Green Chemistry Articles of Interest to the Pharmaceutical Industry

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Organic Process Research & Development

Green Chemistry Highlights

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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 principles into the pharmaceutical industry. The Roundtable currently has 16 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, 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. This review period covers the first 6 months of 2012.

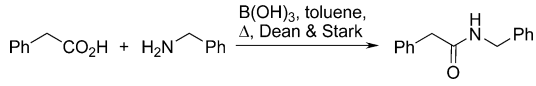
These articles of interest represent the opinions of the authors and do not necessarily represent the views of the member companies. Some articles are included because, whilst not currently being regarded as green, the chemistry has the potential to improve the current state of the art if developed further. 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

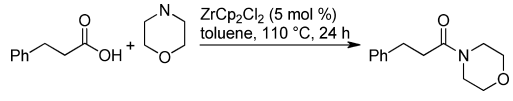
γ-Valerolactone has several interesting characteristics making it a potential candidate to be used as a green solvent. It is available naturally and can be obtained from levulinic acid and its esters, in turn obtained by acid hydrolysis of lignocellulosic biomass. γ-Valerolactone (GVA) has a low melting point (−31 °C), high boiling (207 °C) and flash points (96 °C), high solubility in water, and is nontoxic. Galletti et al. have recently investigated hydrogenation of aqueous streams of levulinic acid using a variety of metal catalysts and conditions. After several screenings, they discovered that use of a heterogeneous cocatalyst such as Amberlyst resins with ruthenium-based catalysts gave yields of GVA in excess of 90%. The heterogeneous catalyst system can be isolated by simple filtration of the reaction mixture and recyclable up to 5 times without loss in yield or selectivity (*Green Chem.* **2012**, *14*, 688−694). Duan Zhang-Qun and Hu Fei described the use of γ-valerolactone as a reaction medium for enzymatic biotransformations. In the studied system, the enzyme-mediated phosphatidylserine synthesis, yields up to 95% were achieved using γ-valerolactone as solvent, and the results were compared to those classical biphasic systems consisting of a water-immiscible organic solvent phase (*Green Chem.* **2012**, *14*, 1581−1583). An article by Moity et al. analyzed 153 solvents and grouped them into different clusters, aprotic dipolar, apolar, polar aprotic, etc. and identified the more sustainable solvents in each cluster (*Green Chem.* **2012**, *14*, 1132−1145).

3. AMIDE FORMATION

The direct amidation of acids and amines catalyzed by boric acid or boronic acids has attracted much interest recently. Grosjean et al. have reported on the importance of the rate of boiling in this reaction and the benefits of applying a systematic approach to the study of such reactions. In some cases the acceleration due to the heat input per unit volume Q_{boil} is greater than the acceleration due to the catalyst, so it is vital that the volumetric heat input rate is also reported in studies of different catalysts. Although this requires a rigorous approach, the equipment to do such experiments is inexpensive and can be found in any synthetic laboratory (*Org. Process Res. Dev.* **2012**, *16*, 781−787).



Allen et al. studied the thermal amidation of unactivated carboxylic acids with amines, reasoning that this reaction should be more facile in nonpolar solvents since the formation of charged species such as ammonium salts would be disfavored in such media. Indeed, the thermal amidation of a range of substrates occurred in toluene at 110 °C. In addition, a range of catalysts was screened for the potential to further improve the reaction rate. $ZrCl_4$ and, in particular, $ZrCp_2Cl_2$ were found to be suitable catalysts for the transformation. Reaction in toluene at 110 °C with 5 mol % of $ZrCl_4$ demonstrated a 6-fold increase in conversion when compared to the reaction without catalyst. A range of substrates was tested using these systems, and the reactions were shown to proceed in high yield with good functional group tolerance, and in the case of chiral substrates, no racemization was observed. Anilines and benzoic acid derivatives displayed limited reactivity in this system, and required the use of the more active catalyst, $ZrCp_2Cl_2$ (*Chem. Commun.* **2012**, *48*, 666−668).



In a similar manner, Lundberg et al. exploited the use of $ZrCl_4$ to accelerate this transformation. Again, good functional group tolerance was observed, with no racemization. This system typically employed 2−10 mol % of the catalyst at 70 °C with added 4 Å molecular sieves. A range of solvents was shown to be effective, with THF being the preferred solvent. Again, aromatic acids proved to be problematic, and the reaction showed some sensitivity towards sterically hindered substrates. Increasing the temperature to 100 °C for these more

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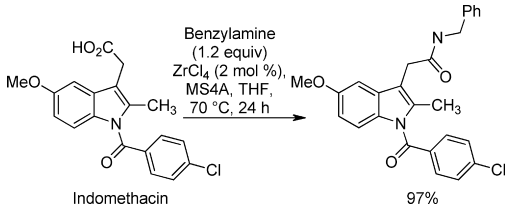
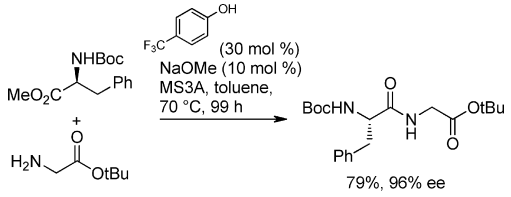
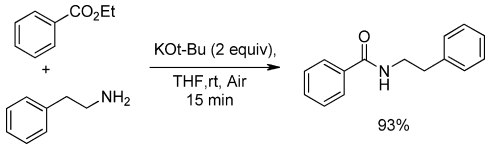
difficult substrates increased the yield (*Chem.—Eur. J.* **2012**, *18*, 3822−3826).



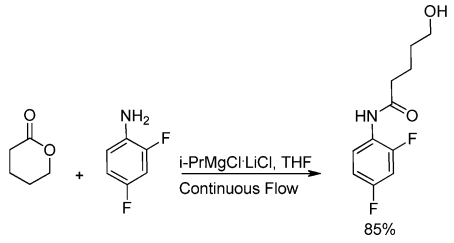
Direct amidation of esters under mild conditions also represents an attractive transformation from an environmental perspective. Ohshima and co-workers have screened a range of catalysts for this transformation, and found that sodium methoxide is a highly effective catalyst for the reaction. A range of solvents under strictly anhydrous conditions could be utilized with 5 mol % of catalyst at 50 °C for good conversions to be obtained. Steric bulk of the ester was shown to be important with only trace amounts of product being observed with *tert*-butyl esters. For chiral substrates, it was found that these conditions resulted in complete epimerization. However, this could be avoided by addition of an acidic alcohol such as 2,2,2-trifluoroethanol or various phenols to modulate the basicity of sodium methoxide. Increased acidity of the added alcohol increased the enantiomeric excess of the product, but also decreased the yield, and so it was critical to balance these two factors (*Chem.—Eur. J.* **2012**, *18*, 5434−5436).



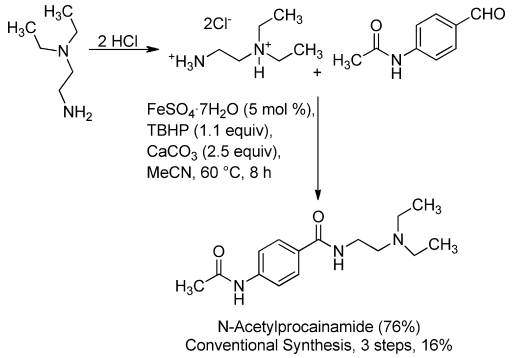
Kim and co-workers reported on a similar transformation using potassium *tert*-butoxide to mediate the amidation of esters. In this study, 2 equiv of potassium *tert*-butoxide were employed with technical grade THF (0.2% H_2O) shown to be the solvent of choice. Carrying out the reaction under water-free or oxygen-free conditions led to a shutdown in the reaction pathway, although excess water also proved to be problematic owing to competing ester hydrolysis. Ethyl esters were shown to be the optimal substrates, and a range of examples is provided. Functional group tolerance proved to be a problem with some substrates, and the reaction was proposed to proceed via a radical-based mechanism (*Synthesis* **2012**, *44*, 42−50).



Muñoz et al. have reported on the amidation of esters mediated by isopropylmagnesium chloride under continuous flow conditions. The Bodroux reaction has been known since the 1950s, although its use has been limited due to a lack of systematic study of the scope and limitations of the reaction as well as the high reactivity of Grignard reagents potentially compromising the reaction selectivity. The current study adapts this reaction to flow conditions using two microreactors. Initially, the amine and Grignard reagent are mixed to generate the magnesium amide, which is combined with the ester in a second reactor. The optimized conditions use THF as solvent at room temperature with a reagent ratio of 1:1.5:3 (ester/amine/Grignard reagent) and residence times of 6 and 14 min. A wide range of examples is provided, showing excellent functional group compatibility and several selectivity advantages over the corresponding batch processes (*Green Chem.* **2012**, *14*, 1355−1341).



Ghosh and co-workers have developed a promising method and described the oxidative amidation of aldehydes with amine salts that uses relatively inexpensive and easily accessible iron compounds as catalysts. The optimized conditions utilized iron sulfate as the catalyst (5 mol %), T-Hydro (70% aqueous *tert*-butyl hydroperoxide) as the stoichiometric oxidant, and calcium carbonate as the base with acetonitrile as the solvent. The use of the weak base proved to be critical in slowly releasing the free amine from the salt form. The reactions were carried out at 60 °C with good yields being obtained typically after 6 h reaction times. A wide substrate scope was demonstrated for both secondary and tertiary amides, and amino acids were shown to couple without detectable racemization. The in situ formation of amine salts was developed to extend the substrate scope of the reaction. The reaction is proposed to proceed through initial hemi-aminal formation, which is oxidized by TBHP via an iron-catalyzed oxidation occurring through a free radical mechanism to the desired amides (*Adv. Synth. Catal.* **2012**, *354*, 1407−1412).



4. OXIDATIONS

Four reviews of note on green oxidations were published during the first half of 2012. Shi et al. authored a comprehensive review of the past 5 years of transition metal-catalyzed oxidations using molecular oxygen, with a focus on new areas of oxidation research such as oxidative Heck reactions, coupling reactions via oxidative dehydrogenation and free radical reactions (*Chem. Soc. Rev.* **2012**, *41*, 3381−3430).

Parmeggiani and Cardona reviewed the literature of the past 15 years on aerobic oxidations of alcohols to the corresponding

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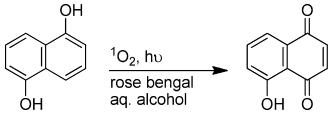
carbonyl compounds using transition metal catalysis, focusing on homogeneous and heterogeneous (primarily nanoparticle) reactions involving Cu, Pd, Ru, Au, Fe, V, Ir, Co, and Os. Alternative solvents for these transformations were also discussed, including ionic liquids, fluorous solvents, water, and supercritical CO_2, as well as solvent-free conditions. The authors identified which methods are optimal for a particular type of substrate and compared methods regarding reactivity and selectivity where possible. The authors concluded by noting that most of these reactions have been developed on simple alcohols and studies with more complex and functionalized substrates need to be investigated to render these protocols synthetically useful (*Green Chem.* **2012**, *14*, 547−564).

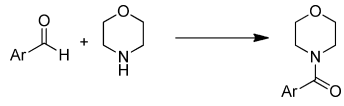
Della Pina et al. provided an overview of oxidations employing gold catalysis published within the past 3 years, including oxidations of hydrocarbons (alkanes, benzylic, alkenes), phenols, alcohols, sugars, carbonyl compounds, and amines. The article concludes with a brief but insightful section on mechanistic studies, including recent experimental and theoretical studies on the mode of adsorption and activation of oxygen on the metal surface, and the nature of the active catalytic species (*Chem. Soc. Rev* **2012**, *41*, 350−369).

Campbell and Stahl reviewed research from the Stahl laboratories regarding Pd- and Cu-mediated site-selective C−H oxidations using oxygen as the stoichiometric oxidant. While many transition metal-mediated oxidations require stoichiometric metal or organic oxidants, the Stahl group has designed and developed reactions using only molecular oxygen as the stoichiometric oxidant with catalytic quantities of metals. Reactions covered in this review include allylic C−H acetoxylation, oxidative coupling of arenes without directing groups, dehydrogenation of cyclohexanones to phenols, and Cu(II)-catalyzed C−H oxidation. The critical role of ligands in promoting reactivity and selectivity is a key part of each section, and preliminary mechanistic pathways for the role of the ligands are discussed (*Acc. Chem. Res.* **2012**, *45*, 851−862).

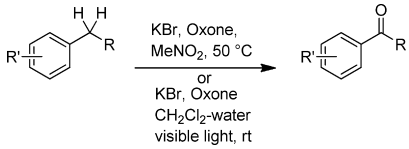
Using light as an energy source and avoiding the use of hazardous reagents, dye-sensitized photooxidation is an attractive green oxidation methodology. Sun et al. described the use of iridium complexes for visible light photooxidation of 1,5-dihydroxynaphthalene to 5-hydroxy-1,4-napthoquinone (*Chem. Commun.* **2012**, *48*, 4169−4171). In combination with continuous processing, these transformations are now becoming more practical and scalable. The same transformation was reported by Yavorskyy et al. using a bubble column reactor with rose bengal as sensitizer. Several other singlet oxygen photooxidations were also studied by this group to demonstrate the scope of the method in their flow apparatus (*Green Chem.* **2012**, *14*, 888−892).



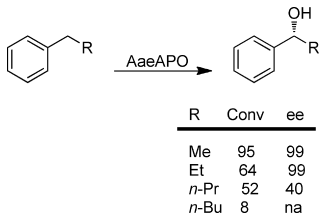
Liu and Jensen describe a continuous flow microreactor for a metal-free oxidative amidation of aromatic aldehydes with secondary amines (4−10 equiv) in acetonitrile or *t*-BuOH as solvent using 30% aq hydrogen peroxide as the sole reagent. Given the ease of changing reaction parameters in a flow system, each reaction pair was optimized with respect to reaction time, concentration, and temperature, with yields typically in the 80−90% range. The carboxylic acid was the main byproduct (5−10%). Amino acid esters provided good yields with no racemization (*Green Chem.* **2012**, *14*, 1471−1474).



Moriyama et al. described a metal-free benzylic oxidation of alkylarenes using KBr and oxone under either thermal or photochemical conditions. They proposed the reaction proceeds initially via oxidation of KBr to generate a bromide radical, which then initiates hydrogen atom abstraction from the benzylic position, generating a benzyl radical. In the thermal reaction, the radical is further oxidized to the cation which reacts with oxone to produce the peroxysulfate intermediate followed by β-cleavage to afford the ketone. In contrast, the photochemical reaction is thought to proceed via the α,α-dibromo intermediate which is hydrolyzed to the ketone. The authors have demonstrated the method on a variety of functionalized arenes (*Org. Lett.* **2012**, *14*, 2414−2417).



Biocatalytic oxidations have not played as important a role in synthetic chemistry as biocatalytic reductions or hydrolytic reactions, but it is an area of active research and growing viability. Kluge et al. reported stereoselective benzylic hydroxylations of alkylbenzenes using the extracellular *Agrocybe aegerita* peroxygenase that operates by transferring oxygen to substrates via peroxide. Best results were obtained with ethyl and propylbenzene, while the longer-chain substrates gave lower conversion and ee. The production of (*R*)-1-phenylethanol was optimized in a fed-batch reactor, achieving a turnover number of 43000 (*Green Chem.* **2012**, *14*, 440−446).



R	Conv	ee
Me	95	99
Et	64	99
n-Pr	52	40
n-Bu	8	na

5. ASYMMETRIC HYDROGENATIONS

Asymmetric hydrogenations are one of the most important transformations to access chirally pure synthetically and medicinally useful materials. In general, several metals (e.g., Ir, Rh, etc.) have been used in combination with chiral ligands for this purpose. Recently, Patureay et al. have developed neutral complexes of PN-S-N types. In particular, phosphorylated sulfonimidamides (SIAPhos) take part in ion exchange with cationic complexes, $[Rh(cod)_2BF_4]$ and $[Ir(cod)_2BarF]$, or neutral complexes $[Rh(cod)Cl]_2$ and $[Ir(cod)Cl]_2$ affording PN-S-N chelates. The resulting iridium complexes performed well in asymmetric hydrogenation reactions of tri- and tetra-substituted enamides to afford products in 55−98% yield with enantioselectivities ranging between 70 and 92% ee. This is the best combination of yield and ee reported for asymmetric hydrogenation of such challenging olefins by using catalytic amounts of neutral complexes (*Adv. Synth. Catal.* **2012**, *354*, 59−64).

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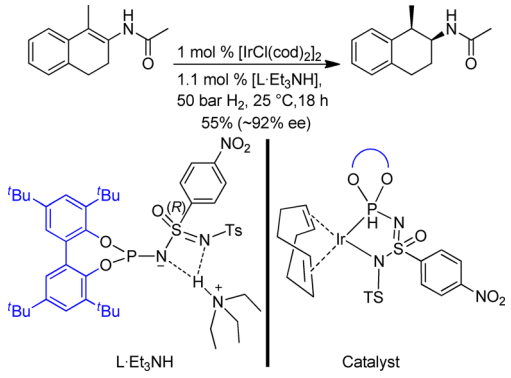
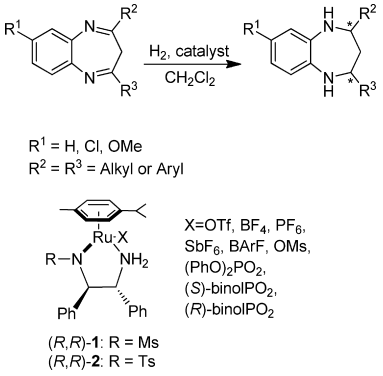
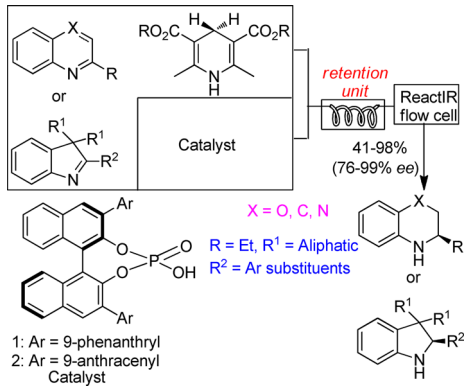


Ding et al. developed a highly enantioselective hydrogenation of 2,4-disubstituted-1,5-benzodiazepines employing chiral cationic ruthenium diamine catalysts. Interestingly, both enantiomers of 2,4-diaryl-2,3,4,5 tetrahydro-1*H*-benzodiazepine derivatives can be accessed by using the same chirality in the ligand with different nonchiral counterions. Further modification in the ligand by varying the *N*-substitution (Ms to Ts) allowed access to greater than 98% ee of a single enantiomer, regardless of any chiral or nonchiral counterions used, although some erosion of diastereoselectivity was observed between different counterions. Interestingly, this strategy allows access to both enantiomers without changing the chiral components of the catalyst adding green features to the strategy (*Angew. Chem., Int. Ed.* **2012**, *51*, 5706−5710).

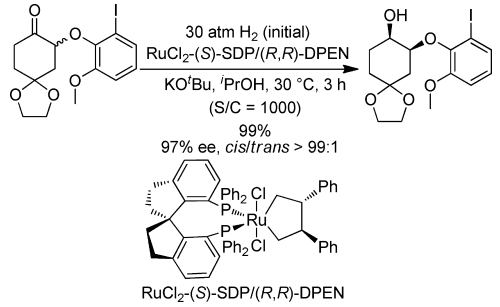


Microreactor technology has been viewed as one of the most important process tools amenable to complement scale-up strategies. Rueping et al. have elegantly demonstrated the potential application of a FTIR-enabled microreactor in asymmetric continuous flow hydrogenations of several hetereocyles, i.e. benzoxazines, quinolines, quinoxalines, and 3*H*-indoles in high yields and excellent enantioselectivities in many cases. The continuous way of conducting chemistry in combination with real-time flow optimization led to the development of a robust process which is considered to be green due to increased reaction control, increased process safety, and a shorter developmental cycle (*Beilstein J. Org. Chem.* **2012**, *8*, 300−307).

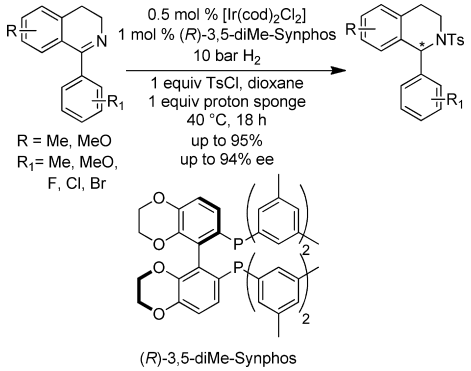
Chen et al. have developed an efficient ruthenium-catalyzed asymmetric hydrogenation of racemic α-aryloxy cyclohexanones based on the dynamic kinetic resolution (DKR) concept, producing chiral β-aryloxy cycloalkanols in excellent enantioselectivities. This provided direct access to an advanced intermediate for the synthesis of medicinally relevant alkaloids. The chiral ruthenium catalyst $RuCl_2$-(*S*)-SDP/(*R*,*R*)-DPEN was used for hydrogenation of aryloxy cyclic ketones to afford



chiral β-aryloxy cyclohexanol in high yields (99%), excellent enantio- (97% ee) and *cis*-selectivities (*cis*/*trans* > 99:1) (*Org. Lett.* **2012**, *14*, 2714−2717).



(*R*)-3,5-diMe-Synphos has been shown to be an efficient ligand for the Ir-catalyzed asymmetric hydrogenation of extremely challenging dihydroisoquinoline derivatives. Berhal et al. have demonstrated, in addition to model substrates, the synthesis of pharmaceutically relevant chiral 1-aryl-ThIQ compounds in high yields and enantioselectivities. *N*-activation with a Ts group provides an extra coordinating group which is critical to achieve high conversion and selectivity, whereas the Proton sponge is employed to avoid the formation of detosylated product (*Org. Lett.* **2012**, *14*, 3308−3311).



Pignataro et al. have devised a library approach to the development of BenzaPhos analogues as highly efficient chiral supramolecular ligands in combination with Rh for asymmetric hydrogenations. This method was amenable to high-throughput screening and robust ligand optimization by conveniently varying the benzamide group in the ligands. The extraordinary stereocontrol (>99% ee) achieved was due to presence of a functional group in the ligand system capable of exerting a substrate orientating effect. *In silico* and experimental studies suggest that preferred orientation of the substrate takes place in

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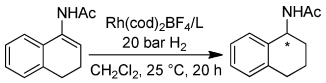
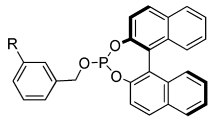
the catalytic cycle by formation of a hydrogen bond between the amide oxygen and hydrogen atoms of the ligand and substrate, respectively (*Chem.—Eur. J.* **2012**, *18*, 10368−10381).



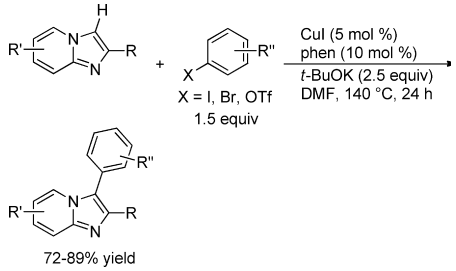
Ligand(L)	Conv.(%)	ee (abs. conf.)
1	100	97, (*R*)
2	100	98, (*R*)
3	100	98, (*R*)



L: R = 1: -NHCOPh; 2: -CH_2NHCOPh
3: -CH_2CH_2NHCOPh

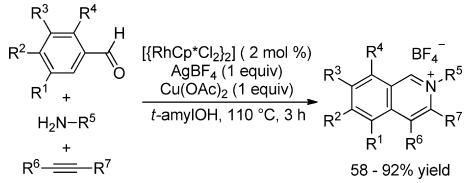
6. C−H ACTIVATION

Cao et al. have developed a copper-catalyzed C-3 arylation of imidazo[1,2-*a*]pyridine derivatives. A combination of 5 mol % CuI, 10 mol % 1,10-phenanthroline, and 2.5 equiv of *t*-BuOK at 140 °C for 24 h promoted the cross-coupling in 72−89% yield. The authors demonstrated that sterically hindered and electronically diverse aryl iodides react well, and they provided several examples that use aryl bromides and aryl triflates. In all cases the aryl halide component is used in excess (1.5 equiv). The authors also showed that substituted imidazo[1,2-*a*]-pyridines can be used (*Org. Lett.* **2012**, *14*, 1688−1691).

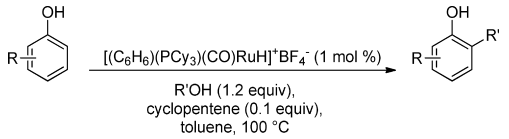


A three-component coupling of benzaldehydes, amines, and alkynes was developed to provide rapid access to isoquinolinium salts. The reaction was catalyzed by 2 mol % [{RhCp*Cl_2}$_2$], 1 equiv of Cu(OAc)$_2$, and 1 equiv of $AgBF_4$ in *tert*-amyl alcohol at 110 °C for 3 h. Cu(OAc)$_2$ was required as the terminal oxidant, while $AgBF_4$ served a dual role of generating the catalytically active cationic rhodium complex and providing an inert counterion for isoquinolinium salt isolation. The authors systematically varied each component to determine the reaction scope. Benzaldehydes with electron-donating substituents provided the highest yields. Notably, the reaction demonstrated ∼11:1 regioselectivity for the C−H arylation of meta-substituted benzaldehydes. Both symmetrical and asymmetrical alkynes worked well, with the latter producing a single regioisomeric product. In addition, alkyl and aryl amines provided comparable results. The authors demonstrated the utility of the method through the synthesis of the isoquinoline alkaloid oxychelerythrine (*Angew. Chem., Int. Ed.* **2012**, *51*, 197−200).

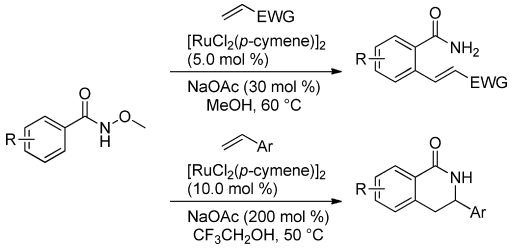
Li et al. have demonstrated a selective dehydrative C−H alkylation of phenols at the ortho position with water as the only byproduct. The transformation worked well with both secondary and primary alcohols, and the primary examples resulted exclusively in the linear alkylation product utilizing 1 mol % of the ruthenium hydride complex. A methoxy group at the meta position promoted the coupling, whereas chloride required a longer reaction time. Yields of 67−95% were realized



in a 6−12 h reaction time for these substrates. Cyclic alcohols resulted in C−H alkenylation products via an alkylation and subsequent dehydrogenation sequence in the presence of excess cyclopentene. Finally, the synthesis of benzofurans was realized by reacting phenols with 1,2-diols under the same reaction conditions. All reactions were performed in a glovebox with the use of Schlenk techniques. Overall, a very effective method requiring low catalyst loading and inexpensive reagents resulting in the formation of water and cyclopentane as the only side products has been developed (*J. Am. Chem. Soc.* **2012**, *134*, 7325−7328).



The use of a methoxyamide to serve as an oxidizing and directing group to form ortho-substituted benzamides from alkenes has been developed by Li et al. utilizing a ruthenium catalyst. All reactions were performed under an argon atmosphere utilizing Schlenk techniques. Para-substituted starting materials were very tolerant of electron-rich and electron-poor functionality, generating very good *E*-selectivity upon reaction with various acrylates where yields ranged from 45−95%. Good selectivity was also observed with reactions for meta-substituted benzamides driven by sterics with the exception of electron-donating groups, which resulted in a mix of the two ortho isomers. When styrenes were utilized in the presence of 2,2,2-trifluoroethanol, the corresponding dihydroisoquinolinones were generated in 47−87% yield. This reaction was also tolerant of donating and withdrawing groups and functionality at the para position on the styrene aryl group, although strained alkenes gave very poor yields under these reaction conditions. For all cases at least 1.8 equiv of the alkene is required (*Org. Lett.* **2012**, *14*, 736−739).



7. GREENER FLUORINATION

Bi et al. reported a highly efficient approach to α-monofluoro acetoacetamides. The process is carried out with Selectfluor in PEG-400 and results in monofluorination with remarkable selectivity. The reported conversions are quantitative in all cases, regardless of the electronic nature of the various substituents, and the ratio of mono- to difluorinated products is greater than 30:1.

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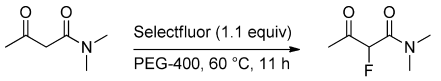
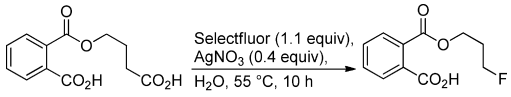
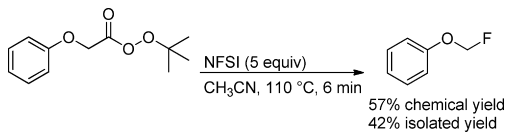
Additional benefits include the absence of base or metal catalyst, and a straightforward isolation and purification by simple crystallization or evaporation. The generality of the methodology was demonstrated on a wide range of acetoacetamides (primary, secondary, alkyl, and aromatic). The operational simplicity, the overall process mass intensity, and sustainability make the reported process a very appealing option for this challenging transformation and should find some resonance in other areas (*Green Chem.* **2012**, *14*, 1159−1162).



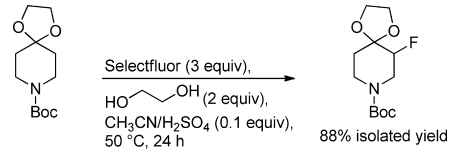
Yin et al. described a novel silver-catalyzed decarboxylative fluorination of aliphatic carboxylic acids using Selectfluor and $AgNO_3$ as the catalyst. The new methodology describes an efficient and remarkable approach for site-specific C(sp^3)−F bond formation that could thus far not be conducted in a practical way. The difference in reactivity of carboxylic acids (tertiary > secondary > primary ≫ aromatic) allows for a valuable handle for further selectivity and successful implementation of chemoselective fluorodecarboxylation. The ready availability and low cost of the fluorine reagent and catalyst, the mild experimental conditions, the remarkable chemoselectivity, and the wide functional group compatibility render this new radical fluorination method of practical value in the synthesis of fluorinated molecules (*J. Am. Chem. Soc.* **20012**, *134*, 10401−10404).



A radical-based methodology for fluorine transfer to alkyl radicals, complementary to the more classical use of anionic or cationic fluoride sources was reported by Rueda-Becerril et al. In their paper, the authors described the first example of fluorine transfer from *N*-fluorobenzenesulfonimide (NFSI) via decarboxylative radical fluorination onto peroxides. The methodology is still at its infancy as it requires suboptimal conditions, but the approach is applicable to a broad range of alkyl radicals, including tertiary, benzylic, and heteroaromatic stabilized radicals. Furthermore, the compatibility of functional groups could allow for rapid expansion of the scope and the utility of the reaction as a complementary tool vs better understood ionic fluorination processes (*J. Am. Chem. Soc.* **2012**, *134*, 4026−4029).



A remarkable acid-catalyzed rate acceleration on the electrophilic fluorination of enols derived from ketones, ketals, and enamides was reported by Liu et al. The authors demonstrated the kinetic effect of catalytic sulfuric acid used with Selectfluor. Methanol, acetonitrile, and even sulfuric acid, when compatible with the reactants, were shown to be the best solvents for the reaction. The reaction appears to proceed in a way analogous to that of acid-catalyzed enol formation and occurs in good yields with excellent selectivity for the formation of the monofluorinated products. Enamides could also be fluorinated using Selectfluor, although the greater nucleophilic character of these compounds is such that catalytic sulfuric acid is not required (*Tetrahedron Lett.* **2012**, *53*, 2971−2975).

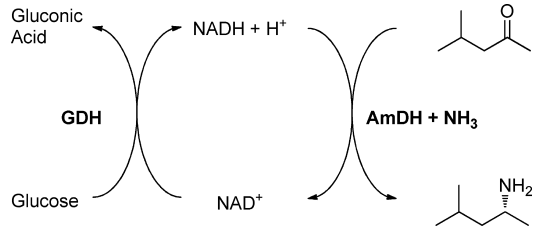


McPake and Sanford published a review highlighting selective continuous processes using fluorine gas. The combination of flow chemistry to address both the high exotherm inherent to the direct fluorination (−430 kJ mol^{-1} for the replacement of hydrogen bonded to sp^3 carbon) and the difficulty in handling fluorine gas, rarely used directly for the manufacture of chemical products, are described. The use of flow chemistry provides a valuable option for the potential manufacture of fluorinated derivatives by atom-efficient and inexpensive processes. A section on the use of fluorine as an oxidizing agent exemplifies the remarkable versatility and efficiency of fluorine gas used in flow regime (*Org. Process Res. Dev* **2012**, *16*, 844−851).

8. BIOCATALYSIS

Alcohol dehydrogenases comprise one of the most popular enzyme classes used in biotransformations. In order to be viable at large scale these processes require a cofactor recycling system, and typically isopropyl alcohol (IPA) is used as this avoids the use of a second enzyme. However, as the IPA is oxidized to acetone, a thermodynamic equilibrium is established between all four components: substrate, product, IPA, and acetone. This equilibrium determines the maximum conversion to product and is independent of catalyst or kinetics. To circumvent this problem, Calvin et al. have reported the removal of acetone by distillation, thus shifting the equilibrium and maximising conversion (*Org. Process Res. Dev* **2012**, *16*, 82−86).

Enzymatic routes using transaminases provide a method of chiral amine synthesis, but this requires the use of a sacrificial amine source. This gives an undesired ketone byproduct which must then be removed in order to shift the reaction equilibrium beyond ∼50% conversion. Abrahamson et al. report the development of an amine dehydrogenase (AmDH) to circumvent this issue. Starting from the wild-type leucine dehydrogenase, several rounds of site-specific protein engineering create the amine dehydrogenase, inverting the enzyme's specificity. The enantioselectivity of the wild-type is maintained and gives (*R*)-1,3-dimethylbenzylamine in 93% and 99.8% ee (*Angew. Chem., Int. Ed.* **2012**, *51*, 3969−3972).



Simon et al. have reported the use of transaminases for the regio- and stereoselective monoamination of diketones. Using alanine as the amine donor, a range of diketones was aminated

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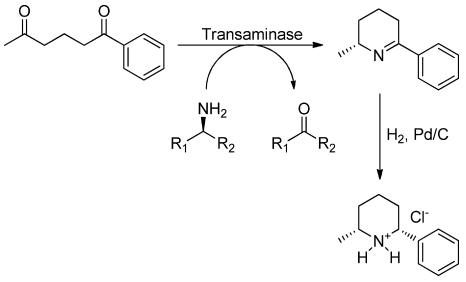
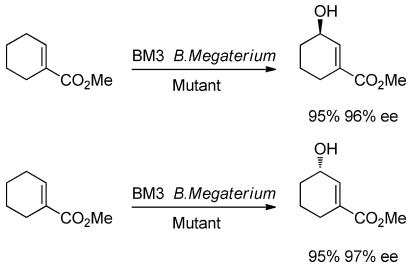
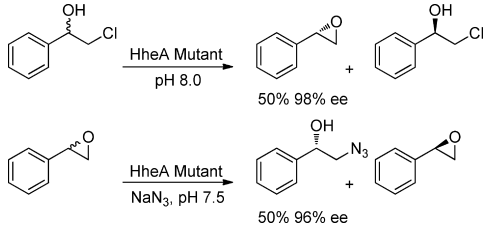


and then spontaneously cyclized to form chiral dihydropiperidines. The second chiral centre could then be introduced via hydrogenation. A range of 2,6-disubstituted piperidines was produced in very good yield and near-perfect enantio- and diastereoselectivity by a range of ω-transaminases (*Angew. Chem., Int. Ed.* **2012**, *51*, 6713−6716).

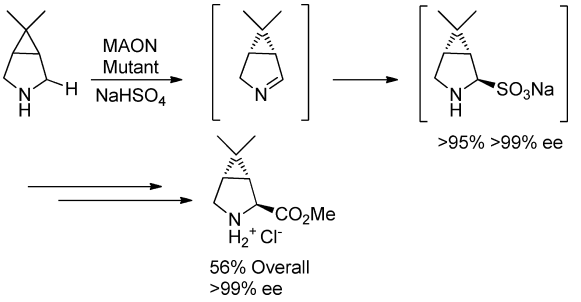
Regio- and stereoselective oxidative C−H activation is a current challenge in synthetic organic chemistry. Agudo et al. reported the regio- and stereoselective hydroxylation of substituted cyclohexene and pentene substrates catalyzed by an evolved cytochrome P450-BM3 from *Bacillus megaterium*. By use of iterative saturation mutagenesis libraries in the form of a combinatorial active-site saturation test (CAST) both (*R*)- and (*S*)-selective mutants were evolved with >90% ee and >95% conversion (*ChemBioChem* **2012**, *13*, 1465−1473).



Synthesis of epoxides is possible enzymatically by the use of halohydrin dehalogenases which catalyze the reverse reaction of epoxide opening with halogens. Tang et al. reported the use of an evolved halohydrin dehalogenase from *Arthrobacter* sp. strain AD2 (HheA) for the kinetic resolution of both 2-chloro-1-phenylethanol and styrene oxide. Saturation mutagenesis produced a mutant capable of resolving 2-chloro-1-phenylethanol in 50% yield and 98% ee (*Appl. Environ. Microbiol.* **2012**, *78*, 2631−2637).



Imine preparation by amine oxidation is desirable as a synthetic tool as it opens opportunities for C−C bond formation. Li et al. reported a manufacturing process of an intermediate towards boceprevir based upon imine formation catalyzed by a mutant monoamine oxidase (MAO). Initially, a collection of monoamine oxidases was screened to find candidates for enzyme optimization. A number of rounds of evolution consisting of mutagenesis using error-prone PCR and gene shuffling techniques improved both the enzyme activity (8- fold increase compared to that of wild type) and stability (stable at 50 °C). The imine product of the oxidation was volatile and a strong inhibitor of MAO. As a result, it was converted in situ into the corresponding bisulfite adduct in >95% solution yield and >99% ee on 65-g scale. The bisulfite adduct was then converted into the desired methyl ester in 56% isolated yield and >99% ee in a telescoped process (*J. Am. Chem. Soc.* **2007**, *134*, 6467−6472).



Balke et al. have reviewed the discovery, application, and protein engineering of Baeyer−Villiger monooxygenases (BVMO) in organic synthesis. The number of these enzymes used in recent years has increased, and tools have been developed to overcome factors limiting their use. This has led in turn to the first large-scale applications of BVMO (*Org. Biomol. Chem.* **2012**, *10*, 6249−6265).

The first half of 2012 saw the publication of a useful book for chemists interested in enzymatic transformations, *Practical Methods for Biocatalysis and Biotransformations*; Wiley: New York, 2012; Vol. 2 (Whittall, J. and Sutton, P., Eds.). *Practical Methods 2* focuses on the applications of enzymes and strains of microorganisms with up-to-date protocols and industry examples to describe the function of biocatalysts in cutting-edge applications. The second volume can be used on its own or in combination with the first volume and concentrates on new techniques and new enzyme families that have been reported since the first volume.

9. REDUCTIONS

Two methods for the reduction of imines to amine were reported. The first procedure, from the laboratory of Matthias Beller, features hydrogenation of imines using 5 mol % zinc triflate, 80 bar H_2 pressure in toluene at 120 °C. A variety of substituent classes, including halogens and other heterocycles, were tolerated and delivered the product amines in good yields. Unfortunately, *N*-benzylic and *N*-aliphatic imines did not react under these conditions.

Also reported in this paper is the reductive hydroamination of alkynes, again forming substituted amines as the product. A survey of various metal catalysts identified zinc triflate as the best catalyst for this transformation. As with the previous example, high temperature and high hydrogen pressure are required; however, a wide variety of alkyl- and aryl-substituted alkynes reacted with aryl amines, including secondary aryl amines, to form the amine product in yields often in excess of 70%. Similar functional group tolerability was observed.

While the conditions for both transformations still require high pressure and temperature, this procedure does not require precious metals or ligands, is operationally simple, and produces the desired products cleanly and in good yields (*ChemSusChem* **2012**, *5*, 777−782).

Imine reduction that uses a hydrosilation strategy was also reported by Bin Li et al. Reaction of various imines with 2 equiv

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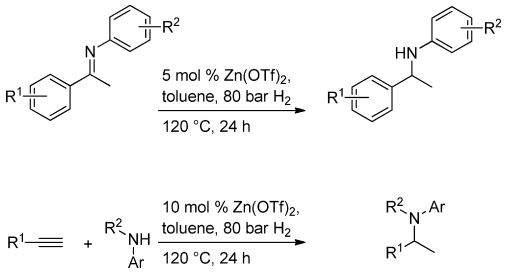
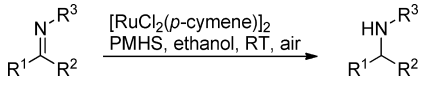
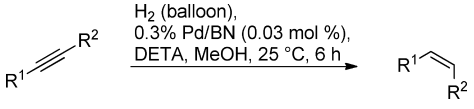


of polymethylhydroxysilane (PMHS) catalyzed by 1−2 mol % $[RuCl_2(p\text{-cymene})]_2$ in ethanol gave the amine products in high yields, under mild conditions. These reactions were even stable to run under air and, more significantly, did not require a further desilylation step. The reaction was tolerant of other reducible functions such as nitro, ketone, ester, and olefin substituents, as well as disubstituted imines. However, in the case of disubstituted and some bulky monosubstituted imines, 2 mol % of the catalyst and elevated temperatures were required (*ChemSusChem* **2012**, *5*, 396−399).

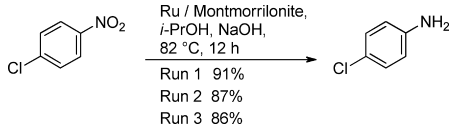


Semireduction of alkynes represents a powerful method for entry into *cis*-olefin compounds. The most common approach is through hydrogenation over a heterogeneous Pd catalyst, typically Lindlar's catalyst: $Pd/CaCO_3$ poisoned with $Pb(OAc)_2$. However, this approach has several disadvantages, primarily in the use of $Pb(OAc)_2$ in catalyst preparation but also in frequent over-reduction of primary alkynes to alkanes. A solution to these issues was provided by Yabe et al. Their approach was to support palladium on solid boron nitride (a crystalline, inert, and benign powder), the hypothesis being that the lone pairs of the nitrogen atoms of the boron nitride would act to reduce catalytic activity. By simply stirring a suspension of boron nitride and $Pd(OAc)_2$ in methanol for 5 days, the isolated powder had consistent and homogeneous Pd distribution of approximately 0.3 wt % and was useful in hydrogenation reactions at room temperature, with 1 atm H_2.

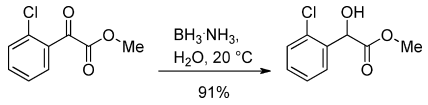
This powder itself was prone to over-reduction of the alkynes, which required an amine additive, diethylenetriamine (DETA), to further attenuate reactivity and give the desired reduction product. The optimized conditions used 0.5−1.3 equiv of DETA, 0.3 wt % Pd/BN powder (0.03 mol % Pd) in methanol at room temperature, and H_2 gas introduced using a balloon. This reaction is extremely tolerant of other functional groups, even reducible groups such as nitro, CBz, and benzyl groups, and workup is simple. The catalyst is removed by filtration and can be reused as many as three times without any erosion in yield or selectivity (although 2.2% Pd leaching was reported after the first use) (*Adv. Synth. Catal.* **2012**, *354*, 1264−1268).



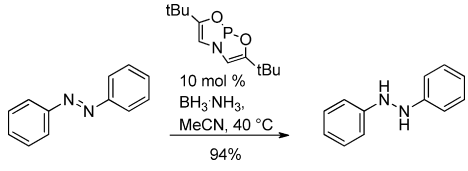
Methods for the reduction of nitro groups continue to be of wide interest. Increased functional group tolerance is a key driver as illustrated by the report from Sarmah and Dutta who have used ruthenium nanoparticles (5 nm) supported on montmorillonite clay to catalyze hydrogen transfer from isopropanol. The ruthenium nanoparticles were prepared by reduction of pre-impregnated $RuCl_3$ by ethylene glycol and were subject to extensive solid-state characterization both before and after reaction. A range of substituents was tolerated including halogen, phenol, and aniline, and catalyst recycling was demonstrated. Improvements are needed however for this to be a viable industrial process as catalyst loadings are currently too high (~10% Ru), and reactions were only run at 0.01 M relative to substrate (*Green Chem.* **2012**, *14*, 1086−1093).



Borane−ammonia complex is under investigation as a system for hydrogen storage, reflecting its ability to release most of its high % weight hydrogen as hydrogen gas. Shi et al. have used borane−ammonia to reduce aldehydes and ketones in neat water in good yield and with good selectivity. Most reactions were conducted at ambient temperature and with good functional tolerance. The reaction of both α- and β-ketoesters led to the corresponding hydroxyester in 86−92% yield, and over-reduction to the 1,2-diol could be avoided by simple temperature control unlike the reaction using sodium borohydride (*Green Chem.* **2012**, *14*, 1372−1375).



There is always interest in avoiding the use of heavy metals in processing. Dunn et al. have also used borane−ammonia as a hydrogen donor in the presence of catalytic amounts of a planar phosphorous compound. Intramolecular arrangements of boranes and phosphines have previously been demonstrated as components in frustrated ion pair species offering potential as catalytic reductants. This work is conceptually different in that it involves 2-electron redox catalysis at the phosphorous center, and only a few examples of this reactivity have been reported previously. Only one reduction example is presented in the paper, and while reduction of azobenzene to the corresponding hydrazine is not of general interest to pharma, it does highlight the potential for such metal-free systems to be viable for other more interesting reductions. Borane−ammonia itself was not capable of performing the reduction. Other phosphorous species (e.g., PPh_3, $(Me_2N)_3P$) were less reactive, giving low conversions requiring stoichiometric loading and higher reaction temperature, suggesting there is some scope for optimization and application to a broader range of reactions (*J. Am. Chem. Soc* **2012**, *134*, 11330−11333).



Solvents such as dipolar aprotics are extremely useful, but legislation such as Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) in the EU is likely to restrict their availability in the future. Hence, it is always interesting to see alternative reaction media that may offer alternatives. Deep eutectic salts differ from ionic liquids in that

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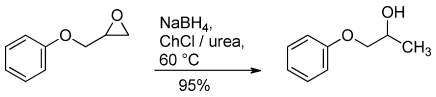
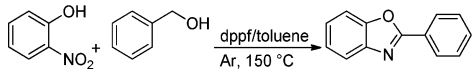
they combine complexing a quaternary ammonium halide with a hydrogen bond donor. In the case of Azizi et al., choline chloride/urea was used as a solvent for the reduction of epoxides and carbonyl compounds. They were able to demonstrate that sodium borohydride could reductively open epoxides in the absence of added Lewis acids. Regioselectivity showed a preference for opening at the least substituted center, and reactivity followed the order aldehyde > epoxide > imine with the ability to chemoselectively reduce an aldehyde in the presence of an epoxide. While there was still a need to use an organic solvent to extract product from a water quench, there was some effort to consider scale up, and reactions were run at 4 M concentration (*RSC Adv.* **2012**, *2*, 2289−2293).

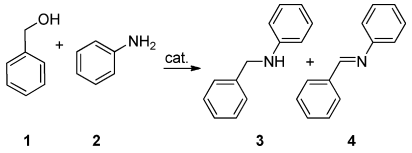


10. ALCOHOL ACTIVATION FOR NUCLEOPHILIC DISPLACEMENT

Wu et al. report direct access to 2-arylbenzoxazoles via an iron-catalyzed coupling of benzylic alcohols with *o*-nitrophenols in toluene at 150 °C under argon. Optimization of reaction conditions revealed dppf [1,1′-bis(diphenylphosphino)-ferrocene] and toluene as the catalyst and solvent of choice, respectively. Reaction under air gave a 75% yield of the model reaction product vs 89% under argon, indicating that a N_2 atmosphere should also work well. No mention was made of gas pressurization of head space, and reactions were performed in sealed vessels. This method delivered good yields for variously substituted aryl components of both starting materials, including electron withdrawing and donating in any position; 2- and 3-pyridine-methanol also coupled well. 2-Aminophenol gave a poor yield, indicating the function of the nitro group as an acceptor in the redox hydrogen transfer mechanism (*Org. Lett.* **2012**, *14*, 2722−2725).

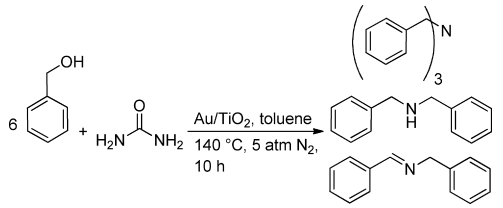


N-Alkylation of amines with alcohols was effected by Sun et al. utilizing a Ni−Cu nanoparticle catalyst on alumina and optimized through inclusion of $CaCl_2$ and NaOH in boiling *o*-xylene. The optimum reaction time was considered 12 h, as an increase to 18 h provided very minimal improvement of the ratio of 3:4 in the model reaction. Candidates for alcohol **1** included variously para-substituted benzyl alcohols as well as primary and secondary aliphatic examples. Examples of reactant **2** included aniline, benzylamine, *N*-cyclohexylamine, and 2-aminopyridine. All reactions showed good conversion with typically a good ratio of amine over imine product (*Catal. Commun.* **2012**, *24*, 30−33).

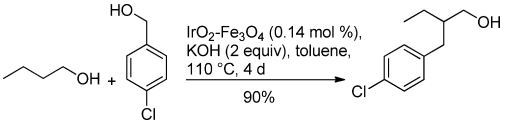


Commercially available Au/TiO_2 catalyst was employed by Zotova et al. to perform *N*-alkylation chemistry with alcohols in toluene at high pressure and temperature in a flow reactor apparatus. Optimum conditions for the model reaction were determined to be 50 bar nitrogen at 180 °C with 0.9 mol % catalyst loading providing a ratio of better than 97:2 for **3** vs **4** with <1% benzaldehyde byproduct, much better than realized at lower pressure in boiling toluene as a batch reaction. Low catalyst loading also provided better selectivity than higher amounts of catalyst in the flow reactor procedure. Examples including aliphatic and aromatic primary and secondary alcohols and primary amines typically gave good conversion with excellent selectivity. Exclusion of moisture and active drying of the flow stream revealed an associated dramatic decrease in catalyst activity and reaction selectivity (*Green Chem.* **2012**, *14*, 226−232).

A procedure to produce secondary and tertiary amines from alcohols and urea utilizing Au/TiO_2 catalyst was presented by He et al. The use of urea as a feedstock is preferable over ammonia, considering handling issues and cost. The model stoichiometric reaction provided 92% yield of the tribenzyl-amine with 2% dibenzylamine and 1% dibenzylimine. The reaction conditions delivered similar results with a wide range of substituted benzyl alcohols and 1-hexanol. Secondary alcohols, including 1-phenylethanol, cyclopentanol, cyclohex-anol, and 2-hexanol, produced good yields of secondary amines under these conditions. The model reaction also proceeds to high yield in solvent free conditions at 180 °C over 72 h with only 0.03 mol % of catalyst (*ChemSusChem* **2012**, *5*, 621−624).



Cano et al. used iridium oxide impregnated magnetite as a heterogeneous catalyst for the cross-alkylation of primary alcohols. A range of phenethyl and aliphatic primary alcohols were treated with the catalyst and potassium hydroxide in toluene at 110 °C over 4 days. Separation of the catalyst was achieved with a magnet, and the catalyst can be reused at least 10 times with minimal loss of efficacy. The authors presented deuterium-labeling studies to probe the proposed mechanism: oxidation of the potassium alkoxides, cross-aldol condensation, and reduction via 1,4-hydride addition from the iridium hydride species formed during the oxidation (*Chem. Commun.* **2012**, *48*, 7628−7630).



C-Alkylation of secondary alcohols with primary alcohols is described by Liao et al. in an extension of the aerobic relay methodology developed by the Xu group. A range of benzylic and aliphatic secondary alcohols is alkylated with benzyl, substituted benzyl, and aliphatic primary alcohols in the presence of copper acetate and potassium hydroxide. The reactions are run neat at 120 °C under air and afford alkylation products in high yield with generally low levels of the ketone byproduct. The authors argue that the presence of oxygen facilitates the initial alcohol to aldehyde/ketone oxidation, improving the overall efficiency of the methodology, and transfer hydrogenation is achieved via a Meerwein−Pondorf−Varley cyclic transition state. Reactions involving aliphatic

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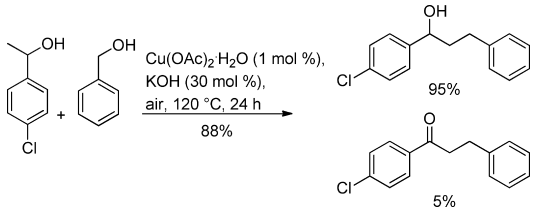
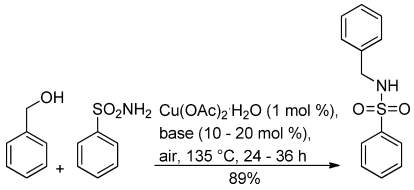
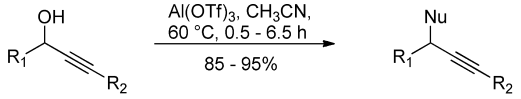
alcohols proceed in lower yield (38−71%) but with >99:1 product selectivity (*Org. Biomol. Chem.* **2012**, *10*, 2973−2978).



In the preceding paper by the same group, Li et al. utilized similar methodology for the N-alkylation of amino-arenes and sulfonamides with a range of benzyl alcohols. The benzyl alcohols (1.3−1.5 equiv) are reacted neat with sulfonamides and amino-arenes at 135 °C in the presence of catalytic copper acetate and a base (10−20 mol % K_2CO_3 for sulfonamides, 40 mol % NaOH or CsOH for amino-arenes). Isolated yields are generally >80%. The authors also present mechanistic studies into the aerobic relay methodology (*Org. Biomol. Chem.* **2012**, *10*, 2966−2972).



Gohain et al. use aluminium triflate to catalyze the nucleophilic substitution of C−1 arene substituted propargyl alcohols with a range of oxygen, nitrogen, sulfur, and arene nucleophiles. Reactions are run in acetonitrile, and the catalyst can be recovered from the aqueous layer during workup of the reaction. The recovered catalyst was reused three times with no loss of efficacy (*Tetrahedron Lett.* **2012**, *53*, 1048−1050).



R_1 = Ph, 4-$MeOC_6H_4$, 4-ClC_6H_4
R_2 = Ph, n-C_4H_9

Nu = MeOH, EtOH, $PhCH_2OH$, phenol, anisole, thiophene, pyrrole, $PhCONH_2$, PhSH, $PhCH_2SH$, $PhSO_2NH_2$, 4-$MeC_6H_4SO_2NH_2$, 4-$NO_2C_6H_4NH_2$,

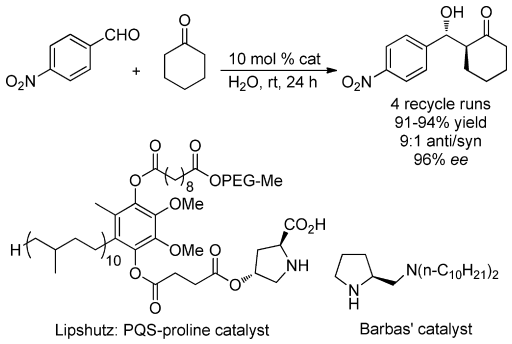
Bandini et al. have published a short review of catalytic enantioselective alkylations of allylic alcohols, focussing on reactions of prochiral or racemic substrates with chiral catalyst systems. The review covers C−C, C−O, and C−N bond formation under redox metal catalysis using low-valent iridium, palladium, and ruthenium systems. Electrophilic activation of the C=C bond, using gold or mercury salts, and organo-catalyzed S_N1 substitutions are also included (*Synthesis* **2012**, *44*, 504−512).

11. CHEMISTRY IN WATER

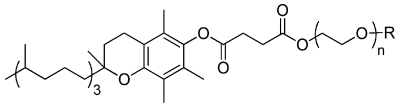
In a recent *Tetrahedron* report various examples of organic reactions in subcritical (100 °C < *T* < 374 °C) and supercritical water are discussed by N. S. Kus. Whereas supercritical water has been applied mainly for bond-breaking reactions and oxidative organic waste destruction, the milder conditions of subcritical water can also be used for bond-forming and rearrangement reactions. An additional advantage of subcritical water is that the decreasing dielectric constant (ε = 6 near the critical point of 374 °C/221 bar, similar to those of organic solvents such as MeOH or EtOH) results in a positive effect on the solubility of organic molecules (*Tetrahedron* **2012**, *68*, 949−958).

Lipschutz and Ghorai designed an L-proline-substituted surfactant able to form nanomicelles in water for application as an organocatalyst in asymmetric aldol reactions (*Org. Lett.* **2012**, *14*, 422−425).

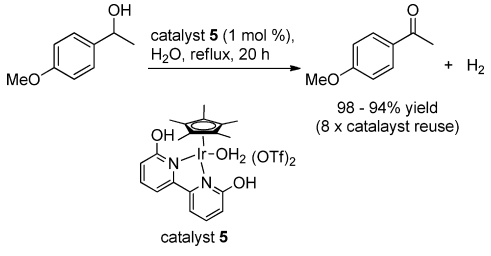
The main advantage of this PQS-proline surfactant is that, after removal of the aldol product by extraction, the aqueous solution containing the catalyst can be recycled without any further purification. This was exemplified by four recycle runs for the reaction above. Although the reaction did not proceed with simple L-proline derivatives, similar results were obtained previously for this reaction by Mase et al. (*J. Am. Chem. Soc.* **2006**, *128*, 734−735),



albeit without recycling of the catalyst. In addition, both authors present an overview of the surfactant design from PTS to TPGS-750-M and the use for various transition-metal-catalyzed cross-coupling reactions in aqueous micellar solution of these surfactants (*Aldrichchim. Acta* **2012**, *45*, 3−16).



The dehydrogenative oxidation in boiling water of primary and secondary alcohols to aldehydes and ketones, respectively, has been described by Kawahara et al. The reaction is catalyzed by water-soluble Cp*Ir complexes of which catalyst **5** (0.02−3 mol %) is preferred. The reaction proceeds with evolution of hydrogen gas, and no additional oxidants are needed. After isolation of the product, the aqueous phase containing catalyst **5** could be reused several times without loss of activity. The catalyst could also be recovered and used again in other dehydrogenative oxidation reactions (*J. Am. Chem. Soc.* **2007**, *134*, 3643−3646).



Over the years various Diels−Alder reactions and 1,3-dipolar cycloaddition reactions have been successfully performed in/on water. Trogu et al. describe the acid−base-catalyzed formation of

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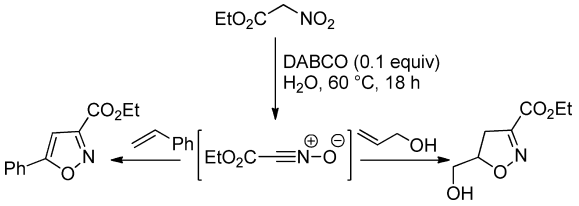
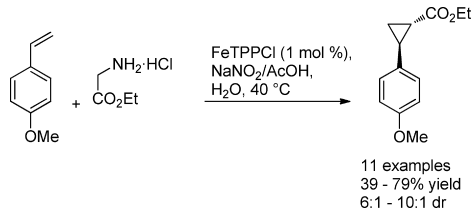
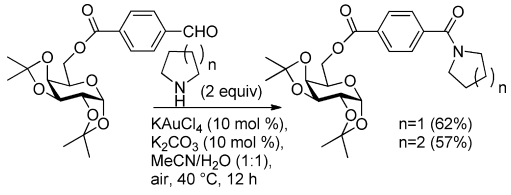
isoxazolines and isoxazoles in water from nitroacetate esters and different dipolarophiles. Although the reaction proceeds via (irreversible) acid-catalyzed water elimination, the condensation reaction proceeds much faster in water than in organic solvents. In an extensive kinetic study the authors suggest that reaction of the partially soluble reagents occurs in water. Concentrations used are acceptable for preparative application, and a wide range of functional groups are accepted as substituents of the (mostly terminal) alkene or alkyne dipolarophile (*Chem.—Eur. J.* **2012**, *18*, 2081−2093).



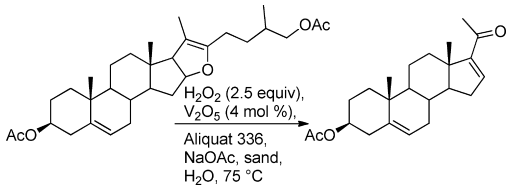
Safe handling of diazo compounds is an important issue on large scale. Morandi et al. have described the tandem diazotization/cyclopropanation in water by in situ generation of ethyl diazoacetate from glycine ethyl ester. Catalyzed by 1 mol % of an inexpensive iron−porphyrin complex, *trans*-cyclopropyl esters are obtained in high yield and diastereomeric ratios of 6:1−10:1 (*Org. Lett.* **2012**, *14*, 2162−2163).



Efficient gold-catalyzed amide synthesis from aldehydes and amines under mild aqueous conditions has been described by Li et al. This method is especially useful for the preparation of tertiary amides. Isolated yields up to 99% are reported for aromatic as well as aliphatic aldehydes, and the method is also described for aldehydes from mono- and trisaccharides (without effecting ketal or silyl protecting groups). The reaction is performed in 1:1 MeCN/H_2O although rather high $KAuCl_4$ catalyst loadings of 1−10 mol % are needed. Without water, nearly no reaction occurs. Air oxygen is used for the reoxidation of the Au(I) to the Au(III) catalyst (*Chem. Commun* **2012**, *48*, 4112−4114).



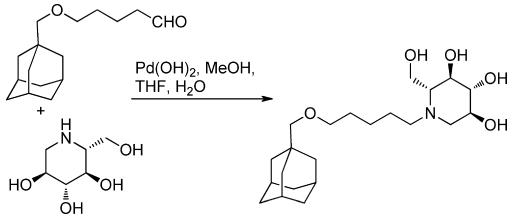
Cui et al. present a practical solution to the problem of performing reactions with poorly soluble solid organic compounds in aqueous solvents. The method consists of mechanical stirring of the organic substrate in water with catalytic Aliquat 336 and sand. As an example, 0.1 g of steroid suspended in 5 mL of water (solubility 4.4×10^{-7} M) is oxidized with H_2O_2, using V_2O_5 as catalyst, with complete conversion in 6.5 h and an isolated yield of 71%. The method is further illustrated for the KBH_4 reduction of steroids in water, saponification of esters of alkaloids and steroids, and oxime/hydrazone formation in water of poorly soluble aromatic aldehydes and alkaloids (*Green Chem.* **2012**, *14*, 668−672).



In the Green Chemistry Special Issue 4 of *Chem. Soc. Rev.* Simon and Li present various examples of organic reactions in water. The attention of this review is not only on enhanced reactivity and selectivity of the organic reactions but also on improvements in workup, catalyst recycling, milder reaction conditions, and water purification (*Chem. Soc. Rev.* **2012**, *41*, 1415−1427).

12. CONTINUOUS PROCESSING AND PROCESS INTENSIFICATION

Two publications utilising continuous hydrogenation highlight the fact that continuous processing is being seen as an effective way to facilitate pressure reactions requiring extreme processing conditions. Genzyme chemists made use of a kilo-lab scale fixed-bed reactor, H-cube Midi, catalytic hydrogenation reactor to facilitate the reductive amination of an aldehyde at 150 °C under 100 bar pressure. Such fixed-bed reactors offer the advantage of very high catalyst loadings per unit volume of the reactor, offering faster kinetics, and can be operated under extreme conditions (as no moving parts, e.g. agitators, are involved) whilst maintaining a low material handling (*Org. Process Res. Dev.* **2012**, *16*, 1090−1097).



Johnson et al. have used a 73-L tubular plug flow reactor to carry out high-pressure (70 bar) rhodium-based asymmetric catalytic hydrogenation and coupled it with downstream unit operations: solvent swap and continuous crystallization to generate 144 kg of material within a laboratory environment, thus saving considerable capital investment required for setting up high-pressure pilot-plant equipment (*Org. Process Res. Dev. (OPRD)* **2012**, *16*, 1017−1038).

Both of the contributions described above are part of a Continuous Processing Special Feature Section of OPRD (*Org. Process Res. Dev.* **2012**, *16*, 843−1153) which contains numerous examples of continuous processing applied to various pharmaceutical chemical transformations.

Gernaey et al. published a perspective article on the role of process systems engineering (PSE) methods and tools in pharmaceutical process development efforts including alternate processing methodologies such as continuous processing coupled with process analytical techniques (PAT) (*Comput. Chem. Eng.* **2012**, *42*, 15−29).

13. GENERAL GREEN CHEMISTRY

A publication by Assaf et al. gives an excellent account of the use of green chemistry metrics in real time to influence a chemical development program for the synthesis of the drug candidate (*S,S*)-reboxetine succinate (*Green Chem.* **2012**, *14*, 123−129).

A themed issue of *Chemical Society Reviews* is dedicated to "Green Chemistry: Present and Future" with guest editors

dx.doi.org/10.1021/op4000434 | *Org. Process Res. Dev.* 2013, 17, 615−626

Chao-Jun Li and Paul Anastas. There is a tutorial review by Sheldon which discusses reaction design to increase synthetic efficiency (*Chem. Soc. Rev.* **2012**, *41*, 1437−1451). A tutorial review by Dunn is designed as an easy-to-read introduction to green chemistry for synthetic organic chemists (*Chem. Soc. Rev.* **2012**, *41*, 1452−1461), and a paper by Jimenez-Gonzalez et al. discusses the use of metrics to evaluate chemical processes at GSK (*Chem. Soc. Rev.* **2012**, *41*, 1485−1498).

A survey by Watson looks at how 21 pharmaceutical companies and one fine chemical company approach green chemistry and, in particular, provides results on metrics which companies routinely collect (*Green Chem.* **2012**, *14*, 251−259).

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