roy et al. (*Tetrahedron* **2011**, *67*, 2161−2195) and Furuya et al. (*Nature* **2011**, *473*, 470−477), respectively.



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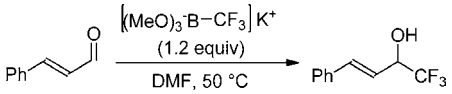
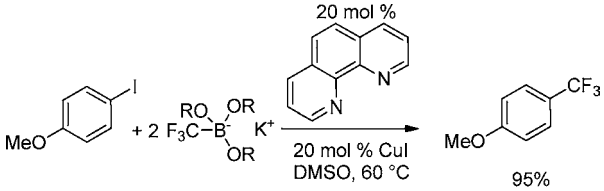
The 1,2-addition of shelf-stable trifluoroborate salts to carbonyl compounds or imines has been reported by Levin et al. Nucleophilic addition to aldehydes, ketones or imines was performed and resulted in formation of the corresponding trifluoromethylated alcohols or amines in high yields. The scope of the reaction was studied by using dimethylformamide as solvent, though initial solvent screening has shown that acetonitrile leads to similar good results (*Tetrahedron Lett.* **2011**, *52* , 281−284).



97%

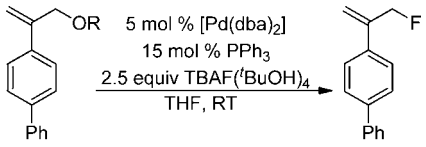
Knauber et al. have used similar CF_3-trialkoxyborate salts in a copper-catalysed coupling with aryl iodides. A range of aryl and heteroaryl iodides were examined (*Chem. Eur. J.* **2011**, *17*, 2689−2697.



95%

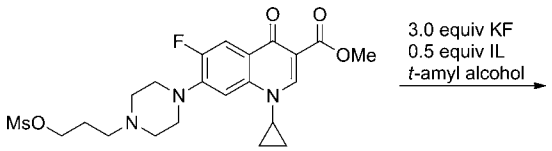
R = CH_2CH_2OMe

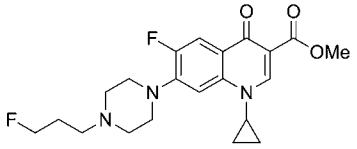
Hollingworth et al. have described the preparation of allyl fluorides by a palladium-catalyzed allylic substitution reaction. Optimization of the reaction conditions revealed tetrabutylammonium tetra (*tert*-butyl alcohol)-coordinated fluoride as reagent of choice, possessing a low hygroscopicity, good nucleophilicity, and low basicity. The scope includes different 2- and 3-arylsubstituted propenyl esters, which were effectively transformed into the corresponding allyl fluorides with a catalyst loading of 5 mol %. However the reaction proved to be limited to the utilization of *p*-nitrobenzoates as leaving group (*Angew. Chem., Int. Ed.* **2011**, *50*, 2613−2617).



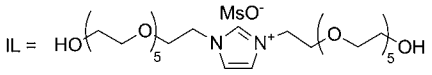
R = CO-*p*-$C_6H_4NO_2$ 95%

Ionic liquids have attracted interest as potential eco-friendly alternative solvent systems because of a number of properties e.g. low volatility. Jadhav et al. have published the utilization of tailor-made ionic liquids as phase transfer catalysts in the nucleophilic substitution reaction. The PTC catalyst made it possible to use cheap potassium fluoride in *tert*-amyl alcohol to convert various mesylates, tosylates and bromides into the corresponding fluoride compounds. General applicability was proven by also employing secondary alkyl bromides and tosylates, which resulted dominantly in an elimination reaction without PTC, but substitution product could be obtained in high yield in presence of the ionic liquid. The concept was also extended to the synthesis of bioactive molecules (*Org. Lett.* **2011**, *13*, 2502−2505).



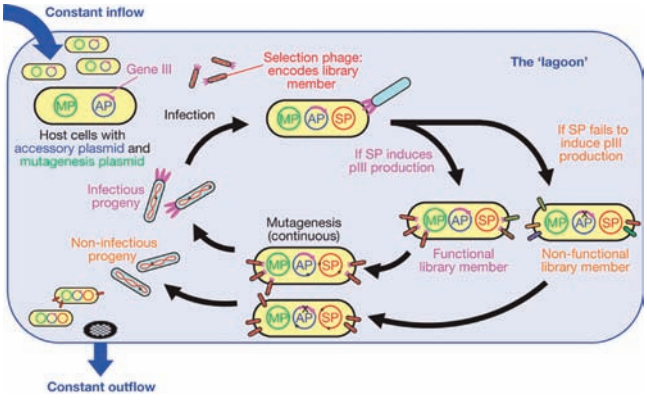


92%



8. BIOCATALYSIS

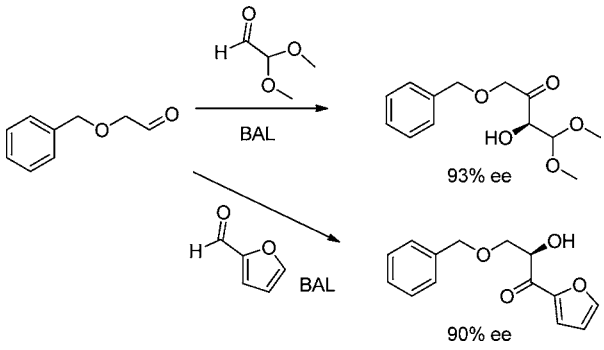
Laboratory evolution has generated many biomolecules with attractive properties, but a single round of mutation typically requires days or longer with frequent human intervention. Because success is dependent on the number of rounds performed, a laboratory process of continuous evolution would dramatically enhance its effectiveness. Esvelt et al. have now reported a new system to do this: phage-assisted continuous evolution (PACE). The method uses a virus (phage) to transfer the evolving genes from host cell to host cell through a modified lifecycle, which is dependent on the activity of interest. This means that phage not displaying the desired activity, are essentially unable to infect new host cells. In addition, those with the highest activity will produce infectious phage at the fastest rate and thus infect more host cells than phage encoding less active genes. In one example, this powerful method executed 200 rounds of evolution in eight days. PACE has the potential to reduce evolution costs and provide solutions to otherwise intractable directed evolution problems (*Nature* **2011**, *472*, 499−503).



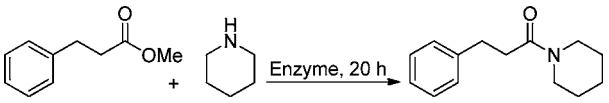
PACE in a single lagoon is illustrated above. [Reprinted by permission from Macmillan Publishers Ltd.: (*Nature* **2011**, *472*, 499−503), copyright 2011.] Host cells continuously flow through a lagoon, where they are infected with selection phage (SP) encoding library members. Functional library members induce production of pIII from the accessory plasmid (AP) and release progeny capable of infecting new host cells, whereas nonfunctional library members do not. Increased mutagenesis is triggered through induction of the mutagenesis plasmid (MP). Host cells flow out of the lagoon on average faster than

they can replicate, confining the accumulation of mutations to replicating phage.

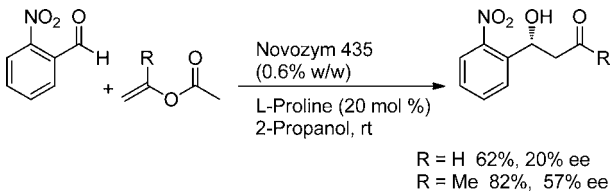
Ayhan et al. have reported the enantioselective self-and cross-condensation reactions of aldehydes catalysed by benzaldehyde lyase (BAL). Selectivity in the BAL-catalysed cross condensation of benzyloxyacetaldehyde was dependent upon the partner aldehyde used. Products from self-condensation were only detectable when one of the substrates was used in excess (*Org. Biomol. Chem.* **2011**, *9*, 2602−2605).



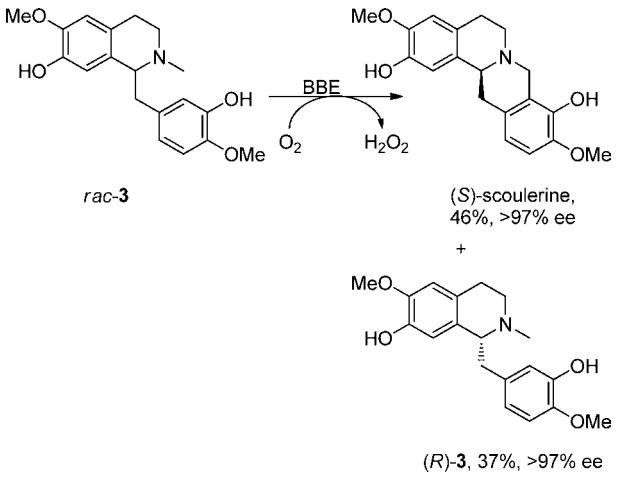
The number one reaction class in the ACS GCIPR for which companies would like better reagents is amidation. A new biocatalyst for this transformation, *Pseudomonas stutzeri* lipase (PSL), has been reported by Van Pelt et al. PSL was investigated in a range of amidation reactions with bulky methyl esters and amines, comparing favorably to Novozym 435 (immobilised *Candida antarctica* Lipase B, NOV435) (*Green Chem.* **2011**, *13*, 1791−1798).



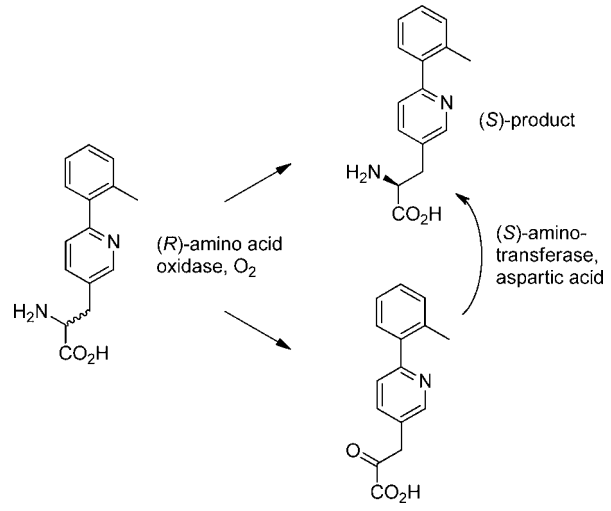
Novozym 435 was also utilised by Kumar et al. who report its use in tandem with an organocatalyst for vinyl/isopropenyl acetate-mediated cross-aldol reactions. The reaction apparently involves lipase-catalysed in situ generation of acetaldehyde and acetone, followed by organocatalysed cross-aldol reaction with aromatic aldehydes to prepare *β*-hydroxy aldehydes or ketones, respectively (*Adv. Synth. Catal.* **2011**, *353*, 1207−1212).



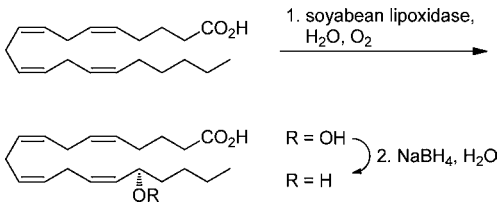
Schrittwieser et al. have reported a chemoenzymatic synthesis of (*S*)-scoulerine, a sedative and muscle relaxing agent. The key step employs an enantioselective oxidative C−C bond formation catalysed by berberine bridge enzyme (BBE). The reaction takes place via oxidative C−H activation of the substrate's *N*-methyl group at the expense of molecular oxygen, a transformation unparalleled in organic synthesis. The approach was applied to 14 enantiomerically pure alkaloids (*J. Org. Chem.* **2011**, *76*, 6703−6714).



An efficient synthesis of an *α*-amino acid by deracemization has been described by Chen et al. The (*R*)-enantiomer of the racemate was oxidised with a (*R*)-selective amino acid oxidase to the *α*-keto acid. This was in turn converted to the (*S*)-amino acid with a (*S*)-aminotransferase and aspartate as the amine donor. The product was isolated in 66% yield and 99.9% ee. Several other biocatalytic routes to the same target molecule were examined. A chemoenzymatic dynamic resolution of the racemic amino acid was examined using (*R*)-amino acid oxidase in combination with chemical reduction of the intermediate imine, which is the initial product of the oxidase reaction. This reduction with NH_3−BH_3 regenerates the racemic amino acid whilst the (*S*)-amino acid accumulates. Yields of 76−79% were obtained with >99.9% ee. In addition to the transaminase, a (*S*)-amino acid dehydrogenase/ammonium formate/NADH system could also be used to convert the *α*-keto acid to the desired (*S*)-product (*Org. Process Res. Dev.* **2011**, *15*, 241−248).



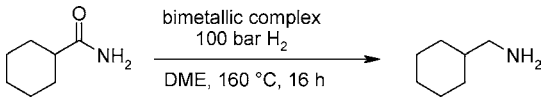
Whilst not a commonly used enzyme in organic synthesis, Conrow et al. have reported the application of a lipoxidase to directly oxidise arachidonic acid to the corresponding 15-(*S*)-alcohol after reduction of the initially formed hydroperoxide with $NaBH_4$. The product was isolated in ∼40% overall yield, 98.5% purity, and >99% ee (*Org. Process Res. Dev.* **2011**, *15*, 301−304).



Sheldon has published a review article on the preparation and use of cross-linked enzyme aggregates (CLEAs) as robust and versatile industrial biocatalysts (*Org. Process Res. Dev.* **2011**, *15*, 213−223).

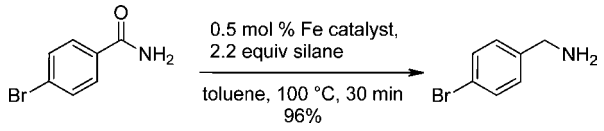
9. REDUCTIONS

Following on from their earlier work on Ru/Mo catalysis, Beamson et al. have published research on the hydrogenation of amides using Ru/Re and Rh/Re catalysts (*J. Catal.* **2011**, *278*, 228−238). The active catalysts are formed in situ from either $Ru_3(CO)_{12}/Re_2(CO)_{10}$ or $Rh_6(CO)_{16}/Re_2(CO)_{10}$, and evidence for the active components of these catalysts containing bimetallic Ru/Re and Rh/Re nanoclusters is presented. Good conversions and product selectivity are reported; for example cyclohexanecarboxamide is hydrogenated to the corresponding amine in up to quantitative conversion and with 95% selectivity for the primary amine product. The reaction conditions are comparable to the authors' previously reported Ru/Mo system (*Adv. Synth. Catal.* **2010**, *352*, 869−883) and much milder than traditional copper chromite-based catalysts (typically 200 bar H_2, 250 °C). Potential mechanistic pathways for amide hydrogenation are also presented.



In a very accessible paper, David Cantillo has employed DFT calculations to study the ruthenium-catalysed hydrogenation of amides. Both the C−O and C−N cleavage modes are compared using a bipyridyl-based Ru^{II} pincer complex as catalyst in the calculations. The author reports that the computed energy barrier for the C−N cleavage is lower than that for C−O cleavage by greater than 10 kcal/mol (*Eur. J. Inorg. Chem.* **2011**, 3008−3013).

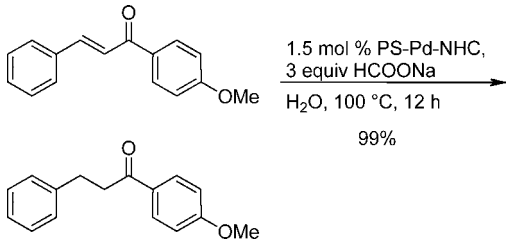
Tsutsumi and co-workers have described a new catalyst system for the iron-catalysed hydrosilane reduction of amides. A heptanuclear iron carbonyl cluster, $[Fe_3(CO)_{11}(\mu\text{-}H)]_2$−$Fe(DMF)_4$, was found to be a highly efficient catalyst for the reduction of various amides by 1,2-bis(dimethylsilyl)benzene. The reaction is carried out in toluene at 100 °C, typical catalyst loading is 0.5 mol % with respect to Fe, and 2.2 equiv of silane is employed. A variety of aromatic and aliphatic amides are exemplified, aromatic halides appear to be well tolerated, and a reaction mechanism is postulated (*Chem. Commun.* **2011**, *47*, 6581−6583).



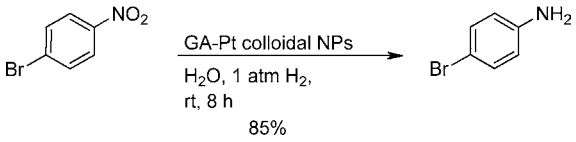
Rueping et al. have published a comprehensive review focussing on recent advances in the use of dihydropyridines for the development of catalytic metal-free transfer hydrogenations. Such catalysts offer a serious alternative to conventional metal- and biocatalysed systems (*Green Chem.* **2011**, *13*, 1084−1105).

In a recent 'Conspectus', Alonso et al. describe the use of nickel nanoparticles (NiNPs) in a variety of hydrogen-transfer processes. Transfer hydrogenation reactions, such as the reduction of alkenes and carbonyl compounds, as well as the reductive amination of aldehydes are discussed along with hydrogen transfer processes such as the hydrogen borrowing approach to C−C and C−N bond formation. In this context, the authors discuss the activation of primary alcohols for the α-alkylation of ketones and the reductive aza-Wittig reaction, with the latter yielding secondary amines in modest yield (*Acc. Chem. Res.* **2011**, *44*, 379−391).

Continuing the theme of aqueous-based transfer hydrogenation, Bagal et al. have reported the development of a polymer supported palladium-N-heterocyclic carbene complex for the conjugate reduction of α,β-unsaturated carbonyls. The reactions are carried out in water with sodium formate as hydrogen source, and the authors report good to excellent conversion and high selectivity for the olefinic double bond across a wide range of substrates (*Green Chem.* **2011**, *13*, 1490−1494).



Finally, Sreedhar et al. have described the selective hydrogenation of nitroarenes using gum acacia-supported colloidal platinum in aqueous medium. Mild conditions and excellent yields and chemoselectivity are reported. A simple procedure for catalyst preparation and reuse is also described (*Catal. Commun.* **2011**, *12*, 1009−1014)).



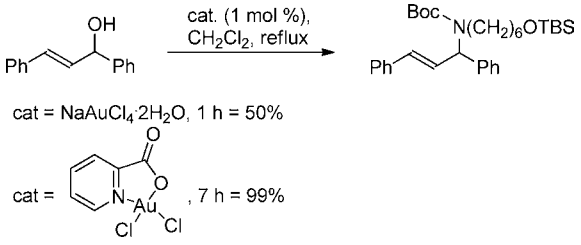
10. ALCOHOL ACTIVATION FOR NUCLEOPHILIC DISPLACEMENT

There are two generally recognised mechanisms for the direct nucleophilic substitution of alcohols: S_N1-type reactions of allylic, benzylic, and propargylic alcohols via carbocation formation and the hydrogen auto-transfer, or "hydrogen borrowing" mechanism. Emer et al. review the former approach. Their comprehensive review covers nucleophilic substitution of allylic, benzylic, and propargylic alcohols, promoted by stoichiometric, or catalytic, amounts of Brønsted or Lewis acids, catalytic metal complexes, and direct substitutions in water. Articles from the literature up to mid 2010 are covered, and a discussion of Mayr's predictive rule of thumb for determining the outcome of a reaction between an electrophile and a nucleophile is also discussed (*Eur. J. Org. Chem.* **2011**, 647−666).

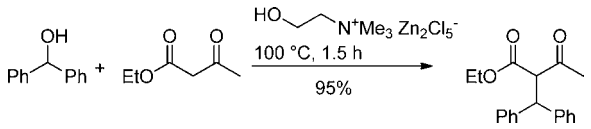
Ohshima et al. report the use of gold(III) catalysts for the substitution of allylic and benzylic alcohols with amines protected with acid-sensitive functional groups [e.g., *tert*-butoxycarbonyl (Boc) and *tert*-butylsulfonyl (Bus)]; substrates

dx.doi.org/10.1021/op300068d | *Org. Process Res. Dev.* 2012, 16, 535−544

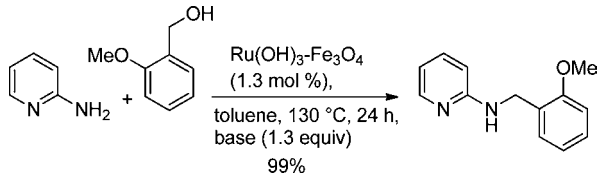
which have not been successfully utilised in Lewis acid-catalyzed substitutions. The reaction is catalyzed by sodium tetrachloroaurate(III)·dihydrate or (picolinoyloxy)gold(III) chloride for amines with sensitive functional groups (e.g., TBS and THP). Reactions are conducted in dichloromethane and alternative, more preferable, solvents were not screened. Yields are generally high and could be improved for less reactive alcohols by the addition of thiophene. The authors suggest a carbocation mechanism (*Chem. Commun.* **2011**, *47*, 8322−8324).



Ultraviolet evidence for carbocation intermediates in the zinc-based ionic liquid-mediated nucleophilic substitution of allylic and benzylic alcohols with aniline, amide, hydrazine, sulphonamide, and carbon nucleophiles is presented by Zhu et al. Heating equimolar amounts of the substrates with 1.5 equivalents of the ionic liquid, formed from a 1:2 mixture of choline chloride and zinc chloride at 100 °C for 1−3 h, typically affords products in greater than 90% yield. The products are isolated by addition of water followed by filtration; the ionic liquid could be recovered, dried, and reused at least five times. The authors discuss the significance of the choline hydroxyl group in the success of this ionic liquid over others examined (*Green Chem.* **2011**, *13*, 1244−1250).



Cano et al. report the use of ruthenium hydroxide impregnated magnetite as a catalyst for the selective N-monoalkylation of poorly nucleophilic amines, e.g. aromatic and heteroaromatic amines, sulfonamides, and nitroarenes, using alcohols via a hydrogen auto-transfer process. The substrates are heated under argon in toluene at 130 °C with 1.3 equivalents of potassium hydroxide and 1.3 mol % catalyst, which can be separated from the mixture with a magnet and reused. The reaction stops at the imine when sodium hydroxide is used in place of potassium hydroxide.

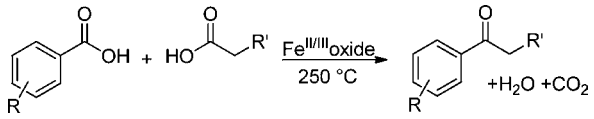


The authors also report the first alkylation of sulfinamides by this strategy, and alkylation of chiral sulfinamides with secondary alcohols affords the alkylated compound with a diastereomeric ratio of 92:8, albeit in modest (28%) yield (*J. Org. Chem.* **2011**, *76*, 5547−5557).

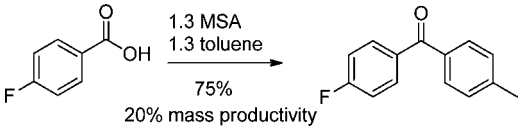
Liu et al. postulate a new mechanism in the air-promoted, metal-catalyzed, aerobic N-alkylation of amides, amines, and sulphonamides with alcohols. Their methodology typically heats the neat substrates at 135 °C in a sealed tube under an air atmosphere in the presence of potassium carbonate. Commonly available iridium, rhodium, or ruthenium catalysts are utilized, and yields are generally good to excellent. Although the reaction conditions are not readily scaled up, extensive studies into the possible mechanism provide insight and a possible, safe way forward. The authors suggest the initial, rate-limiting, step is dehydrogenation of the primary alcohol to aldehyde which can be overcome by aerobic oxidation. The resulting aldehyde reacts with the amine, producing an imine and water with the active catalyst, a metal hydride, generated during the alcohol oxidation. The base promotes dehydrogenation of alcohol to aldehyde in a transfer hydrogenation of the imine as the catalytic cycle which the authors suggest is analogous to a relay, although it may be difficult to differentiate this from hydrogen auto transfer. Supporting experiments using catalytic amounts of air or aldehyde to promote the reaction offer a potentially safer way forward. The paper provides insight into the significance of catalyst activation and the role of base in the reaction, which was noted but not discussed in Cano's paper. Overall, the oxidative initiation protocol enabling the use of cheaper metal salts should prove advantageous (*J. Org. Chem.* **2011**, *76*, 5759−5773).

11. FRIEDEL−CRAFTS CHEMISTRY

A magnetite-catalyzed protocol for the selective decarboxylative cross-ketonisation between an aryl- and alkylcarboxylic acid is described by Gooßen, et al. Mechanistic considerations coupled with extensive catalyst trials provided selectivity for the cross-coupling with very low contamination from dialkylketone formation albeit at very high temperature. The decarboxylation of the aromatic acid also helps ensure regioselectivity compared to typical F−C acylations. The model reaction between 3-toluic acid and phenylacetic acid was optimized to an 80% theoretical yield with a 9:1 ratio of the desired cross-coupled product over the dialkyl ketone utilizing a nanopowder mixture of Fe(II)/Fe(III) oxide within a particular size range heated in Dowtherm A as solvent at 250 °C over 21 h (*Adv. Synth. Catal.* **2011**, *353*, 57−63).



Wilkinson outlines a metal- and halogen-free green alternative for F−C acylations promoted by methanesulfonic anhydride (MSAA) to provide aryl ketones. Reaction of variously substituted benzoic acids with arenes, including electron-deficient examples, were performed neat, typically using no more than 2 mol equiv of the arene and 1.3 equivalents of MSAA, providing reasonably good yields and regioselectivity along with impressive mass productivity. Chlorobenzene coupling required extended heating (32 h) and a second charge (0.35 equiv) of MSAA for a 53% yield, but could be further catalyzed by introduction of 2 mol % $In(OTf)_3$ if reaction time enhancement (9 h) is deemed a priority over waste stream content. Nitroaromatic reactions were unsuccessful. 4-Methanesulfonyl-phenylacetic acid coupled well with toluene to provide the ethanone product in 69% yield with 91:9 regioselectivity. Reactions utilizing alkylacids and lower-boiling arenes benefitted from the use of small amounts of cosolvents (*Org. Lett.* **2011**, *13*, 2232−2235).



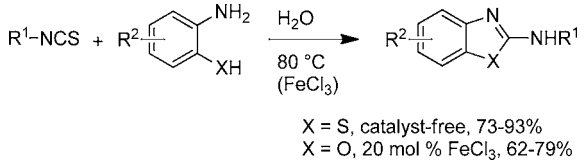
Smith and El-Hiti provide a critical review focussed on the use of zeolite catalysts for greener F−C aromatic substitution reactions resulting in enhanced para selectivity. They provide a brief insight into structural variation in zeolite-type catalysts followed by sections on specific reaction types including nitration, halogenation, alkylation, acylation, methanesulfonylation, and acetylation with all including regioselectivity discussions (*Green Chem.* **2011**, *13*, 1579−1608).

Sartori and Maggi present a review update concentrating on various solid catalysts used in acylation reactions of specific classes of substrates; arenes, aromatic ethers, thioethers, phenolic substrates, including Fries rearrangements, and heterocycles. Solid catalysts include zeolites, as well as clays, metal oxides, heteropoly acids, and Nafion (*Chem. Rev.* **2011**, *111*, PR181−PR214).

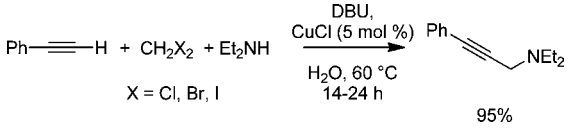
Each review provides copious references on its subject.

12. CHEMISTRY IN WATER

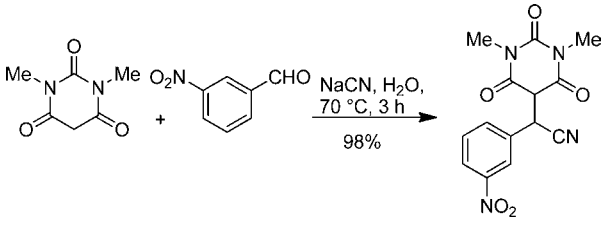
A variety of 2-aminobenzthiazoles have been synthesized by an efficient tandem reaction of isothiocyanates with 2-aminothiophenols. Zhang and co-workers observed a significant rate acceleration of this catalyst-free reaction when performed in water. The reaction has been extended to the $FeCl_3$-catalyzed coupling of isothiocyanates and 2-aminophenols to 2-aminobenzoxazoles (*Green Chem.* **2011**, *13*, 413−418).



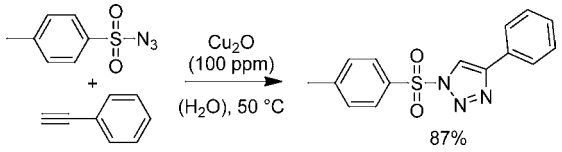
Different multicomponent reactions (MCRs) have been described recently using water as a beneficial solvent. The three-component coupling of terminal alkynes, dihalomethane, and amines to form propargyl amines has been described by Yu and Zhang. High yields of 90−95% have been obtained using 5 mol % CuCl as a catalyst and DBU (1 equiv) as a base (*Adv. Synth. Catal.* **2011**, *353*, 163−169).



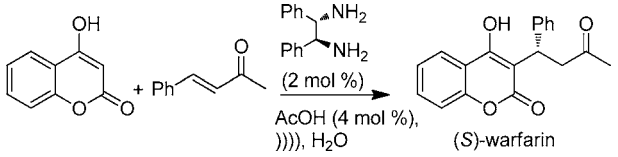
The MCR reaction described by Soleimani et al. of different 1,3-diketo compounds, substituted benzaldehydes, and NaCN affords alkyl cyanides in a tandem Knoevenagel condensation and Michael addition reaction. Water acts as both solvent and catalyst for the reaction (*Green Chem.* **2011**, *13*, 566−569).



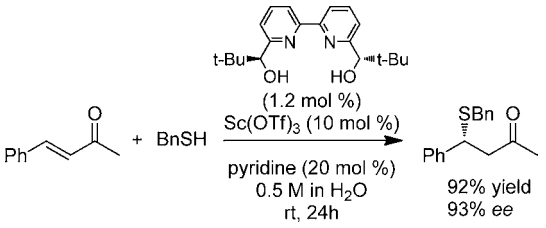
An efficient Cu_2O-catalyzed azide−alkyne cycloaddition reaction in water has been described by Wang et al. As a result of the high catalytic activity of the Cu_2O/H_2O system, the reaction could be run neat, and the catalyst loading could be decreased to ppm levels using water only as an additive (*Green Chem.* **2011**, *13*, 562−565).



Asymmetric organocatalysis in water has been applied by Rogozińska et al. for the synthesis of the anticoagulant warfarin (currently marketed as racemate). The reaction performed "on water" with 2 mol % of chiral diamine and 4 mol % of acetic acid as additive under ultrasound conditions gave (*S*)-warfarin in >99% ee and 52% yield after enrichment by crystallization (*Green Chem.* **2011**, *13*, 1155−1157).



Kobayashi and co-workers have described the chiral scandium-catalyzed asymmetric 1,4-addition of thiols to enones in water. Substoichiometric amounts of pyridine or NaOH have been used as base to reach enantiomeric excesses >90%. Of the different solvents tested remarkably the best results were obtained in water (*Org. Biomol. Chem.* **2011**, *9*, 2619−2621).



The ring-opening of epoxides in water with various nucleophiles has been reviewed by Bonollo et al. (*Eur. J. Org. Chem.* **2011**, 2587−2598).

13. CONTINUOUS PROCESSING AND PROCESS INTENSIFICATION

An article on application of continuous crystallisation in pharmaceutical API manufacturing has been reported as part of a perspective on Pharmaceutical Crystallisation by Chen et al. From an industrial viewpoint this article provides an impressive analysis of the advantages and disadvantages along with details on commonly used techniques, challenges and impact on regulatory issues (*Cryst. Growth Des.* **2011**, *11*, 887−895).

In a publication by Browne et al., an agitated cell reactor which uses transverse mixing motion to maintain solid suspension has been used to carry out a salt formation process and demonstrate the feasibility of such a reactor in handling slurries. The reactor which maintains its mixing using a shaking platform is suggested suitable for medium scale processing of solid forming reactions (*Org. Process Res. Dev.* **2011**, *15*, 693−697).

dx.doi.org/10.1021/op300068d | *Org. Process Res. Dev.* 2012, 16, 535−544

An article by Wegner et al. highlights ten key issues in modern flow chemistry; the authors also highlight the practical challenges in transferring from a lab to a manufacturing scale (*Chem. Commun.* **2011**, *47*, 4583−4592).

14. GENERAL GREEN CHEMISTRY

Professor Bruce Lipshutz (University of California at Santa Barbara) won the academic award in the 2011 Presidential Green Chemistry Awards for his work in designing a second-generation surfactant TPGS-750-M. The surfactant which is commercially available allows a variety of metal-catalysed reactions (e.g., Grubbs, Suzuki, Heck and Sonogashira) to be carried out in high yield in water; details can be found in (*J. Org. Chem.* **2011**, *76*, 4379−4391).

Sanderson published an article in *Nature* summarising the first 20 years of Green Chemistry based on interviews with Paul Anastas, Eric Beckman, John Warner, Peter Dunn, Pete Licence, Walter Leitner, Neil Winterton, and Robert Kavlock (*Nature* **2011**, *468*, 18−20).

Concepts such as Atom Economy, E-Factor, and Process Mass Intensity are now widely used by synthetic chemists to assess the "greenness" of their processes and reactions. Hartman et al. from Merck have suggested Analytical Method Volume Intensity (AMVI) as a metric to assess the efficiency of HPLC analytical methodology from an environmental perspective (*Green Chem.* **2011**, *13*, 934−939).

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