

Key green chemistry research areas—a perspective from pharmaceutical manufacturers

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In 2005, the ACS Green Chemistry Institute (GCI) and the global pharmaceutical corporations developed the ACS GCI Pharmaceutical Roundtable to encourage the integration of green chemistry and green engineering into the pharmaceutical industry. The Roundtable has developed a list of key research areas. The purpose of this perspective is to summarise how that list was agreed, provide an assessment of the current state of the art in those areas and to highlight areas for future improvement.

Introduction to the ACS Green Chemistry Institute Pharmaceutical Roundtable

In 2005, the American Chemical Society (ACS), Green Chemistry Institute (GCI)¹ and several leading global pharmaceutical corporations developed the ACS GCI Pharmaceutical Roundtable (ACS GCIPR, hereafter referred to as the Roundtable)² to encourage innovation while catalysing the integration of green chemistry and green engineering into the business of drug discovery, development and production. The pharmaceutical industry is devoted to inventing medicines that allow patients to live longer, healthier, and more productive lives. In addition these pharmaceutical companies are also committed to bringing key medicines to the patient with minimum impact on the environment.

The Roundtable's mission is to catalyse the implementation of green chemistry and green engineering in the global pharmaceutical industry. To achieve this mission, the Roundtable identified four strategic priorities.

1. Inform and influence the research agenda

To identify and to monitor new research opportunities for more efficient process development and production. To

influence the technical agendas of federal/international funding agencies by defining needs and advocating investment in specific areas of green chemistry and engineering innovation. To encourage external funding support for research in academic and government laboratories that will have direct value to the pharmaceutical industry.

2. Tools for innovation

To identify, design, and provide tools available to member companies to promote green chemistry and engineering innovation within the industry. To provide a centralised resource for accumulating alternatives, sharing tools, maintaining the toolbox, and minimising duplication of effort.

3. Education resource

To educate and influence today's and tomorrow's pharmaceutical leaders on the business value and scientific merit of applying green chemistry and engineering in the pharmaceutical industry.

4. Global collaboration

To provide green chemistry and engineering expertise to pharmaceutical corporations worldwide by utilising the GCI network of international affiliates and researchers and by sharing best practices among our members.

Membership to the Roundtable is open to all pharmaceutical research, development, and manufacturing companies. Members at the time of writing this paper were (in alphabetical order): AstraZeneca, Eli Lilly & Company, GlaxoSmithKline, Johnson & Johnson, Merck & Co., Inc., Pfizer, Inc., and Schering-Plough Corporation. Each company has a green chemistry program in various stages of development from infancy through more mature; however, the work of the Roundtable addresses the generally consistent underlying needs of all programs, thereby providing value to all members.

The activities of the Roundtable reflect the joint belief that the pursuit of green chemistry and green engineering is imperative

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for a sustainable business and environment. Collaboration results in a strong organisation to prioritise research needs and to influence the technical research agendas of national/international funding agencies and to improve the cost effectiveness of investment in the design and implementation of green chemistry and engineering tools specific to the industry. The work presented in this paper reflects the collaborative efforts of member companies to identify key green chemistry research areas of need for the industry. With this information, we seek to influence research agendas and directly fund research through the ACS GCI Pharmaceutical Roundtable Research Grant Program, with the objective to provide our scientists with readily available, proven greener alternatives to current pharmaceutical process development methods.

Process for identifying and agreeing on the key green chemistry research areas

The process of identifying and agreeing on the key research areas is shown diagrammatically in Fig. 1. The process started with gathering ideas from all the companies *via* a brainstorming exercise, followed by a cross company debate and assessment of the research areas, then concluded by a voting exercise where each Roundtable company had an equal vote.

The output of the brainstorming exercise is shown below. The ideas were grouped into three categories: (i) reactions that pharmaceutical companies use, but would strongly prefer better and greener reagents, (ii) more aspirational reactions (*i.e.* reactions that companies would like to use, if they were available, as they offer potentially cleaner synthetic approaches to the current art) and (iii) ideas outside of the reaction theme (concerned with solvent use). We felt that all the ideas on the brainstorming list were good and worthy of research, but from a pragmatic point of view the ideas needed to be prioritised.

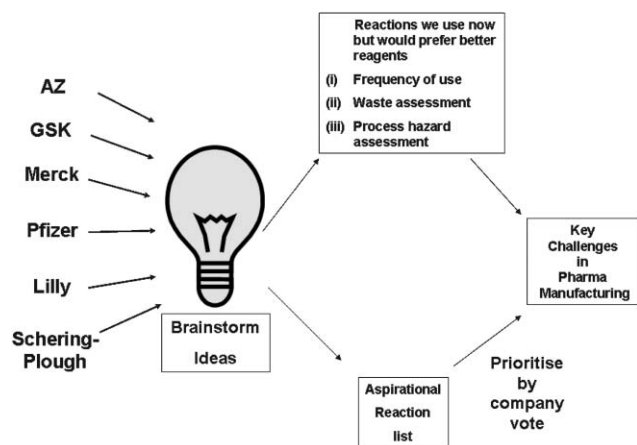


Fig. 1 The process for identifying and agreeing on the key research areas.

Brainstorm output on key research areas

Reactions currently used but better reagents preferred

Safer and more environmentally friendly Mitsunobu reactions

Reduction of amides avoiding LiAlH_4 or B_2H_6
 Bromination reactions
 Sulfonation reactions
 Amide formation avoiding poor atom economy reagents
 Nitration reactions
 Demethylation reactions
 Friedel–Crafts reactions on unactivated substrates
 Ester hydrolysis
 OH activation for nucleophilic substitution
 Epoxidation
 Wittig chemistry without (Ph_3PO)
 Radical chemistry without Bu_3SnH

More aspirational reactions

Asymmetric hydrocyanation
 Aldehyde or ketone + NH_3 + “X” to give a chiral amine
N-Centred chemistry avoiding azides, hydrazine *etc.*
 Asymmetric hydrolysis of nitriles
 Asymmetric hydrogenation of unfunctionalised olefins/enamines/imines
 Asymmetric hydroformylation
 C–H activation of aromatics (cross-coupling reactions avoiding the preparation of haloaromatics)
 C–H activation of alkyl groups
 New greener fluorination methods
 Oxygen nucleophiles with high reactivity
 Green sources of electrophilic nitrogen
 Asymmetric hydroamination of olefins
 Organocatalysis
 $\text{ROH} + \text{ArCl}$ to give ROAr

Solvent themes

Solvent-less reactor cleaning
 Replacements for polar aprotic solvents, NMP, DMAc, DMF *etc.*
 Alternatives to chlorinated solvents

For the reactions which companies currently use but better alternatives are needed, we decided to use a three point assessment. We looked at how often the reactions were used in making pharmaceutical products, taking advantage of a survey recently published by three of the Roundtable member companies.³ Another key component was to consider how much waste each reaction generated, and a GSK database was used to give a qualitative assessment. The third part of the assessment concerned process safety, for which data from the Pfizer database of reaction assessments (Toxtherm) was used to make the judgment. In addition, literature data and data on reported explosion hazards was taken into consideration. For example Barton and Nolan report⁴ that after polymerisation, the second and third most common causes of explosions are nitration and sulfonation reactions.

The voting process

Each company consulted its green chemistry teams and some of its most senior scientists in chemical development before coming to a company vote. All companies agreed that the

Table 1 Reactions companies use now but would strongly prefer better reagents

Research Area	Number of Roundtable companies voting for this research area as a priority area
Amide formation avoiding poor atom economy reagents	6 votes
OH activation for nucleophilic substitution	5 votes
Reduction of a mides without hydride reagents	4 votes
Oxidation/Epoxidation methods without the use of chlorinated solvents	4 votes
Safer and more environmentally friendly Mitsunobu reactions	3 votes
Friedel–Crafts reaction on unactivated systems	2 votes
Nitrations	2 votes

solvent-less reactor cleaning and replacements for polar aprotic solvents were critical and hence made the final list. Next, each company identified the top five areas within the two reaction categories.

A summary of the voting is shown in Tables 1 and 2.

One of the key messages was that there was a lot of commonality in the company votes. For example all 6 companies voted for amide formation,⁵ reflecting the high level of use (9.1%)⁶ and the poor atom efficiency of many current methods. All companies voted for cross couplings without preparation of haloaromatics, showing the high use of Suzuki⁷ and related reactions and a concern for the high level of waste that these palladium cross coupling reactions generate.

Hence the final list of the 12 key green chemistry research areas is the following: amide formation, OH activation, amide reduction, oxidations/epoxidation methods without the use of chlorinated solvents, safer and more environmentally friendly Mitsunobu reactions, C–H activation of aromatics, chiral amine synthesis, asymmetric hydrogenation, greener fluorination methods, *N*-centred chemistry, greener alternatives to polar aprotic solvents and solvent-less reactor cleaning Each one of these key research areas is discussed in more detail.

(i) Amide formation avoiding poor atom economy reagents

An analysis of drug candidates prepared by three leading pharmaceutical companies found that amide bond formation was utilised in the synthesis of 84 (65%) of the 128 candidates surveyed.³ Forty four percent were based on acid chloride intermediate, a relatively environmentally benign approach where, for example if thionyl chloride is employed to make the acid chloride, the by-products, SO₂ and HCl, can be removed by scrubbing through a basic solution. About 36% of the 84 amide bond forming reactions were carried out by means of a coupling reagent such as *N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide hydrochloride [EDCI·HCl, catalysed by

HOBt (the triazole is a high energy molecule and potential explosive)], 1-propylphosphonic acid cyclic anhydride or *N,N'*-carbonyldiimidazole (CDI). These methods are less “atom economical” in that they generate greater quantities of waste as measured by their mass intensity factor (MI), (defined as the ratio of a total mass in a process divided by mass of product in kg).⁸ Commercial examples of amide formation using CDI include sildenafil⁹ and sunitinib,¹⁰ however this method still generates by-products with a combined molecular weight of 180 to accomplish a dehydration reaction, ten times more mass than if water itself were the only by-product.

Amide bond formation using enzymatic catalysis eliminates some of the issues associated poor atom economy as well as the potential hazards associated with non-aqueous chemical based approaches. Hydrolysis of nitriles catalyzed by nitrile hydrolases and lipase-catalysed amidation of carboxylic acids and esters with ammonia leading to the formation of primary amides are clean, safe and efficient.¹¹ For example, in a process practiced by Mitsubishi Rayon Corporation, both the %-conversion of acrylonitrile and the %-yield of acrylamide reach 99% under standard operating conditions of 0–5 °C, pH 7.5–8.5.¹² Likewise, enzyme-catalysed amide bond formation catalysed by peptidases and acylases eliminates the use of highly reactive coupling reagents and minimises the need for protection/deprotection steps, thus improving the MI significantly.¹³ Moreover, mild reaction conditions and the excellent stereo- and regioselectivity of enzymes precludes racemisation and guarantees structural fidelity of the product. Despite significant progress in biocatalytic amide synthesis and some commercial success, the narrow substrate specificity of the currently available enzymes severely limits their practical use. The development of new molecular biology tools has enabled the expansion of the numerous functional properties of biocatalysts, and is expected to increase their commercial utility in the next 3–5 years.

Table 2 More aspirational reactions

Research Area	Number of Roundtable companies voting for this research area as a priority area
C–H activation of aromatics (cross coupling reactions avoiding the preparation of haloaromatics)	6 votes
Aldehyde or ketone + NH₃ + “X” to give chiral amine	4 votes
Asymmetric hydrogenation of unfunctionalised olefins/enamines/imines	4 votes
New greener fluorination methods	4 votes
<i>N</i>-Centred chemistry avoiding azides, hydrazine etc	3 votes
Asymmetric hydramination	2 votes
Green sources of electrophilic nitrogen (not TsN ₃ , nitroso, or diimide)	2 votes
Asymmetric hydrocyanation	2 votes

In summary, amide bond formations are one of the most common transformations carried out in pharmaceutical synthesis. Their efficiency, however, is hampered by widespread use of reagents with poor atom economy. Therefore, development of reagents with lower MI-factors or, ideally, catalytic methods, such as the exciting use of boric acid to catalyse amide formation,¹⁴ would favourably impact the environmental profile of many processes.

(ii) Alcohol activation for nucleophilic substitution

The substitution of activated alcohols is a frequently used approach for the preparation of active pharmaceutical ingredients (APIs). In a recent survey, 2% of transformations comprised conversions of alcohols to halides or sulfonate esters (invariably for further use), and 64% of all nitrogen substitution reactions were alkylations.³ Direct nucleophilic substitution of an alcohol is attractive as it should yield water as the by-product, however, hydroxide is a poor leaving group usually requiring activation. Direct substitution of some allylic, benzylic and tertiary alcohols may be achieved *via* an S_N1 reaction but this approach typically requires excess Brønsted or stoichiometric amounts of Lewis acids and does not afford control over stereochemistry. Secondary alcohols can be substituted with good stereospecificity using a Mitsunobu protocol, the issues of which are discussed below. Activation is wasteful as it requires additional processing and the activating group, once displaced, also has to be separated from the product and the resulting waste must be disposed. The consequences of activation are illustrated by the synthesis of the dopamine agonist ropinirole **1** (Scheme 1).¹⁵ The toluenesulfonate (**2**, R = OTs) is displaced with dipropylamine affording ropinirole in 85% yield. Whilst affording a significant improvement over an earlier route, where displacement of bromide (**3**, R = Br) gave ropinirole in 57% yield due to competing elimination, the net conversion of alcohol (**4**, R = OH) is achieved in 74% yield. The preparation of **2** from **4** had a mass intensity of 25 kg kg⁻¹.¹⁵

There are encouraging recent advances in this area. Catalytic activation of allylic and benzylic alcohols has been demonstrated using indium(III) chloride for displacement with acetylenic, allylic or propargylic silanes,¹⁶ and activation by 4-toluenesulfonic acid, including polymer bound acid, allows for displacement of the alcohol with a range of carbon, nitrogen, oxygen and sulfur nucleophiles.¹⁷ A wider range of alcohols, including primary and secondary, have been substituted with amines by *in situ* oxidation and reduction

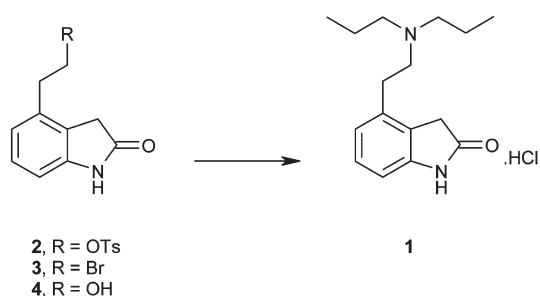
catalysed by iridium complexes.¹⁸ This approach has been extended to the preparation of carbon–carbon bonds, for example using a ruthenium catalyst.¹⁹ The challenge of achieving a method of activation for secondary alcohols that maintains control over the stereochemistry of the reaction remains.

(iii) Reduction of amides without hydride reagents

Essentially all medicines and current drug candidates contain at least one basic nitrogen atom. A common approach to the synthesis of amines is to reduce the corresponding amide with a hydride reagent such as LiAlH₄, DIBAL, RedAl, B₂H₆, Et₃SiH, or polymethylhydroxysilane (PMHS). The reaction survey³ reported that reduction of amides to amines was used in only 0.6% of chemical transformations; this number would surely be higher if safer methods for use on scale were available. The survey indicated that the number of amide reductions was equally split between diborane and hydride reagents. Lithium aluminium hydride, having a molecular weight of 38 and four hydrides per molecule, has the highest hydride density and is frequently used, even though it co-generates an inorganic by-product (lithium aluminum hydroxide) which is difficult to separate from the product. The workup procedure recommended by one bulk supplier (Chemetall) is to precipitate and filter the aluminum hydroxide salts. However, slow filtrations and product loss through occlusion or adsorption are typical problems that can be encountered. Options for disposal of the cake include dissolving in water and sending to a waste water treatment plant or drying the cake and sending to a chemical waste dump that accepts solids.²⁰ Both options have an environmental impact. Therefore, a generally applicable, safe, environmentally benign and economically viable method for the reduction of amides to amines would have an appreciable benefit to numerous processes.

Hydrogen gas is the ideal reductant because the only by-product is water. Thus, much research has been directed towards discovery of a transition metal catalyst selective for hydrogenation of amides. However, even with the best catalysts, both high temperature (~150 °C) and pressure (>100 bar) are required. These conditions involve expensive high pressure hydrogenation equipment not typically available in a common pharmaceutical manufacturing plant. The harsh conditions also preclude the use of these catalysts with substrates that contain other reducible or thermally labile functional groups. Recent research has led to the discovery of catalysts that are effective at lower temperature and pressure, giving encouragement that the goal of finding a selective, low pressure/temperature catalyst is realistic.²¹

Another approach would be to use a biotransformation to reduce the amide. It is notable that a number of bacteria and fungi reduce carboxylic acids to aldehydes or ketones.²² The usual fate of amides in biological pathways is hydrolysis. However, an anaerobic bacteria, *Clostridium sporogenes*, has been reported to reduce benzamide to benzylamine.²³ A key challenge in this technology area is gaining a detailed understanding of these complex enzyme-catalysed processes that require ATP/NADPH co-factor recycling, and getting the



Scheme 1 The synthesis of ropinirole **1**.

enzymes cloned and produced on a large scale in suitable expression systems.

The acylation/reduction strategy for *N*-alkylation avoids the need to handle alkylating agents and would be more widely used if a safer, more atom economical or preferably catalytic method for amide reduction were developed. The solution to this problem could be either chemical or biochemical.

(iv) Oxidation/epoxidation methods without the use of chlorinated solvents

The pharmaceutical industry performs more reduction reactions than oxidation reactions. The reaction survey³ shows that oxidations covered 3.9% of reactions whereas reductions were used in 14% of transformations. Oxidation reactions encompass transformations that either remove hydrogen from the molecule (for example, alcohol to aldehyde), or insert an oxygen into a C–C (Baeyer–Villiger, epoxidation) or C–H bond (aldehyde to acid).²⁴ By definition an oxidant is involved, and hence the reactions are generally of high energy in nature. While much progress has been made on the development of greener oxidation reagents (Ru^I/BuO₂H, TEMPO/NaOCl, Pd-catalysed aerobic oxidations), and the use of stoichiometric high valent metals (Mn, Os, Cr) have virtually been eliminated from pharmaceutical processes, several deficiencies among existing methods need to be addressed or supplanted with greener technologies. First, a great majority of oxidation reactions are conducted in inert, nonflammable chlorinated solvents. Second, catalysts containing heavy metals must be removed or recycled for toxicological, environmental or economic reasons. Third, transportation and storage of organic peracids, commonly used for epoxidation, incur significant business costs. Last, there is much to be desired in the choice of available oxidants. Molecular oxygen or air is the ideal oxidant; however, aerating flammable solvents is a significant safety concern that can only be fully addressed if the reaction can be conducted efficiently in water. Hydrogen peroxide is the second best choice with respect to atom economy, but utilisation, efficiency and narrow range of scope limit its application. Sodium hypochlorite is one of the most economical oxidants. However, it usually comes in the form of dilute aqueous solutions, which leads to the generation of large volumes of aqueous waste from the process. Several alternatives to Cl⁺, most prominently TCIA (trichloroisocyanuric acid), offer distinct advantages.²⁵ Yet, the preferred reaction medium still remains a chlorinated solvent. Developers of new reactions should bear in mind that any useful and widely adopted new reaction should offer certain advantages over existing methods. New reactions should target green reagents and solvents, safer and milder conditions, or improved selectivity. One unmet need for green oxidation is allylic oxidation. The insertion of oxygen into a C–H bond adjacent to a double bond can only be reliably achieved using a stoichiometric amount of SeO₂.

Biocatalysis is much further advanced in the area of oxidation than in reduction.²⁶ A classic example of the power of bio-oxidation is in the field of steroid synthesis. Without the development of highly regio- and enantioselective monooxygenase reactions, many potent steroidal medications would not

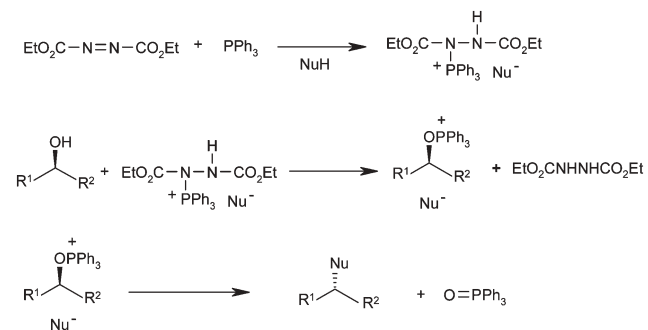
be available on scale at an economic price. However many challenges remain to be solved in this potentially highly valuable field.

The oxidation of methyl groups to produce certain functionalised aromatics and heteroaromatics has been scaled-up into production, but is by no means yet a universal solution. Some advances are being made into the understanding of how to scale-up reactions using redox enzymes thought to be too unstable to ever use—chloroperoxidase and Baeyer–Villiger monooxygenase being good examples.²⁷ Other exciting areas are the growth in the study of air oxidations catalysed by laccases with or without organic co-catalysts²⁸ and the use of peroxides and lipases to prepare epoxides.²⁹ It is interesting to note the serendipitous discovery of ‘ozonolysis-like reactions’ by several oxidising enzymes.³⁰ Could this be further developed into a useful technology to use in organic synthesis?

(v) A “greener” Mitsunobu reaction

The “redox” condensation reaction of alcohols with compounds having an active hydrogen (NuH), mediated by triphenylphosphine and dialkyl azodicarboxylates, has become known as the Mitsunobu reaction (Scheme 2) in recognition of his pioneering research during the 1960’s and 1970’s.³¹ This transformation has become a powerful and widely used reaction for organic chemists over the past 40 years due to several key attributes, which include: (1) chiral secondary alcohols are displaced with inversion with high stereospecificity; (2) extraordinary scope, including nucleophiles derived from oxygen, nitrogen, sulfur, and carbon, and a wide variety of alcohols; (3) compatibility with a broad range of functional groups; and (4) ease of operation, with most protocols requiring only simple addition of reagents to a flask and operating temperatures generally near room temperature.

The primary shortcoming of the Mitsunobu reaction is the use of stoichiometric quantities of the azodicarboxylate and triphenylphosphine, which overall function to eliminate water from this condensation reaction. Thus, waste products totaling more than 450 in molecular weight are generated to remove water, a highly atom-inefficient process. In addition, removal of these by-products requires additional processing, such as chromatography, to purify the product, producing additional waste. As well as the environmental considerations, diethyl azodicarboxylate is a high energy molecule and the Pfizer data base reports a decomposition energy of 1000 J g⁻¹. For these



Scheme 2 The Mitsunobu reaction.

reasons, commercial application of the Mitsunobu reaction has been very limited, and the reaction survey³² reports that only 0.2% of chemical transformations are Mitsunobu reactions.

Some research has been directed toward reducing the high environmental impact of the Mitsunobu reaction. Most of the work to date has focused on the use of polymer-bound triphenylphosphine.³³ The polymer bound reagent simplifies purification, allows for recycling and multiple use of the resin after reactivation, and minimises solvent usage. Use of both polymeric triphenylphosphine and polymeric azodicarboxylate equivalents was recently described by Toy and co-workers.³⁴ These polymer-bound reagents simplify product isolation, but recycling still requires cumbersome protocols and harsh reagents.

An alternate approach, that is also greener, is the use of the reagent cyanomethylenetriethylphosphorane, which combines both redox partners in a single reagent. The by-products of this reagent include acetonitrile and trimethylphosphine oxide, which are improvements over the original Mitsunobu reagents.³⁵

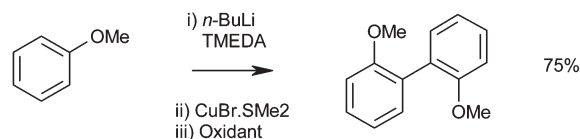
The ideal Mitsunobu reaction would be catalytic in nature, with the stoichiometric oxidant and reductant generating innocuous by-products. A first approach to this goal has been recently published by Toy and co-workers.³⁶ In their work, iodosobenzene diacetate is used as the stoichiometric oxidant, which produces the environmentally less burdensome by-products, acetic acid and iodobenzene, instead of the hydrazide. Triphenylphosphine is still employed (2 equiv.), so considerable research is still required to devise a reaction that is catalytic in both reagents.

The Mitsunobu reaction has become a powerful and popular transformation in the organic chemistry laboratory. Further research towards making this transformation green is required to realise its full potential in commercial applications.

(vi) C–H activation of aromatics

Aromatic groups are by far the most essential pharmacophores for medicinal chemistry and drug development. A cursory review of recent phase III and marketed pharmaceuticals reveals that more than 75% of them contain at least one aryl or heteroaryl group. A great number of the aryl groups, especially phenyls, are incorporated into the API preassembled. No aromatic ring synthesis was exercised in the process and virtually all of them are procured from basic or specialty chemical sources. Recent advances in metal-catalysed cross-coupling reactions have greatly facilitated the versatility of incorporating aryls for medicinal chemistry. However, most of these reactions rely on the availability of aryl bromides or iodides. Direct activation of aryl hydrogen (converting Ar–H into Ar–Ar) will be of great potential.

Directed metallation has gained popularity for its versatility at introducing electrophiles onto the aryl ring. A recent example of biaryl formation *via* an organocuprate oxidation without a preceding metal halogen exchange from an aryl halide is shown in Scheme 3. This directed lithiation avoids the separate preparation or purchase of an aryl halide, however, a prerequisite is the presence of a directing group at the *ortho* position.³⁷



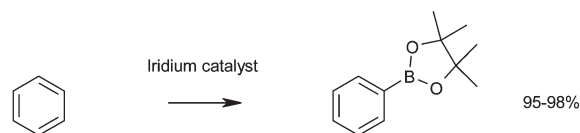
Scheme 3 C–H activation by directed metalation.

An unmet need for green chemistry is direct C–H activation using catalytic methods. An example is the iridium-catalysed C–H activation of aromatics (Scheme 4).³⁸ This chemistry provides the desired arylboronic acid directly from the C–H activation without the use of the aryl halide. The subsequent Pd-catalysed reaction with a second activated aryl group *via* known methods (for example aryl halides in a Suzuki–Miyaura coupling) provides efficient access to biaryls. However, new reactions that enable chemists to form a bond between aryl groups without having to go through any aryl halide (ArX) would be highly useful. An encouraging sign is that there has been a surge of exciting results in this area in the last few years.³⁹

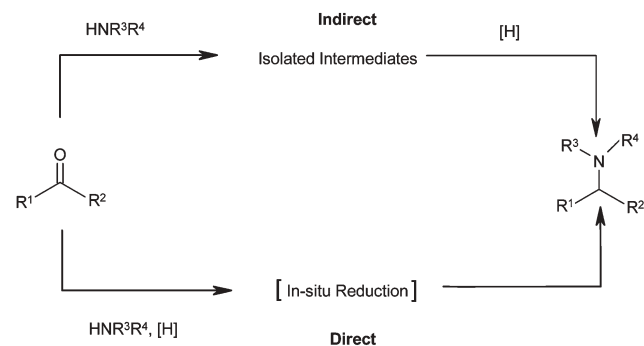
(vii) Asymmetric synthesis of amines from prochiral ketones

Over the past few decades researchers in academia and industry have explored the synthesis of α -chiral aliphatic amines from prochiral ketones. However, reports of general methods in high enantiomeric excess are rare.⁴⁰ In most cases, indirect reductive amination methods are used. These are generally limited to specific cases such as enamine hydrogenation,⁴¹ enantioselective alkylmetal addition to aliphatic aldimines,⁴² enantioselective transfer hydrogenation of ketimine derivatives,⁴³ diastereoselective addition to chiral imines,⁴⁴ or diastereoselective reduction of chiral methylbenzyl ketimine derivatives.⁴⁵

The direct reductive amination of ketones has been shown to be a very efficient methodology for the synthesis of racemic amines (Scheme 5). Development of asymmetric versions of



Scheme 4 Iridium catalysed C–H activation of aromatics.



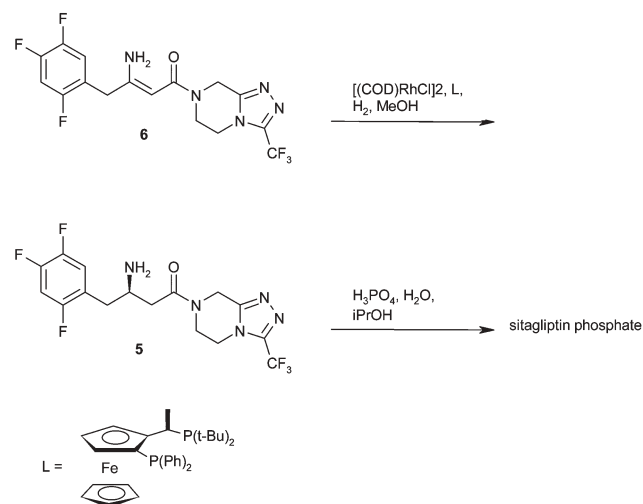
Scheme 5 Asymmetric synthesis of amines from prochiral ketones.

this reaction, on the other hand, have been difficult to realise.⁴⁶ A general methodology for the direct synthesis of α -chiral aliphatic amines from prochiral ketones would be an extremely valuable addition to the chemical transformation toolbox. Apart from the elimination of extra steps to prepare and isolate the imine substrates, the direct reductive amination of ketones could have major advantages in terms of overall efficiency and environmental impact.

(viii) Asymmetric hydrogenation of unfunctionalised olefins/enamines/imines

The reaction survey³ found that the predominant strategy for the introduction of chirality was through classical chemical resolutions as opposed to introductions through biotransformation or transition metal or organometallic catalytic means. Asymmetric hydrogenation provides an elegant methodology for the introduction of chirality, meeting many of the goals of green chemistry and is finding increasing application in API synthesis.⁴⁷ The efficiency of this approach is elegantly exemplified by the Merck second generation synthesis of sitagliptin **5** (Scheme 6), where an unprecedented final stage asymmetric hydrogenation of the unprotected enamide **6**⁴¹ resulted in an increase in overall yield of almost 50% and produced 100 kg less waste per kg sitagliptin⁴⁸ when compared with the first generation approach.⁴⁹

There are challenging areas remaining within the field, for example, the hydrogenation of enamides and related substrates in the synthesis of amino acids has numerous examples⁵⁰ but few examples exist for unsubstituted enamines⁴¹ and imines. Some classes of alkene offer additional challenges.⁵¹ For the pharmaceutical industry, the limited time for synthetic route identification is an issue and access to catalyst and ligand diversity is required to ensure the application of this approach.⁵² Some pharmaceutical companies have synthesised their own ligands and have found very effective catalysts.⁵³ The majority of academic asymmetric hydrogenation approaches are based on homogeneous catalysis to overcome issues of activation and mass transfer. For pharmaceutical use, efficient catalyst and ligand recovery, and eliminating heavy



Scheme 6 The synthesis of sitagliptin.

metal contamination of the API are significant requirements for the industry. These controls are often easier to achieve with heterogeneous methodology where there are less examples.⁵⁰ The demonstration of organocatalytic hydride transfer offers the possibility of future access to metal free asymmetric hydrogenations.⁵⁴

(ix) New greener fluorination methods

Owing to its unique stereoelectronic properties, fluorine has increasingly been used to block metabolism sites or to modulate electronic properties of the drug candidate without introducing steric bulk. Fluorine containing molecules account for 10% and 14% of launched pharmaceuticals and drug candidates currently in phase III clinical trials, respectively. The possibilities for fluorine incorporation only seem limited by the chemistry of forming the F–C bond. Unfortunately, there are only a handful of methods for introducing fluorine into target compounds—most of them involving harsh reaction conditions and the use of corrosive and hazardous reagents. As a result, chemists rely heavily on purchased starting materials with fluorine already incorporated, limiting their ability to explore all structure–activity relationship (SAR) spaces. Three categories for fluorination are commonly used (Scheme 7):

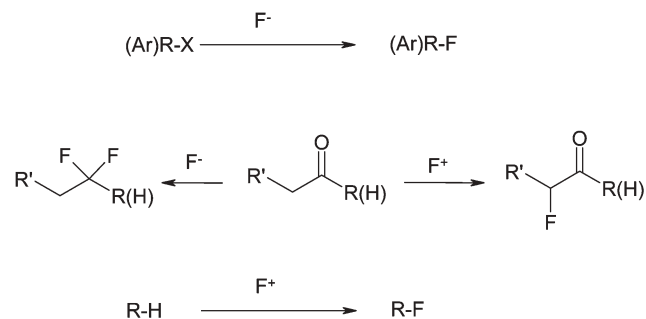
1. Fluorine exchange with a leaving group (Cl, Br, I, OH, OSO₂R, etc.) using either HF, or its alkali/ammonium salt.

2. Deoxyfluorination: converting either an aldehyde or ketone into a gemdifluoromethylene (R₁R₂C=O → R₁R₂CF₂), or an alcohol into an aliphatic fluoride (R₁R₂CHOH → R₁R₂CHF). For this purpose DAST has long ago replaced the notorious SF₄, and in recent years a more stable and user-friendly version (Deoxo-FluorTM) has emerged.⁵⁵

3. Direct fluorination from an electrophilic (F⁺) source (e.g. SelectfluorTM).⁵⁵ This usually requires a carbon nucleophile, such as the enolate of an aldehyde, ester or amide.

Fluorination is a very active area of research and new reagents are appearing all the time, for example 2,2-difluoro-1,3-dimethylimidazoline (DFI) which exchanges a fluorine for a hydroxyl group.⁵⁶

Unmet needs in the realm of incorporating fluorine into drug molecules include catalysts for increasing the nucleophilicity of F[−], milder conditions for conducting fluorine exchange reactions (ArCl → ArF), and safer and more economical sources of electrophilic fluorine.



Scheme 7 Common methods to introduce fluorine.

(x) *N*-Centered chemistry avoiding azides, hydrazine, etc

The “hydroxyl to amine” transformation is important in pharmaceutical synthesis. Sodium azide is frequently used to effect the “hydroxyl to amine” transformation. It is popular in organic chemistry because it reliably affords high yields of products with predictable stereochemistry (enforced by the S_N2 mechanism) under relatively mild conditions. The “rule of six” states that six carbons (or other atoms of about the same size) per energetic functional group (azide or diazo or nitro) provides sufficient dilution to make a compound relatively safe.⁵⁷ However all Roundtable companies would consider organic azides intrinsically hazardous and would usually subject them to extensive safety testing using reaction calorimetry and adiabatic calorimetry techniques before considering scale-up of such chemistry. The preparation of amines requires treatment of a halide or sulfonate with aqueous sodium azide, a hazardous process due to the formation of heavy metal azides which are contact explosives. Sodium azide is a staple in every medicinal chemist’s shelf of reagents: for example Sharpless’ “click chemistry”⁵⁷ relies on alkyl azides, synthesis of beta lactams is based on azidoacetyl chloride, and that of 1,2,3-triazoles and tetrazoles is based on sodium azide. Tetrazoles, standard isosteres for carboxylic acids commonly used in medicinal chemistry are synthesised by cycloaddition of tri-*n*-butyltin azide to nitriles. Thus, there is a critical need in the industry to develop a technique for the safe handling of azides or more preferably chemistry which does not involve azides. The principal concern in azide chemistry is the risk of formation of heavy metal azide salts which are shock sensitive. The cadmium plated screws typically used to repair glass connectors in modern production plant equipment, and waste water pipes made of lead in older plants, present particularly high risk by potentially forming highly explosive cadmium or lead azides.⁵⁸ These realities make the handling of sodium azide in the plant environment hazardous. To address these issues, compounds like AZT are made in dedicated facilities which are designed and maintained at significant expense to handle azide compounds safely. Pyrazoles are generally made from hydrazine or a substituted hydrazine, examples such as sildenafil and celebrex are made from a substituted hydrazines, which require special handling and/or specialised facilities.

Considering the complexity of handling azides, many process units opt to use substitute reagents. Ironically, these substitute reagents generally have much higher MI-factors than azide or hydrazine. For example, the classical Gabriel synthesis involves displacing the leaving group with a bulky potassium phthalimide,⁵⁹ and then removing the phthalic acid group under harsh conditions.⁶⁰ Even though a number of equivalents of the Gabriel synthesis have been developed,⁶¹ they all require an activating, protecting, or blocking group, resulting in processes with elevated MI-factors. Nitrogen nucleophiles with lower MI-factors are also known, but they are generally insufficiently nucleophilic and tend to undergo polyalkylation (e.g., ammonia).⁶² Moreover, the inability to displace a sulfonate on a carbohydrate pyranose ring with clean inversion of configuration (without competing elimination) limits their synthetic utility.

Interestingly, even though azide is highly nucleophilic, sodium azide is not always the most effective reagent. For example, in the case of diacetone glucose tosylate, sodium azide gives no reaction, while ammonia and hydrazine displace the tosylate with inversion of configuration.⁶³ It is postulated that azide fails to displace tosylate because it is charged, and expulsion of a charged anionic leaving group into a non-polar environment is disfavored. Ammonia and hydrazine are more effective because the leaving group is not expelled as a charged anion, but rather as an ammonium salt into the non-polar environment. Therefore, even though the new azide-alternatives are unlikely to replace azide’s standing as the most nucleophilic nitrogen anion, their use in non-traditional media might address environmental and safety issues associated with the use of azide and its current replacements.

(xi) Replacements for dipolar aprotic solvents

This is a class of solvents of tremendous utility to chemists given their ability to solubilise a large number of chemicals and their support or promotion of a variety of chemistries through their polarity. However, solvents such as *N*-methylpyrrolidin-2-one (NMP), *N,N*-dimethylformamide (DMF) and *N,N*-dimethylacetamide (DMAc) have been found to have human reproductive risks and are therefore becoming targets of increasing regulatory constraint. They have also always been problematic from an environmental perspective because reaction work-ups usually involve large quantities of water, and the preferred disposal method for mixed aqueous/organic wastes has generally been incineration. Mixed aqueous/organic wastes of this type generally require additional fuel to incinerate, and have the added burden of NO_x formation. Given the high biological oxygen demand/chemical oxygen demand and nitrogen loadings these types of wastes have if they are discharged to a waste water treatment plant, there is reluctance to discharge to biological treatment, especially plants with tight NH_3 limits. Separation of the solvent from mixed aqueous waste streams is difficult in the batch chemical context, generally capital and energy intensive, and therefore not usually undertaken.

Therefore, given the utility of these solvents from a chemical perspective but the environmental and health risks they pose, suitable replacements of lower risk and less impact are required.

(xii) Solvent-less reactor cleaning

Organic solvents account for 75–80% of the waste associated with the synthesis of APIs. In addition to serving as media for reactions and separations, solvents are routinely used to clean reaction vessels following a campaign. Strict limits on cleanliness (typically 10–20 ppm) are followed by most pharmaceutical companies. In pilot plant operation, the volume of solvent used for cleaning is generally 2–3 times greater than the amount of solvent used in the reaction itself. Cleaning solvents are generally relatively green (e.g. methanol and acetone) and are sometimes recovered for subsequent reuse.⁶⁴ In the best case scenario, waste solvent is recycled; however distillation is frequently required, making the process energy and time intensive. Solvent waste disposal adds cost to

API production. Eliminating cleaning solvent would therefore decrease the environmental footprint of most pharmaceutical processes significantly.⁶⁵

Cleaning using solvent rinse and boil-out are generally inefficient. Frequently, the contaminants to be removed are structurally dissimilar from the product, and may have vastly different solubility properties from the desired product. For this reason, other cleaning systems have been evaluated. Aqueous hydrogen peroxide was found to be a suitable cleaning agent for the dissolution of certain organic residues.⁶⁶ Recent work utilising high-pressure water jet technology to clean reactors has proven beneficial.⁶⁷ The relationship between jet properties (e.g. temperature, pressure, composition, and impingement conditions) and cleaning efficiency has been defined. Development of efficient detergents acceptable for API equipment and research toward making vessel cleaning solvent less in commercial setting will have a major impact on reducing the environmental impact of pharmaceutical processes, while ensuring the integrity and quality of pharmaceutical products.

Conclusions

The Roundtable first announced the key research areas at the 10th Annual Green Chemistry and Engineering Conference in Washington (June 2006).⁶⁸ At the meeting the Roundtable announced that it would be launching a grant program for research in the 12 key research areas. A call for research proposals was made in November 2006 and the response from the academic community was outstanding, with 32 research proposals received within 1 month. The announcement of the award was made in December 2006.⁶⁹ The Roundtable sees the research grant program as an ongoing commitment.⁷⁰

It should be noted that great progress has been made over the last few years. For example, 20 years ago the industry was still using stoichiometric oxidations with chromium(VI) reagents whereas today bleach based oxidations catalysed by nitroxyl radicals are commonplace. There has also been a huge growth of large scale use of asymmetric reactions over the same time period. The idea of identifying and supporting research in the key research areas was to continue and to accelerate that improvement.

Of course chemistry changes quickly and almost certainly it will be necessary to refine and update the key research areas at some point in the future.

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