Organic Process Research & Development **2008,** *12,* 807–816

Green Chemistry Highlights

Green Chemistry Articles of Interest to the Pharmaceutical Industry

1. Introduction

Pharmaceutical companies and the American Chemical Society's (ACS) Green Chemistry Institute (GCI) developed the ACS GCI Pharmaceutical Roundtable (Roundtable) in 2005 to encourage the integration of green chemistry and green engineering into the global pharmaceutical industry. The Roundtable now consists of nine member companies including AstraZeneca, Boehringer-Ingelheim, Eli Lilly and Company, GlaxoSmithKline, Johnson & Johnson, Merck & Co., Inc., Pfizer, Schering-Plough, and Wyeth. One of the strategic priorities of the Roundtable is to inform and influence the research agenda. An initial step to achieve this objective was to publish a paper outlining key green chemistry research areas from a pharmaceutical perspective (*Green Chem.* **2007**, *9*, 411−420). Beginning in 2007 we undertook a literature review program against the strategic research areas for the purpose of sharing that information within the companies represented in the Roundtable.

This document covers the whole of 2007, and sections for new strategic research areas have been added: Chemistry in Water, Process Intensification, Friedel−Crafts Chemistry, and SFC Separations. For the new sections, the review period is 2006 and 2007.

These articles of interest represent the opinions of the authors and do not necessarily represent the views of the various companies. 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

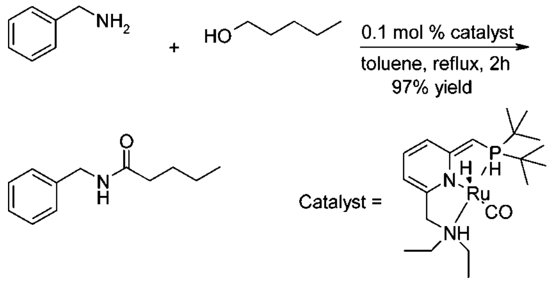
Slater and Savelski from Rowan University published a method to characterize the greenness of solvents used in pharmaceutical manufacture and used the methodology in two case studies: (i) a development compound from Bristol-Meyers Squibb and (ii) sildenafil citrate from Pfizer. (*J. Environ. Sci. Health* **2007**, *42*, 1595−1605). In both cases the Rowan Greenness score was assessed all the way from medicinal chemistry through to pilot plant or the commercial synthesis.

Leeke et al. reported on a Suzuki reaction between a boronic acid and an aryl iodide which is carried in supercritical CO_2 containing a small amount of a toluene and methanol cosolvent. (*Org. Process Res. Dev.* **2007**, *11*, 144−148)

Imperato et al. published a microreview on ionic solvents from renewable resources. The toxicity of ionic liquids to fish and aquatic species is often problematic for industrial applications. The use of ionic liquids derived from biorenewable and biodegradable materials are of considerable interest. (*Eur. J. Org. Chem.* **2007**, 1049−1058)

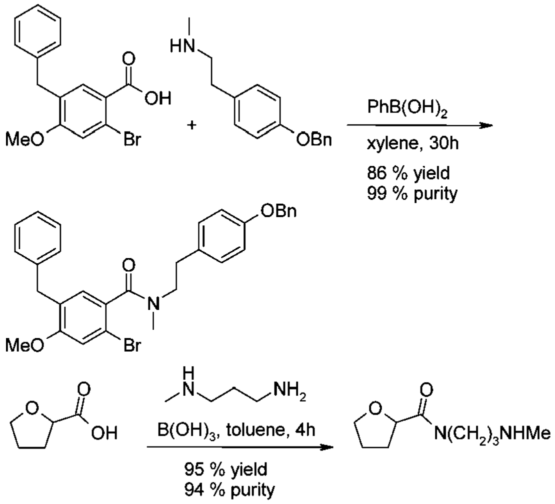
Solvent-free and highly concentrated reactions are often a way to reduce environmental impact. Walsh et al. reports on these types of conditions in combination with asymmetric catalysis. (*Chem. Rev.* **2007**, *107*, 2503−2545)

3. Amide Formation



Milstein et al. published an account of the reaction of primary alcohols with amines catalyzed by 0.1 mol % of a ruthenium catalyst to give an amide or ester with the liberation of two moles of hydrogen gas. (*Science* **2007**, *317*, 790−792) The reaction is very sensitive to steric hindrance at the α-position of the alcohol, so this reaction may not have the wide utility preferred for pharmaceutical applications. Nevertheless, conceptually this is a very interesting reaction which is in principle more environmentally benign than traditional alternatives.

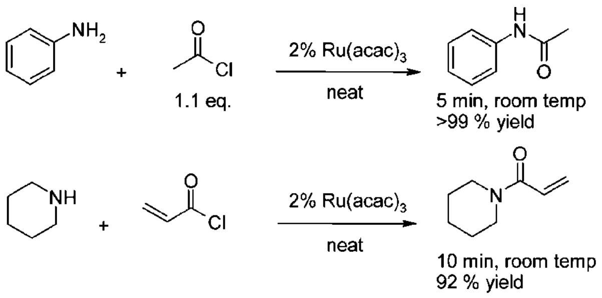
Bandichhor et al. published a paper describing the use of boric acid to catalyze the reaction between acids and amines to prepare seven drug substance-related molecules. Boric acid is cheap, environmentally benign, and easy to remove by filtration or washing. (*Org. Process Res. Dev.* **2007**, *11*, 1065−1068)



Varala et al. published a communication detailing the use of catalytic $Ru(acac)_3$ to acetylate phenols, alcohols, and amines under neat conditions. (*Can. J. Chem.* **2007**, *85*, 148−152) This solvent-free and highly atom-economic reaction (in the case of

10.1021/op800175p CCC: $40.75

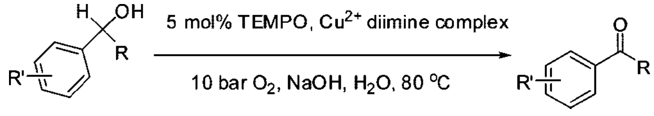
amide formation) is expanded to illustrate other esters and amides that can be prepared.



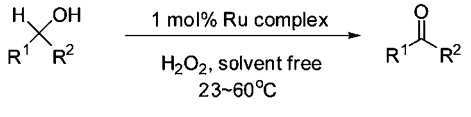
4. Oxidations

The selective catalytic oxidation of alcohols to their corresponding carbonyl compounds is an important but challenging task for modern organic synthesis and the chemical industry. Many stoichiometric oxidants are known for the oxidation of alcohols such as chromates, hypochlorite, permanganates, and others. However, their main disadvantage is that most of them are toxic and produce large amounts of waste. Nonwaste-producing oxidants such as air and hydrogen peroxide provide a base for more environmentally friendly and relatively cheap systems.

Figiel et al. recently demonstrated an aerobic oxidation of benzylic alcohols catalyzed by in situ-generated copper (II) diimine and TEMPO in aqueous alkaline solutions, where dioxygen was used as an end oxidant. (*Adv. Synth. Catal.* **2007**, *349*, 1173−1179) This simple catalytic system turned out to be highly efficient and selective in the oxidation of primary and secondary benzylic alcohols to their corresponding carbonyl compounds under mild conditions [5 mol% of TEMPO, 3 mol% of copper (II) diimine, pH 12.6−13.5, 80 °C, 10 bar O_2]. A plausible reaction mechanism was proposed for the oxidation reaction according to ESI-MS studies.

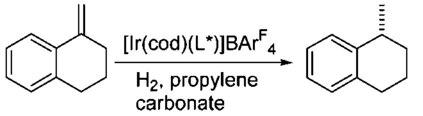


Besides molecular oxygen, hydrogen peroxide is a suitable green and waste-avoiding oxidant. Shi et al. reported aliphatic and benzylic alcohols are oxidized to the corresponding aldehydes or ketones in the presence of [Ru(terpyridine)(2,6-pyridinedicarboxylate)] with high selectivity by using hydrogen peroxide as the oxidant. (*Chem. Asian J.* **2007**, *2*, 411−415) There is no need for the addition of cocatalysts or organic solvents. By applying an optimized reaction protocol, high catalyst productivity (turnover number greater than 10,000) and activity (turnover frequency up to 14,800 h^{-1}) has been achieved.

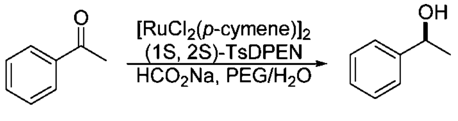


5. Asymmetric Hydrogenations

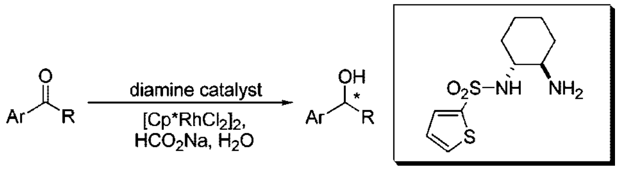
Borner et al. report the successful use of propylene carbonate as solvent for asymmetric hydrogenation reactions. (*Angew. Chem., Int. Ed.*, **2007**, *46*, 5971−5974) Propylene carbonate is a dipolar aprotic solvent that is nontoxic and biodegradable. Using iridium catalysts with commercially available diphosphane ligands, catalytic activities and enantioselectivities are obtained that are comparable to conventional solvents. Another advantage of this approach is that the catalyst can be recycled if the product is soluble in a nonpolar solvent and if the catalyst is soluble in propylene carbonate.



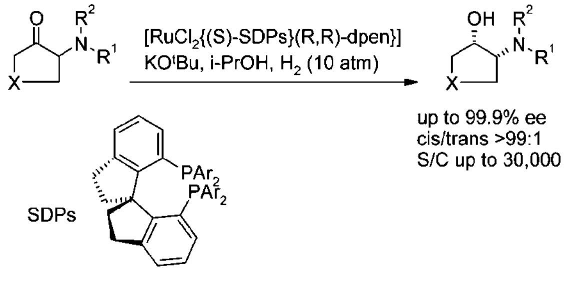
Chan et al. report that asymmetric transfer hydrogenations can be conducted in a mixture of poly(ethylene glycol) (PEG) and water. (*J. Mol. Catal. A: Chem.* **2007**, *275*, 47−53) PEG polymers are inexpensive and nontoxic. By performing the reaction in PEG/H_2O and extracting the reaction mixture with a nonpolar solvent (assuming the product is soluble in this solvent), the catalyst can be immobilized in the PEG/H_2O layer and can be recycled (the catalyst is insoluble in nonpolar solvents such as hexane). High activity and enantioselectivity are obtained for the asymmetric transfer hydrogenation of a variety of aromatic ketones. The catalyst can be recovered and reused at least 14 times without any loss of enantioselectivity.



Somanathan et al. reported on the successful use of new water-soluble chiral monosulfonamide ligands for the asymmetric transfer hydrogenation of ketones. (*Tetrahedron Lett.* **2007**, *48*, 4335−4338) By replacing the tosyl group of the previously reported ligands with a more water-soluble, heteroatom-containing sulfonamide, the activity of the asymmetric transfer hydrogenation catalyst was increased in water compared to isopropanol. Using a rhodium catalyst complexed with the diamine and sodium formate as the hydrogen source, secondary alcohols were produced with >93% ee and >89% yield.



Zhou et al. recently reported a highly efficient method for preparing optically active *N*, *N*-disubstituted *cis*-aminocycloalkanols involving the dynamic kinetic resolution (DKR) of racemic α-aminocycloalkanones by ruthenium-catalyzed asymmetric hydrogenation. (*Angew. Chem., Int. Ed.* **2007**, *46*, 7506−7508) Excellent enantioselectivities (up to 99.9%) and *cis*-diastereoselectivities (*cis*/*trans* > 99:1) are obtained with S/C ratios of up to 30,000 using a series of [(diphosphine)Ru(II) diamine] complexes containing SDP ligands (**1**). The hydrogenation results indicate a tolerance for different substituents on the dialkylamino group in terms of both enantioselectivity and diastereoselectivity.



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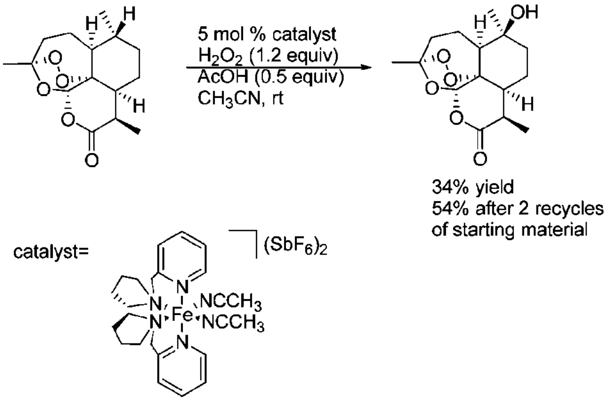
Wu and Xiao published a review on the asymmetric transfer hydrogenation of ketones in water. (*Chem. Commun.* **2007**, 2449−2466) Asymmetric transfer hydrogenations in water using normal (organic-soluble) catalysts, water-soluble catalysts, supported catalysts, and biomimetic analogues are reviewed. The benefits and limitations of performing these reactions in water are also discussed.

A special issue of *Accounts of Chemical Research* on hydrogenation features some excellent reviews on asymmetric hydrogenation. (*Acc. Chem. Res.* **2007**, 40, 1237−1419) Reviews by Zhou on the asymmetric hydrogenation of heteroaromatic compounds, by Pfaltz and Roseblade on iridium-catalyzed asymmetric hydrogenation of olefins, and reviews by four industrial groups on the commercial application of this technology have been released on the Web.

6. C−H Activation

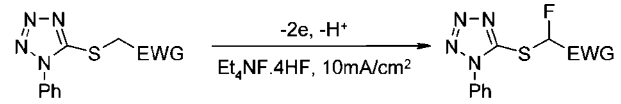
Chen and White report on the selective oxidation of unactivated, aliphatic C−H bonds without the requirement of directing groups and with the use of hydrogen peroxide as the oxidant. (*Science* **2007**, *318*, 783−787) Either sterics (least hindered) or electronics (preference for tertiary C−H, remote from EWGs) can be used to selectively and predictably oxidize a single C−H bond even in complex natural product examples in moderate yields (54% after recycling the starting material twice). Although a directing group is not required, carboxylic acids can be used to direct lactone formation. Stereochemical integrity is maintained at the reacting centre. Although the scope is narrow and the yields are still moderate, this is an impressive example of C−H activation.



7. Greener Fluorination

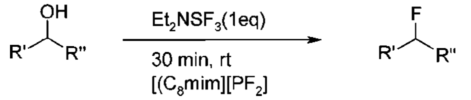
Mason et al. published a review on microreactor technology with a section on the synthesis of fluorine-containing molecules. (*Chem. Rev.* **2007** *107*, 2300−2318) The microreactor technology is much safer than using F$_2$/HF in batch reactors.

Meanwhile, electrolytic partial fluorination was also demonstrated by Fuchigami et al. (*J. Fluorine Chem.* **2007**, *128*, 1168−1173) Anodic electrochemical fluorination is selective. Although the yields are sometimes modest, it is a green way to avoid Selectfluor and *N*-fluoropyridinium salts.

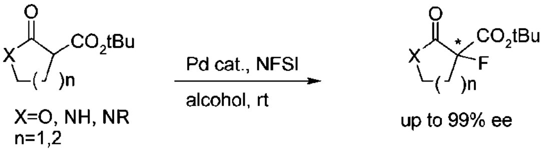


Stavber et al. demonstrated direct fluorination under solvent-free conditions using electrophilic fluorinating reagents from the N−F class. (*Tetrahedron Lett.* **2007**, *48*, 2671−2673) Solvent-free fluorination was efficiently and selectively achieved on a variety of β-diketones, β-keto esters, acetylated monoketones, and activated aromatic derivatives.

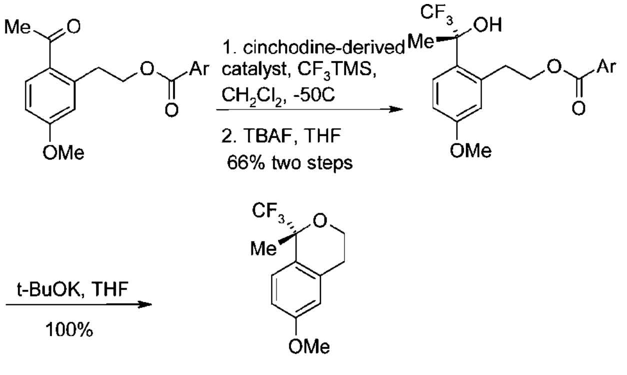
Das et al. reported ionic liquids as recyclable solvents for diethylaminosulfur trifluoride (DAST)-mediated fluorination of alcohols and carbonyl compounds. (*Tetrahedron Lett.* **2007**, *48*, 5305−5307) The ionic liquids replace chlorinated solvents.



Suzuki et al. published enantioselective fluorination of *tert*-butoxycarbonyl lactones and lactams catalyzed by chiral Pd(II)−bisphosphine complexes. (*J. Org. Chem.* **2007**, *72*, 246−250) The synthesis of chiral fluorine molecules from active methylene compounds shows high efficiency (yield, ee) at ambient temperature in alcohols.

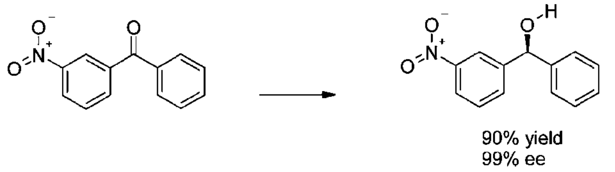


An enantioselective trifluoromethyl addition to a ketone was demonstrated by a process group at Pfizer to prepare a key chiral intermediate toward a chiral isochroman. (*Org. Process Res. Dev.* **2007**, *11*, 1015−1024) This chemistry avoids a resolution and much of the expected C−F chemistry using trifluoroacetic anhydride.

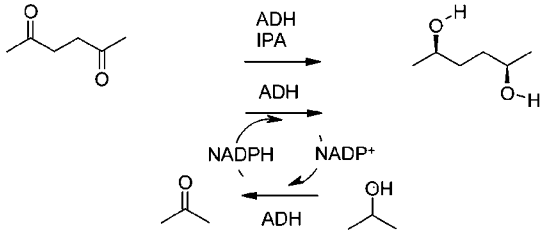


8. Biocatalysis

Alcohol dehydrogenases are rapidly becoming the technology of choice for the reduction of ketones to chiral alcohols. (*Acc. Chem. Res.* **2007**, *40*, 1260−1266) A recent paper from the Merck group reported the very efficient reduction of diaryl ketones to give chiral alcohols that would be difficult to synthesize by other means. (*Org. Lett.* **2007**, *9*, 335 − 338)

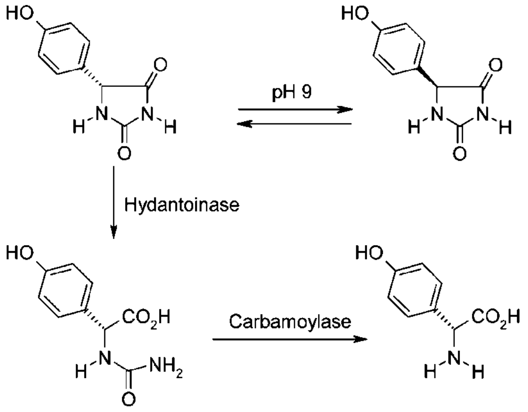


The efficient recycling of the NAD/NADP cofactors is crucial to the economic success of any ADH reaction. Schroer et al. reported the use of isopropanol in the reduction of 2,5-cyclohexadione to (*R,R*)-2,5-cyclohexanediol. (*Org. Process Res. Dev.* **2007** *11*, 836−841) The use of pervaporation to remove acetone increased the yield from 54% to 90%.



Other publications in the area of ADH chemistry include the combined use of ADH and nitrilase enzymes to prepare homochiral β-hydroxy acids from β-ketonitriles (*Org. Lett.* **2007**, *9*, 2561−2563) and a paper by Faber et al. which described the use of an ADH from *Rhodococcus ruber* in aqueous-solvent microemulsions for the reduction of poorly water-soluble ketones. (*Org. Lett.* **2007**, *9*, 2163−2166)

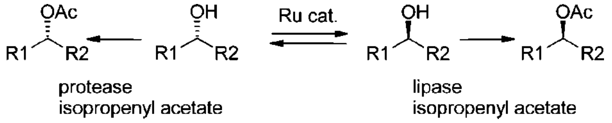
The Kaneka group published a manufacturing route to D-*p*-hydroxyphenyl glycine using a dual enzyme system comprising a hydantoinase and carbamoylase. (*Org. Process Res. Dev.* **2007**, *11*, 503−508) The unwanted enantiomer undergoes spontaneous racemization under the reaction conditions, thus driving the reaction to one homochiral product. The product is used in the manufacture of amoxicillin, and the technology can be used for the manufacture of other amino acids.



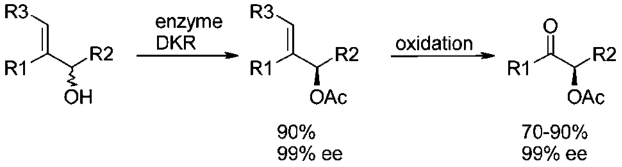
A large-scale synthesis of statin intermediates using ADH enzymes was also described.

Conversion of racemic mixtures into single enantiomers via deracemization, stereoinversion, or dynamic kinetic resolution is an efficient and clean way to produce chiral synthons. Arosio et al. describe an efficient DKR reaction using a readily available detergent protease. (*Adv. Synth. Catal.* **2007**, *349*, 1345−1348) The use of a thio ester enables racemization of the unreacted ester enantiomer under the conditions used for the bioresolution.

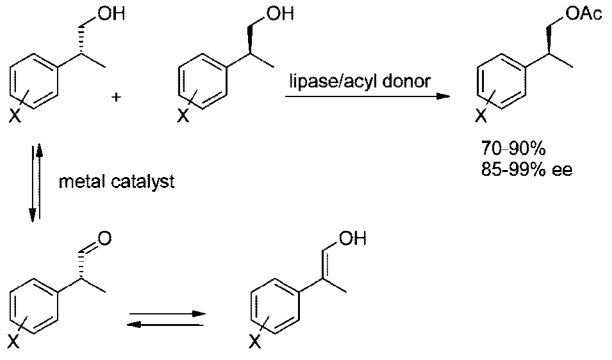
Park et al. reported a further improvement to the redox catalyst in their DKR reaction. (*J. Org. Chem.* **2007**, *72*, 6860−6864) The new catalyst is air-stable, works at ambient temperature and can tolerate isopropenyl acetate as the acyl donor. The improvement arises from replacement of a CO ligand in the Ru complex with an R_3P ligand. One drawback is that Ag_2O needs to be present as a cocatalyst. (*R*)- or (*S*)-alcohols can be produced, depending on the enzyme stereoselectivity.



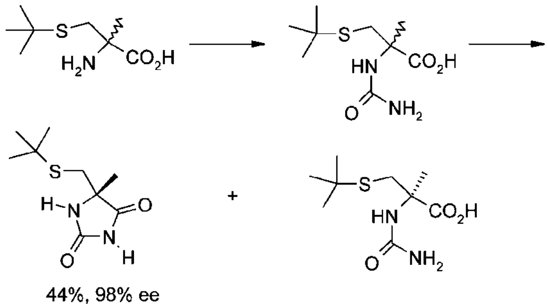
The key to a successful DKR is the identification of a redox catalyst that will work in tandem with the enzyme. Usually these are fairly complex molecular ruthenium complexes, but Zhu et al. report success with a Zr-doped zeolite material. (*Chem. Eur. J.* **2007**, *13*, 541−547) A further example of a DKR, to prepare chiral acyloin acetates through resolution of an allylic alcohol, is reported by Bogar et al. (*Org. Lett.* **2007**, *9*, 3401−3404)



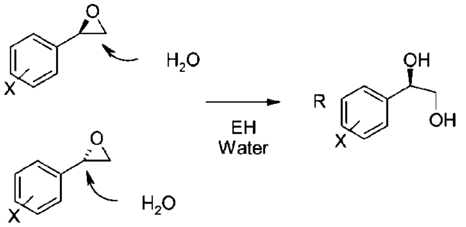
Most enzyme-catalyzed DKR reactions are limited to producing acids, amines, and secondary alcohols. Bäckvall et al. report a DKR that produces a chiral primary alcohol where the chiral centre is β from the hydroxyl function. (*Adv. Synth. Catal.* **2007**, *349*, 1577−1581) The undesired enantiomer is racemized in situ via the aldehyde. The product ester is unaffected.



The Kaneka group report an unusual stereoselective ring closure in water catalyzed by a hydantoinase. (*Tetrahedron Lett.* **2007**, *48*, 3437−3440) The technology can be used to prepare useful chiral quaternary amino acids or hydantoins.

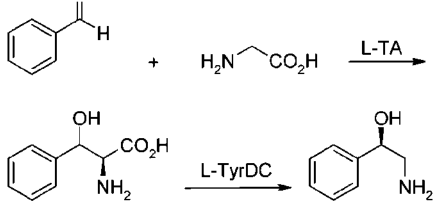


Epoxide hydrolases (EH) are an emerging class of enzymes that have a great deal of potential in the green synthesis of chiral diols. Factors holding back the adoption of this technology on scale are poor throughput and sensitivity of the EH enzymes under processing conditions. Mateo et al. published an interesting study where large improvements have been demonstrated by enzyme immobilization. (*Tetrahedron: Asymmetry* **2007**, *18*, 1233−1238) The EH from *Solanum tuberosum* acts in an enantioconvergent fashion by hydrolyzing each enantiomer either at the benzylic or primary carbon to give only one diol in high enantiomeric excess.

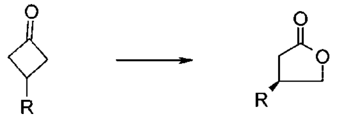


A DSM group describes the synthesis of β-hydroxyl amino acids using threonine aldolase (TA), thereby allowing access to complex chiral molecules from simple aldehydes and glycine. L-selective TA give products with high ee (99%) and de (99%). D-TA give high ee (99%), but poor de (~50%). (*Tetrahedron* **2007** *63*, 918−926)

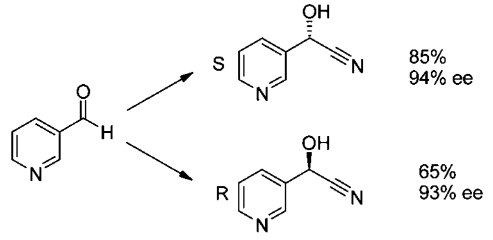
Combination of threonine aldolase with L-tyrosine decarboxylase (L-TyrDC) yields chiral β-amino alcohols. (*Angew. Chem., Int. Ed.* **2007**, *46*, 1624−1626)

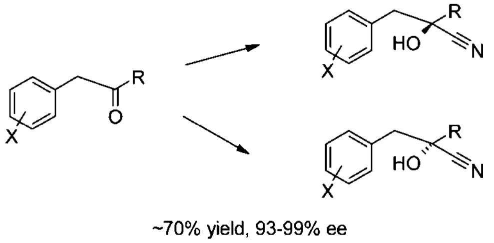


The use and uptake of cyclohexanone monooxygenases capable of carrying out chiral Baeyer−Villiger oxidations have been severely limited by substrate/product inhibition and enzyme stability under process conditions. Wohlgemuth reports the progress made in the use of ISPR to increase substrate concentrations from ~0.5 g L^{-1} to 25 or more g L^{-1}, making these reactions a much more attractive prospect for scale-up. (*Biocatal. Biotransform.* **2007**, *25*, 178−185).

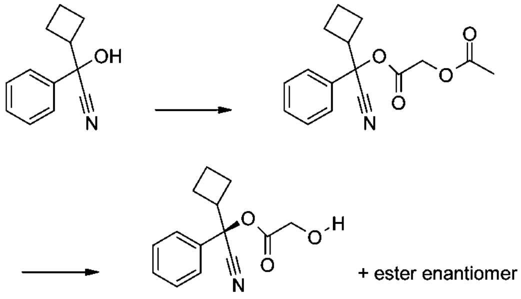


Chiral cyanohydrins are useful for the preparation of a wide variety of pharmaceutical intermediates. Two papers from the Merck group describe the use of hydroxyl nitrile lyases (HNL) to make chiral cyanohydrins from aldehydes and ketones. (*Tetrahedron Lett.* **2007**, *48*, 1473−1477; *Tetrahedron: Asymmetry* **2007**, *18*, 208−214) The enzymes are used as cross-linked aggregates, thus facilitating removal from the reaction mixture and reuse. Both isomers are available since both *R*- and *S*-selective HNLs are available.





Hindered cyanohydrins can be problematic to prepare as single enantiomers using HNL chemistry. Recuero published a resolution using simple spacer groups to move the site of enzyme hydrolysis away from the hindered quaternary carbon. (*Tetrahedron: Asymmetry* **2007**, *18*, 994−1002) Products are usually obtained in excellent ee (99%) using simple lipases like those of *Candida antarctica* or *Pseudomonas cepecia*. The stereochemistry of the product is governed by choice of lipase.

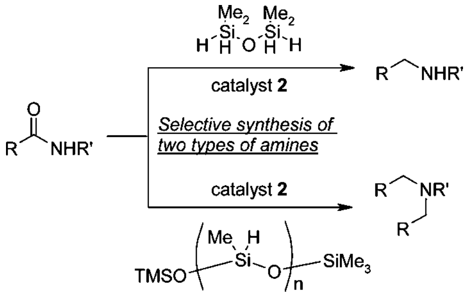


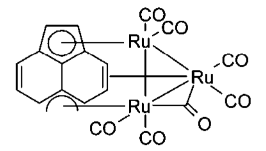
Pig liver esterase has been shown to be a highly useful enzyme in biocatalysis, often showing complementary enantioselectivity and reactivity patterns to those of most lipases. This enzyme is often used for the resolution of bulky substrates and the desymmeterization of meso compounds. However, its use on a large scale for pharmaceutical intermediates is hampered by concerns over the viral and TSE contamination. A DSM group reports that they have cloned and overexpressed an isoenzyme of pig liver esterase into a yeast. (*J. Biotechnol.* **2008**, *133*, 301−310) This totally non-mammalian esterase can be produced on a large scale and used for the manufacture of chiral synthons at scale.

Finally, Sheldon published a comprehensive review looking at enzyme immobilization and microchannel reactors for biocatalysis. (*Adv. Synth. Catal.* **2007**, *349*, 1289−1307)

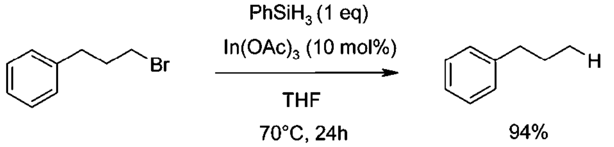
9. Reductions

Amide reduction using hydrosiloxanes or hydrosilanes present air- and moisture-stable alternatives to conventional metal hydride reagents. They have recently been used to good effect for tertiary amide reductions, but secondary amides have remained problematic. Nagashima et al. have successfully met this challenge through the use of a catalytic ruthenium cluster complex to activate various hydrosiloxanes, achieving selective reduction of secondary amides to either secondary amines or tertiary amines via judicious choice of hydrosilane. (*J. Org. Chem.* **2007**, *72*, 7551−7559) In a related approach, Fernandes and Romão access both secondary and tertiary amines *via* dioxomolybdenum dichloride-catalyzed silane reductions of the corresponding amides. (*J. Mol. Cat. A: Chem.* **2007**, *272*, 60−63)

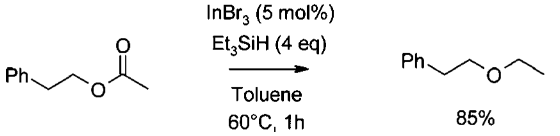



catalyst **2**

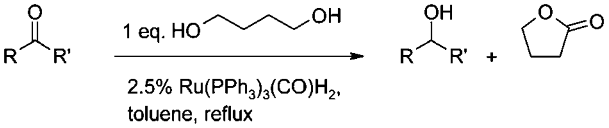
Also recently reported are reductions of a wide range of other functionalities, using metal-catalyzed hydrosilane reductants that, while not without limitations, generally offer improvements to conventionally utilized alternatives. Miura et al. and Brookhart used indium- and iridium-catalyzed alkyl halide reductions, respectively, in approaches that present alternatives to toxic tin or expensive (TMS)$_3$SiH reductants. (*J. Org. Chem.* **2007**, *72*, 787−792 and *J. Am. Chem. Soc.* **2007**, *129*, 12656−12657)



Mandal and McMurray use Pd−C-induced catalytic transfer hydrogenation with triethylsilane to reduce a wide range of substrates containing multiple bonds, azides, imines, and nitro groups under mild, neutral conditions. (*J. Org. Chem.* **2007**, *72*, 6599−6601) Yun et al. report enantioselective conjugate reduction of unsaturated nitriles via copper hydride catalysis, generated by the action of copper (II) acetate, Josiphos ligand, and inexpensive polymeric hydrosiloxane. (*Synthesis* **2007**, 2233−2235) Lemaire et al. report a potentially useful approach to phosphine oxide reduction via Ti(O-^{i}Pr)$_4$-catalyzed hydrosiloxanes. (*Synlett* **2007**, 1545−1548) Finally, Sakai et al. report a one-pot procedure for a direct reductive conversion of the carbonyl function of esters to the corresponding ethers by Et$_3$SiH in the presence of catalytic InBr$_3$. (*J. Org. Chem.* **2007**, *72*, 5920−5922)

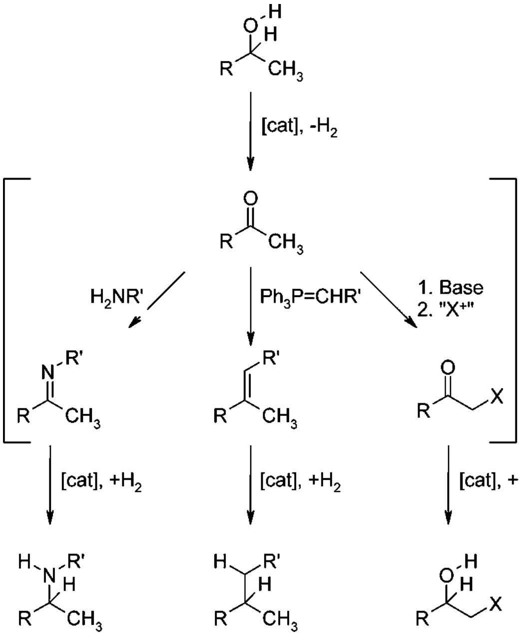


Williams et al. published a transfer hydrogenation method for carbonyl moieties utilizing 1,4-butanediol as the hydrogen source in conjunction with a ruthenium catalyst. (*Org. Lett.* **2007**, *9*, 4387−4389) The butanediol provides hydrogen, irreversibly resulting in ring closure to γ-butyrolactone, thus eliminating the necessity for a large molar excess of a hydrogen donor as is necessary when using isopropanol or similar sources. A number of aldehydes and benzylic ketones are exemplified, with isolated yields typically between 80 and 90%.



10. Alcohol Activation for Nucleophilic Displacement

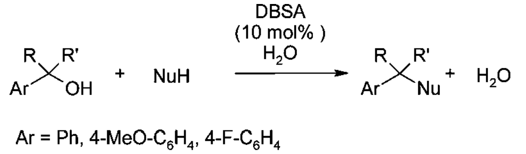
Hydrogen autotransfer (metal-catalyzed oxidative hydrogen elimination, reaction of the resulting aldehyde and reductive hydrogen addition to the double bond of the product) is a productive method for alcohol activation. Typically, an iridium or ruthenium catalyst is used. A recent review by Williams et al. covers the literature to 2006 and includes progress with the amination of alcohols, formation of nitrogen heterocycles, N-heterocyclization, C−C bond formation, and β-functionalization. (*Adv. Synth. Catal.* **2007**, *349*, 1555−1575).



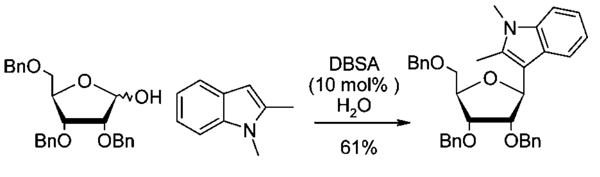
Milstein and co-workers have elaborated the approach to the first synthesis of amides from alcohols and amines, as discussed in section 3.

Brønsted acid activation of allylic, benzylic, and propargylic alcohols towards nucelophilic substitution has been applied to a variety of reactions. Shirakawa and

Kobayashi reacted benzyl alcohols with a range of carbon-centred nucleophiles in water using dodecylbenzenesulfonic acid as a surfactant-type Brønsted acid. (Org. Lett. **2007**, 9, 311−314) C-Glycosylation of 1-hydroxy sugars is achieved with good (>20:1) β-selectivity.

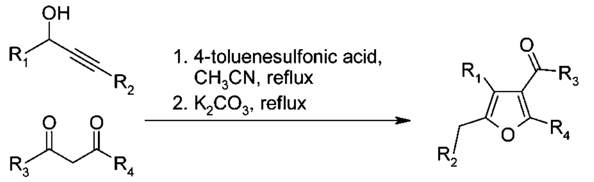


Ar = Ph, 4-MeO-C_6H_4, 4-F-C_6H_4

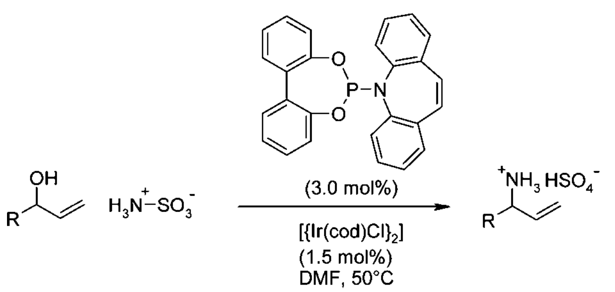


DBSA = $C_{12}H_{25}$-$C_6H_4SO_3H$

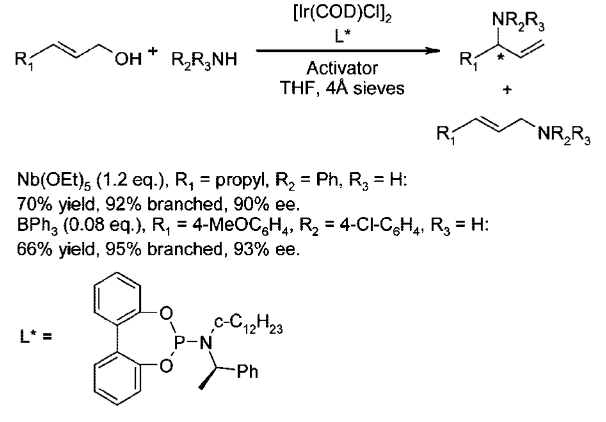
Kaneda et al. demonstrate the use of montmorillonite catalysts to react allylic, benzylic, and cyclohexyl alcohols with amines, activated aromatic compounds, 1,3-dicarbonyl compounds, and allyl silanes. (*J. Org. Chem.* **2007**, 72, 6006−6015) Zhou et al. alkylate 1,3-dicarbonyl compounds (diketones, diesters, and β-keto esters) with a range of allylic and benzylic alcohols in the presence of catalytic ytterbium triflate. (*Tetrahedron Lett.* **2007**, 48, 3969−3973) Sanz et al. use catalytic *p*-toluenesulfonic acid monohydrate in the propargylation of 1,3-diketones in good yield; yields are lower with a β-keto ester. (*Org. Lett.* **2007**, 9, 727−730) Subsequent treatment with potassium carbonate affords a one-pot synthesis of tetrasubstituted furans.



Iridium catalysts have been used to activate allylic alcohols towards amination. Carreira et al. use sulfamic acid as an ammonia equivalent. (*Angew. Chem., Int. Ed.* **2007**, 46, 3139−3143) Reactions are run in DMF. The solvent may participate in generation of a reactive intermediate for the amination. Use of a chiral phosphoramidite ligand results in a 70% ee.



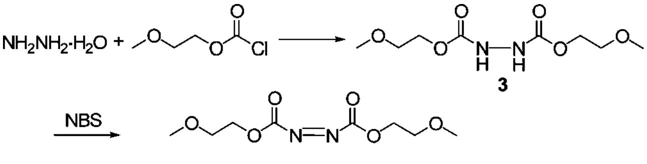
In related work, Hartwig et al. achieve asymmetric amination of terminal allylic alcohols with a range of anilines, using chiral phosphoramidite ligands and an activator, either stoichiometric niobium ethoxide or catalytic triphenylborane. (*J. Am. Chem. Soc.* **2007**, 129, 7508−7509) Good selectivity for branched over terminal amines is achieved, and enantiomeric excess is typically between high 80 and mid 90% ee.



$Nb(OEt)_5$ (1.2 eq.), R_1 = propyl, R_2 = Ph, R_3 = H:
70% yield, 92% branched, 90% ee.
BPh_3 (0.08 eq.), R_1 = 4-$MeOC_6H_4$, R_2 = 4-Cl-C_6H_4, R_3 = H:
66% yield, 95% branched, 93% ee.

11. Greener Mitsunobu Reaction

Sugimura recently developed di-2-methoxyethyl azodicarboxylate (DMEAD) as an alternative to DEAD (diethyl azodicarboxylate), the classical reagent used in the Mitsunobu reaction. (*Chem. Lett.* **2007**, 36, 566−567) DMEAD is prepared in a two-step sequence. Hydrazine hydrate is treated with 2-methoxyethyl chloroformate to produce di-2-dimethoxyethyl hydrazine carboxylate (**3**). Subsequent NBS-mediated oxidation provides DMEAD in good yield.



3

DMEAD

Hydrazine dicarboxylate **3** is a key byproduct of the Mitsunobu reaction. DMEAD's primary advantage over DEAD, and DIAD (diisopropyl azodicarboxylate) lies in the fact that the hydrazine carboxylate **3** byproduct is water soluble (0.55 g/mL). As such, it is readily removed from the reaction mixture by extraction with neutral water, as opposed to silica gel column chromatography. *Further, **3** can be recovered after concentration and recycled back to DMEAD for reuse.* The method still suffers from the classical problem of removing the $Ph_3P{=}O$ byproduct (typically done by silica gel column chromatography). Sugimura also does a head-to-head comparison of the use of DMEAD and DIAD in terms of purity and yield. In all cited examples, DMEAD perform as well or better than DIAD.[1]

12. Friedel−Crafts Chemistry

Baba et al. highlight the application of In(III)-mediated chemoselective dehydrogenative interaction of $ClMe_2SIH$ with carboxylic acids, via in situ acid chloride synthesis. (*Org. Lett.* **2007**, 9, 405−408) Despite the majority of examples involving the use of both activated aromatic partners (i.e., anisole) and chlorinated solvents (1,2-DCE), some exceptions are reported,

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(1) The author did note that Lipshutz recently reported preparation of di-*p*-chlorobenzyl azodicarboxylate (DCAD), where the hydrazine dicarboxylate can be removed via crystallization. See: Lipshutz, B. H.; Chung, D. W.; Rich, B.; Corral, R. *Org. Lett.* **2006**, 22, 5069−5072, for details. http://dx.doi.org/10.1021/ol0618757.

such as intramolecular reactions on unactivated aromatics, the use of toluene (competitive acylation was not observed), or the absence of solvent in several examples. Of particular interest is the unusual application of this mild and moisture-tolerant indium catalyst in the presence of free hydroxyl moieties and also the ability to use only 5−30 mol % metal catalyst, compared to stoichiometric $AlCl_3$.

See also the section on acid catalysis in section 16: General Green Chemistry.

13. Chemistry in Water

Water is an environmentally benign solvent. Organic reactions in water have received tremendous attention in recent years. Chao-Jun Li et al. updated the progress made over the past decade on developing organic reactions in aqueous media. (*Chem. Rev.* **2005**, *105*, 3095−3165 and *Chem. Soc. Rev.* **2006**, *35*, 68−82) Another well-received book *Organic Reactions in Water*; Lindström, U. M., Ed., was published in 2007 by Blackwell Publishing Ltd., Oxford, U.K. (ISBN: 9781405138901), covering various topics including acid catalysis, metal-mediated C−C bond formation, pericyclic reactions, nucleophilic additions/substitutions, and biocatalysis in water.

Blackmond et al. warned about the simplistic approach that all reactions in water are green. (*Angew. Chem., Int. Ed.* **2007**, *46*, 3798−3800) For example, pure water is nontoxic, but a water stream contaminated with organics is not. “Water should only be considered a green solvent if the aqueous waste stream can be directly discharged to a biological effluent treatment plant.”

See also the *Chem. Commun.* paper by Wu and Xiao in the asymmetric hydrogenation section (section 5) for reports of these reactions performed in water.

14. Process Intensification

Process intensification refers to an approach to engineering design that strives to increase process efficiency and ultimately reduce the size of plant process equipment by 10 to 1000 times. The main driver behind process intensification is the economic benefit of smaller plant equipment with equal capacity. However, there are many side benefits that stem from this approach. Some of the environmental benefits of process intensification are reductions in energy consumption, solvent usage, and waste stream production. There are several approaches to process intensification, including continuous processing, intensive reactor designs with high heat- and mass-transfer rates, “multifunctional” process equipment that combines two or more unit operations, and concurrently improving process technology and underlying chemistry (atom efficiency). Process intensification is not new to the broader chemical industry. However, the introduction in the fine chemicals and pharmaceutical industries has been more gradual. Recently, Professor Steven Ley’s group at Cambridge has been involved in telescoped multistep syntheses of complex molecules using immobilized reagents, scavengers, and catch-and-release protocols (*Chem. Commun.* **2006**, 4835−4837) Jensen et al. recently reported a continuous multistep microchemical synthesis of carbamates from azide via an isocyanate intermediate without isolation. (*Angew. Chem., Int. Ed.* **2007**, *46*, 5704−5708) Yoshida et al. demonstrated the use of microreactors for effectively controlling reactions involving highly unstable intermediates such as *o*-bromophenyllithium, which is known to decompose to benzyne very quickly even at −78 °C. (*J. Am. Chem. Soc.* **2007**, *129*, 3046−3047) Professor Livingston’s group has recently published a novel idea for continuous dynamic kinetic resolution involving two catalysts. One of the catalysts is retained in a lower temperature vessel with a microfiltration membrane, allowing the racemization to occur efficiently in a higher-temperature vessel (membrane-enhanced dynamic kinetic resolution” (MEDKR) concept) as shown in the figure below. (*Chem. Commun.* **2007**, 3462−3463)

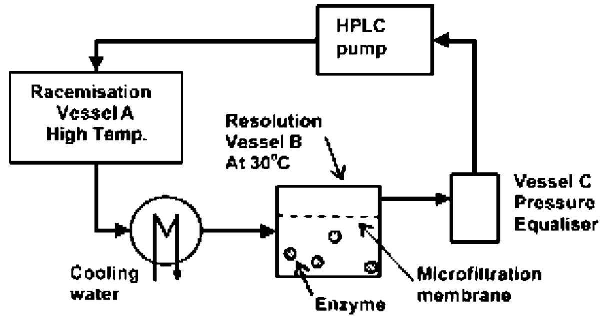

Figure 1. **Schematic of the proposed MEDKR process.**

Enache et al. explored the use of heat-exchange reactors with millimeter-scale channels to provide process intensification for homogeneously catalyzed gas−liquid reactions. (*Catal. Today* **2007**, *128*, 18−25) A solvent-free process for the hydroformylation of cyclodecatriene was developed. A similar approach was taken for heterogeneously catalyzed multiphase reactions. (*Catal. Today* **2007**, *128*, 26−35) The hydrogenation of resorcinol was used as a demonstrative example.

Datsevich et al. presented a process for intensifying three-phase reactions using fixed-bed catalyst reactors. (*Catal. Today* **2007**, *120*, 71−77) While fixed-bed catalyst reactors do not necessarily lead directly to process intensification, Datsevich et al. used a liquid phase that is presaturated with gas (presaturated one-liquid flow (POLF) (see Figure 2)). This allows for more efficient mass transfer between the three phases. In addition, it allows for the use of smaller catalyst particles by reducing the energy demands of gas recycling compared to traditional stationary catalyst processes such as trickle-bed, bubble column, and multitubular reactors.

15. Supercritical Fluid Chromatography (SFC) Separations

Helmy et al. published an article describing the improvement of sensitivity of analytical SFC in analysis and release of drug compounds. (*Chirality* **2007**, *19*, 787−792) This describes how SFC can be used as a cGMP tool for the release of drug compounds with the improvements in the signal-to-noise ratio. On a single-instrument basis the impact may not be apparent, but considering that there are thousands of HPLCs being used in most pharmaceutical companies, converting a number of them to SFC will significantly reduce the quantity of waste produced yearly by analysis, validation, and release testing.

West et al. published a report on the evaluation of stationary phase for use with SFC. (*J. Chromatogr., A* **2007** *1169*, 205−219) Although previously considered a “normal phase”

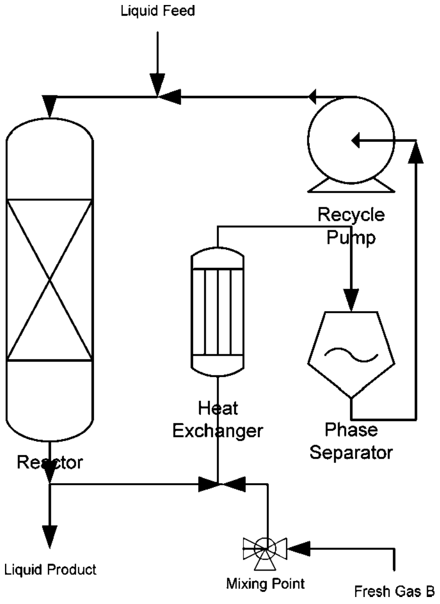

Figure 2. **Simplified one-stage POLF technology.**

technique, the report strongly supports the use of both normal phase and reversed phase stationary phases.

Leonard et al. published an article on the use of preparative SFC in the delivery of a preclinical candidate. (Chirality **2007**, *19*, 693−700) The report also presents a direct comparison of HPLC to SFC, describing the time, solvent, and cost savings associated with implementation of the latter method.

Yan et al. reported three case studies on the use of steady-state recycling (SSR) and SFC for the chiral resolution of pharmaceutical intermediates in place of HPLC. (J. Chromatogr., A **2007**, *1156*, 220−227)

In all three cases both SFC and SSR had higher productivity and reduced solvent needs which allowed for fast delivery times.

The first International Conference on SFC was held in Pittsburgh, PA, U.S.A., from September 23−25, 2007. The conferences had attendees from the pharmaceutical industry, academia, and the food industry coming from North America, Africa, Europe, and Asia. Electronic copies of the presentation and posters can be found on the conference Web site: http://www.greenchemistrygroup.org/index.html

16. General Green Chemistry

The 2007 academic award in the Presidential Green Chemistry Challenge was awarded to Professor Michael Krische from the University of Texas at Austin. The award was for his work in "Hydrogen-Mediated Carbon−Carbon Bond Formation." (J. Am. Chem. Soc. **2007** *129*, 8432−8433)

Roger Sheldon published an interesting article entitled "The E-Factor: 15 years on". (Green Chem. **2007** *9*, 1273−1283) This article details many efficient industrial syntheses and makes the claim that the pharmaceutical industry in particular has become much more focused on waste minimization since the first publication of the E-Factor.

Dewulf and colleagues from Johnson and Johnson have published a detailed resource analysis of two chemical processes (crystallization vs chromatography) to separate a pair of diastereoisomers. This analysis involved materials, energy, and environmental considerations; essentially materials and energy are converted to the same common currency to allow easier cross comparison. In this particular analysis the crystallization process proved superior to chromatographic separation. (Green Chem. **2007**, *9*, 785−791)

In the field of acid catalysis, Harmer reported a new and simplified route to the superacid 1,1,2,2-tetra-fluoroethanesulfonic acid (TFESA) (a potential replacement for trifluoromethanesulfonic acid with lower volatility and hence easier handling and improved safety). (Green Chem. **2007**, *9*, 30−37) Multiple applications were discussed (including acylation, Fries, and alkylation reactions) for both TFESA and a silica-supported version of the catalyst, which thereby enables reactions in nonpolar reaction media and aids recycling. On a related theme, Clark outlines the potential uses of Starbon acid (a renewable, sustainable, and environmentally compatible mesoporous carbonaceous catalyst obtained from biomass) as an effective catalyst for acid esterification, alcohol acylation, and aromatic alkylation. (Chem. Commun. **2007**, 634 − 636)

Issue 6 of 2007 *Chemical Reviews* is devoted to green chemistry topics. Keith, Gron, and Young review green analytical methodologies. (Chem. Rev. **2007**, *107*, 2695−2708) The review covers alternative analytical methods for extractions and analysis that are greener than standard versions but are equally as effective, safer to use, and more beneficial to the environment. Methods which do not require pretreatment, use few reagents, or work with aqueous solvent have a green advantage. Some methods which fit this category are: pH, ion chromatography, flame atomic absorption, graphite furnace atomic absorption, spectroscopy, elemental analysis using X-ray fluorescence, gas chromatography, and total organic carbon analysis. The authors apply their selection criteria to methods listed in the National Environmental Methods Index (NEMI). This database was released in 2002 and contains a growing number of green analytical methods.

Stephen Challenger
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GlaxoSmithKline, Leigh Nr Tonbridge, Kent, U.K.

Jimmy DaSilva
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