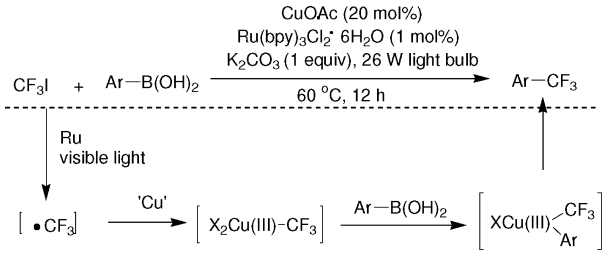
Organic Process Research & Development

Highlights from the Literature

pubs.acs.org/OPRD

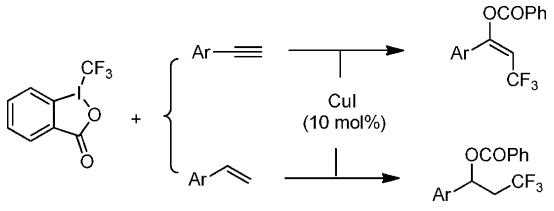
Some Items of Interest to Process R&D Chemists and Engineers

COPPER-CATALYZED TRIFLUOROMETHYLATION OF BORONIC ACIDS WITH TRIFLUOROMETHYL IODIDE



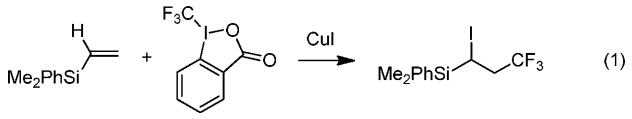
A mild method for the cross-coupling of arylboronic acids with CF_3I via the merger of photoredox (to generate CF_3 radical) and Cu catalysis (to generate reactive Cu−aryl species) was developed by Professor Sanford and her co-worker of University of Michigan (*J. Am. Chem. Soc.* **2012**, *134*, 9034−9037). Potassium carbonate was found a base of choice for the promotion of transmetalation in DMF solvent. This method demonstrates the feasibility of achieving Cu-catalyzed trifluoromethylation via a radical pathway of a wide variety of aromatic and heteroaromatic substrates bearing many common functional groups. Aromatic boronic acids bearing either electron-donating (*tert*-butyl, methoxy) or electron-withdrawing (cyano, trifluoromethyl, fluoro, methyl ester) substituents underwent trifluoromethylation to give the trifluoromethylated products in high yield. A variety of different potentially reactive functional groups (such as hydroxy, iodo, ketone, aldehyde, ester, and amide) was well-tolerated. Boronic acids derived from heteroaromatics such as pyridine, quinoline, furan, and thiophene could be trifluoromethylated in modest to good yields.

COPPER-CATALYZED TRIFLUOROMETHYLATION OF ALKENES AND ALKYNES

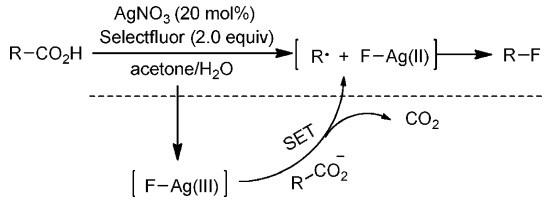


Regio- and stereoselective trifluoromethylation of alkynes and alkenes was achieved via Cu-catalyzed addition of hypervalent iodine reagent (*Org. Lett.* **2012**, *14*, 2882−2885). Using hypervalent iodine as CF_3 source in the presence of CuI reactions of various alkenes and alkynes afforded the corresponding trifluoromethyl-benzoyloxylated alkanes and alkenes, respectively. Because of the electrophilic character of the addition reaction, reactions of alkenes or substrates bearing electron-donating substituents proceed faster than those of alkynes or electron-poor substrates.

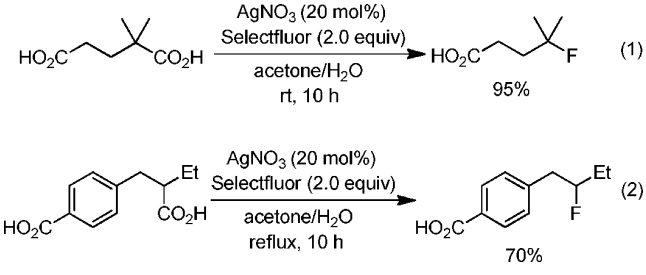
In the case of vinyl silane substrate, trifluoromethylhalogenation took place instead of the expected benzoyloxylation, giving dimethyl(phenyl)(3,3,3-trifluoro-1-iodopropyl)silane (eq 1).



SILVER-CATALYZED DECARBOXYLATIVE FLUORINATION OF ALIPHATIC CARBOXYLIC ACIDS



A report (*J. Am. Chem. Soc.* **2012**, *134*, 10401−10404) describes a site-specific $C(sp^3)$−F bond formation via a silver-catalyzed decarboxylative fluorination of aliphatic carboxylic acids with SELECTFLUOR reagent in aqueous solution. With $AgNO_3$ (20 mol %) as a catalyst, the reaction of carboxylic acids with SELECTFLUOR reagent in 1:1 (v:v) acetone/H_2O solution at refluxing temperature led to a clean formation of the fluorinated alkanes in good to excellent yields. The reaction was suggested to proceed through an oxidative radical decarboxylation mechanism likely involving the divalent silver intermediate, Ag(II)−F, and an alkyl radical, being generated via a SET process between trivalent silver species and carboxylate anion. Water was found to be essential as no decarboxylation was observed in any of the anhydrous organic solvents such as acetone, DMF, or DMSO. The reactivity of carboxylic acids decreases in the order tertiary >secondary > primary. Aromatic acids such as benzoic acid, 4-chlorobenzoic acid, and 2-nitrobenzoic acid failed to give any desired products under the standard reaction conditions. Consequently, chemoselective decarboxylation of diacids was demonstrated (eqs 1 and 2) giving the corresponding fluorinated acids.

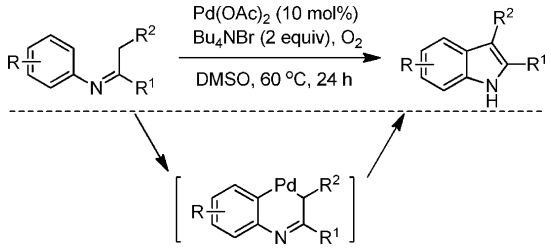


Published: October 10, 2012

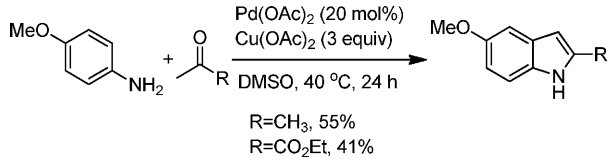
   dx.doi.org/10.1021/op300253y | *Org. Process Res. Dev.* 2012, 16, 1574−1581

The reaction tolerates a variety of functional groups, including amide, ester, carbonyl, halide, and ether.

INDOLE SYNTHESIS VIA PALLADIUM-CATALYZED AEROBIC OXIDATIVE CYCLIZATION

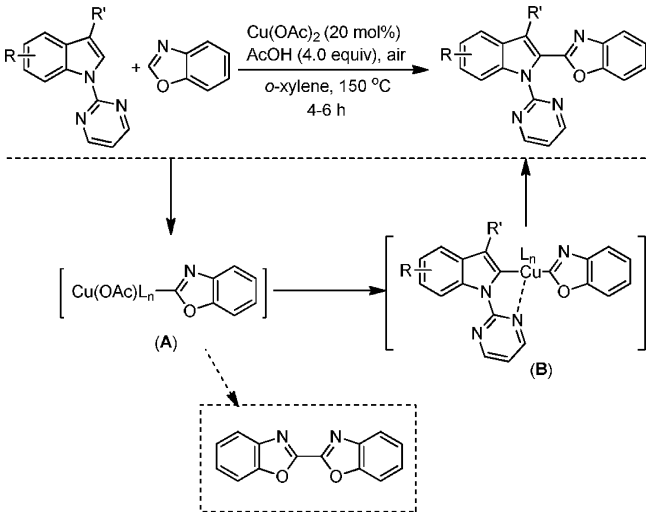


An approach to indoles was developed involving a palladium(II)-catalyzed cyclization reaction of *N*-aryl imines (*J. Am. Chem. Soc.* **2012**, *134*, 9098−9101). Mechanistically, the reaction undergoes a reductive elimination of a palladacycle intermediate to give the indole product and Pd(0) that would be oxidized to Pd(II) catalyst by O_2. The reaction system ($Pd(OAc)_2/Bu_4NBr/O_2$) tolerates both electron-rich and electron-poor functional groups including methyl, methoxy, nitro, cyano, amide, trifluoromethyl, chloro, bromo, and fluoro groups.

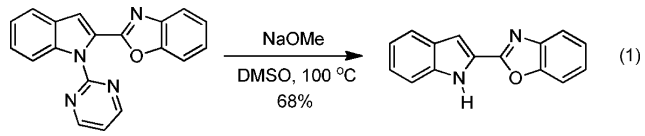


One-pot oxidative condensation of aniline with ketones was demonstrated under modified conditions ($Pd(OAc)_2/Cu(OAc)_2$), providing the corresponding products in 55% (R = CH_3) and 41% (R = CO_2Et), respectively.

COPPER-CATALYZED CROSS-COUPLING OF INDOLES AND 1,3-AZOLES

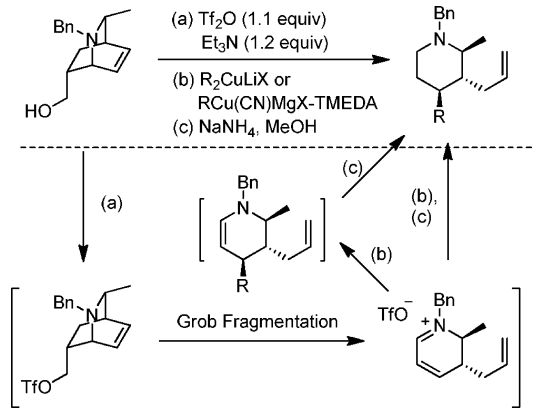


A copper-mediated intermolecular cross-coupling of 1,3-azoles and indoles bearing the 2-pyrimidyl group for chelation assistance was developed by Professor Miura and co-workers of Osaka University, Japan (*Angew. Chem., Int. Ed.* **2012**, *51*, 6993−6997). Treatment of a mixture of *N*-(2-pyrimidyl)indole and benzoxazole with $Cu(OAc)_2$ (20 mol %) and AcOH (4.0 equiv) in boiling *o*-xylene under atmospheric conditions produced the corresponding cross-coupling product in good yield. Mechanistically, two intermediates (**A** and **B**) were involved in the cross-coupling process: an initial carboxylate ligand-assisted cupration of the relatively acidic C−H bond, generating a heteroaryl−copper intermediate **A**, followed by 2-pyrimidyl chelation-assisted C−H metalation of indole, forming a bis(heteroaryl) copper species **B** as a key intermediate. Finally, O_2-promoted irreversible reductive elimination provides the corresponding cross-coupling product along with regeneration of the starting copper complex to complete the catalytic cycle. A side cupration reaction of intermediate **A** with the second benzoxazole competes to generate a bis(benzoxazole)copper, en route to the homocoupling product. Fortunately, the highly electron-deficient nature of the 1,3-azolyl ligand on **A** makes the process preferential for cross-coupling over homocoupling. As a chelation-directing group, the *N*-pyrimidyl group could be eliminated upon treatment of the cross-coupling product with NaOMe in DMSO at 100 °C, as illustrated in eq 1.The electronic nature of the functional



group at the 3-position of the indole substrates influences the reaction outcome, for example, 3-methylindole resulting in a moderate yield even at higher temperature, while the cyano analogue gave the coupling very smoothly to afford the product in good yield. The Cu-based reactions tolerated functional groups (R) such as methoxy and chloro on the benzene ring.

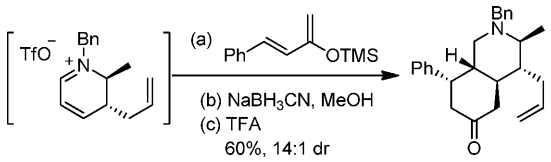
STEREOSELECTIVE SYNTHESIS OF 2,3,4-TRISUBSTITUTED PIPERIDINES VIA GROB FRAGMENTATION OF 2-AZABICYCLO[2.2.2]OCT-7-ENE



In addition to the recent publication (*J. Org. Chem.* **2010**, *75*, 7465−7467) regarding the synthesis of 2,3,6-trisubstituted tetrahydropyridines, an approach for access to 2,3,4-trisubstituted piperidines was disclosed (*J. Org. Chem.* **2012**, *77*, 5832−5837). Exposure of azabicyclo[2.2.2]octane to a mixture of Tf_2O and Et_3N in methylene chloride followed by treatment with organocuprates and sodium borohydride provided 2,3,4-trisubstituted piperidines in good yields and high

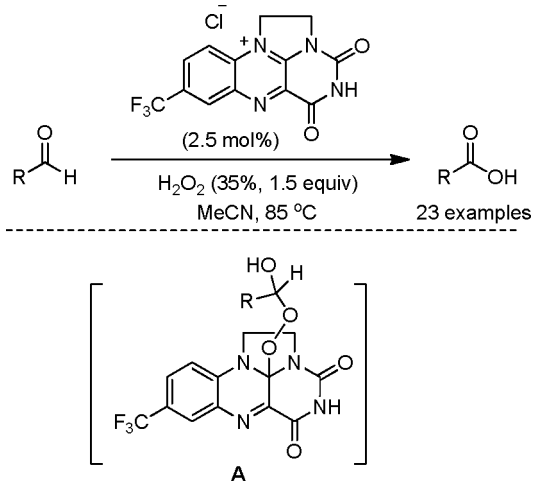
dx.doi.org/10.1021/op300253y | *Org. Process Res. Dev.* 2012, 16, 1574−1581

stereoselectivity. The three-step, one-pot process involves a Grob fragmentation, stereoselective 1,4-nucleophilic addition, and reduction. This reaction protocol avoided the potential dimerization of the enamine intermediates during the workup and purification by reduction of the tetrahydropyridine in situ into the corresponding piperidine.



In addition, as a dienophile the dihydropyridinium intermediate could also participate in a Diels–Alder reaction with siloxy dienes to give octahydroisoquinolinone in good overall yield after the sequential reduction with $NaBH_3CN$ and treatment with TFA.

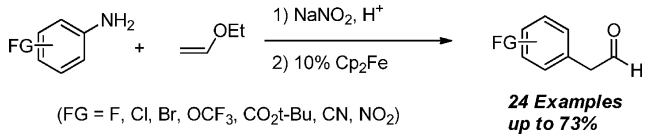
BIOMIMETIC FLAVIN-CATALYZED ALDEHYDE OXIDATION



The oxidation of alkyl and aryl aldehydes to their corresponding carboxylic acids was achieved with hydrogen peroxide mediated by a biomimetic bridged flavin catalyst (*Org. Lett.* **2012**, *14*, 3656–3659). The protocol is relatively simple: treatment of the aldehydes with 35% hydrogen peroxide (1.5 equiv) and flavin catalyst (2.5 mol %) at 85 °C in acetonitrile. Both aryl and alkyl aldehydes are suitable substrates for the oxidation, affording the carboxylic acids in good yields. This flavin-catalyzed oxidation proceeds through a hypothesized adduct intermediate, peroxyhemiacetal **A**. This adduct then undergoes thermal collapse via 1,2-hydride migration with resultant O–O bond cleavage to form carboxylic acid and hydrated flavin. Apparently, a main competitive side reaction is Dakin oxidation with migration of the R group, resulting in the formation of a formate ester which hydrolyzes under the reaction conditions. Indeed, such Dakin oxidation was observed when the R was an electron-rich aryl or a tertiary alkyl group, giving phenol or *tert*-butyl alcohol.

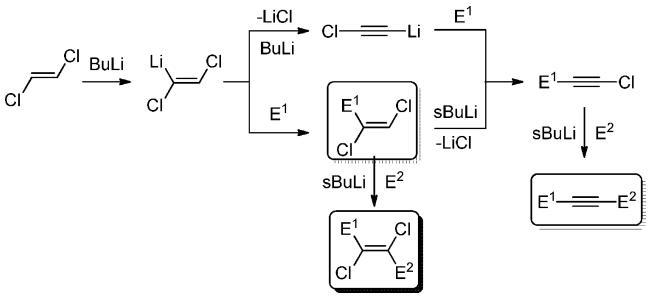
CONTINUOUS-FLOW SYNTHESIS OF MONOARYLATED ACETALDEHYDES USING ARYLDIAZONIUM SALTS

Buchwald et al. from MIT have reported recently that anilines and ethyl vinyl ether can be used as precursors for an efficient



continuous flow process that is the synthetic equivalent of the α-arylation of acetaldehyde enolate (*J. Am. Chem. Soc.* **2012**, *134*, 12466–12469). This Meerwein arylation reaction allows for high functional group tolerance to give a number of synthetically valuable monoarylated acetaldehydes with the absence of base. Under the mild reaction conditions, the use of anilines as aryl group donors provides a facile entry into a wide range of polyhalogenated products, thus addressing the shortcomings of traditional transition-metal-catalyzed enolate arylation methodologies relying on aryl halides. Moreover, the continuous-flow method provides a general solution for the efficient and safe generation of a range of unstable aryldiazonium salts, enabling a scalable synthesis of arylacetaldehydes. As shown in the scheme above, 24 examples succeed via this methodology with up to 73% yield.

LITHIATION OF 1,2-DICHLOROETHENE IN FLOW MICROREACTORS: VERSATILE SYNTHESIS OF ALKENES AND ALKYNES BY PRECISE RESIDENCE-TIME CONTROL

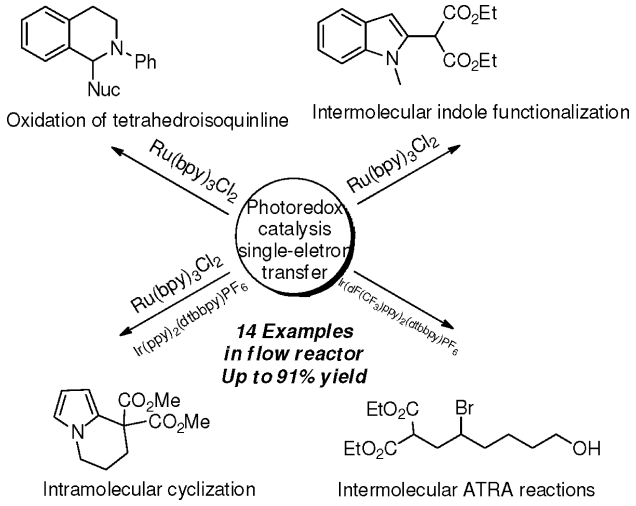


The J.-i. Yoshida group from Kyoto University in Japan reported recently about the lithiation of 1,2-dichloroethene in flow microreactors and the resulting transformations based on precise residence time control (*Angew. Chem., Int. Ed.* **2012**, *51*, 3245–3248). Starting from *trans*-1,2-dichloroethene, a highly reactive and unstable intermediate 1,2-dichlorovinyllithium can be generated, which can be used in a subsequent reaction before it decomposes (due to β-elimination) by virtue of a "space integration" strategy. As shown in the scheme above, this flash chemistry allows for versatile syntheses via the reaction pathway switch, either producing monosubstituted, disubstituted 1,2-dichloroethenes or asymmetric disubstituted alkynes.

VISIBLE-LIGHT PHOTOREDOX CATALYSIS IN FLOW

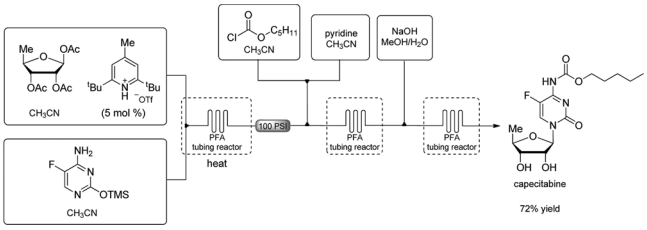
The Stephenson group from Boston University and the Jamison group from MIT reported on joint research about a convenient and readily operable photochemical flow reactor, which enables the marked acceleration of a variety of transformations mediated by photoredox catalysis via the single-electron transfer process (*Angew. Chem., Int. Ed.* **2012**, *51*, 4144–4147). The entire setup has a sufficiently small footprint to easily fit into a standard fume hood and can be assembled quickly and inexpensively. On the basis of photoredox catalysts such as $Ru(bpy)_3Cl_2$ and $Ir(ppy)_2(dtbbpy)PF_6$, this flow

dx.doi.org/10.1021/op300253y | *Org. Process Res. Dev.* 2012, 16, 1574–1581



reactor has shown an increased efficiency in terms of material throughput for all the transformations studied, including oxidation of tetrahydroisoquinolines, intramolecular cyclization via radical reactions, intermolecular indole functionalization/coupling, and intermolecular atom transfer radical addition (ATRA) reaction in flow. Compared with that of a batch reactor, the high surface area-to-volume ratios typical of flow reactors allow for more efficient irradiation of a reaction mixture. Even higher rates of substrate conversion (in terms of mmol of material per hour) are possible simply by employing a photoreactor with a greater internal volume.

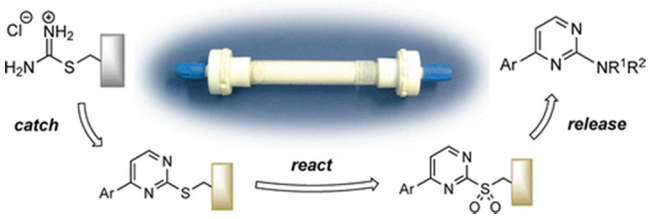
RAPID CONTINUOUS SYNTHESIS OF 5′-DEOXYRIBONUCLEOSIDES IN FLOW VIA BRØNSTED ACID-CATALYZED GLYCOSYLATION



A rapid continuous synthesis of 5′-deoxyribonucleosides as important pharmaceuticals in flow via Brønsted acid-catalyzed glycosylation has been reported by the Jamison group from MIT (*Org. Lett.* **2012**, *14*, 3348−3351). The use of a Brønsted acid organocatalyst in this glycosylation reaction in continuous flow renders this method greener and more efficient than those requiring stoichiometric amounts (or more) of Lewis acids. The one-flow, multistep sequence circumvents purification of the intermediate products and produces unprotected target compounds in a streamlined manner, as demonstrated by the syntheses of the important drugs doxifluridine, galocitabine, and capecitabine.

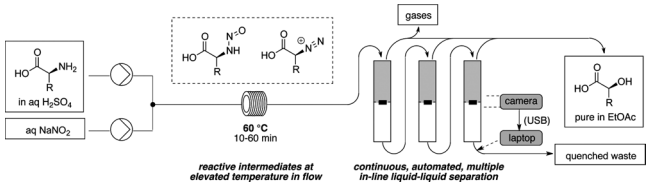
A "CATCH−REACT−RELEASE" METHOD FOR THE FLOW SYNTHESIS OF 2-AMINOPYRIMIDINES AND PREPARATION OF THE IMATINIB BASE

Steven V. Ley group from University of Cambridge has reported recently the development of a monolith-supported synthetic procedure (*Org. Lett.* **2012**, *14*, 3920−3923). By taking advantage of flow processing and the superior flow



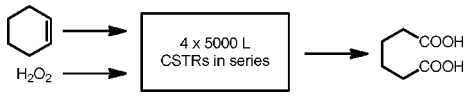
characteristics of monolithic reagents over gel-phase beads, this "Catch−React−Release" method allows facile access to an important family of 2-aminopyrimidine derivatives from readily available enaminones and amines, such as a key precursor aminopyrimidine en route to Imatinib (as shown in the scheme: Ar = 3-pyridyl, R^1 = 2-methyl-5-nitrobenzyl, R^2 = H). Compared with solution-phase synthesis, the supported variant of this reagent thiouronium salt offers many advantages including simplified isolation of the product, the potential for automation, and containment of toxic and malodorous byproducts. The new monolithic reagent also offers benefits over traditional polymer bead reagents, in particular, a more suitable morphology for effective use in a continuous flow regime and a low-cost and accessible preparation procedure. Only one purification operation is required over three steps, and the compounds are retrieved in comparable yields to batch routes to similar targets.

CONTINUOUS MULTIPLE LIQUID−LIQUID SEPARATION: DIAZOTIZATION OF AMINO ACIDS IN FLOW



The Steven V. Ley group from the University of Cambridge has recently reported a device capable of multiple liquid−liquid extractions/phase separations, which was applied to the first examples of amino acid diazotization in flow on multigram scales (*Org. Lett.* **2012**, *14*, 4246−4249). The device is easy to assemble manually, and instructions along with the source code for the machine are provided. Based on computer-controlled high-pressure pumps and a high resolution digital camera, this second-generation laboratory-scale, modular liquid−liquid separation device first witnesses the diazotization of amino acids towards valuable chiral hydroxyacids. The use of a triple-separator system in conjuction with the developed diazotization process allows the safe and efficient production and automated isolation on multigram scales. The compatibility of this device with other chemical reaction sequences convinces the authors that in the future, the use of this device will greatly accelerate synthetic preparations in research laboratories and enable more complex multistep sequences.

LARGE-SCALE CONTINUOUS PRODUCTION OF ADIPIC ACID



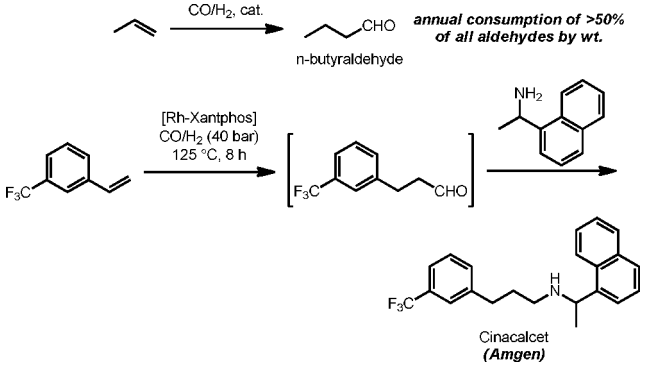
dx.doi.org/10.1021/op300253y | *Org. Process Res. Dev.* 2012, 16, 1574−1581

Wang, Li, and co-workers have reported a large scale continuous flow process for the manufacture of adipic acid using a catalyst system synthesized in situ from H_2WO_4, H_2SO_4, and H_3PO_4 in H_2O_2 (*Green Chem.* **2012**, *14*, 2868−2875). Their process differs from that employed commercially by DuPont and by Asahi Kasei in that no N_2O gas is formed as a byproduct; it does not require solvents, phase transfer catalysts, or additives; and has fewer unit operations. Catalyst recovery and recycle was demonstrated successfully 20 times, and calorimetry and batch scale-up studies were performed to establish process safety. Pilot-plant continuous flow process was run successfully for 350 h in a train of four 5000-L CSTRs in series (representing a 10000-fold scale up), affording the precrystallization product in 95% yield and 99% purity.

DEEP EUTECTIC SOLVENTS: SYNTHESIS, PROPERTIES, AND APPLICATIONS

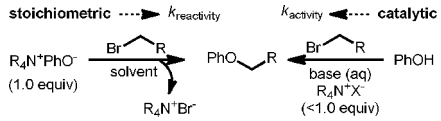
Ionic liquids have been extensively studied as "green" solvents; however their cost and toxicity have rendered them unattractive in industrial organic synthesis. A new class of solvents, deep eutectic solvents (DES), has recently been proposed as ionic liquid surrogates, similar in their properties and applications without the cost/toxicity drawbacks of ionic liquids. A DES is defined as a fluid composed of two or three components capable of self-association through hydrogen bonding, thus forming a eutectic mixture. A review by Jérôme and co-workers highlights this class of solvents (*Chem. Soc. Rev.* **2012**, 10.1039/c2cs35178a). The review starts with a definition of DES and a detailed look at their physiochemical properties and subsequently delves into the applications of DES in dissolution and separation processes, catalysis, organic synthesis, electrochemistry, and material chemistry.

APPLIED HYDROFORMYLATION



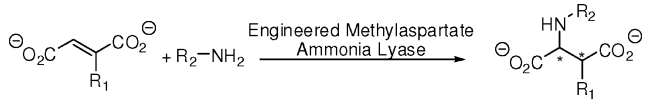
Börner, Franke, and Selent have assembled a detailed review on applied and industrially relevant hydroformylations (*Chem. Rev.* **2012**, 10.1021/cr3001803). The review starts with a classification of bulk hydroformylation processes that have been practiced in the industry for several decades. A detailed discussion on the choice of metals and ligands follows with an emphasis on ligands designed for industrial application. Decomposition of ligands and catalysts under hydroformylation conditions and measures against decomposition are addressed next. An extensive survey of the substrates already developed and those of potential importance in the bulk and fine chemical industries is the centerpiece of the review, which is followed by a section on stereoselective hydroformylations. The review ends with a discussion of potential and less toxic alternatives for syngas.

EFFECTS OF CHARGE SEPARATION, EFFECTIVE CONCENTRATION, AND AGGREGATE FORMATION ON THE PHASE-TRANSFER-CATALYZED ALKYLATION OF PHENOL



Phase transfer catalysis is of prime importance in industrial organic synthesis; however, the underlying mechanistic regimes remain poorly understood, and selection of the catalyst remains largely an empirical exercise. Denmark and co-workers have attempted to tackle this problem by studying the factors that influence the rate of phase-transfer-catalyzed alkylation of phenol (*J. Am. Chem. Soc.* **2012**, *134*, 13415−13429). This was done using an homologous series of quaternary ammonium ion phenolates; the stoichiometric, catalytic, and phase transfer rate constants were compared, their partition equilibria were analyzed, and composition of the species in the organic phase was determined. A major factor influencing catalyst activity was determined to be the effective concentration of the tetraalkylammonium phenoxides in the organic phase.

BIOCATALYTIC SYNTHESIS OF α-AMINO ACIDS



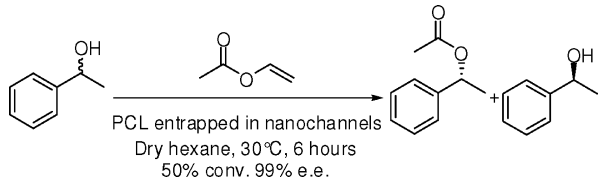
The importance of optically pure α-amino acids as chiral building blocks for different sectors in industry is well-known. However, despite the number of enzymatic processes already developed for the synthesis of these molecules including hydantoinases, dehydrogenases, acylases, aminotransferases, and amidases, the use of ammonia lyases is the most attractive one due to the 100% theoretical yield and the lack of cofactor recycling needed for performing the reaction. The 3-methylaspartate ammonia lyase (MAL) is an enzyme which catalyses the reversible addition of ammonia to a double bond as shown in the scheme. Unfortunately, the substrate scope of MAL is very narrow and only a few small substituted amines and fumarates are reasonably active, yielding a limited number of substituted aspartic acids.

The work of Poelarends and co-workers, recently published (*Nature Chem* **2012**, *4*, 478−484), describes a structure-based engineering of methylaspartate ammonia lyase (which in nature catalyses the conversion of 3-methylaspartate to ammonia and 2-methylfumarate) to accept a variety of substituted amines and fumarates and catalyse the asymmetric synthesis of aspartic acid derivatives. The results obtained show that a single amino acid substitution can dramatically expand the scope of substrate specificity of MAL and identified that Q73 and L384 residues could represent good targets for further development for enhanced substrate scope utilization.

IMPROVING LIPASE ACTIVITY BY IMMOBILIZATION ON MESOPOROUS SILICA DERIVATIVES

The development of different techniques for enzyme immobilization brought several advantages to the use of biocatalysis

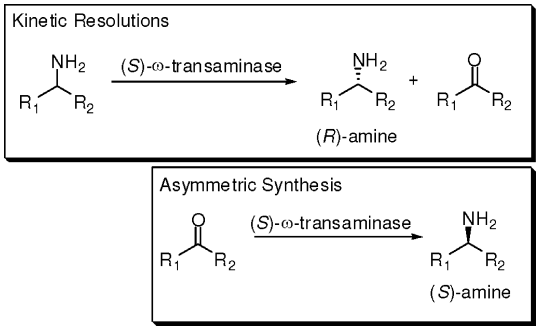
dx.doi.org/10.1021/op300253y | *Org. Process Res. Dev.* 2012, 16, 1574−1581



in process chemistry, such as easier recovery from reaction media and improved stability/efficiency. A brief search of the literature gives several supports and different immobilization procedures. However recently, the use of mesoporous silica materials as supports for enzyme immobilization has attracted a lot of attention, mainly due to the properties of these materials which fit well with the requirements for enzyme immobilization.

Yang, Li, and co-workers have recently published their work on the use of polymer-modified mesoporous silica for lipase immobilization and found improved catalytic performance for the studied lipase (*Langmuir* **2012**, *28*, 9788−9796). The modification of the nanopore microenvironment has the objective to balance the hydrophobic/hydrophilic ratio in order to improve the performance of the heterogeneous biocatalyst. In order to achieve the desired hydrophilic/hydrophobic ratio a series of mesoporous silicas were modified by a co-condensation method under mild acid conditions with hydrophilic polymer SURFONAMINE-B200 or hydrophobic polymer SURFONAMINE-L207. The results presented by the authors show that immobilization of *Pseudomonas cepacia* (PCL) onto a mesoporous silica support with a moderate hydrophobic microenvironment led to the best performance with higher activity than the free enzyme and the enzyme immobilized on mesoporous silica without modification. For example, the kinetic resolution of *sec*-phenyl ethanol was performed with high conversion (50%) and enantiomeric excess (ee) (99%) by the *P. cepacia* (PCL) immobilized on mesoporous silica support with a moderate hydrophobic microenvironment, whereas the immobilization on mesoporous silica support without modification led to just 8.2% conversion with high ee.

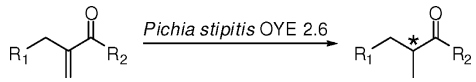
OPTICALLY PURE AMINES BY THE USE OF ω-TRANSAMINASES



Chiral amines are important building blocks for the synthesis of biologically active molecules for the pharmaceutical and agrochemical industries. However, in the last decades, just a few well-established biocatalytic methods for the preparation of such intermediates have been published, with the use of lipases under kinetic or dynamic resolution conditions the best option. The strategy of using lipases for this kind of transformation suffers from long reaction times and expensive catalysts/harsh conditions for the racemization step on dynamic resolutions.

Recently, improvements in the field of enzyme engineering and screening made the discovery and development of new transformations easier. ω-Transaminases are one of these enzymes which gained attention in the past decade. Matthew and Yun have published a review article (*ACS Catal.* **2012**, *2*, 993−1001) about the use of ω-transaminases in the syntheses of optically pure amines and unnatural amino acids. This review covers not only the application of ω-transaminases on the production of chiral amines but also the different strategies for identification and engineering of novel transaminases.

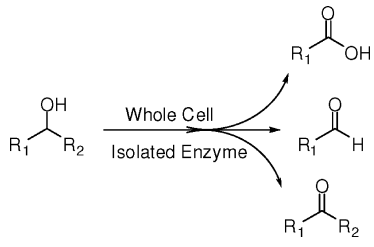
ASYMMETRIC ALKENE REDUCTIONS BY *Pichia stipitis* OYE 2.6



In the recent years much attention has been given to the identification of biocatalysts which could increase the toolbox of organic synthesis. Reduction of double bonds is an important transformation and is well established with whole cells or isolated enzymes when a ketone is used as the substrate. The reduction of carbon−carbon double bound by the use of alkene reductase has emerged in recent years as a powerful transformation catalysed by enzymes.

The first work on this field was done in 1995 when Old Yellow Enzyme (OYE1) was used for the reduction of electron-deficient double bonds. Recently, Stewart and co-workers have published their work on the structural and catalytic characterization of *Pichia stipitis* OYE 2.6 (*Adv. Synth. Catal.* **2012**, *354*, 1949−1960). The authors observed that the local environment of the flavin mononucleotide cofactor was very similar to that for other OYE members; however, differences on substrate binding were found. Site saturation mutagenesis was also performed on four different sites, and the results obtained revealed that replacement of some amino acids could lead to a wide range of activities while low impact on stereoselectivity was observed.

OXIDATION OF ALCOHOLS BY BIOCATALYSTS



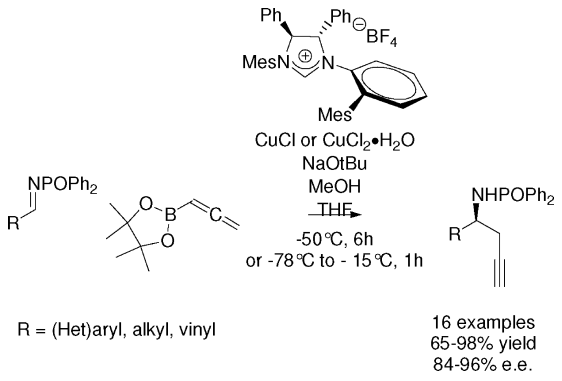
Oxidation of primary and secondary alcohols is an important transformation in organic chemistry, but most of the traditional methods employed for chemical oxidation have potential disadvantages in terms of environmental impact and do not follow green chemistry principles. On the other hand, biocatalytic oxidations take place under mild conditions leading to the desired products with high chemo-, regio-, and stereoselectivity.

Molinari and co-workers (*ChemCatChem* **2012**, *4*, 739−749) have recently published a review paper on preparative methods for the biological oxidation of alcohols, where advantages and limitations of the use of this approach are highlighted. Issues related to cofactor recycling and product inhibition and recovery are addressed. Several protocols regarding oxidations

dx.doi.org/10.1021/op300253y | *Org. Process Res. Dev.* 2012, 16, 1574−1581

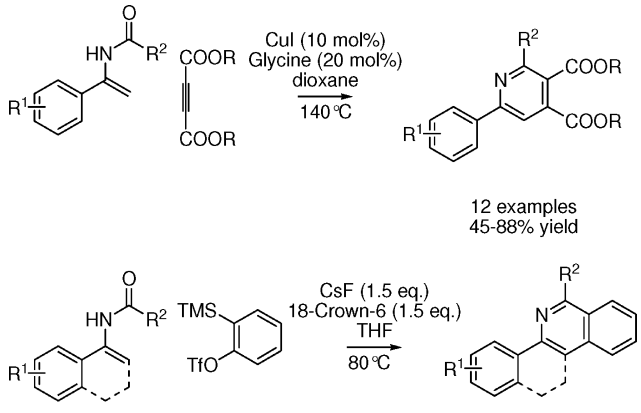
of alcohols to aldehydes and carboxylic acids are examined as well as the oxidation of secondary alcohols and diols and deracemization/stereoinversion protocols.

COPPER-CATALYZED ENANTIOSELECTIVE SYNTHESIS OF HOMOPROPARGYL AMINES



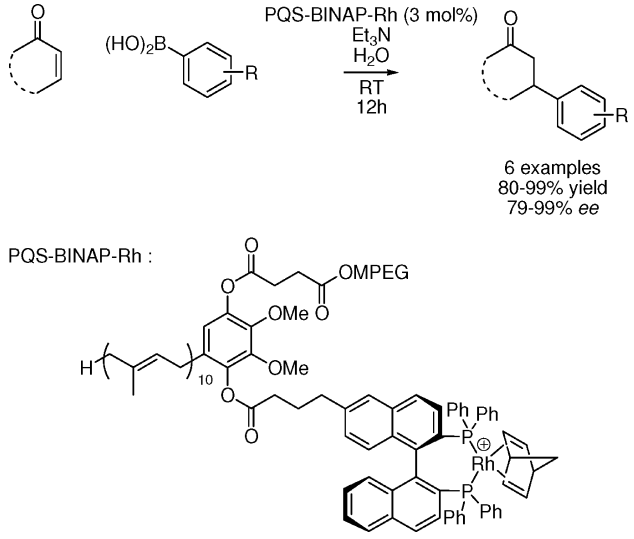
Enantiomerically enriched amines are highly valuable intermediates, and there are few examples of robust protocols to generate them. Hoveyda's group has reported an efficient catalytic enantioselective method for the production of homopropargyl amines (*Angew. Chem., Int. Ed.* **2012**, *51*, 6618−6621). This protocol relies on the addition of allenylboron to *N*-phosphonoyl imines catalyzed by a complex formed from a chiral imidazolium salt and a copper source (CuCl or $CuCl_2 \cdot H_2O$). Interestingly, the isolation procedure only involves the trituration of *N*-phosphonoyl amides which are very prone to crystallize, and the reaction can be carried out without recourse to strictly anhydrous or oxygen-free conditions. The substrate scope is very large, as aliphatic as well as variously substituted (hetero)aromatic imines provide the desired product in uniformly high yield and enantiomeric excess.

COPPER-CATALYZED SYNTHESIS OF PYRIDINES AND ISOQUINOLINES FROM ENAMIDES



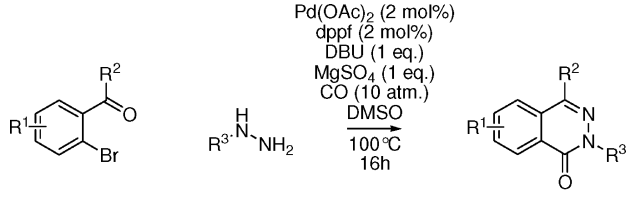
Although numerous methods for the synthesis of pyridines and isoquinolines are known, new alternatives that allow simple access to these important heterocycles continue to be actively sought after. A Chinese group has described the coupling of enamides with dimethyl acetylene dicarboxylate or aryne to generate respectively pyridines or isoquinolines (*Chem. Commun.* **2012**, *48*, 8105−8107). In the first case, the best conditions involve the use of copper iodide and glycine in dioxane at 140 °C, whereas coupling with aryne only required the use of CsF and 18-crown-6 (as the copper catalyst facilitates the cyclotrimerization of benzyne). Both reactions tolerate a number of functional groups on the enamide coupling partner including halogens.

RHODIUM-CATALYZED ASYMMETRIC 1,4-ADDITIONS IN WATER AT ROOM TEMPERATURE



Pursuing his successful work on micellar catalysis, Lipshutz and co-workers have described the first example of nonracemically ligated transition metal catalyst-tethered amphiphile (*Adv. Synth Catal.* **2012**, 10.1002/adsc.201200160). The catalyst, synthesized by the attachment of a BINAP derivative to the PQS skeleton (polyethylene glycol ubiquinol sebacate) followed by complexation with rhodium(I), efficiently promotes the asymmetric 1,4-addition of arylboronic acids to enones. Under the optimized conditions, which require only 3 equiv of triethylamine in water at room temperature, the products are obtained in high yield and enantiomeric excess. Noteworthy is that the water-soluble catalyst is conducive to in-flask recycling; after removal of the product from the first run by extraction, reintroduction of all reactants, except the catalyst, results in the clean formation of a second batch of the product. Although no loss of the metal is detected in the organic extract, the yield drops significantly after the fourth run while maintaining high enantiomeric excess, showing a possible instability of the rhodium complex under the developed conditions.

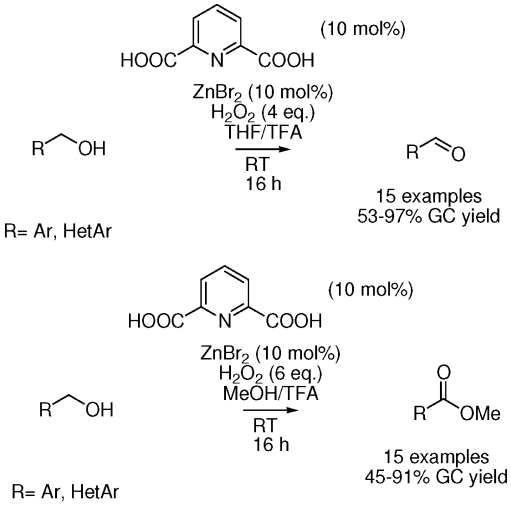
PALLADIUM-CATALYZED SYNTHESIS OF PHTHALAZINONES



dx.doi.org/10.1021/op300253y | *Org. Process Res. Dev.* 2012, 16, 1574−1581

Phthalazinones are structural motifs often encountered in bioactive molecules. Beller's group described a practical synthesis of this class of compounds that avoids common shortcomings such as the use of strongly basic or acidic conditions (*Chem. Eur. J.* **2012**, *18*, 8596−8599). Their synthesis relies on the formation of hydrazone from 2-bromobenzaldehyde and a hydrazine, followed by carbonylation and the formation of a carbon−nitrogen bond. Extensive screening revealed that the optimal ligand/base combination was dppf/DBU and that the addition of magnesium sulfate significantly improves the yield. Electron-donating and -withdrawing substituted bromobenzaldehydes as well as various aryl- and alkylhydrazines performed equally well under the reaction conditions.

ZINC-CATALYZED OXIDATION OF BENZYL ALCOHOLS TO ALDEHYDES AND ESTERS



Xiao-Feng Wu has described a simple and efficient protocol for the oxidation of benzyl alcohols to aldehydes and esters (*Chem.—Eur. J.* **2012**, *18*, 8912−8915). Both reactions take place at room temperature and are catalyzed by zinc(II) bromide with pyridine 2,6-dicarboxylic acid as ligand and TFA as additive. The formation of aldehydes is performed in THF with 4 equiv of hydrogen peroxide while the esters are obtained in MeOH with 6 equiv of the oxidant. Variously substituted benzyl alcohols (and two furylmethanols) furnished the corresponding oxidized product in fair to high yields.

REVIEW OF LASER REFLECTANCE MEASUREMENT TECHNOLOGY

The article, *Chem. Eng. Technol.* **2012**, *35*, 967−979, presents a recent review which discusses the focused beam reflectance (FBRM, Lasentec/Mettler Toledo) and three-fold dynamical optical reflectance measurement devices (3D ORM, MTS Düsseldorf), respectively. The article covers the measurement principles, the chord length deconvolution, and the influence of suspension density on counts and size distribution. Several works that focus on the crystallization kinetics determination are highlighted.

PRODUCTION OF SUBMICROMETER PARTICLES USING ELECTROSPRAYING

The electrospray crystallization process was the subject of investigation as a promising candidate for the continuous production of submicrometer particles. In a recent work (*Cryst. Growth Design* **2012**, *12*, 3514−3520) the following process parameters have been closely studied: nozzle diameter, flow rate, potential difference, initial solute concentration, and distance between the nozzle tip and grounded plate. The authors concluded that submicrometer particles in the 200−800-nm range can be produced; however, the operation range is limited by agglomeration. This work also investigated the effect of the D-mannitol and Poloxamer 188 on the size of the particles and eventually on the dissolution rate; the study has shown that the dissolution rate can be significantly enhanced by the presence of these excipients.

Another study on the topic of electrospray processing (*J. Pharm. Sci.* **2012**, *101*, 1178−1188) investigated the influence of the carbamazepine concentration, solution conductivity, flow rate, voltage, and current on the particle diameter, morphology, and solid state. The obtained particle size was between 320 and 1756 nm, and it was found that the size increases with the flow rate. The obtained particles were mostly amorphous.

Wenyi Zhao

Jacobus Pharmaceutical Co. Inc., Princeton, New Jersey 08540, United States. E-mail: Wenyi38@hotmail.com

Dongbo Zhao

Bayer Technology & Engineering (Shanghai) Co., Ltd., 82 Mu Hua Road, Shanghai Chemical Industry Park, Shanghai 201507, P.R. China.
E-mail: tony.zhao@bayer.com

Aman A. Desai

Process Science, Core R&D, The Dow Chemical Co., 1710 Building, Midland, Michigan 48674, United States.
E-mail: AADesai@dow.com

Rodrigo Octavio Mendonça Alves de Souza

Chemistry Institute, Federal University of Rio de Janeiro, Athos da Silveira Ramos Street, 149, Rio de Janeiro 24230153, Brazil.
E-mail: souzarod21@gmail.com

Sylvain Guizzetti

Building A: Chemistry, NovAlix, Bioparc, bld, Sébastien Brant BP 30170, F-67405 Illkirch Cedex, France.
E-mail: sg@novalix-pharma.com

Levente Simon

BASF Schweiz AG, Rheinfelderstrasse, CH 4133, Schweizerhalle, Switzerland.
E-mail: levente.simon@basf.com

John Knight*

Scientific Update LLP, Maycroft Place, Stone Cross Mayfield, East Sussex TN20 6EW, United Kingdom.

AUTHOR INFORMATION

Corresponding Author

*john@scientificupdate.co.uk