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 16 member companies as compared to 3 in 2005. The membership scope has also broadened to include contract research/manufacturing organizations, generic pharmaceuticals, and related companies. Members currently include ACS GCI, Amgen, AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Codexis, Dr. Reddy's, DSM Pharmaceutical Products, Eli Lilly and Company, GlaxoSmithKline, Johnson & Johnson, Merck & Co., Inc., Novartis, Pfizer, Inc., Roche, and Sanofi.

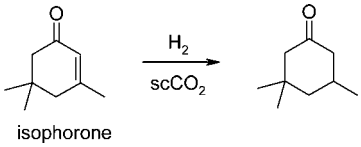
One of the strategic priorities of the Roundtable is to inform and influence the research agenda. Two of the first steps to achieve this objective were to publish a paper outlining key green chemistry research areas from a pharmaceutical perspective (*Green Chem.* **2007**, *9*, 411−420) and to establish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

Pereira et al. have published a tutorial review on ethyl lactate which covers the synthesis of the material from renewable sources; very detailed information is given on its physical properties, and there are also some references to its use as a solvent for synthesis (*Green Chem.* **2011**, *13*, 2658−2671).

Stevens et al. have reported on the hydrogenation of isophorone in $scCO_2$. This is a long-standing project between



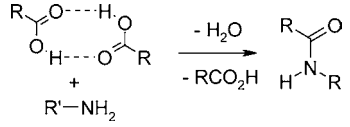
isophorone

the Poliakoff group at Nottingham University and Thomas Swann & Co. Ltd. About a decade ago Thomas Swann built a plant to hydrogenate around 1000 tonnes per annum of isophorone. The project was a technical success, but compressing CO_2 is energy intensive, and sharply rising energy costs made the process uncompetitive. This latest paper looks at using CO_2 from carbon capture and storage (i.e., from a power station). Such CO_2 contains a number of impurities, e.g. N_2, H_2O, and CO. The paper examines the effects of the impurities on this particular reaction and concludes that they do not give insuperable problems (*Green Chem.* **2011**, *13*, 2727−2733).

Reduction reactions are of fundamental industrial importance. Besides the fact that an immense number of catalysts have been described, the search for more environmentally benign reaction conditions remains relevant. In a mini-review the authors focus on greener strategies to recycle and reuse catalysts using solvents such as water, supercritical CO_2, and ionic liquids as a replacement for typical organic solvents (*ChemSusChem* **2011**, *4*, 1035−1048).

3. AMIDE FORMATION

Charville et al. from Durham University in collaboration with Syngenta have reported detailed mechanistic studies on the uncatalyzed direct amidation reaction between a carboxylic acid and an amine. The studies were performed with a combination of ^1H NMR studies in D_8-toluene and calorimetric studies and were supported by DFT computational calculations. It is proposed that for favorable substrates the reaction proceeds via a dimer (*Eur. J. Org. Chem.* **2011**, 5981−5990).

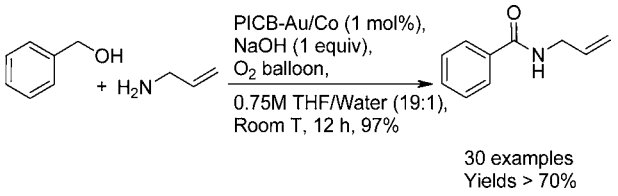


Kobayahsi and co-workers have developed an alternative pathway for amide synthesis from alcohols and amines through a tandem oxidative process (TOP) using their polymer-incarcerated (carbon black) catalysts (PICB catalysts). The reactions proceed in a THF/water system with the addition of one equivalent of sodium hydroxide using either a balloon of oxygen or air as the oxidant. The authors found that the most effective catalyst for the transformation was a combination of gold and cobalt (PICB−Au/Co), and they rationalize that the cobalt has the dual benefit of stabilizing the intermediate carbinolamine, whilst also tempering the reactivity of the gold nanoparticles in the initial oxidation step. Reactions were conducted with 1−1.5 mol % of the catalyst at either 25 or 40 °C. Good substrate scope was demonstrated for both the amine (including the use of aqueous ammonia to generate a primary amide) and the alcohol component, and the catalysts could easily be recycled (*J. Am. Chem. Soc.* **2011**, *133*, 18550−18553).

Pattabiraman and Bode have published a review which highlights the significant limitations of the current methods for amide bond formation, indicating particularly the growing concerns about the waste and expense of these methods. Furthermore, this review explores a diverse array of novel

Received: September 10, 2012
Accepted: September 24, 2012
Published: October 17, 2012

dx.doi.org/10.1021/op300251d | *Org. Process Res. Dev.* 2012, 16, 1887−1896



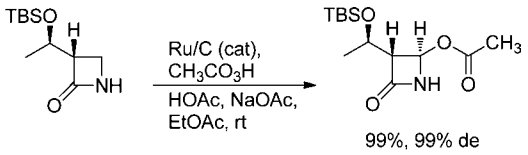
current strategies being developed for the reaction, including new acylation reactions of amines, use of amine surrogates for amidation, transamidation reactions, and novel chemoselective ligation methods. Several current synthetic challenges are also discussed such as catalytic amide bond formation and the production of therapeutic peptides, and progress towards practical solutions to these issues is presented (*Nature* **2011**, *480*, 471−479).

4. OXIDATIONS

Two reviews of note on green oxidations were published in the second half of 2011.

Mizuno and Kameta reviewed homogeneous and heterogeneous oxidations of hydrocarbon substrates with H_2O_2 catalyzed by vanadium complexes. Vanadium-based polyoxometalates are of particular interest since their properties can be finely tuned for high activity and selectivity. The complexes are generally stable under thermal and oxidative conditions, offering the potential for low catalyst loadings and catalyst recycling (*Coord. Chem. Rev.* **2011**, *255*, 2358−2370).

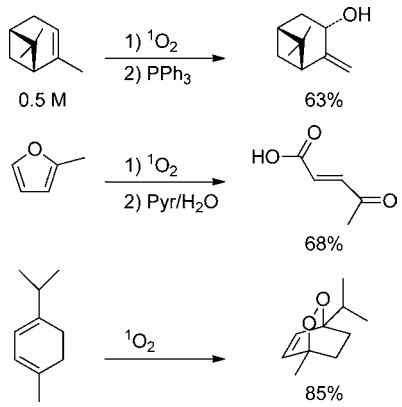
S.-I. Murahashi reviewed 30 years of pioneering research from his laboratory on biomimetic transition-metal-catalyzed oxidations, offering insights into the birth and subsequent exponential growth in the field of C−H activation. Of the many achievements during his career, the seminal discovery of an acetoxylation reaction to produce 4-acetoxy-azetidinone has led to cheaper and more efficient manufacture of many carbapenem antibiotics. This intermediate is now produced on a 100 t scale annually (*Proc. Jpn. Acad. Ser. B* **2011**, *87*, 242−253).



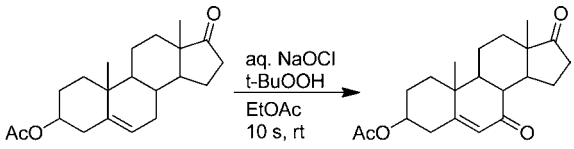
Kuang et al. describe organic, solvent-free oxidations of alcohols to aldehydes and ketones using 1-methyl-2-azaadamantane *N*-oxyl radical (1-Me-AZADO) at the 0.5 mol % level with aq HNO_3, $NaNO_2$, and oxygen. The catalyst is recycled by taking advantage of the differing solubilities of its oxidation states. Under acidic conditions, the protonated radical (R_2N−OH) distributes to the organic phase (neat alcohol at the start of the reaction). Upon addition of the terminal oxidant (O_2 and $NaNO_2$), the oxidized form (R_2N^+=O) is transferred to the aq phase. Upon completion of the reaction, the layers are separated, and the aq phase containing catalyst can be reused. After eight cycles, the catalyst was still providing 90% conversion with about 50% of the catalyst recovered (*Green Chem.* **2011**, *13*, 1659−1663).

While many publications over the past decade have touted methodologies using green oxidants such as molecular oxygen, ozone, and hydrogen peroxide, often these methodologies cannot be adopted in industry due to inherent and unacceptable safety risks. Therefore, oxidation reactions have become a recent focus of continuous processing, where the total volume of a reaction can be kept small, reaction times short, and heat transfer rapid. Four flow oxidation papers of note were published during the latter half of 2011.

Levesque and Seeberger described photochemical generation of singlet oxygen in a photochemical flow reactor for the oxidation of alkenes, 1,3-dienes, and thioethers. A 14 mL photochemical flow reactor was constructed. With a flow rate of 5 mL/min (residence time 0.8 min) using a 0.5 M solution of substrate and 12 mL/min oxygen, 20−30 g of substrate could be processed in one hour (*Org. Lett.* **2011**, *13*, 5008−5011).



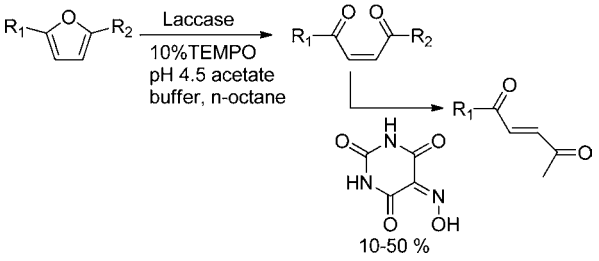
Lv et al. reported metal-free benzylic oxidations in a flow reactor using aq NaOCl in combination with *t*-BuOOH, obtaining high yields and good selectivity with a residence time of 10 s at ambient temperature. The allylic oxidation of a steroid provided a demonstration of the methodology on a relatively complex substrate (*Synth. Commun.* **2011**, *41*, 3215−3222).



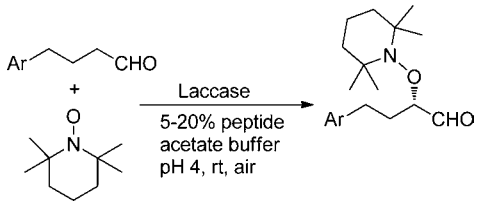
Two papers describe ozonolysis reactions in continuous systems. Roydhouse et al. provided a detailed analysis of the ozonolysis of 1-decene to nonanal in a flow capillary reactor (*Org. Process Res. Dev* **2011**, *15*, 989−996) while Allian et al. provided an in-depth discussion of two continuous reactors for the ozonolysis of an undisclosed isobutylene substrate. A continuous stirred tank reactor (CSTR) was designed and optimized to provide 300 g of product and a continuous bubble reactor employed to prepare 2.5 kg. FTIR, calorimetry, and kinetics guided the development of a safe and high-yielding reaction (*Org. Process Res. Dev* **2011**, *15*, 91−97).

Biocatalytic oxidations offer another approach to avoid hazardous conditions inherent in oxidations using oxygen, since these reactions can be carried out in primarily aq media. However, biocatalytic oxidations have been less well developed relative to other enzymatic reactions such as hydrolysis and ketoreductions, thus offering a fertile area for green oxidation research. During the second half of 2011, two groups reported oxidations using the laccase enzyme, a copper-based oxidase. Asta et al. demonstrated the oxidative ring-opening of 2,5-dialkylfurans in water and an air atmosphere. Using TEMPO as cocatalyst, the *Z*-1,4-dione isomer is formed exclusively. The *E*-isomer can be formed by addition of violuric acid, which

apparently provides an acid-catalyzed Michael−retro-Michael pathway to isomerize the *Z*-isomer to the more thermodynamic stable *E*-isomer. A number of symmetrical and unsymmetrical furans were oxidized to the synthetically useful *Z*-isomer products in 22−65% yields (*Green Chem.* **2011**, *13*, 3066−3069.

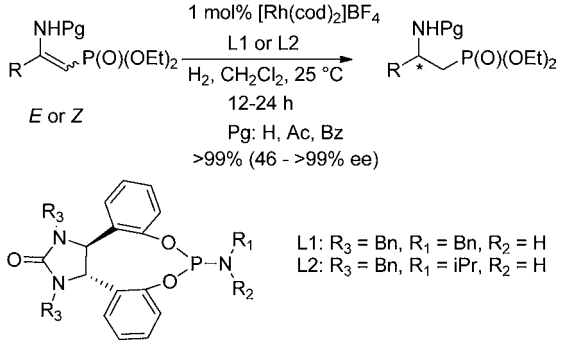


Akagawa and Kudo used laccase-mediated oxidations for the enantioselective α-oxyamination of aldehydes with TEMPO in aq media under an air atmosphere, using a peptide catalyst to induce asymmetry. Yields of 65−80% with enantiomeric excesses (ee's) of 86−90% were achieved with 4-arylbutanals. When Tween 80 was added to the reaction, concomitant oxidation of the aldehyde to carboxylic acid occurred, with similar yields and ee's. The peptide catalyst could be reduced to 5 mol % with only minimal loss of yield or ee (*Org. Lett.* **2011**, *13*, 3498−3501).

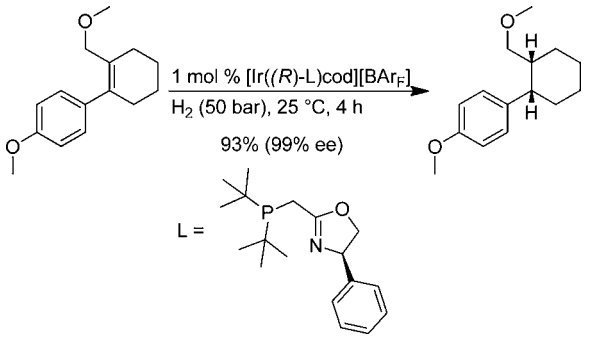


5. ASYMMETRIC HYDROGENATION

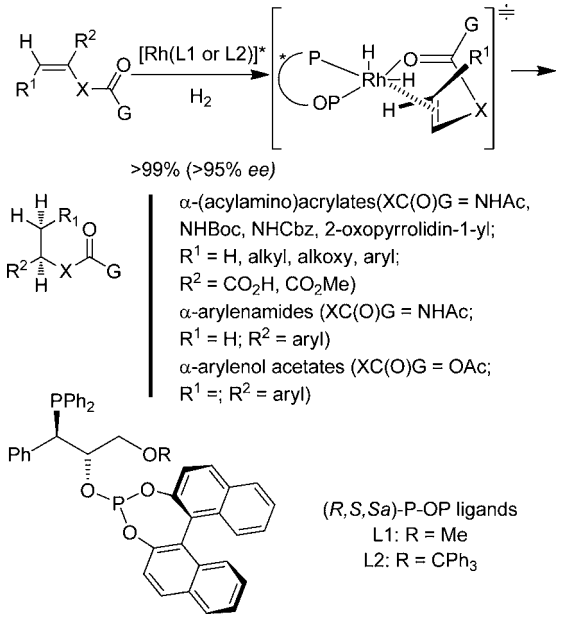
Zhang et al. report primary amine containing chiral monodentate phosphoramidite DpenPhos ligands [(*S*,*S*)-L1-L2]-derived Rh(I) catalysts are found to affect asymmetric hydrogenation of various naked or α- and β-aryl or heteroaryl- or alkyl-substituted enamido phosphonates. Asymmetric hydrogenation using L1 afforded 96−99% ee with a turnover number of 1800/h at 4 atm H_2 pressure. This asymmetric hydrogenation strategy enabled the synthesis of (*S*)-phospholeucine (the (*R*)-isomer is an amino peptidase inhibitor) and the antibacterial agent alafosfalin with high yields and ee. These catalysts (derived from L1 or L2) were also employed in the asymmetric hydrogenation of various β-substituted (*Z*)- or (*E*)-β-enamidophosphonate esters affording products in excellent yields and ee (*Angew. Chem., Int. Ed.* **2011**, *50*, 11743−11747).



A series of tetra-substituted cyclic alkenes were subjected to Ir-catalyzed hydrogenations to access *cis*-1-methoxymethyl-2-arylcyclohexanes in high yields and ee by using phosphinomethyloxazolines as ligands. Apart from excellent yields, the greener features of this transformation are that the reactions have been performed at room temperature in 4 h whilst using very low catalyst loading (*Chem.—Eur. J.* **2011**, *17*, 13502−13509).



Etayo et al. have developed enantioselective hydrogenation reactions of a number of alkenes catalyzed by Rh complexes of a set of P-OP ligands (L1, L2, and ent-L2) in high yields and ee. This strategy provided the means to access amines, alcohols, and α-amino acids of pharmaceutical significance. The reactions are performed at room temperature in 18 h when using a low catalyst loading (*Chem.—Eur. J.* **2011**, *17*, 13978−13982).



An atom economical and clean enantioselective hydrogenation route to pharmaceutically interesting 3-amino-chroman derivatives is presented by Wu et al. Asymmetric hydrogenation of trisubstituted enamides derived from chromanone derivatives catalyzed by Ru-synphos led to the desired product in high yields and ee up to 96% (*Org. Lett.* **2011**, *13*, 3782−3785).

New iridium catalysts with tridentate spiro ligands were designed by Xie et al. for the hydrogenation of simple ketones. The paper includes synthesis of the ligands, screening, and optimization of reactions conditions. The best-performing ligand was then used to reduce a variety of ketone substrates, mostly focussing on aryl methyl ketones. The chiral alcohols

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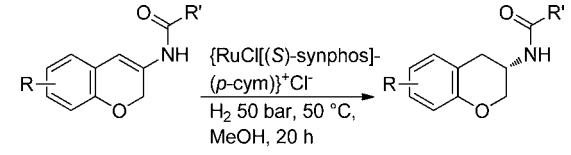
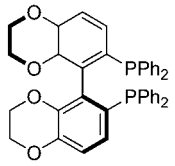


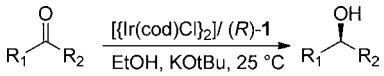
R = Me, MeO, F, Cl, Br
R' = Me, Et, Pr, *t*-Bu, Ph, OBn

Up to 97% Yield
up to 96% *ee*

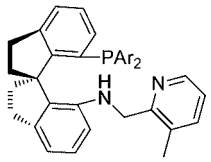


(*S*)-synphos

were obtained in up to 99% ee, and the TON for the catalysts was as high as 4.5 million (*Angew. Chem., Int. Ed.* **2011**, *50*, 7329−7332).



R_1 = aryl, alkyl
R_2 = Me, Et, nBu



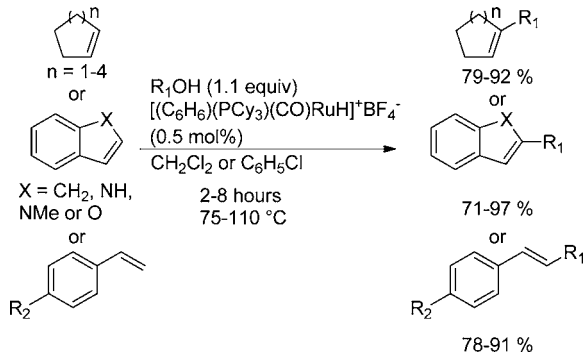
(*R*)-**1** (Ar = 3, 5-(t-Bu)$_2$C$_6$H$_3$

6. C−H ACTIVATION

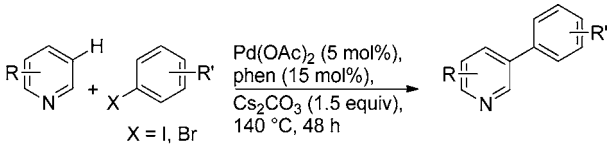
Pan et al. describe an enantioselective secondary sp^3 C−H bond activation of 2-(alkylamino)-pyridine in the presence of a chiral Ir(I) catalyst in an oxygen-free atmosphere. A screening of catalysts and ligands revealed the BF_4^- counterion, and (*S*)-tolBINAP gave the best yield and enantiomeric excess (ee). A variety of styrenes were investigated, and styrenes with electron-withdrawing groups gave the best yield and ee. No significant steric effect was observed with differently substituted styrenes (para vs meta vs ortho). Yields of up to 81% and up to 89% ee were possible in the case of 4-methylstyrene. The paper also details the removal of the pyridyl group to generate the corresponding chiral primary amine. In the case of R^1 = methyl and R^2 = 4-MeOC$_6$H$_4$, this conversion can be accomplished in 81% yield (*Org. Lett.* **2011**, *13*, 4692−4695).

67-81% yield
84-89 %ee

A catalytic C−H alkylation of alkenes with alcohols was developed by Lee et al. utilizing [(C$_6$H$_6$)(PCy$_3$)(CO)RuH]$^+$BF$_4^-$. Substrate functionality was well tolerated, and cyclic olefins, heteroarenes, and styrenes all alkylate readily. Heteroarenes selectively alkylated adjacent to the heteroatom, while styrenes provided a mix of olefins (>98% trans) and reduced hydrogenation products (typically 10−15%). Aliphatic and aryl-substituted primary alcohols worked very well in a short time frame, but secondary aliphatic alcohols were much slower. While methylene chloride and chlorobenzene were the best solvents, toluene and THF also worked, but at a slower rate. All reactions were run in an oxygen-free atmosphere. No additives or cocatalysts were required, and the only side product of the reaction is one equivalent of water, which is very appealing from a sustainable reaction perspective. Overall, a very green robust system has been identified for the alkylation of alkenes, where the only side product is water and turnover numbers of up to 102,000 were possible (*Science* **2011**, *333*, 1613−1616).



Ye et al. have developed the first example of a nondirected, regioselective C-3 arylation of pyridines. A combination of 5 mol % Pd(OAc)$_2$, 15 mol % 1,10-phenanthroline, and 1.5 equiv Cs$_2$CO$_3$ at 140 °C promoted the cross-coupling in 54−90% yield. The reaction showed useful scope for both the arene and pyridine substrate. A wide array of sterically- and electronically diverse aryl iodides and aryl bromides underwent coupling with pyridine in >10:1 regioselectivity. Several pyridine derivatives such as 3-picoline and 2-methoxypyridine provided good reactivity with iodobenzene. However, quinoline provided the arylated product with a modest 3:1 regioselectivity. The current method is most useful for pyridine and simple pyridine derivatives as a large excess of this reagent is required (>50 equiv) relative to the arene (*J. Am. Chem. Soc.* **2011**, *133*, 19090−19093).



X = I, Br

7. GREENER FLUORINATION

Noël et al. described a palladium-catalyzed C−F bond formation with a microflow packed-bed reactor. The previous batch process required a large excess of CsF, and the amount of waste made this strategy unattractive. A packed-bed reactor design allowed the easy handling of large quantities of insoluble CsF with excellent mixing, precise control over reaction times, and the ability to safely handle elevated temperatures and pressures. A single syringe pump was used to inject a toluene solution of various aryl triflates, [(cinnamyl)PdCl]$_2$, and *t*-BuBrettPhos through a CsF packed-bed reactor at 120−140 °C. Full conversion was achieved with a residence time of only 20 min in most cases. Aryl triflates bearing esters, ketones, and cyano groups were well tolerated (*Angew. Chem., Int. Ed.* **2011**, *50*, 8900−8903).

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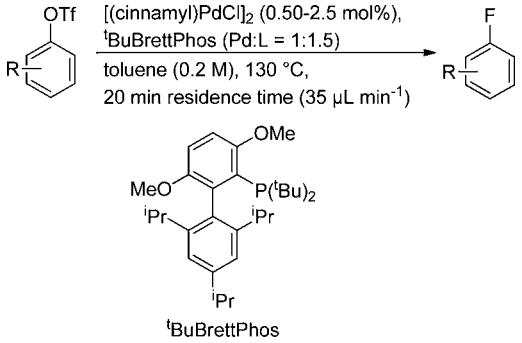
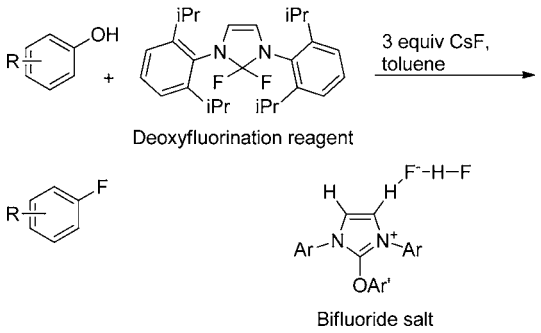
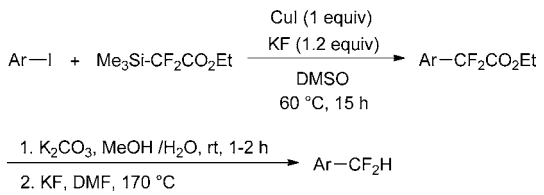


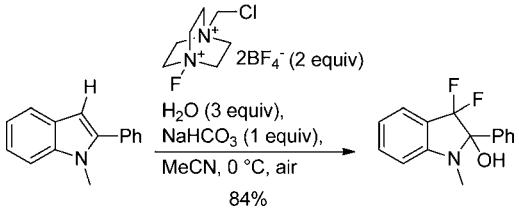
Tang et al. have reported a fluorinating reagent that delivers aryl fluorides from phenols by a one-step ipso substitution. The deoxyfluorination reagent can be handled in air as a solid or stored as a dry toluene solution for at least two months. Both electron−deficient and electron-rich phenols can be fluorinated by the reagent. It is noteworthy that even 4-fluoroaniline can be prepared by the presented method. The proposed mechanism for fluorination involves a 2-phenoxyimidazolium bifluoride salt that is formed by condensation of a phenol with the reagent. Hydrogen bonding appears to be crucial for the fluorination reaction (*J. Am. Chem. Soc.* **2011**, *133*, 11482−11484).



The copper-mediated cross-coupling reaction for aromatic trifluoromethylation has been widely investigated. However, the cross-coupling of HCF_2Cu with aromatic halides has never been accomplished due to the lack of thermal stability of HCF_2Cu species. Fujikawa et al. have developed a new reaction sequence leading to an efficient synthesis of difluoromethylated aromatic compounds from aryl iodides *via* 2,2-difluoroacetates. Aryl iodides reacted with α-silyldifluoroacetates upon treatment with cuprous iodide catalyst in DMSO to give the corresponding aryldifluoroacetates in moderate to good yields. The subsequent hydrolysis of aryldifluoroacetates and KF (or CsF)-promoted decarboxylation afforded a variety of difluoromethyl aromatics (*Org. Lett.* **2011**, *13*, 5560−5563).



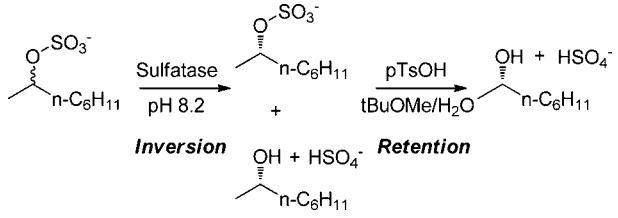
Lin et al. report an efficient difluorohydroxylation of N-substituted indoles leading to 3,3-difluoroindolin-2-ols in good yields by using Selectfluor as the electrophilic fluorinating reagent. The indole ring is difluorinated regioselectively at C3. Unsubstituted indoles eliminate to 3,3-difluoro-3*H*-indoles; replacing water with alcohols in the presence of molecular sieves affords the corresponding ether at C2. The authors discuss the mechanism (*Org. Lett.* **2011**, *13*, 4498−4501).



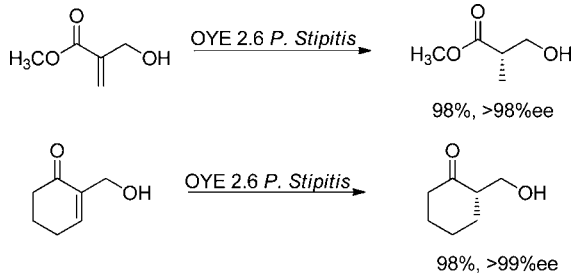
Fuchigami and Inagi have published a review discussing the selective electrochemical fluorination of organic molecules and macromolecules in ionic liquid fluoride salts. The authors highlight that organic electrosynthesis is recognized as an environmentally friendly process and that reactions often proceed under mild conditions. The review details the influence of solvent effects on the selectivity of the fluorination reactions and then describes the significant advantages of switching to ionic liquids for these processes. Finally, an overview of strategies such as ultrasonication, mixed solvent systems, and use of mediators is provided to stimulate further research in this area (*Chem. Commun.* **2011**, *47*, 10211−10223).

8. BIOCATALYSIS

Schober et al. report a method for deracemization of secondary alcohols using an alkylsulfatase. The enzyme utilises acid-catalysed hydrolysis to give inversion of configuration by attack of water at the carbon atom. The remaining enantiomer is chemically hydrolysed under acid conditions by attack at the sulfur atom, giving retention of configuration at carbon (*Org. Lett.* **2011**, *13*, 4296−4299).



Walton et al. have reported the use of enoate reductases for the reduction of adducts from Baylis−Hillman reactions. From a library of enzymes, old yellow enzyme (OYE) 2.6 from *Pichia stipitis* was the only one to show excellent levels of conversion and enantioselectivity towards the Roche ester. The wild-type enzyme produced the (*S*)-enantiomer, whilst site mutagenesis of the Trp116 residue gave mutants which displayed good selectivity for the (*R*)-enantiomer (*ACS Catal.* **2011**, *1*, 989−993).



Regio- and stereoselective oxidative C−H activation is a current challenge in synthetic organic chemistry. Kille et al. report the regio- and stereoselective hydroxylation of steroids

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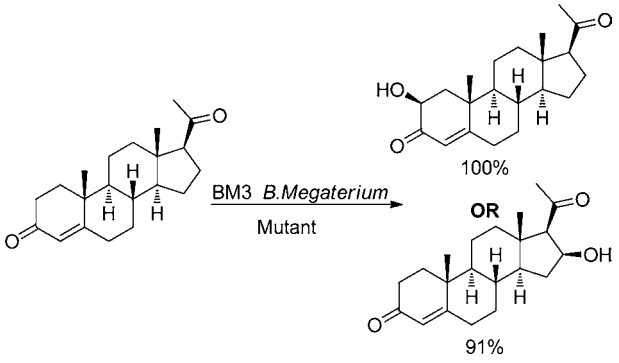
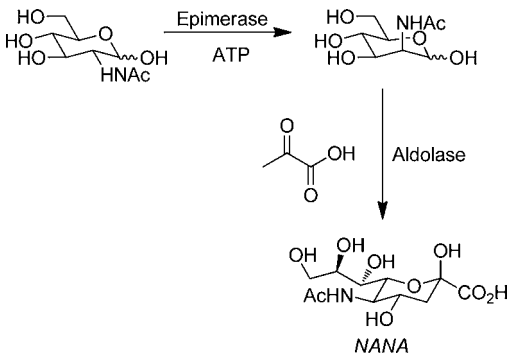
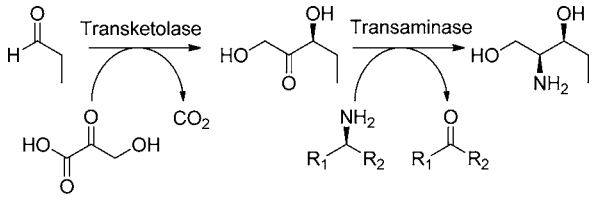
catalysed by the cytochrome P450 BM3 from *Bacillus megaterium*. A number of saturation mutagenesis libraries were created which showed good to excellent conversion of testosterone and progesterone to a variety of hydroxylated products (*Nature Chem.* **2011**, *3*, 738−743).



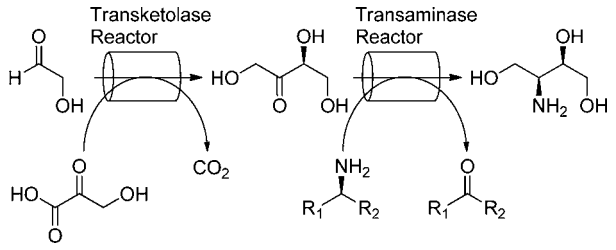
The use of whole-cell biocatalysts is becoming an important tool in the synthesis of pharmaceutical intermediates and starting materials. Tao et al. have recently published an example of this with a one-pot biosynthesis of *N*-acetyl-D-neuraminic acid (NANA), several derivatives of which are commercial products. Whole-cell approaches can suffer from problems with side reactions, mass transfer of materials in/out of the cell, and the use of expensive chemical induction systems. To overcome these factors, a variety of methods were used. Side reactions were reduced by eliminating the cell's *N*-acetyl-D-glucosamine phosphotransferase. Mass transfer in and out of the cell was increased by adding cetyltrimethylammonium bromide and using a temperature induction system. NANA production of 59 g/L is possible using this system (*Sci. Rep.* **2011**, *1*, 142).



Rios-Solis et al. have also combined two enzymes in one microbial host. In this case a transketolase and a transaminase, each on a separate plasmid, where combined in *Escherichia coli* for a whole-cell biotransformation. Complete conversion of propionaldehyde to 2*S*,3*S*-amino-1,3-diol in one pot is observed, although concentrations are still low (10 mM). In addition, the strain containing the two plasmids had half of the growth rate of the strains containing only one plasmid-type (*Biocatal. Biotrans* **2011**, *29*, 192−203).



Matosevic et al. have reported similar chemistry using microreactors with the transketolase and transaminase enzymes immobilized onto the inner jackets of glass capillaries. To bind the enzymes, the derivatised glass surface was treated with Ni-sulfate, and the histidine-tagged enzyme was then loaded. The reaction was monitored by using an online flow-through UV-spectroscopic cell. The tandem enzyme reaction showed 5% conversion over 1 h (initial conc. of 10 mM) due in part to the transaminase step being slower than the transketolase step. An overview of multistep-enzyme processes in microreactor systems is also reported (*J. Biotechnol.* **2011**, *155*, 320−329).



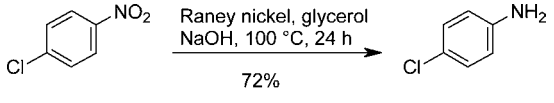
Wang et al. have reported a new ketoreductase from *Streptomyces coelicolor*. The enzyme is NADH dependent and was found to reduce a variety of aromatic and aliphatic ketones, producing the (*R*)-enantiomer of the corresponding alcohol. Yields and ee's are good with a substrate concentration of 5 mg/mL (*Bioresour. Technol.* **2011**, *102*, 7023−7028).

(*R*)-Selective transaminases are much rarer than (*S*)-selective ones, making them valuable biocatalysts for producing enantiopure (*R*)-amines. Schätzle et al. have identified a number of new (*R*)-selective transaminases from several microorganisms by *in silico* genome research. These were then expressed in *E. coli*, isolated, and tested against a variety of prochiral ketones. Enantiopure (>99%) (*R*)-amines could be produced, however volumes and concentrations are rather low (*Adv. Synth. Catal.* **2011**, *353*, 2439−2445).

Several reviews have also been published in this period. Turner has reviewed enantioselective oxidation of C−O and C−N bonds (*Chem. Rev.* **2011**, *111*, 4073−4087). Hollmann et al. have reviewed enzymatic reductions (*Green Chem.* **2011**, *13*, 2285−2314) and Wenda et al. summarize the advantages, disadvantages, and potential uses of biocatalysis to undertake greener chemistry (*Green Chem.* **2011**, *13*, 3007−3047).

9. REDUCTIONS

Glycerol is a significant byproduct of biodiesel production (~10% yield) and offers good solvent properties combined with low toxicity. Most reactions in glycerol operate at elevated temperatures which significantly reduce its viscosity. It is also active as a hydrogen donor in hydrogen-transfer reactions. Tavor et al. have used it to reduce nitro-aromatics to anilines with Raney nickel in the presence of sodium hydroxide. Recycling of Raney nickel was demonstrated for simple substrates, although the addition of fresh base was required (*Synth. Commun.* **2011**, *41*, 3409−3416).



The reduction of allylic alcohols using $RuCl_2(\eta^6\text{-}C_6H_6)$-(DAPTA) in glycerol was reported by Diaz-Alvaraz et al. Pleasingly from a green perspective, it was possible to use

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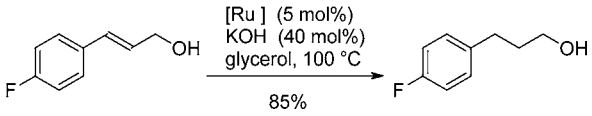
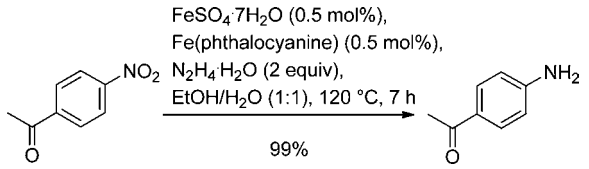
technical grade glycerol rather than highly purified solvent, and substrate concentrations up to 1 M were demonstrated. Screening single-variable changes identified the reported system which presents a good lead for further refinement. This system presents an advance over the previous conditions from this group in that scope for catalyst recycling was demonstrated, albeit for simple substrates (*Catal. Commun.* **2011**, *13*, 91−96).

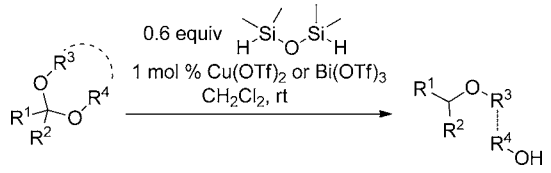


The use of water, supercritical CO_2 and ionic liquids as solvents for reduction reactions has been reviewed by Alvarez de Cienfugos et al. (*ChemSusChem* **2011**, *4*, 1035−1068).

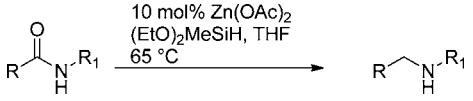
Despite its toxicity, the use of hydrazine as a reductant continues to attract interest. Sharma et al. reported the use of catalytic $FeSO_4{\cdot}7H_2O$, Fe(phthalocyanine)$_2$, or a 1:1 mixture to cleanly reduce nitroaromatics to the corresponding anilines. Low catalyst loadings (0.5 mol %) were required, and chemoselectivity was good, showing compatibility with halogen, ketone, and phenol functionality among others. Solvent choice was also made with an eye on industrial application using aqueous ethanol or ethylene glycol. It should be noted that hydrazine is on the Annex XVII register under the REACH legislation within the EU as a potential substance of very high concern (*Chem.—Eur. J.* **2011**, *17*, 5903−5907).



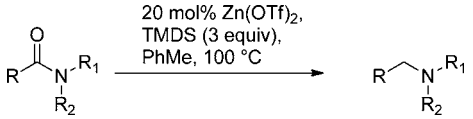
Metal-catalyzed hydrosilylation presents an attractive methodology for the reduction of C−O bonds. Zhang et al. have recently published a metal triflate-catalyzed reductive cleavage of acetals to ethers. Of the metal catalysts screened, Cu(OTf)$_3$ and Bi(OTf)$_3$ stood out as providing the best combination of reactivity and selectivity (vs diether formation) when 1,1,3,3-tetramethyldisiloxane (TMDS) was employed as the reducing agent. Ethanol, water, toluene, and THF were limited as solvents, either providing incomplete conversion, eroded selectivity, or in the case of water, decomposition of the acetal to the aldehyde. Dichloromethane was thus identified for optimization of the reaction conditions. While both catalysts provided high conversion, Bi(OTf)$_3$ provided the best selectivity in most cases, and when employed at 1 mol % relative to the acetal, it cleanly reduced a wide variety of acetals to the ether−alcohol product at room temperature, in the presence of 0.6 equiv of TMDS (1.2 equiv Si−H). Additionally, these conditions proved to be tolerable of hydroxyl, nitrile, nitro, and ester functionalities (*Green Chem.* **2011**, *13*, 2737−2742).



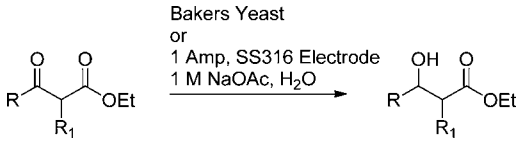
Preparation of amines via reduction of carboxamides was the focus of a recent paper from Das et al. Reduction of tertiary amides using 10 mol % zinc acetate with methyldiethoxysilane (3 equiv) in THF occurred smoothly at 65 °C. A variety of aromatic and heteroaromatic amides were reduced in yields up to 93%. While electronic effects of the aromatic rings had marginal effect on the reaction, steric crowding around the amine part of the amide bond significantly reduced reaction rate. Various substituents such as hydroxy, nitro, azo, nitrile, ester, and ether moieties were well tolerated under these reaction conditions; however, methylthio and keto groups were not tolerated. In the latter case, reduction of the ketone was the major side reaction.



Reduction of secondary amides was also reported, this time using zinc triflate as the catalyst and TMDS as the reducing agent. Solvent selection is critical, as ethereal solvents gave poor reaction rates and led to low yield. Optimization of the reaction conditions led to 20 mol % zinc triflate, TMDS (3 equiv) in toluene at 100 °C. Under these conditions, a wide array of aromatic and heteroaromatic amides were reduced to the respective amine products in isolated yields ranging from 50 to 85%. As with the aforementioned reduction of tertiary amides, these reaction conditions were tolerant of common substituents (*Chem.—Eur. J.* **2011**, *17*, 12186−12192).



Enzymatic transformations are highly regarded for their high enantioselectivtiy, mild reaction conditions, and low environmental impact. A recent paper by Ojha et al. described reduction of various keto-esters using both free and immobilized Baker's yeast as the reductant. High yield and excellent stereoselectivity were reported for various alkyl-substituted keto esters. Use of immobilized Baker's yeast provided for a rapid and simple isolation protocol and was recyclable. Also described by the authors was an interesting electrochemical reduction of alkyl-substituted keto-esters using a stainless steel electrode. The reduction reaction favored high pH and was conducted in aq sodium acetate, rendering hydrogen gas and hydroxyl ion as the major byproduct of the reaction. Unlike the enzymatic process, the electrochemical technique provided no enantioselectivity, and extremely low substrate concentration (0.001 M) greatly increases the amount of solvent and therefore limits execution of this procedure at production scale (*Int. J. ChemTech Res.* **2011**, *3*, 917−927).

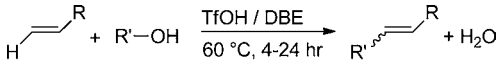


10. ALCOHOL ACTIVATION FOR NUCLEOPHILIC DISPLACEMENT

Yue et al. provide methodology for direct coupling of benzylic, allylic, and propargylic alcohols with aromatic and aliphatic alkenes run under air, utilizing trifluoromethanesulfonic acid as

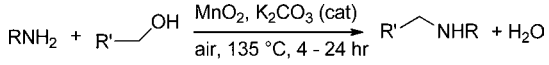
dx.doi.org/10.1021/op300251d | *Org. Process Res. Dev.* 2012, 16, 1887−1896

catalyst. Unfortunately, although the reaction works in toluene or DCE, it is more effective in chloroform or 1,2-dibromoethane (DBE). Various benzyl alcohols reacted readily with elaborated styrenes regardless of aromatic activation to generally provide good yields. Reaction of similar alcohols with a variety of cyclic alkenes also proceeded well at 60 °C for 4 to 24 h. Double bond migration was noted via hydride shift in some common cycloalkenes. Other particular examples and thoughts on mechanistic possibilities are discussed (*Adv. Synth. Catal.* **2011**, *353*, 3139−3145).



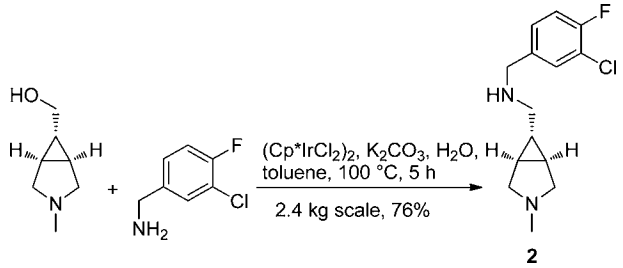
R = benzylic, allylic, propargylic

Yu et al. report a MnO_2-catalyzed dehydrative coupling of alcohols with amines and sulfonamides performed neat under air with catalytic base included. An array of sulfonamides as well as anilines and aminopyridines were treated with various benzyl alcohols under air, typically with 10−20 mol % each of MnO_2 and K_2CO_3 providing the coupled product in high yields within 24 h at 135 °C. Nitrogen atmosphere inhibited completion of the reaction drastically. The authors propose a hydrogen-borrowing mechanism, assisted by aerobic oxidation to regenerate the MnO_2 catalyst (*Org. Lett.* **2011**, *13*, 6184−6187).



Berliner et al. have published the application of the hydrogen-borrowing strategy, utilising Yamaguchi's catalyst, in the synthesis of **2**, an intermediate to a GlyT1 inhibitor.

The approach replaced a sequential Swern oxidation and reductive amination procedure, and the publication discusses the scale-up and optimization of the process. Optimization of the catalyst loading and methods for iridium removal to acceptable levels are also discussed (*Org. Process Res. Dev* **2011**, *15*, 1052−1062).

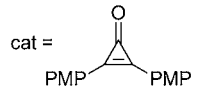


2

Two complementary approaches toward organocatalytic nucleophilic substitution of alcohols that offer clean inversion of chiral alcohols have been published. Denton et al. report a modified Appel chlorination using catalytic triphenylphosphine oxide. Treatment of the catalyst with oxalyl chloride affords a chlorophosphonium intermediate which reacts with the alcohol, and the resulting product is displaced with chloride, regenerating triphenylphosphine oxide. Their procedure avoids the use of stoichiometric amounts of carbon tetrachloride and triphenylphosphine. A range of primary and secondary alcohols are chlorinated in good yield. Bromination can be achieved using a mixture of oxalyl chloride and lithium bromide (*J. Org. Chem.* **2011**, *76*, 6749−6767). Vanos and Lambert use substituted cyclopropenones as the catalyst reacting with oxalyl chloride to form an intermediate chlorocyclopropenium chloride salt which reacts with the alcohol, and the resulting product is displaced with chloride, regenerating the cyclopropenone. Bis-*p*-methoxyphenylcyclopropenone was the most efficient catalyst (*Angew. Chem., Int. Ed.* **2011**, *50*, 12222−12226). Both publications include studies into the mechanism. The predominant use of chlorinated solvents in both methods is a current drawback, although Denton et al. have shown that ethyl acetate may be used with a slight loss in yield.

Denton et al. Ph_3PO (0.15 equiv), $(COCl)_2$, $CHCl_3$, 7 h, RT, 80%

Vanos & Lambert cat (0.1 equiv), $(COCl)_2$, CH_2Cl_2, 1 h, RT, 84%



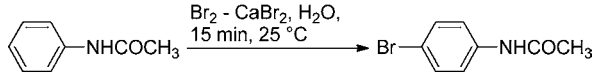
PMP = p-methoxyphenyl

11. CHEMISTRY IN WATER

A recent review paper by C.-J. Li presents an overview of various metal-mediated C−C bond-forming reactions in water. This review focuses on organometallic addition reactions to carbonyl derivatives, transition-metal-catalyzed nucleophilic addition via C−H activation, and iron- and copper-catalyzed dehydrogenative cross-coupling reactions (*Sci. China Chem.* **2011**, *54*, 1815−1830).

Catalytic asymmetric carbon−carbon bond-forming reactions under aqueous conditions have been reviewed by Bhowmick and Bhowmick. Enantioselective aldol reactions, 1,4-conjugate additions, Mannich reactions and Diels−Alder reactions both via organocatalysis and chiral metal complexes are summarized (*Tetrahedron: Asymmetry* **2011**, *22*, 1945−1979).

Bromination of activated aromatic compounds using aqueous Br_2CaBr_2 has been described by Kumar et al. Mono, di-, and tribrominated products can be prepared in high yield and selectivity simply by varying the equivalents of bromine. Reactions are typically complete within 30 min and show a high degree of functional group tolerance. Isolation of the brominated product is accomplished by filtration of the reaction mixture. Neutralization of the HBr in the filtrate using $Ca(OH)_2$ regenerates the bromination system and can be reused by addition of bromine and substrate. As many as four recycles were reported with little erosion in isolated yield. (*Green Chem.* **2011**, *13*, 2187−2196).



96% yield

In a paper by Ma et al. the asymmetric Michael addition of isobutyraldehyde to nitroalkenes in both organic solvents and water were compared. By using the diastereomeric amphiphilic amine−thiourea catalyst **3a** or **3b**, both enantiomers of the Michael product could be isolated in good yields and high ee. Reduction in catalyst loading as low as 5 mol % **3a** had no deleterious effect on enantioselectivity under aqueous conditions. However, at low catalyst loading the reaction rate suffered, requiring long reaction times at room temperature. As

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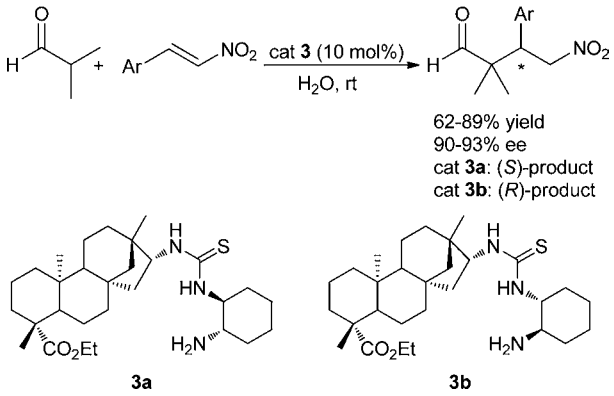
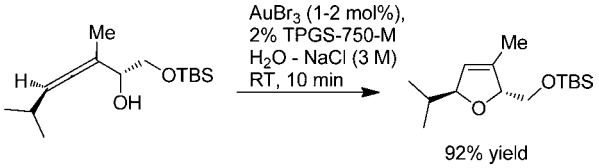
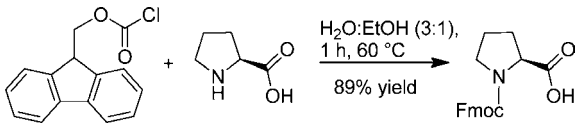
the diastereomeric catalysts are readily prepared from "natural" isosteviol and either enantiomer of cyclohexane-1,2-diamine, either the (*S*)- or (*R*)-enantiomer of the product is accessible (*Eur. J. Org. Chem.* **2011**, 6747−6754).



The gold-catalyzed cycloisomerization of α-functionalized allenes in water has been described by Minkler et al. Excellent yields of 78−92% are obtained using $AuBr_3$ as catalyst in micellar systems of the vitamin E-derived amphiphiles PTS or TPGS-750-M. α-Hydroxy as well as tosylated α-amines are cyclized under these conditions. By tuning the micellar diameter with different concentrations of NaCl (0−3 M) the $AuBr_3$ loading can be reduced to 1−2 mol % without noticeable reduction in chemical yield. In addition, the aqueous micellar system affords air-stable gold catalyst solutions with good recyclability after *n*-hexane extraction of the product and PTS derivatives. In over four runs only 0.29% of the gold catalyst is lost by leaching (*Angew. Chem.* **2011**, *50*, 7820−7823).



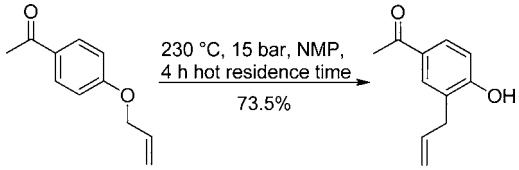
The 9-fluorenylmethoxycarbonyl (Fmoc) group has found wide application in solid-phase as well as solution-phase peptide synthesis. Gawande and Branco have now described a simple, fast, and efficient procedure for the Fmoc protection of amines and α-amino acids in aqueous media. By reaction in pure water or water/ethanol 3:1 at 60 °C, yields up to 92% have been obtained without addition of any further catalyst. The E factor and mass intensity of this procedure is compared with alternative Fmoc protection methods reported in the literature (*Green Chem.* **2011**, *13*, 3355−3359).



12. CONTINUOUS PROCESSING AND PROCESS INTENSIFICATION

Noël and Buchwald have published a critical review on the use of flow processing in cross-coupling reaction covering advances in the field for all the major transformations. This article will be of significant interest to the pharmaceutical process development community, keeping in mind the increasing use of such transformations in commercial route development (*Chem. Soc. Rev.* **2011**, *40*, 5010−5029).

Rincón et al. at Eli Lilly successfully developed an efficient continuous process for ortho-Claisen thermal rearrangement of 1-[4-(allyloxy)phenyl]acetone in NMP as a solvent under extreme conditions of 230 °C and 15 bar pressure to overcome apparent processing limitations and safety issues associated with batch processing under such conditions (*Org. Process Res. Dev* **2011**, *15*, 1428−1432).



Browne et al. reported low-temperature syntheses of various (hetero)aromatic boronic acids and esters via lithium−halogen exchange using a new lab-scale cryogenic mesoscale flow reactor that can attain temperatures as low as −89 °C (*Org. Lett.* **2011**, *13*, 3312−3315).

Reductions of various nitriles to aldehydes using diisobutylaluminium hydride were carried out in a continuous fashion by Muñoz et al. at Janssen to overcome both the instability issues associated with the reaction intermediates and non-robustness on scale (*Tetrahedron Lett.* **2011**, *52*, 6058−6060).

13. GENERAL GREEN CHEMISTRY

The scarcity of key elements is an important sustainability consideration for all chemicals based industries. The British Geological Survey has published its survey of 52 elements ranking them by equal consideration of four criteria: scarcity (based on crustal abundance), production concentration (the global spread of production), reserve base distribution (an indication of future sources), and governance (a measure of political stability). The platinum group metals, fundamental to many of the methods cited in the Articles of Interest above, rank second in the list and are categorized as a very high risk. (The link for the Risk List 2011 may be found at: http://www.bgs.ac.uk/mineralsuk/statistics/riskList.html.)

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Notes

The Green Chemistry Articles of Interest are produced on behalf of The ACS GCI Pharmaceutical Roundtable.