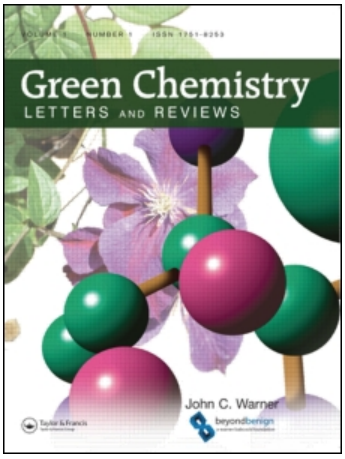

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INDUSTRY REVIEW

Green process chemistry in the pharmaceutical industry

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Key factors for deriving environmentally sustainable processes in the synthesis of pharmaceutical intermediates and products are discussed. The selection and use of solvents is emphasized as regards methods to minimize environmental impact. Case studies of successful process development to attain improved green processes are included.

Keywords: green chemistry; pharmaceuticals; solvent utilization strategies

Introduction

> Green Chemistry: "hurt not the earth, neither the sea, nor the trees."
>
> Ronald C.D. Breslow (*1*)

The development of new pharmaceutical products by organic synthesis over the past century has contributed to a revolution in medical care, enabling dramatic reductions in hospitalization, suffering, and death. However, this achievement is flawed if the environment is adversely impacted. With the increasing emphasis on green chemistry (*2,3*) recently, pharmaceutical process chemists have concentrated their focus and creative energies toward minimizing the environmental impact of their craft. This review will present a selective overview of useful means to achieve this goal, and discuss case studies of the successful modification of processes to achieve reduced resource requirements, waste generation or energy consumption.

The manufacture of chemicals has the potential to generate significant amounts of waste by-products and pollutants, such as contaminated solvents, depleted reagents, and air pollutants. Pharmaceutical manufacture can be a significant contributor of these factors. For a comparison of the efficiency of the sectors of chemical manufacture, Table 1 reveals that the manufacture of drugs generates more waste and by-products in comparison to all others (*4*). This must be taken in context, since the medical and regulatory requirements of pharmaceutical purity will naturally lead to more waste per kilogram product as compared to making less sophisticated compounds of less stringent purity, however, it does underline the challenge and opportunity for improvement presented to the pharmaceutical industry.

The problem is further elaborated by a report from GlaxoSmithKline (GSK) (*5,6*). A life cycle study of waste produced from their Active Pharmaceutical Ingredient (API) manufacturing facilities estimated that 80% of their waste is solvent-related. Assuming other pharmaceutical companies produce a similar percentage of solvent waste, this suggests that addressing the selection, use, recovery, and disposal of solvents will contribute dramatically to alleviating this problem. While not the only means for greening pharmaceutical manufacture, solvent considerations will appear frequently in the case histories of drug process development in this review.

Solvents in pharmaceutical process development and greenness factors (*7,8*)

The selection of solvents for the synthesis of pharmaceuticals is critical on a number of levels (*9*). Beyond the obvious function of solvents to allow compounds to react efficiently in solution, they may further influence the particle size of the API and impact manufacturing costs by leading to difficult isolations or requiring milling. Solvents often influence the crystal form of the API, which directly determines dissolution rates, formulation, and bioavailability. The utilization of solvents also brings the disadvantage of solvent incorporation into the API. If they cannot be removed, the amount must be controlled or limited to levels that are safe to the patient. While the

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Table 1. Comparison of chemical industry sectors by quantity of byproduct per kilogram of product (*3*).

Industry sector	Product tonnage	kg byproducts/kg product
Oil refining	10^6–10^8	~0.1
Bulk chemicals	10^4–10^6	<1–5
Fine chemicals	10^2–10^4	5–50
Pharmaceuticals	10–10^3	25–100

presence of solvents in drugs is not usually considered an environmental impact, they may be considered a form of pollution for the purposes of this review as they affect us directly as does other pollution. As a means of evaluating this danger to our health, solvents require categorization. The Center for Drug Evaluation and Research (CDER) of the USA Food and Drug Administration (FDA) lists four classes of solvents organized by patient safety and environmental considerations (*10*). Class I solvents (i.e. benzene, carbon tetrachloride, 1,2-dichloroethane, 1,1-dichloroethylene, and 1,1,1-trichloroethane) are highly undesired based on their unacceptable toxicity or deleterious environmental impact. Class II solvents are most commonly organic solvents, such as acetonitrile, methanol, methylene chloride, tetrahydrofuran, toluene, and hexane (see Table 2). Class III solvents (i.e. acetic acid, acetone, ethanol, ethyl acetate, heptane, and dimethyl sulfoxide) have the lowest toxic potential. The lack of proven human toxicity is the main criterion for being listed as a class three solvent and the potential for demotion to class II or I is always possible. Class IV solvents (i.e. isooctane, isopropyl ether, petroleum ether, and 2-methyltetrahydrofuran) have insufficient toxicological data. Whether any of these solvents are entirely environmentally benign is debatable, which is another reason for carefully assessing the use of these solvents in pharmaceutical manufacture.

Since it is clear that solvents can rarely be avoided for efficient pharmaceutical manufacture, the initial question becomes how to select as green a solvent as possible. Certain solvents may be excluded that pose potential harm to patients, operators, and the environment. Such rarely used solvents along with potential substitutes are listed in Table 3 (*9*).

Tools are available for designing green syntheses. For instance, the Environmental Protection Agency (EPA) offers several useful websites (*11*). The Green Chemistry Expert System (GCES) offers guidelines and support information for devising a green-chemistry process (*12*). This tool includes a green solvents/reaction conditions module, which contains information on green solvent alternatives to traditional choices. Table 4 lists a variety of solvents that are generally recognized as green selection and provides a means for choosing environmentally friendly solvents for manufacture.

Table 2. Class II solvents and their limits in pharmaceutical products.

Solvent	PDE (mg/day)	Concentration limit (ppm)
Acetonitrile	4.1	410
Chlorobenzene	3.6	360
Chloroform	0.6	60
Cyclohexane	38.8	3880
1,2-Dichloroethene	18.7	1870
Dichloromethane	6.0	600
1,2-Dimethoxyethane	1.0	100
N,N-Dimethylacetamide	10.9	1090
N,N-Dimethylforamide	8.8	880
1,4-Dioxane	3.8	380
2-Ethoxyethanol	1.6	160
Ethyleneglycol	6.2	620
Formamide	2.2	220
Hexane	2.9	290
Methanol	30.0	3000
2-Methoxyethanol	0.5	50
Methylbutyl ketone	0.5	50
Methylcyclohexane	11.8	1180
N-Methylpyrrolidone	48.4	4840
Nitromethane	0.5	50
Pyridine	2.0	200
Sulfolane	1.6	160
Tetralin	1.0	100
Toluene	8.9	890
1,1,2-Trichloroethene	0.8	80
Xylene	21.7	2170

From FDA website: http://www.fda.gov/cder/guidance/Q3CT&Lrev1.htm; PDE, permitted daily exposure.

There are two monographs that provide another source of information, one is "Practical Process Research & Development" and the other is "Waste Minimization in Pharmaceutical Process Development: Principles, Practice, and Challenges" (*13,14*). These are excellent sources for consideration of solvents for designing a green process.

In this overview article we will summarize some of the success stories of using green chemistry principles to guide process design and the use of green solvents in the pharmaceutical industry (*15–19*). The selection of green solvents and the improved approaches displayed in these examples were chosen based upon performance criteria, such as optimal yield, chemical reactivity and selectivity, and separation.

Table 3. Solvents with limited use in pharmaceutical scale-up (*9*).

Solvent	Unfavorable issues	Possible alternative solvent(s)
Ethyl ether	Flammable	MTBE
Chloroform, dichloromethane	Toxicity and environmental	$PhCH_3/CH_3CN$, *n*-butanol or trifluorotoluene
Benzene	Toxicity	Toluene
Isopropyl ether	Peroxide formation	MTBE
CCl_4, $ClCH_2CH_2Cl$	Mutagenicity and environmental impact	–
HMPA	Toxicity	N-methylpyrrolidine
Ethylene Glycol	Toxicity	1,2-propanediol
Hexane	Electrostatic discharge	
Neurological toxicity	Heptane	
Pentane	Flammable	Heptane
Dioxane	Teratogen	Tetrahydrofuran (THF) or 2-Me-THF

Case studies of green processes in pharmaceutical development

Sildenafil citrate (*20–23*)

The story of the phosphodiesterase (V) inhibitor sildenafil citrate (Viagra®), the first effective oral treatment for erectile dysfunction, is well known even outside of chemical circles. In addition to alleviating distress for an underserved cohort, it has been an important component of Pfizer's revenues since 1998. Behind its success is a good example of the adaptation of green chemistry in the design of the commercial manufacturing process.

The first viable route developed at Pfizer's UK laboratories was a linear 11 step synthesis, which gave a 4.2% overall yield from 2-pentanone (Scheme 1). While compelling and attractive chemistry, it was not suitable for large scale manufacturing due to low yield and the use of noxious compounds. As regards route selection, particularly unfortunate was the placement of a highly crystalline, easily purified intermediate in the middle of the synthesis rather than near the end. This would require that toxic chlorosulfonic acid would appear subsequent to the point where the chemist would like to purge most impurities. In addition, this chlorosulfonation required excess chlorosulfonic acid as it functioned as both reagent and solvent, guaranteeing that substantial hazardous waste would result.

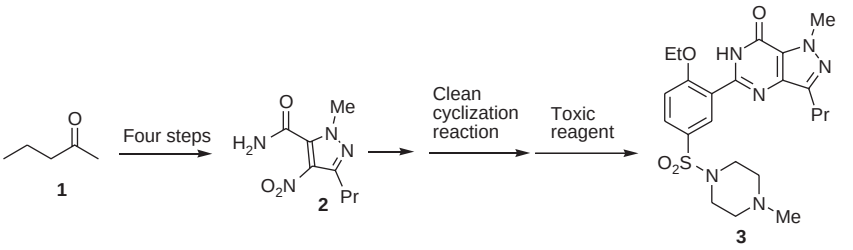
Table 4. Most useful green solvents used in the pharmaceutical industry.

Acetic acid
Water
Ethanol
1-Butanol
2-Butanol
Acetone
Butyl acetate
Propyl acetate
Isobutyl acetate
Isopropyl acetate
Methyl acetate
t-Butanol
Tetrahydrofuran (or 2-Me-THF)
Ethyl acetate

While a convergent strategy is not necessarily a better or shorter synthesis, it often does improve a manufacturing process by permitting the simultaneous preparation of the components of an advanced intermediate. Advanced intermediates may thus be stockpiled and impurities tend to purge easier since when the convergence occurs, non-reacting impurities in the intermediates become dissimilar to the new intermediate. For sildenafil citrate, the redesigned chemistry became beneficial in that it increased the overall yield significantly, (average yield of last three steps = 97% yield). The process redesign placed the cyclization as the last step and utilized the relatively benign reagents *t*-butanol and its potassium base, while the chlorosulfonation was moved earlier into the synthesis (Scheme 2). This permitted the inherent purification of the workups in the steps subsequent to the sulfonation to remove the toxic residues. The final step could now also be run in high concentration, further minimizing solvent waste.

While the improved yields naturally reduced the waste, green solvents, such as water, *t*-butanol, and ethyl acetate had also been introduced in place of ether and chlorinated solvents. Process development established that ethyl acetate could be used over three consecutive steps (hydrogenation, acid activation, and acylation), which simplified the process and removed the need to completely exchange solvents between all steps, a major energy saving and waste elimination.

Pfizer has continued to optimize the sildenafil citrate process since commercial launch. Remarkably, this research has further lowered the ratio of solvent



Scheme 1. First preparative route to sildenafil citrate.

waste/kg product over 17 years from 1300 L/kg to only 7 L/kg by minimizing solvent use, increasing solvent recovery, improving solvent selection, and telescoping steps. Only the solvents *t*-butanol, ethyl acetate, 2-butanone, and a trace of toluene still require disposal.

Sertraline

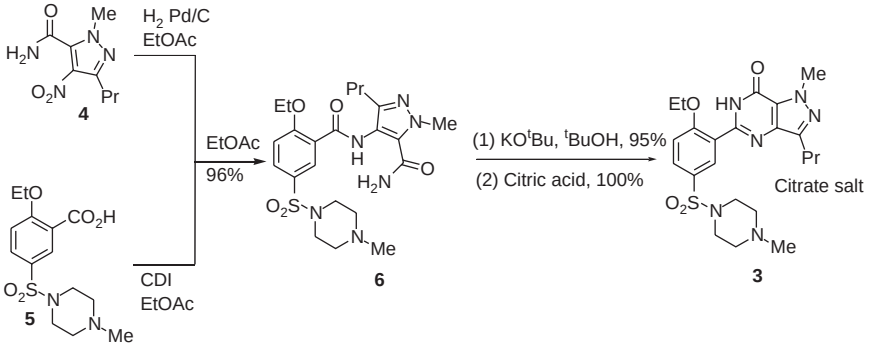
Sertraline (Zoloft®) is an anti-depressant agent launched by Pfizer in 1991 (*24–26*). The original synthesis utilized a Stobbe reaction to couple benzophenone with diethylsuccinate to yield a mono acid (Scheme 3). Hydrolysis and decarboxylation under strongly acidic conditions produced the butenoic acid, which was hydrogenated over a palladium catalyst to the desired 4,4-diarylbutanoic acid **10**. Subsequent Friedel–Crafts acylation and cyclization yielded the key racemic tetralone intermediate **11**. Condensation with methylamine in the presence of titanium tetrachloride followed by catalytic reduction of the imine gave a mixture of *cis* and *trans* amines **12**. The *cis* form was purified as its HCl salt by fractional crystallization and was subsequently resolved with D-(–)mandelic acid to produce the desired (+)-(1*S*, 4*S*)-sertraline **13**.

There are several potential areas for improvement in this synthesis (Scheme 4). Firstly, it required four steps to establish the skeleton of the racemic tetralone, certainly a shorter route existed for this relatively simple compound. Secondly, the Friedel–Crafts acylation required excess $AlCl_3$ and was carried out in the hazardous solvent carbon disulfide. Finally, classic resolution using a chiral salt was required in the final step, requiring significant resources for carrying along the unwanted stereoisomer throughout the entire synthetic sequence. Obviously, this was not a green process since half of the final product was the unused diastereomer and was not recycled.

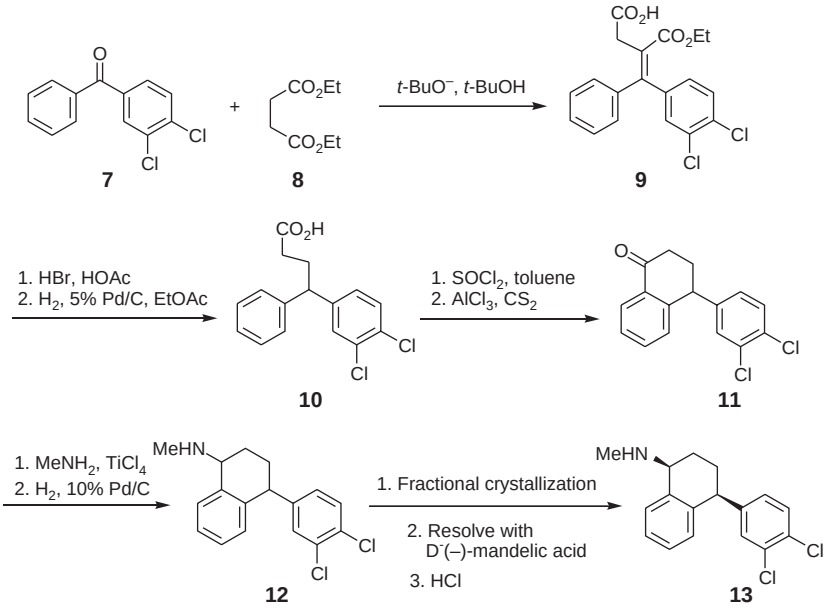
The process chemistry team cleverly determined that the formation of the imine could be pushed to >95% completion by substituting the solvent from tetrahydrofuran (THF) to ethanol. The imine possessed low solubility in alcohols and as a result the equilibrium of the condensation was shifted toward the imine as it precipitated. Ethanol also permitted a telescope into the next step. As $TiCl_4$, was no longer needed for the imine formation, the new process alleviated the difficult separation of the titanium waste and the expensive disposal problem.

Optimization of the imine reduction established that the catalyst $Pd/CaCO_3$ produced better regioselectivity than the existing catalyst system Pd/C. The ratio of *cis* (desired)/*trans* (undesired) isomers had been 6:1, while the revised processed raised the ratio to 17:1 and as a result raised the yield from 78 to 92%.

The first commercial process employed in 1986 had used five solvents, including the neurotoxin hexane. Efficient process research has reduced this number to only ethanol and ethyl acetate. Overall organic solvent



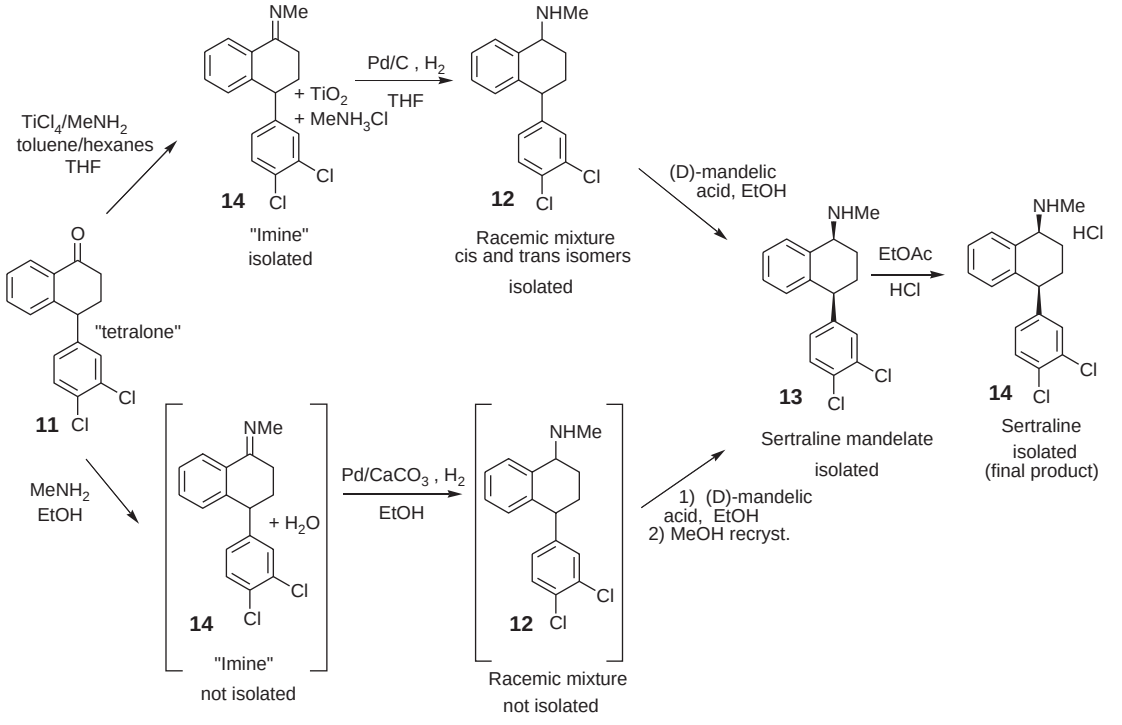
Scheme 2. Convergent commercial preparation of sildenafil citrate.



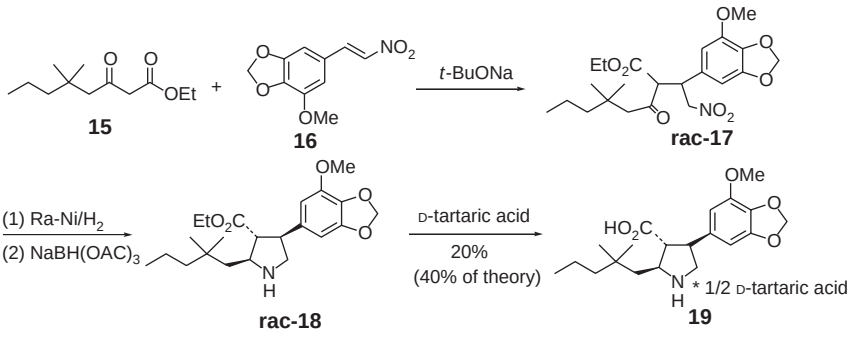
Scheme 3. Early process synthesis of sertraline.

usage has been decreased from 979 L/kg in the first commercial process to 256 L/kg in the current process, due to both process optimization and solvent recycling.

Obviously, the resolution of racemic sertraline is still not efficient if the undesired enantiomer is not recycled. Preferable would be a means to exclusively produce the required diastereomer, allowing removal of the resolution step. It was possible to resolve the tetralone **11** using a simulated moving bed (SMB) chromatography (*25*), followed by racemization of the unwanted enantiomer since the racemic tetralone **11** was prepared in one step from an aluminum trichloride mediated reaction of 1-naphthol and ortho diclorobenzene in high yield (*26*). The racemate was sent back into the separation process with previously



Scheme 4. Comparison of routes between the old and new commercial synthesis of sertraline HCl.



Scheme 5. Resolution route to the pyrrolidine core of ABT-546.

unchromatographed material, essentially effecting a total conversion of the racemic tetralone into the desired enantiomer if run as a reiterative process. Of course, this required significant solvent consumption, but if the solvent is recycled, a greener process still results due to the more efficient use of starting materials.

ABT-546

Developing a selective and efficient catalytic process is usually the best solution when asymmetry arises from prochiral starting materials. The process for the synthesis of the endothelin-A antagonist ABT-546 provides an excellent example (*27–29*). Although a synthetic route was developed to prepare the racemic pyrrolidine core of ABT-546 (Scheme 5), it required subsequent resolution with D-tartaric acid. Yet, this process still required several recrystallizations and the resolved tartrate salt was obtained in only 40% of theory. This motivated a search for an asymmetric synthesis of the pyrrolidine core in order to provide enough material to support upcoming clinical trials.

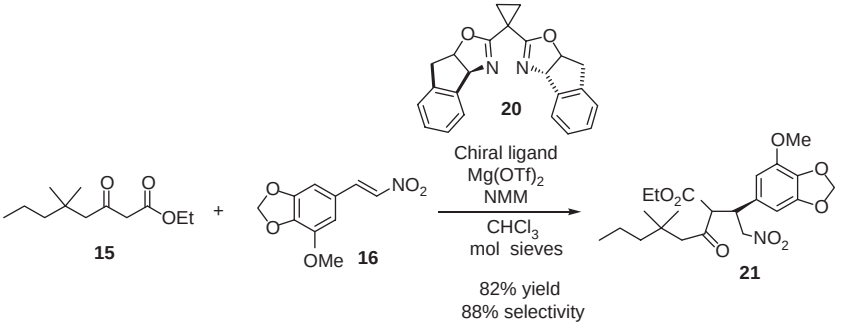
After systematic screening and analysis, a catalytic, highly enantioselective conjugate-addition process was developed in which the β-ketoester anion **15** was added to nitroolefin **16** via catalysis with 4 mole% bis(oxazoline)–$Mg(OTf)_2$ amine complex (Scheme 6). The ability to attain 88% selectivity in this addition allowed less reliance on the tartrate salt for upgrading the chiral purity.

There is a particular advantage to choosing green solvents in the final steps of a drug preparation as any residues remaining in the API produce less concern. The synthesis of ABT-546 was crafted to use water as a co-solvent for the last three steps (Scheme 7). The tartrate salt was broken with K_2CO_3 in THF/water, the free base residing in the THF layer. Next, bromoacetamide was added to the THF solution of free base, along with aqueous $NaHCO_3$, and the reaction was heated until alkylation was complete. After separation, the product in the THF layer was diluted with ethanol. Finally, aqueous NaOH was used for saponification. The three step/one pot sequence provided the free base of ABT-546 in excellent yield (96%) without the need for solvent removal and extraction.

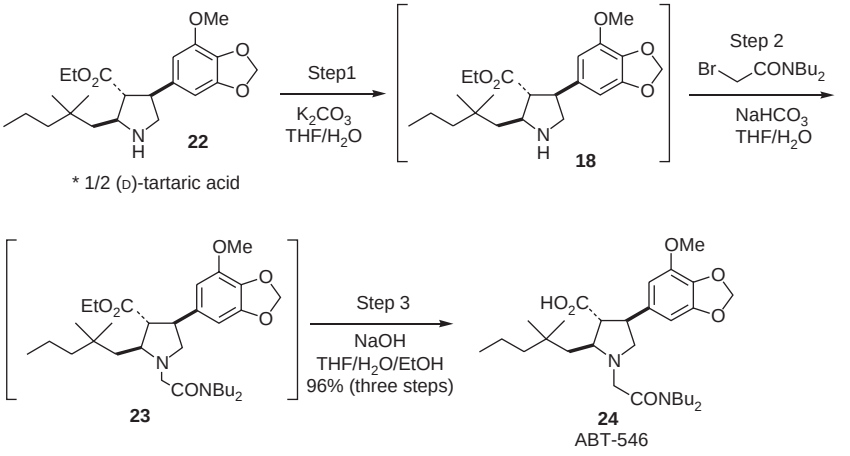
LY300164

LY300164 is a potential therapeutic agent for the treatment of neurodegenerative disorders such as Alzheimer's and Huntington's disease. Lilly's LY-300164 process makes use of environmentally benign protocols, such as air oxidation and a biocatalytic reduction (*30,31*).

The original synthesis consisted of a linear approach of eight steps and provided a 22% overall



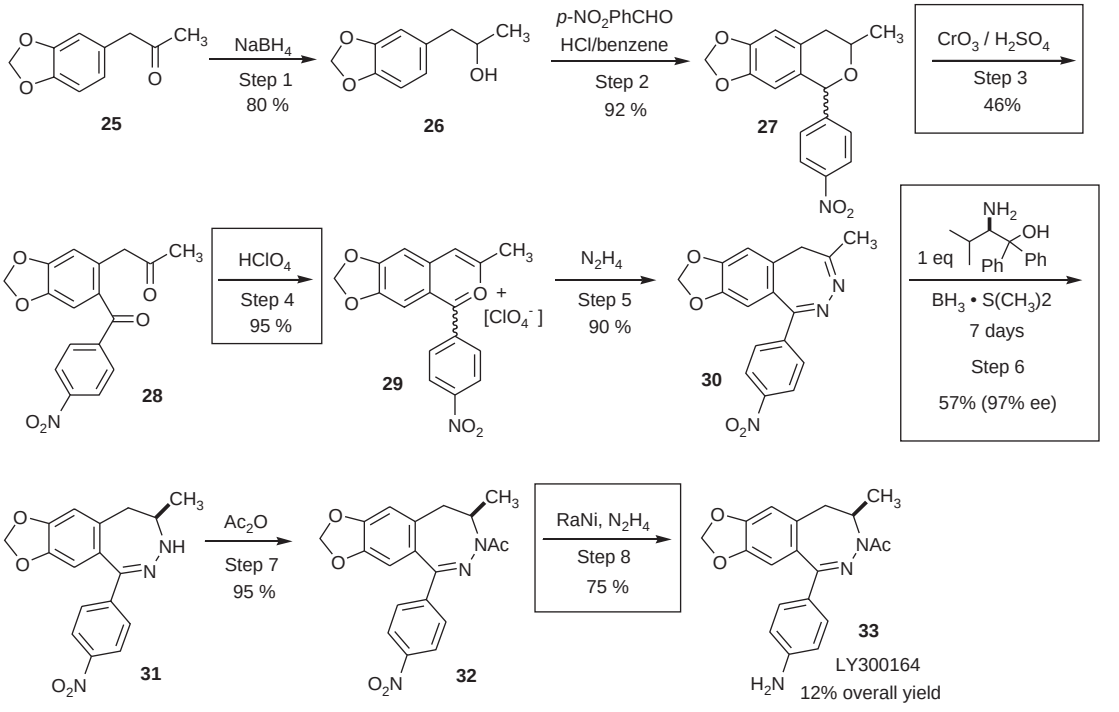
Scheme 6. New approach to synthesis of the core of ABT-546.



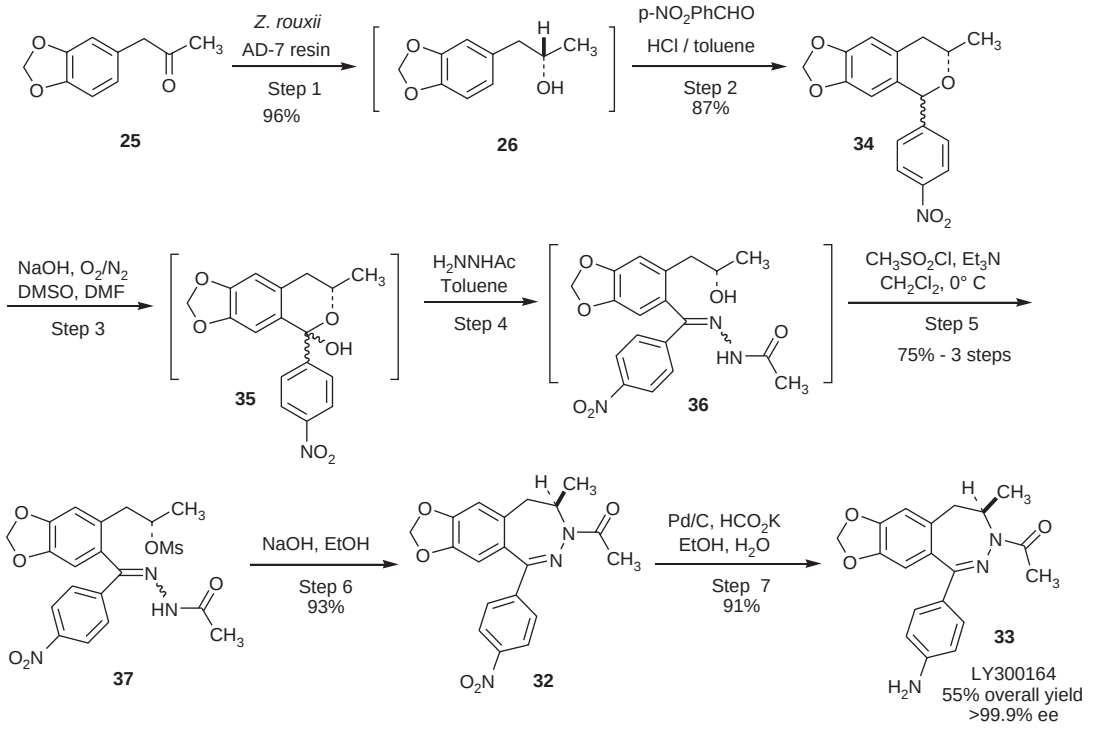
Scheme 7. Final three step in the synthesis of ABT-546.

yield (Scheme 8). Several environmental disadvantages of this approach were the use of chromium trioxide (the only acceptable oxidant for making the diketone at that time), perchloric acid, borane, and hydrazine. The use of hydrazine at the last step where API contamination of genotoxic impurity (GTI) would become a major concern was particularly unfortunate.

The need to dispose of 3 kg of chromium waste per kilogram of product and the heavy metal contamination of reaction vessels were powerful inducements to avoid this metal oxidation. This led to a redesign of the synthetic route which also permitted the incorporation of several other green improvements (Scheme 9). The new route was made possible by introducing the required chirality at the beginning of the sequence by preparing the chiral alcohol **26** enzymatically instead of by the late-stage borane imine reduction. A biocatalytic reduction using resin-bound *Zygosaccharomyces rouxill* in water efficiently provided the chiral alcohol **26** in a remarkable 100% conversion, >99.9% ee and 96% isolated yield. This enzyme has a good process record as it has been used in the food industry for centuries. Additionally, this enzyme



Scheme 8. The initial scalable synthesis of LY300164.



Scheme 9. Improved process route to LY300164.

operated at a relatively high concentration (40 g ketone/L) permitting a high throughput for a biocatalytic reaction.

The chiral alcohol was carried directly into the cyclization step to form the chiral cyclic ether **34**. Instead of oxidizing at this point, which would have also pointlessly destroyed the hard won chirality, a new route was developed to permit an alternative to the oxonium salt route. The oxidation required at the benyzlic center was accomplished by air via a base mediated oxidation using sodium hydroxide in DMSO to establish the hemiketal **35** (Scheme 9).

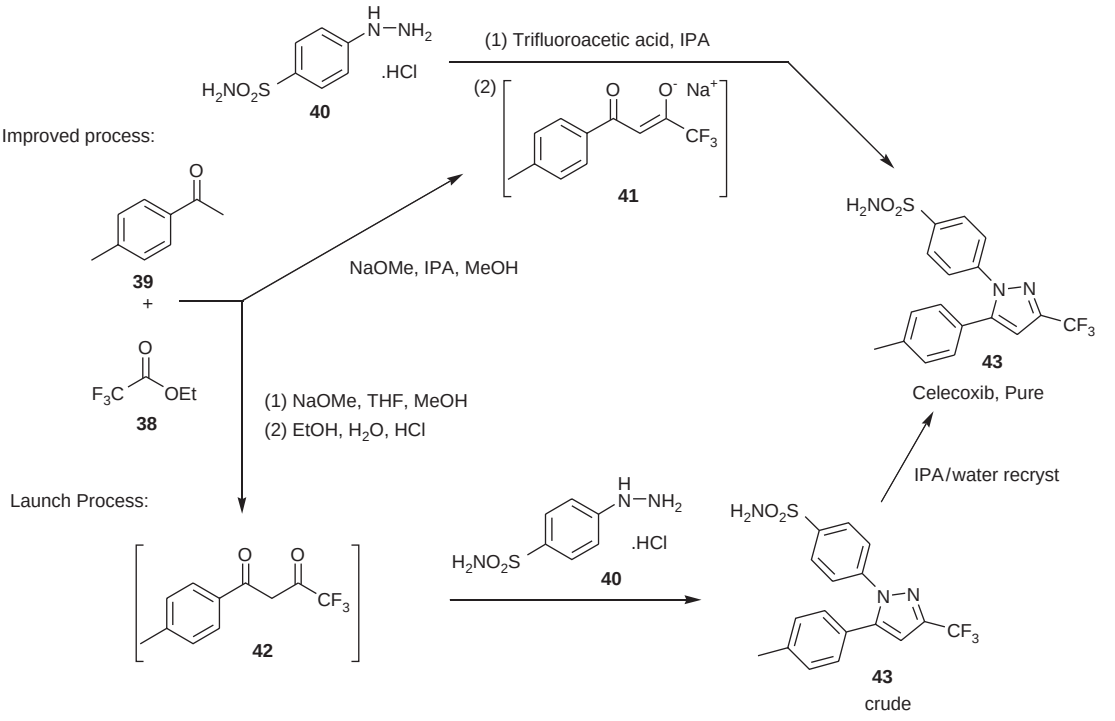
This step was telescoped to react with acetylhydrazine to form **36** and then treated with mesyl chloride and triethylamine, the crystalline mesylate **37** was isolated in 75% overall yield over three steps. The beauty of this design is that chromium has been replaced by air, hydrazine by the less dangerous acetylhydrazine, and there is no further need for the persistent environmental pollutant perchloric acid to form the oxonium salt. The subsequent cyclization cleanly formed the benzodiazepine **32** in 93% isolated yield.

The final step to reduce the nitro group to reveal LY300164 was first conducted with hydrazine and Raney nickel. Since the suspected carcinogen hydrazine had been eliminated from an earlier step, there was strong motivation to excise it entirely from the process. This could be done by catalytic hydrogenation in aqueous ethanol using potassium formate as a hydrogen source. LY300164 was subsequently isolated in 91% yield. The process reconsideration resulted in a much greener process by tripling the overall yield, reducing the number of steps, substituting air for a heavy metal-induced oxidation, and developing a biocatalytic reduction for establishing the chiral center.

Celecoxib

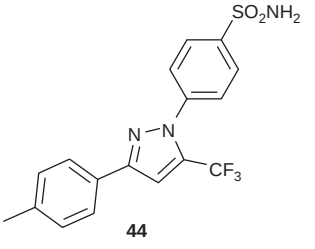
Celecoxib is the active ingredient in Celebrex®, the widely used COX-2 anti-inflammatory agent. This molecule is relatively simple and already possessed a reasonable synthetic process by the time it reached the developmental chemists (Scheme 10) (*32,33*). However, the high daily dose of up to 800 mg suggested additional process work was still mandated for the large quantities of bulk drug that would be needed.

The existing preparation of the pyrazole ring required recrystallizations to remove the unreacted hydrazine **40** and the regioisomers, which were generated during the cyclization. The need for this purification added significantly to the solvent and waste disposal requirements, leading the chemists to target the ring formation for optimization to reduce the ecological footprint of the process.



Scheme 10. Comparison of the commercial launch and improved processes for Celecoxib.

The improvements came from a thorough understanding of the mechanistic underpinnings of the reaction. The key question concerned the formation of the 2–3% levels of impurity **44** (Scheme 11). The experiences with other pyrazoles during the developmental work suggested that the level of regioisomeric impurity could be much lower. The chemists discovered that the presence of water would lead to the hydrate of the diketone, which in turn influenced the formation of **44**, as did the concentration of the hydrazine. Thus, the water concentration was kept low and the hydrazine's effective concentration was reduced by adding it as the HCl salt instead. This salt had limited solubility in the now non-aqueous solution until the diketone sodium salt was added, which neutralized enough salt to lead to a controlled reaction. This clever self-moderating reaction reduced the production of the regioisomer to 0.5%, permitting the direct isolation of pure Celecoxib from the reaction mixture by simple water dilution and cooling. It is unusual to find a process that permits a direct isolation of the API without some additional purification.



Scheme 11. Impurity in the final cyclization (*42,43*).

The green benefits established by the subtle, but significant changes above are numerous. Only two benign solvents (methanol and isopropanol) are now needed. The yield increased from 63 to 84%, decreasing waste production by 35% and reducing the use of the hazardous hydrazine. The reactor throughput increased 50%. The change in reaction conditions now meant that product isolation only required cooling to 20°C instead of 5°C. Finally, the cleaner product permitted a change in the cake wash solvent from 100% isopropanol to 50% aqueous isopropanol. This process eliminated the use of the undesirable solvents methylene chloride and hexane, and when combined with the other changes, eliminated the need for 5200 metric tons of solvent annually. Figures 1 and 2 graphically demonstrate the greening of the Celecoxib manufacture process.

Quinapril

Quinapril hydrochloride (Accupril®) is an angiotensin converting enzyme (ACE) inhibitor for the treatment of hypertension and congestive heart failure (*34*). The original manufacturing route contained a variety of undesired qualities, such as the use of

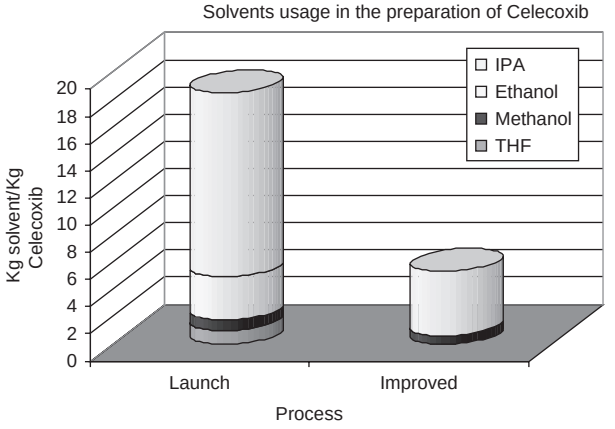


Figure 1. Solvent usage in the preparation of Celecoxib (1995–2002).

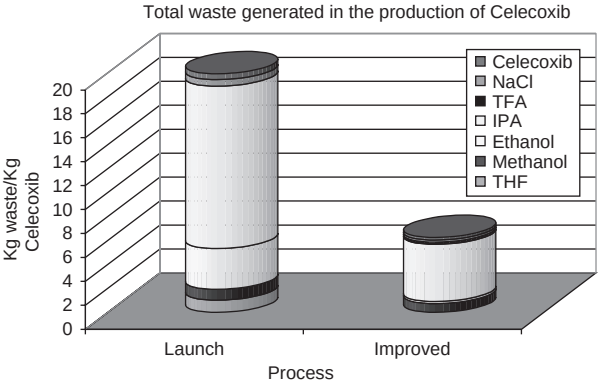


Figure 2. Comparison of the total waste generated in the production of Celecoxib.

methylene chloride, the potentially explosive hydroxybenzotriazole, the sensitizer dicyclohexylcarbodiimide (DCC), and copious toluene volumes for removing acetic acid by solvent exchange. The key to the redesign of the quinapril process was the loss of yield due from an intramolecular cyclization that formed a diketopiperazine impurity. The rate of this side reaction of the product was greatly enhanced, when the reaction mixture was held at $>55^{\circ}C$ during the three acetic acid/toluene azeotropic distillations.

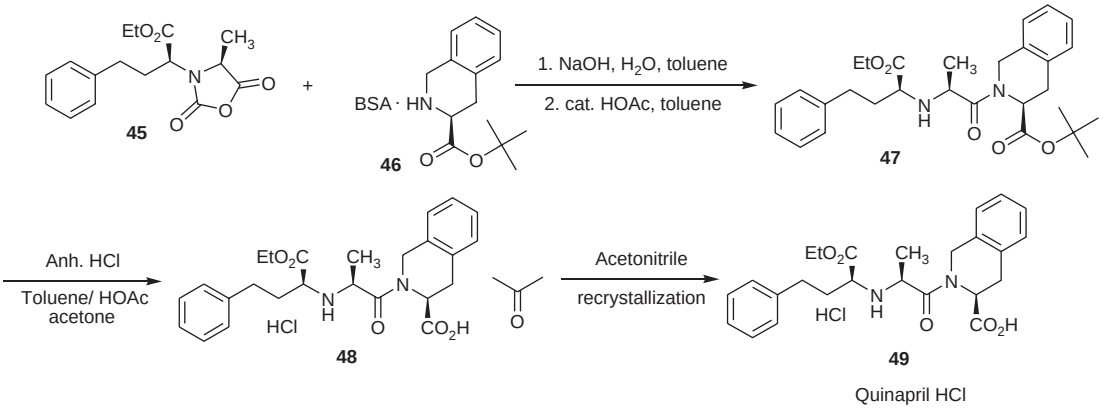
The redesign focused on the elimination of the use of acetic acid, which would permit minimizing diketopiperazine formation. This was accomplished by changing the starting material to the commercially available N-carboxyanhydride **45**. When reacted with the isoquinolinecarboxylic acid *t*-butyl ester salt **46**, the self-activated anhydride led to direct amide coupling, allowing the elimination of DCC, its waste product dicyclohexylurea (DCU), and the need for a chlorinated solvent. The coupling proceeded well in water and toluene (Scheme 12).

The ester was cleaved using a minimum amount of acetic acid/HCl, the salt was formed and isolation proceeded well without a lengthy solvent exchange or drying operation, but by simply adding the anti-solvent acetone. A final recrystallization from acetonitrile produced the API.

As a result, the overall yield increased from 58 to 90%, throughput has quadrupled, waste production has been significantly reduced, and less and greener solvents have been incorporated. Figure 3 represents these improvements graphically.

Sitagliptin

Hydrogenation could be the ultimate manifestation of green chemistry, when the chemical results are weighed against the environmental impact. The addition of hydrogen to unsaturated bonds can establish chirality or the formation of desired functional groups of lower-oxidation state by simple operations and high atom efficiency. Often only trace quantities of catalysts are required or if the catalyst is valuable, means



Scheme 12. New quinapril process.

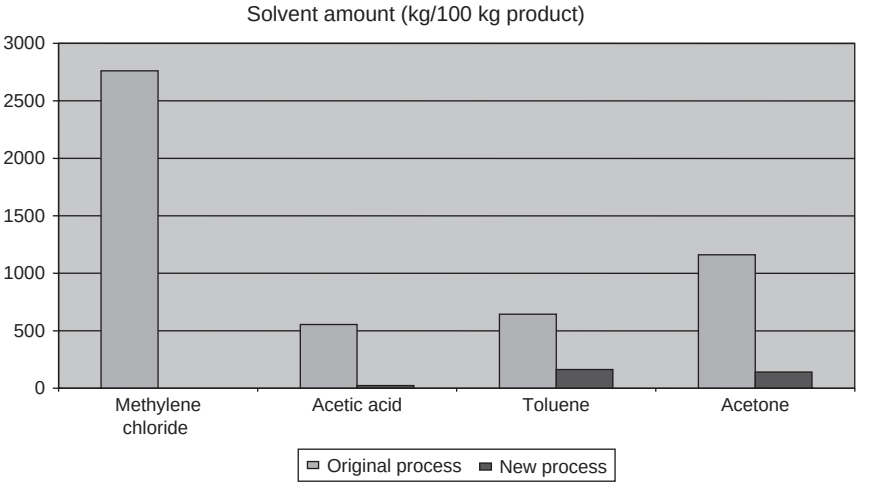
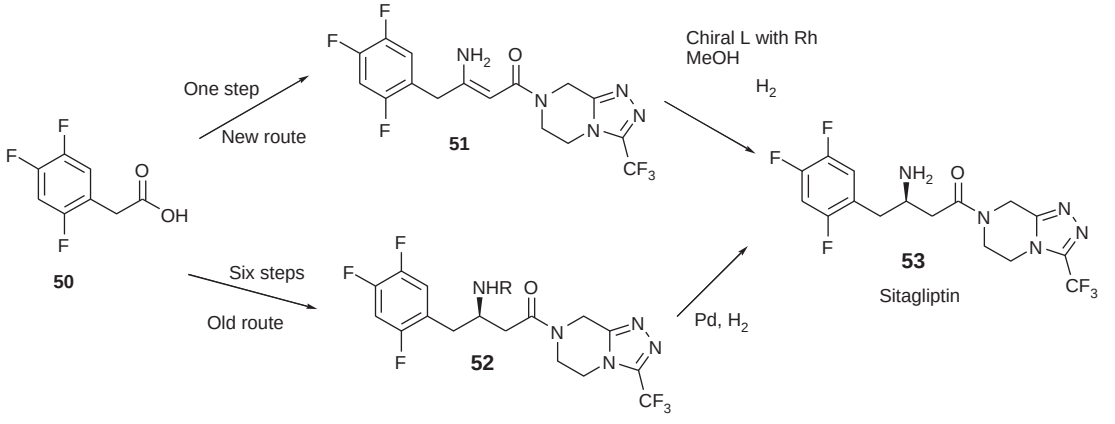


Figure 3. Solvent use comparison in original process and new process.

for its recovery can be designed. The scope of the reaction is broad, the reagent is cheap, and the environmental impact of the reaction is usually minimal if the solvent can be recovered in some manner (*38–41*). The establishment of stereogenic centers via catalytic asymmetric hydrogenation is particularly valued in pharmaceutical process chemistry, since it often permits foregoing resolution or multistep alternative chemistry.

The story of the process development of sitagliptin provides an example of the effective use of this technique (*35–37*). Sitagliptin is a new treatment for type two diabetes via inhibition of the DPP-IV enzyme. Merck used a first-generation synthesis of sitagliptin to prepare about 100 kg for clinical trials, which proceeded by the asymmetric hydrogenation of a β-ketoester catalyzed by (*S*)-binap$RuCl_2$–triethylamine complex in 94% ee (Scheme 13). The ester was hydrolyzed to yield a β-hydroxy carboxylic acid, followed by further transformation to a protected β-lactam and then coupled to a triazole. Subsequent deprotection then revealed the key β-amino acid moiety and the drug was isolated as its phosphoric acid salt. This had potential for evolving into a manufacturing process, however, the numerous steps correspondingly increased the amount of reagents and volume of solvents used. A better process was sought for scale up.

One means for eliminating steps is to avoid the use of protecting groups, effectively removing two steps required to protect the starting material and subsequently deprotect the product. Such an idea was incorporated into the second generation synthesis of sitagliptin. The asymmetric hydrogenation of an enamine would be a more efficient means to synthesize the β-amino acid moiety, but a significant drawback was the requirement of an acyl protecting group on the nitrogen atom. This group is usually considered



Scheme 13. Process incorporating catalytic asymmetric hydrogenation for the preparation of sitagliptin.

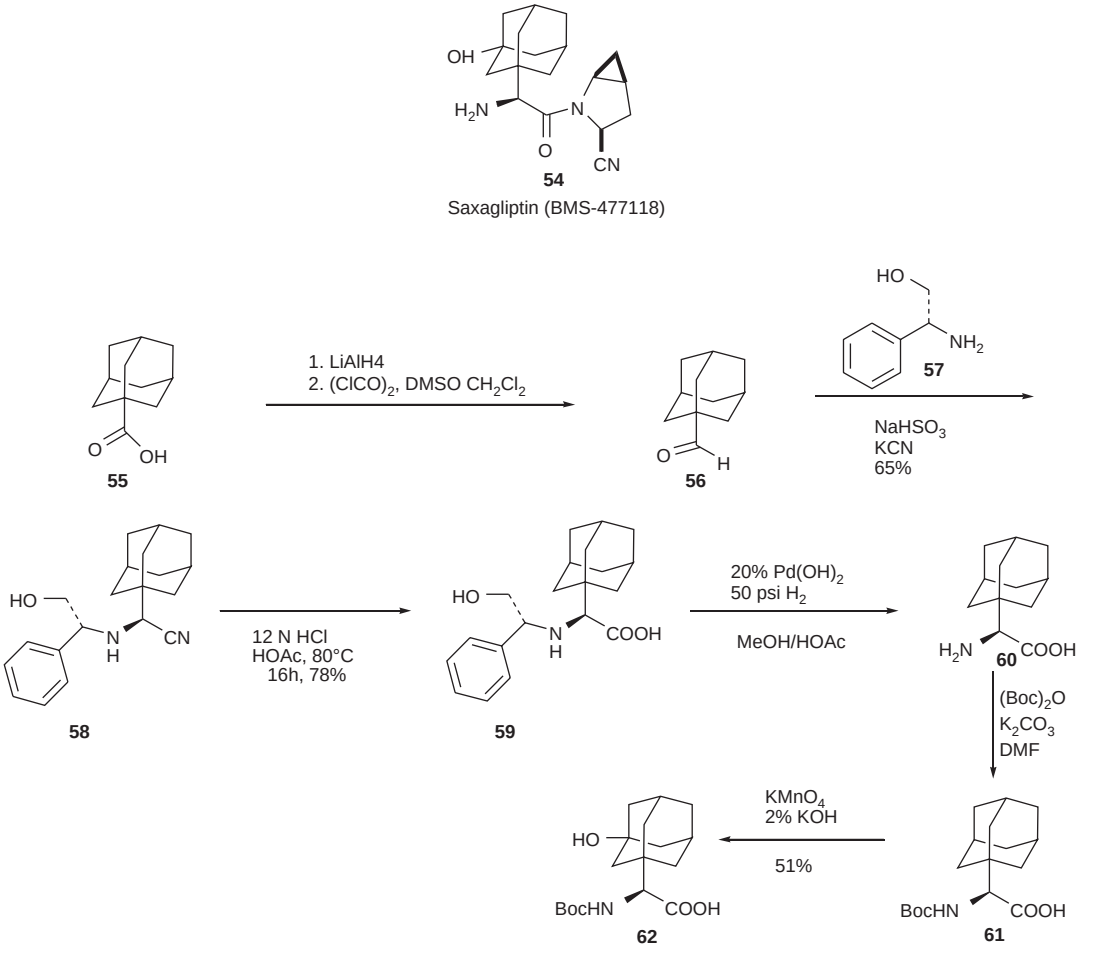
indispensable for chelation between the reactant and the metal catalyst in order to lead to high reactivity and selectivity.

Remarkably, the process chemists discovered a completely unprecedented transformation: the asymmetric catalytic hydrogenation of unprotected enamines in high optical purity and yield, in this case catalyzed by rhodium with a ferrocenyl phosphine ligand (Josiphos). In collaboration with Solvias, this process was perfected and along with several other process changes, it became the manufacturing route. Crafting a new synthetic sequence permitted the reduction step to be run at the end, which minimized the quantity of the expensive catalyst needed, allowed >95% recovery of the rhodium, and only revealed the reactive amino group of sitagliptin in the final step. The new synthesis has only three steps and increases the overall yield by nearly 50%.

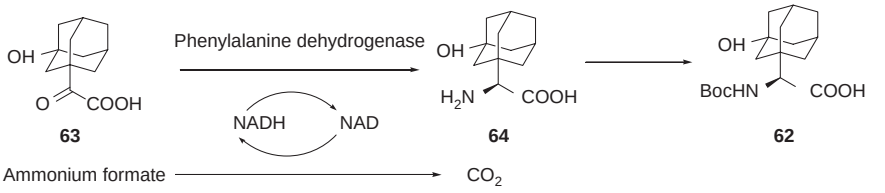
Implementing the new route on a manufacturing scale has reduced the amount of waste by >80% and completely eliminated aqueous waste streams. As this second-generation synthesis will create 220 kg less waste for each kilogram of sitagliptin manufactured, Merck expects to eliminate the formation of at least 150 million kilograms of waste over the lifetime of the drug.

Saxagliptin

Although chiral drugs can be prepared by asymmetric chemical transformations, the use of microbial- or enzyme-catalyzed reactions has advantages over traditional chemical processes. Several have been already described in this review. Many chemoenzymatic processes are stereoselective and can be carried out at ambient temperatures and atmospheric pressure, which typically reduces cost, hazards, and minimizes the probability of undesired side-reactions that may occur under forcing conditions. Furthermore, biocatalytic processes are generally carried out in aqueous



Scheme 14. Original preparative route for the preparation of (*S*)-3-hydroxyadamantylglycine.



Scheme 15. Enzymatic reaction used for preparation of (*S*)-3-hydroxyadamantylglycine.

solutions using less toxic chemicals, potentially minimizing the waste generation.

Saxagliptin (*54*) is a DPP-IV inhibitor under development by Bristol-Myers Squibb (*42,43*). (*S*)-N-BOC-3-hydroxyadamantylglycine **62** is a key intermediate which was originally prepared by an asymmetric Strecker reaction, which is required highly toxic potassium cyanide (Scheme 14). By using a modified phenylalanine dehydrogenase, the Bristol-Myers Squibb (BMS) enzyme technology group successfully set the chiral center in **64** by an enzymatic reductive amination of keto acid **63** (Scheme 15), reducing the number of steps from five to only one by redesigning the process chemistry, eliminating the need for cyanide and the expensive chiral reagent, (*R*)-(–)-2-phenylglycinol, poor oxidation using potassium permanganate in the final step, and this reductive amination used water as solvent.

Enzymes also facilitated a reaction on the dihydropyrrole portion of saxagliptin. *Candida antartica lipase B* (CALB) mediated ammonolysis of the ester with ammonium carbamate as the ammonia donor to yield the amide (Scheme 16). The inclusion of Ascarite® and calcium chloride as adsorbents for carbon dioxide and ethanol byproducts, respectively, increased the yield to 98%, furnishing high purity amide (99.9% ee) in 81% isolated yield with minimal side product formation.

Solvent categories and their utility in pharmaceutical manufacture

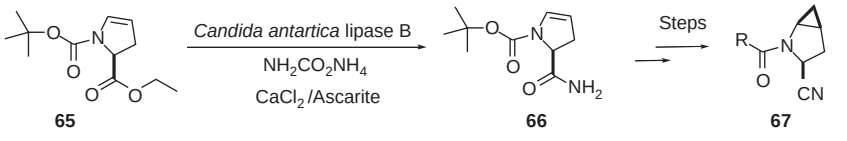
Water as a process solvent

Water is the ultimate green solvent (*44*). Besides its presence in many biocatalytic reactions, water may be used in a surprisingly large variety of reactions as solvent or cosolvent. Several more examples of the use of water as solvent are worth mentioning.

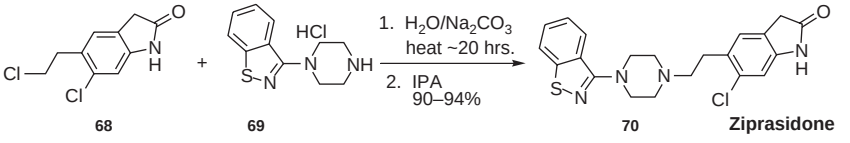
The first synthesis of ziprasidone (Geodon®), an atypical anti-psychotic agent, was not suitable for pilot plant scale-up. Initially, the two fragments were joined by alkylation of **68** with **69** in the presence of NaI and Na_2CO_3 in organic solvent, to produce ziprasidone in 20% yield. When water was used as the solvent to improve the solubility of the reagents, the yield increased to 90–94% (Scheme 17) (*45*).

Danofloxacin **73** is a quinolone anti-bacterial drug for treating infections in livestock (*46–49*). The product-forming amination step was improved by conducting it in pressurized water in order to permit a higher temperature and reaction rate (Scheme 18). It was then isolated in 91% yield and high quality by filtration at the isoelectric pH. In addition, pyridine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), toluene, and alcohols, all used in an earlier process were no longer needed.

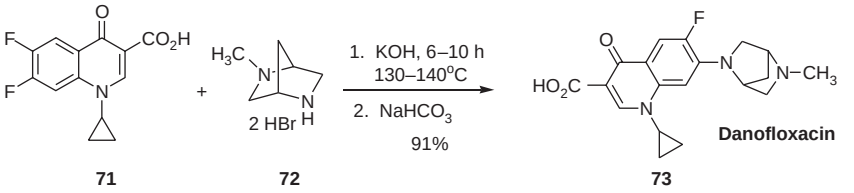
An efficient one-pot synthesis of dibromopyridazinone **77**, an intermediate to ABT-963 (*50*), has been



Scheme 16. Saxagliptin revised process for pyrrole ring amidation.



Scheme 17. Water as solvent during ziprasidone coupling.



Scheme 18. Water as solvent under pressure to permit higher reaction temperature.

developed that incorporates water as a solvent over three consecutive steps (Scheme 19) (*51*). This process was used to prepare 22 kg of dibromopyridazinone **77** in 82% overall yield and 96% purity without further purification.

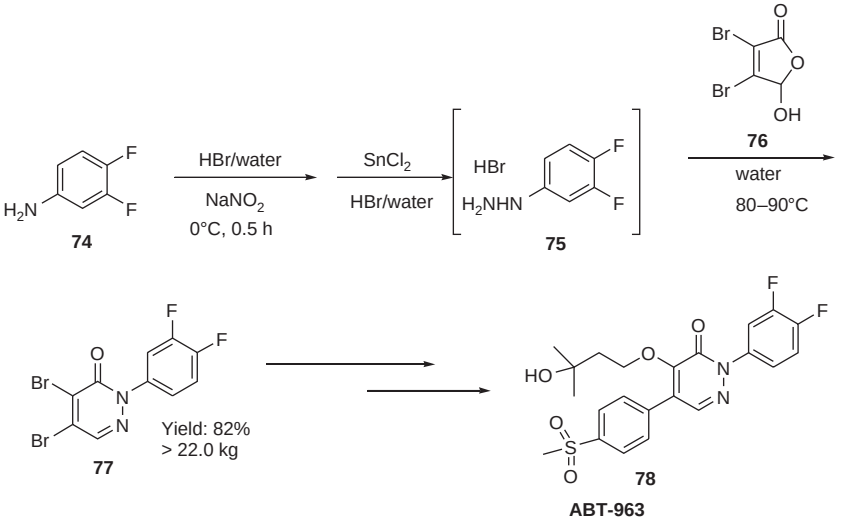
Many drug molecules and intermediates will have limited solubility in water if there are not a sufficient number of hydrophilic groups present. The use of phase-transfer catalysis (PTC) is a special case for water as a process solvent and can often ameliorate solubility problems as well as improve many reactions. PTC technology is simple, cheap, reliable, and has found many applications in industry manufacture. For instance, NaOH may be used as the ring-closing base under PTC conditions (Scheme 20) (*52*). Sodium hydroxide was added to the reagents and catalytic tetrabutylammonium chloride in THF/H_2O at 45°C, leading to the cyclized product in 96% yield.

A practical pilot-scale synthesis of 4-vinyl-2, 3-dihydrobenzofuran **84** is done using PTC for dehydrohalogenation (Scheme 21) (*54*).

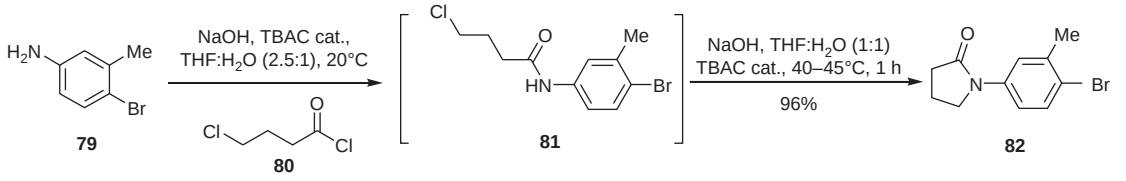
The use of chiral PTC has recently become more common for the preparation of chiral, enantio-enriched compounds from prochiral substances (*55–59*). Chiral PTC often makes use of the cinchona alkaloids because the parent alkaloids are inexpensive, readily available in both pseudoenantiomeric forms, and can be easily quaternarized to a variety of different salts. An illustrative example is the alkylation of a phenylindanone using chiral PTC in 98% yield and 92% ee (Scheme 22) (*60–62*). It was proposed that the chiral induction step involved an ion-pair in which the enolate anion fit on top of the catalyst, positioned by electrostatic and hydrogen-bonding effects, as well as π–π stacking interactions between the aromatic rings in the catalyst and the enolate. The electrophile then preferentially approached the ion-pair from the open top (front) face. A crystal structure of the catalyst supports this interpretation.

Suzuki couplings may be conducted in water as a cosolvent. A multikilogram-scale synthesis of a biphenyl carboxylic acid derivative using a Pd/C-mediated Suzuki coupling in aqueous methanol is possible, which produces an improved yield of the desired product as well as leaves low residual Pd levels in the product (Scheme 23).

Practical and efficient epoxidation of aromatic olefins may be accomplished using Oxone® in ethyl acetate–water (Scheme 24). This oxidant/solvent system is the best choice for the required chemistry for environmental reasons. The reported method is suitable for large-scale synthesis (*53*).



Scheme 19. Water as green solvent in the process chemistry.

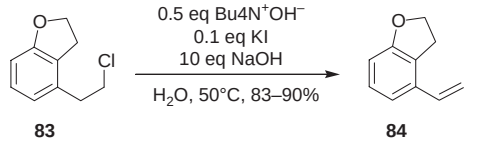


Scheme 20. Water as solvent in ring-closing under PTC condition.

Solvent-free processes (63)

The ultimate of green chemistry could be defined as being totally free of solvents or any other chemicals beyond those that will comprise the product. Solvent-free processes may theoretically eliminate waste and be energy efficient, but for large-scale chemical manufacture it is not hazard-free. Without using solvent as heat transfer media and heat sinks in exothermic reactions, the consequences of a runaway reaction can be devastating. A greater understanding of the thermal characteristics of solvent-free reaction is essential before any increase in scale should be considered (*64*). But there are some instances of solventless chemistry related to pharmaceutical manufacture, if excess reagents are not considered to represent solvent. Dihydropyrimidinone derivatives hold promising biological properties and often may be prepared using modifications of the Biginelli reaction: the acid-catalyzed three-component condensation of a 1,3-dicarbonyl compound, an aldehyde, and urea (Scheme 25). Recently, a simple synthesis of dihydropyrimidinones by a solvent-free and catalyst-free Biginelli condensation has been reported at kilogram scale (*65*). These reaction conditions were also mild enough to tolerate a variety of sensitive functionalities. No solvents or catalyst was used and suggests solvents can be eschewed for narrowly defined structures.

Solvent-free catalytic asymmetric reactions have the potential to be safe, cost saving, and environmental-friendly processes (*66*). In 1997, a breakthrough in the isolation of terminal epoxides with high enantioselectivity by hydrolytic kinetic resolution of epoxides was reported (Scheme 26) (*67*). Such resolved epoxides or diols are useful synthons in pharmaceutical chemistry. Water serves as a nucleophile in the presence of catalytic (salen)Co(OAc) to open epoxides. The reaction possesses the process advantages that the hydrolytic kinetic resolution of



Scheme 21. Dehydrohalogenation under PTC conditions.

propylene oxide has been performed on large scale (>200 kg) and the remaining catalyst can be recycled at least three times without loss of activity or enantioselectivity (*68*).

To control exothermicity, conducting solvent-free reactions at low temperature is a promising means to achieve a viable synthesis. The organocatalytic conjugate addition of nitroalkanes to nitroolefins using a modified cinchona alkaloid catalyst is an example (Scheme 27) (*69*). At 0°C, this solvent-free reaction afforded the desired product in 81% ee and 83% yield. A less attractive feature was that the low temperature also reduced the reaction rate, requiring days for acceptable reaction completion. The reaction was considered safe for operation at large scale once a thermodynamic investigation (differential scanning calorimetry, DSC, and thermal gravimetric analysis, TGA) was completed, always a good idea in process chemistry.

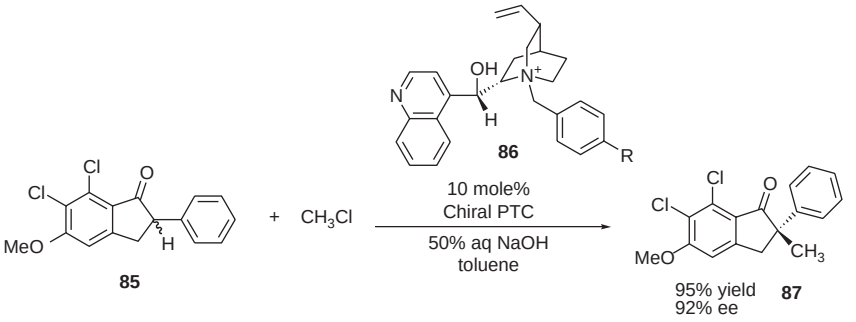
Ionic liquids

There has been an increase in research of ionic liquids as solvents in recent years (*70*). Many of the researchers in this area promote the usefulness of ionic liquids in the synthesis of molecules important to the pharmaceutical industry in reactions, such as Friedel–Crafts alkylations or acylations (*71*), Heck couplings (*72*), alkylations (*73,74*), and various condensations (*75*). It is unclear if any direct pharmaceutical applications have appeared yet.

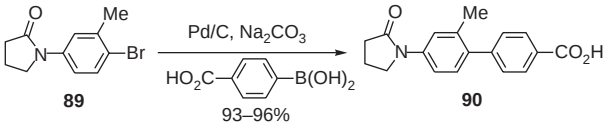
While ionic liquid advocates cite their low volatility and ability to recycle as green attributes, this is only one consideration. Until the issues of cost, safety, regulatory acceptance of ionic solvents residue in APIs, and the lack of generality are addressed, their utility remains undefined.

Supercritical carbon-dioxide (76–78)

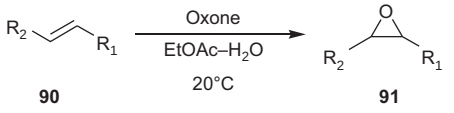
Supercritical fluids are finding application in the pharmaceutical industry for solving difficult process and formulation problems. Supercritical fluids exhibit a pressure-tunable dissolving power with a liquid-like density and gas-like transport properties. They possess the attractive property of easy separation from the substrate once the chemistry is complete by simply



Scheme 22. First chiral PTC for alkylation in pharmaceutical process.



Scheme 23. Water as solvent for a Suzuki coupling reaction.



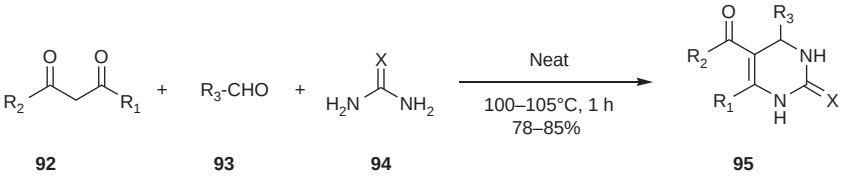
Scheme 24. Oxone epoxidation in two-phase system.

releasing the pressure. This unique combination of properties is ideally suited for developing processes for reacting, extracting, purifying, and recrystallizing pharmaceuticals as well as producing new forms that cannot be obtained by traditional processing technologies. By far the most exploited supercritical fluid has been liquidized carbon-dioxide. This can be a green reaction solvent, assuming the gas is captured after processing.

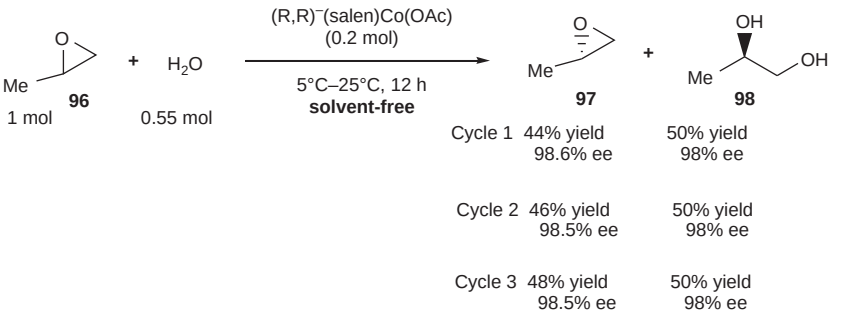
Recently, process chemists in Boehringer Ingelheim Pharmaceuticals developed a practical method for the removal of ruthenium byproducts by supercritical-fluid extraction in the synthesis of macrocyclic compound BILN2061 (*79*). Supercritical carbon-dioxide was used to remove the Ru catalyst and its derived byproducts from a ring-closing metathesis reaction. This method was implemented in a semi-continuous fashion and allowed for efficient removal of the toxic metal impurities to meet the specifications for the final drug substance.

Besides chemistry, this solvent can be profitably used for form establishment. Some pharmaceutical compounds are difficult to micronize by conventional grinding or jet milling. For example, materials that have a low-melting point or are waxy cannot be ground or milled. Some supercritical-fluid processes have been developed to first dissolve the pharmaceutical compound and then effect precipitation by pressure decrease. Alternatively, the gas can act as an anti-solvent causing recrystallization from solution because of a solubility decrease when the gas and liquid solvent contract.

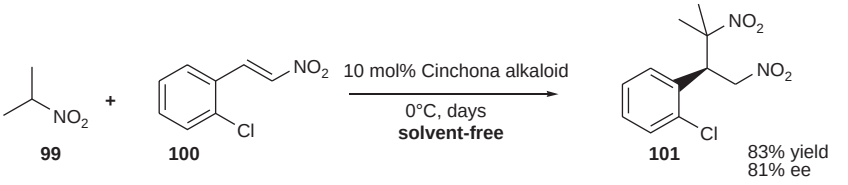
Poor aqueous solubility of drug candidates presents a significant problem in drug development. Among various strategies to address solubility issues, reducing the particle size is a common option. Recently, a processing technique called rapid expansion of a supercritical solution into a liquid solvent (RESOLV) has been used to reduce the drug particle size and offers advantages in clean, non-toxic drug formulation research (*80*). For example, this technology has been applied to a pair of anti-inflammatory drugs: ibuprofen and naproxen. The RESOLV process produced exclusively nanoscale (less than 100 nm) ibuprofen and naproxen particles suspended in aqueous solutions. These suspensions are protected from particle agglomeration and precipitation by using common polymeric and oligomeric stabilizing agents. This technology may serve as a green process for nanosizing other drugs for formulation and



Scheme 25. Solvent-free Biginelli condensation.



Scheme 26. Hydrolytic kinetic resolution of propylene oxide.



Scheme 27. Asymmetric organocatalytic Michael addition under solvent-free conditions.

sustained-release requirements (*81*). Additional applications of supercritical fluids in the controlled release of drugs have appeared (*82*).

Conclusion

Many of the green chemistry principles are not new to pharmaceutical industry chemists, but represent the way good process development is done. They do represent a new area of focus to further reduce manufacturing costs, build in greater process robustness, and to diminish the environmental footprint of the industry. It is clear from the US Presidential Green Chemistry Challenge awards awarded to industry companies that there is much successful activity in redesigning pharmaceutical processes. This trend will certainly continue.

Green chemistry is rapidly being adopted by process chemists and engineers, and not only because it is the right thing to do. Cost is also a factor. A Tufts University study suggests that average R&D costs for developing a drug have increased dramatically since the mid 1970s from $55 million to over $800 million in 2000 (*83,84*). As the industry continues to come under pressure to hold down the cost of drugs, the adoption of an environmentally benign approach to drug candidate synthesis will contribute by reducing the increasing costs of reagent procurement and waste disposal.

In conclusion, we hope the representative examples illustrated in this selective review have provided incentives for further work in developing green pharmaceutical processes. Eventually, there will be no need to emphasize green chemistry to pharmaceutical chemists as it will become the natural course of action when the ultimate good to the company, patient, and environment is considered.

Acknowledgements

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References

(1) Breslow, R. The Greening of Chemistry. *Chem. & Eng. News* **1996**, (Aug 26), 72.
(2) Anastas, P.T.; Williamson, T.C., Eds.; *Green Chemistry: Frontiers in Benign Chemical Syntheses and Processes*; Oxford University Press: Oxford, UK, 1998.
(3) Anastas, P.; Warner, J., Eds.; *Green Chemistry: Theory and Practice*; Oxford University Press: Oxford, UK, 1998.
(4) Sheldon, R.A. *Chem. Ind.* **1992,** *23*, 903–906; Sheldon, R.A. *Chem. Tech.* **1994,** *24,* 38–47.
(5) Jimenez-Gonzalez, C.; Curzons, A.D.; Constable, D.J.C.; Cunningham, V.L. *Int. J. LCA* **2004,** *9,* 115–121.
(6) Curzons, A.D.; Jimenez-Gonzalez, C.; Duncan, A.L.; Constable, D.J.C.; Cunningham, V.L. *Int. J. LCA* **2007,** *12,* 272–280.
(7) Sheldon, R.A. *Green Chem.* **2005,** *7,* 267–278.

(8) Clark, J.H.; Tavener, S.J. *Org. Pro. Res. Dev*. **2007,** *11,* 149–155.
(9) Anderson, N.G. In *Art of Drug Synthesis*; Johnson, D.S., Li, J.J., Eds.; John Wiley & Sons: Hobooken, New Jersey, 2007; pp 11–28.
(10) Guidance for Drugs in USA Food and Drugs Administration. http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm (accessed Oct 15, 2009).
(11) USA Green Chemistry Website. http://www.epa.gov/greenchemistry (accessed Oct 15, 2009).
(12) EPA Green Chemistry GCES Tool. http://www.epa.gov/greenchemistry/pubs/gces.html (accessed Oct 15, 2009).
(13) Gadamasetti, K.G., Ed. *Process Chemistry in the Pharmaceutical Industry*; Marcel Dekker: New York, 1999, pp 3–17 and reference cited therein.
(14) Zhang, T.Y. *In Handbook of Green Chemistry and Technology*; Clark, J., Macquarrie, D., Eds.; Blackwell Science: Oxford, UK, 2002; pp 306–320.
(15) Butters, M.; Catterick, D.; Craig, A.; Curzons, A.; Dale, D.; Gillmore, A.; Green, S.P.; Marziano, I.; Sherlock, J-P.; White, W. *Chem. Rev*. **2006,** *106,* 3002–3027.
(16) Constable, D.J.C.; Dunn, P.J.; Hayler, J.D.; Humphrey, G.R.; Leazer, Jr., J.L.; Linderman, R.J.; Lorenz, K.; Manley, J.; Pearlman, B.A.; Wells, A.; Zaks, A.; Zhang, T.Y. *Green Chem*. **2007,** *9,* 411–420.
(17) Zhang, T.Y. *Chem. Rev*. **2006,** *106,* 2583–2595.
(18) Anderson, N.G., Ed. *Practical Process Research & Development*; Academic Press: San Diego, CA, 2000; pp 81–108.
(19) Nelson, W.M., Ed. *Green Solvents for Chemistry; Perspectives and Practice*; Oxford University Press: New York, 2003.
(20) Dunn, P.J.; Galvin, S.; Hettenbach, K. *Green Chem*. **2004,** *6*, 43–48.
(21) Dunn, P.J. In *Process Chemistry in the Pharmaceutical Industry*; Gadamasetti, K.G., Braish, T., Eds.; CRC Press: Boca Raton, FL, 2008; pp 267–277.
(22) Dale, D.J.; Draper, J.; Dunn, P.J.; Hughes, M.L.; Hussain, F.; Levett, P.C.; Ward, G.B.; Wood, A.S. *Org. Proc. Res. Dev*. **2002,** *6,* 767–772.
(23) Dale, D.J.; Dunn, P.J.; Golightly, C.; Hughes, M.L.; Levett, P.C.; Pearce, A.K.; Searle, P.M.; Ward, G.; Wood, A.S. *Org. Proc. Res. Dev*. **2000,** *4,* 17–22.
(24) Taber, G.P.; Pfisterer, D.M.; Colberg, J.C. *Org. Proc. Res. Dev*. **2004,** *8*, 385–388 and references therein.
(25) Pais, L.S.; Loureiro, J.M.; Rodrigues, A.E. *Separ. Purif. Technol*. **2000,** *20,* 67–77.
(26) *Chem. Eng. News* **2002,** *80* (29), 45–62.
(27) Ji, J.; Barnes, D.M.; Zhang, J.; King, S.A.; Wittenberger, S.J.; Morton, H.E. *J. Am. Chem. Soc*. **1999,** *121,* 10215–10216.
(28) Barnes, D.M.; Ji, J.; Fickes, M.G.; Fitzgerald, M.A.; King, S.A.; Morton, H.E.; Plagge, F.A.; Preskill, M.; Wagaw, S.H.; Wittenberger, S.J.; Zhang, J. *J. Am. Chem. Soc*. **2002,** *124,* 13097–13105.
(29) Barnes, D.M.; Ji, J.; Zhang, J.; King, S.A.; Wittenberger, S.J.; Morton, H.E. *ACS Symposium Series* **2002,** *817* (From Bench to Pilot Plant), 45–59.
(30) Anderson, B.A.; Hansen, M.M.; Vicenzi, J.T.; Zmijewski, M.J. In *Process Chemistry in the Pharmaceutical Industry*; Gadamasetti, K.G., Ed.; Marcel Dekker: New York, 1999, pp 263–282.
(31) Anderson, B.A.; Hansen, M.M.; Harkness, A.R.; Henry, C.L.; Vicenzi, J.T.; Zmijewski, M.J. *J. Am. Chem. Soc*. **1995,** *117,* 12358–12359.
(32) Letendre, L. (Pfizer). Green Chemistry in the Redesign of the Celecoxib Process: Summary for the Presidential Green Chemistry Challenge Awards Program, 2005.
(33) Talley, J.J.; Penning, T.D.; Collins, P.W.; Rogier, Jr., D.J.; Malecha, J.W.; Miyashiro, J.M.; Bertenshaw, S.R.; Khanna, I.K.; Granets, M.J.; (G.D. Searle and Co., USA). WO 95/15316; Penning, T.D.; Talley, J.J.; Bertenshaw, S.R.; Carter, J.S.; Collins, P.W.; Docter, S.; Graneto, M.J.; Lee, L.F.; Malecha, J.W.; Miyashiro, J.M.; Rogers, R.S.; Rogier, D.J.; Yu, S.S.; Anderson, G.D.; Burton, E.G.; Cogburn, J.N.; Gregory, S.A.; Koboldt, C.M.; Perkins, W.E.; Seibert, K.; Veenhuizen, A.W.; Zhang, Y.Y.; Isakson, P.C. *J. Med. Chem*. **1997,** *40,* 1347–1365.
(34) Jennings, S. (Pfizer). A Green Process for the Synthesis of Quinapril Hydrochloride: Summary for the Presidential Green Chemistry Challenge Awards Program, 2005.
(35) Hansen, K.B.; Balsells, J.; Dreher, S.; Hsiao, Y.; Kubryk, M.; Palucki, M.; Rivera, N.; Steinhuebel, D.; Armstrong III, J.D.; Askin, D.; Grabowski, E.J.J. *Org. Proc. Res. Dev*. **2005,** *9,* 634–639.
(36) Hsiao, Y.; Rivera, N.R.; Rosner, T.; Krska, S.W.; Njolito, E.; Wang, F.; Sun, Y.; Armstrong III, J.D.; Grabowski, E.J.J.; Tillyer, R.D.; Spindler, F.; Malan, C. *J. Am. Chem. Soc*. **2004,** *126,* 9918–9919.
(37) Clausen, A.M.; Dziadul, B.; Cappuccio, K.L.; Kaba, M.; Starbuck, C.; Hsiao, Y.; Dowling, T.M. *Org. Proc. Res. Dev*. **2006,** *10,* 723–726.
(38) Blaser, H-U.; Studer, M. *Green Chem*. **2003,** *5,* 112–117.
(39) Blaser, H-U.; Malan, C.; Pugin, B.; Spindler, F.; Steiner, H.; Studer, M. *Adv. Synth. Catal*. **2003,** *345,* 103–151.
(40) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res*. **1997,** *30,* 97–102.
(41) Jessop, P.G.; Ikariya, T.; Noyori, R. *Chem. Rev*. **1999,** *99,* 475–494.
(42) Hanson, R.L.; Goldberg, S.L.; Brzozowski, D.B.; Tully, T.P.; Cazzulino, D.; Parker, W.L.; Lyngberg, O.K.; Vu, T.C.; Wong, M.K.; Patel, R.N. *Adv. Synth. Catal*. **2007,** *349,* 1369–1378.
(43) Augeri, D.J.; Robl, J.A.; Betebenner, D.A.; Magnin, D.R.; Khanna, A.; Robertson, J.G.; Wang, A.; Simpkins, L.M.; Taunk, P.; Huang, Q.; Han, S-P.; Abboa-Offei, B.; Cap, M.; Xin, L.; Tao, L.; Tozzo, E.; Welzel, G.E.; Egan, D.M.; Marcinkeviciene, J.; Chang, S.Y.; Biller, S.A.; Kirby, M.S.; Parker, R.A.; Hamann, L.G. *J. Med. Chem*. **2005,** *48,* 5025–5037.

(44) Li, C-J. *Chem. Rev.* **2005,** *105,* 3095–3166; Li, C-J. In *Organic Reactions in Water*; Lindstroem, U.M., Ed.; Blackwell: Oxford, UK, 2007; p 92.
(45) Bowles, P. (Pfizer Inc., USA). Process for preparing aryl piperazinyl-heterocyclic compounds. US Patent 5206366, April 27, 1993.
(46) McGuirk, P.R.; Jefson, M.R.; Mann, D.D.; Elliott, N.C.; Chang, P.; Cisek, E.P.; Cornell, C.P.; Gootz, T.D.; Haskell, S.L. *J. Med. Chem.* **1992,** *35,* 611–620.
(47) Howard, H.R.; Lowe III, J.A.; Seeger, T.F.; Seymour, P.A.; Zorn, S.H.; Maloney, P.R.; Ewing, F.E.; Newman, M.E.; Schmidt, A. *J. Med. Chem.* **1996,** *39,* 143–148.
(48) Urban, F.J.; Breitenbach, R.; Gonyaw, D. *Synth. Commun.* **1996,** *26,* 1629–1638.
(49) Walinsky, S.W.; Fox, D.E.; Lambert, J.F.; Sinay, T.G. *Org. Proc. Res. Dev.* **1999,** *3,* 126–130.
(50) Kerdesky, F.A.; Leanna, M.R.; Zhang, J.; Li, W.; Lallaman, J.E.; Ji, J.; Morton, H.E. *Org. Process Res. Dev.* **2006,** *10,* 512–517.
(51) Zhang, J.; Morton, H.E.; Ji, J. *Tetrahedron Lett.* **2006,** *47,* 8733–8735.
(52) Ennis, D.S.; McManus, J.; Wood-Kaczmar, W.; Richardson, J.; Smith, G.E.; Carstairs, A. *Org. Proc. Res. Dev.* **1999,** *3,* 248–252.
(53) Hashimoto, N.; Kanda, A. *Org. Proc. Res. Dev.* **2002,** *6,* 405–406.
(54) Rao, M.; Yang, M.; Kuehner, D.; Grosso, J.; Deshpande, R.P. *Org. Proc. Res. Dev.* **2003,** *7,* 547–550.
(55) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2007,** *107,* 5656–5682.
(56) Ooi, T.; Maruoka, K. *Angew. Chem., Int. Ed.* **2007,** *46,* 4222–4266.
(57) O'Donnell, M.J. *Acc. Chem. Res.* **2004**, *37,* 506–517.
(58) Lygo, B.; Andrews, B.I. *Acc. Chem. Res.* **2004,** *37,* 518–525.
(59) O'Donnell, M.J. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; pp 727–756 and reference cited therein.
(60) Hughes, D.; Dolling, U.; Ryan, K.; Schoenwaldt, E.; Grabowski, E. *J. Org. Chem.* **1987,** *52,* 4745–4752.
(61) Dolling, U.; Davis, P.; Grabowski, E. *J. Am. Chem. Soc.* **1984,** *106,* 446–447.
(62) Dolling, U.; Grabowski, E.; Pines, S. Process using achiral co-catalyst promoter for chirl phase transfer alkylation process for an enantiomer of a substituted fluorenyloxyacetic acid. US Patent 4605761, August 12, 1986.
(63) Tanaka, K., Ed. *Solvent-Free Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2003.
(64) Correa, W.H.; Edwards, J.K.; McCluskey, A.; McKinnon, I.; Scott, J.L. *Green Chem.* **2003,** *5,* 30–33.
(65) Ranu, B.C.; Hajra, A.; Dey, S.S. *Org. Proc. Res. Dev.* **2002**, *6*, 817–818.
(66) Walsh, P.J.; Li, H.; de Parrodi, C.A. *Chem. Rev.* **2007,** *107,* 2503–2545.
(67) Tokunaga, M.; Larrow, J.F.; Kakiuchi, F.; Jacobsen, E.N. *Science* **1997,** *277,* 936–939.
(68) Jacobsen, E.N. *Acc. Chem. Res.* **2000,** *33,* 421–431.
(69) Wang, J.; Li, H.; Zu, L.; Jiang, W.; Wang, W. *Adv. Synth. Catal.* **2006,** *348,* 2047–2050.
(70) Hough, W.L.; Rogers, R.D. *Bull. Chem. Soc. Jpn.* **2007,** *80,* 2262–2269.
(71) Jain, N.; Kumar, A.; Chauhan, S.; Chauhan, S.M.S. *Tetrahedron* **2005,** *61,* 1015–1060.
(72) Calo, V.; Nacci, A.; Monopoli, A. *Eur. J. Org. Chem.* **2006,** *17,* 3791–3802.
(73) Earle, M.J. *ACS Symposium Series* **2002,** *818* (Ionic Liquids), 90.
(74) Chowdhury, S.; Mohan, R.; Scott, J.L. *Tetrahedron* **2007,** *63,* 2363.
(75) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007,** *107,* 5606–5655.
(76) Dzyuba, S.V.; Bartsch, R.A. *Angew. Chem. Inter. Ed.* **2003,** *42* (2), 148–150.
(77) Prajapati, D.; Gohain, M. Tetrahedron **2004,** *60* (4), 815–833.
(78) Leitner, W. Acc.Chem. Res. **2002,** *35* (9), 746–756.
(79) Gallou, F.; Saim, S.; Koenig, K.J.; Bochniak, D.; Horhota, S.T.; Yee, N.K.; Senanayake, C.H. *Org. Proc. Res. Dev.* **2006,** *10,* 937–940.
(80) Pathak, P.; Meziani, M.J.; Desai, T.; Sun, Y-P. *J. Am. Chem. Soc.* **2004,** *126* (35), 10842–10843.
(81) Subramaniam, B.; Saim, S.; Rajewski, R.; Stella, V.J. *ACS Symposium Series* **2001,** *766* (Green Engineering), 96–110.
(82) Tom, J.W.; Lim, G.B.; Debenedetti, P.G.; Prud'homme, R.K. *ACS Symposium Series* **1993,** *514* (Supercritical Fluid Engineering Science), 238–257.
(83) DiMasi, J.A.; Hansen, R.W.; Grabowski, H.G. *J. Health Econ* **2003,** *22,* 151–185.
(84) Pisano, G.P.; Wheelwright, S.C. *Harvard Business Rev.* **1995,** *73* (5), 93–105.