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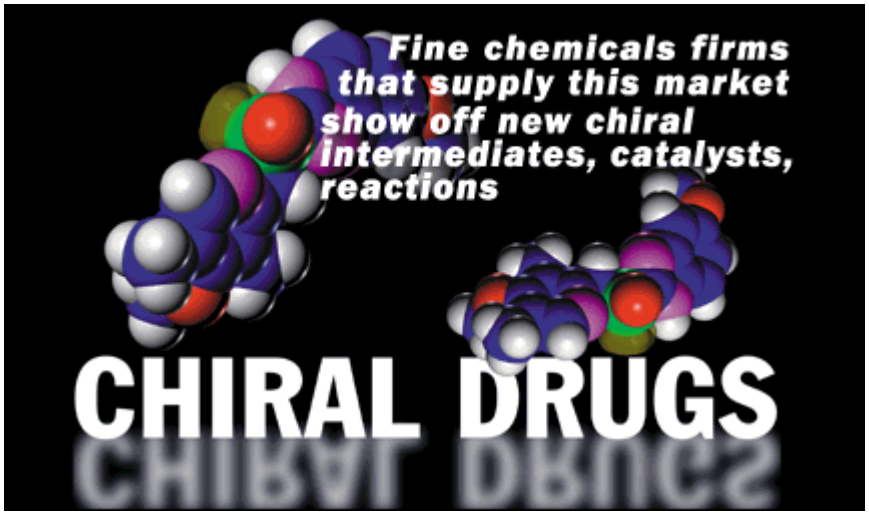

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The chiral drug industry soared through a major milestone last year, as annual sales in this rapidly growing segment of the drug market topped $100 billion for the first time. These compounds now represent close to one-third of all drug sales worldwide.

The industry's continuing growth is rooted, in part, in fundamental biochemistry. The biological messenger molecules and cell surface receptors that medicinal chemists try to affect are chiral, so drug molecules must match their asymmetry.

A second reason for the sector's growth arises from the continuing concern of the Food & Drug Administration that companies make appropriate choices about whether to develop inherently chiral drug molecules in their single-isomer or racemate forms. The logistics of testing are simpler for a single isomer because FDA requires that both enantiomers of a racemate be studied in detail.

Against this backdrop of growing markets, the drug industry and its fine chemicals suppliers will gather next month for the Conference on Pharmaceutical Ingredients (CPhI) in Milan, Italy. There, drugmakers will find that, despite intense involvement in mergers and acquisitions, fine chemicals suppliers have many new products to offer them.

Single-isomer drug sales reached $115 billion worldwide in 1999, up 16% from $99 billion in 1998, according to Richard L. DiCicco, president of the consulting firm Technology Catalysts International Corp. (TCI) , Falls Church, Va. He estimates that this class will grow at an average annual rate of 8% to $146 billion in 2003. Single-isomer drugs accounted for 30% of the $335 billion total drug sales worldwide in 1998, edging up to 32% of the $360 billion market in 1999.

Drug companies are also using chirality as a tool either to extend the patent lives of their blockbuster drugs or to increase their "status," DiCicco notes. A blockbuster is a drug with more than $1 billion per year in sales.

But in this upbeat atmosphere for chiral drugs, DiCicco notes a disturbing number of promising single-isomer blockbuster candidates that have either stumbled or failed this year. These setbacks have been troubling not only to the drug company innovators but also to the fine chemicals producers who had shared the risk of developing the drugs.

Racemic switching

One example of the use of chirality to extend patent protection and so manage a product's life cycle is AstraZeneca's plans for its Prilosec brand of omeprazole antiulcer drug. AstraZeneca has redeveloped a single-enantiomer form of the drug that it had previously been been marketing as a racemate.

AstraZeneca of London, England, and Wayne, Pa., has marketed racemic omeprazole in the U.S. since its approval here in 1995. But the pharmacological activity resides in the (S)-enantiomer, and the patent on the racemate runs out in 2002. So AstraZeneca will make a racemic switch: The company has patented the (S)-isomer separately, which is known by its own generic name esomeprazole. AstraZeneca's Nexium brand of esomeprazole was approved for marketing in Europe in July, and the company expects approval in the U.S. later this year.

Omeprazole is a proton pump inhibitor, which means that it prevents secretion of gastric acid. Because many ulcers result from a local infection by the bacterium *Helicobacter pylori*, omeprazole is often prescribed in combination with such antibiotics as clarithramycin and amoxicillin. The antibiotics eradicate the infection, and omeprazole halts acid secretion to promote healing.

DiCicco estimates U.S. sales of omeprazole in 1999 at $5.9 billion. He expects sales to rise to $7 billion in 2000 and $8 billion in 2001. In 2002, generic producers may get $2 billion of the drug's market, he says, while AstraZeneca's sales fall to $3.1 billion. The decrease in the total value of sales in 2002 comes from the lower prices charged by generic producers.

But AstraZeneca will start reaping sales of $50 million from esomeprazole in 2000, $200 million in 2001, $400 million in 2002, and $750 million in 2003, DiCicco estimates.

All these estimates contain two wild cards, however. One is how AstraZeneca will price single-enantiomer Nexium. The second is how ulcer patients will use the drugs. Pricing is complicated by the fact that a 20-mg tablet of single-isomer esomeprazole contains the same amount of active ingredient as a 40-mg tablet of racemic omeprazole. Many drug marketers believe that the single enantiomer should be priced at a slight discount compared with omeprazole to encourage doctors to change patients' prescriptions to Nexium, particularly when faced with the option of a lower priced generic racemate competitor.

The issue of patient behavior is complex. In order to gauge these effects, as well as doctors' prescribing patterns and to analyze results of clinical trials on sales estimates, DiCicco has begun hiring a panel of physicians that he calls his clinical research analysis group. Physicians working on the TCI staff so far are cardiologist Cathy Groupe, oncologist Wendy L. Schulman, and gastroenterologist Shaw Jones. Analysts Natalie Dearing and Francine Rosenberg work with them to gather data about clinical trials.

Jones has already alerted DiCicco to the subtle effects on sales of ulcer drugs as a result of the behavior of uninsured patients. These patients may delay taking any drug until ulcer pain becomes severe, he says. They may also cut pills in half to stretch out a prescription.

The behavior of insured patients can have an impact, too, particularly if the generic form of a drug is sold as an over-the-counter product. Third-party payers such as insurance companies usually will not reimburse patients for over-the-counter drugs, although they will pay for a prescription version. Thus, insured patients may ask a doctor for a prescription, even when a cheaper over-the-counter product is available.

Another issue affecting sales of patented chiral drugs like omeprazole and esomeprazole is what is called the "economic credentialing" of doctors by health maintenance organizations (HMOs). Doctors who prescribe larger average amounts of these costly drugs than their peers receive "letters" from HMOs and have difficulty with "recredentialing."

Companies like AstraZeneca that develop their own drugs are not the only ones taking advantage of the benefits of switching from racemic to single-isomer forms of chiral drugs. Sepracor of Marlborough, Mass., has been switching the drugs of other companies for years. When Sepracor discovers that the pharmacological activity of another company's racemic drug resides in just one enantiomer, the firm patents that isomer if the innovator company has not already done so. Sepracor is ready to license back the innovator's single-isomer drug but is prepared to go ahead with marketing on its own part if the innovator does not take a license.

For example, Sepracor found that the antidepressant activity of fluoxetine, marketed by Eli Lilly, Indianapolis, as Prozac, is in the (*R*)-enantiomer. Sepracor patented (*R*)-fluoxetine in January 1998 and proceeded with clinical trials. In 1998, Lilly took a license on Sepracor's patent, agreeing to pay a $20 million license fee and $70 million in milestone payments as (*R*)-fluoxetine wends its way through FDA's new drug approval process. Lilly will also pay royalties on sales for years after approval.

But Schering Corp., Kenilworth, N.J., is hanging tough on the levorotatory isomer of its racemic bronchodilator inhalant, albuterol, which it sells under the brand name Proventil to treat asthma. Sepracor patented and went ahead with clinical trials of levalbuterol, got FDA approval in March 1999, and began marketing to allergists, general practitioners, and respiratory physicians under the brand name Xopenex. Since Schering decided not to take a license, Sepracor licensed Abbott Laboratories, North Chicago, Ill., in November 1999 to market Xopenex to pediatricians.

Sepracor is working on scale-up procedures for other chiral drugs as well. Principal chemist Kevin Fang described commercial-scale production of (*S*)-bupropion at the American Chemical Society meeting in Washington, D.C., in August. Glaxo Wellcome, Research Triangle Park, N.C., discovered the racemate and markets it under the trade name Wellbutrin for depression.

At the August ACS meeting, another Sepracor principal chemist, Yaping Hong, talked about a commercial route to (*S*)-desmethylzopiclone. Rhône-Poulenc Rorer, Collegeville, Pa., discovered racemic zopiclone and sells it in Europe as a sleeping pill under the trade names Imovane and Amoban. Desmethylzopiclone is a metabolite of zopiclone in which an N-methyl piperazine has been demethylated.

There is much recent interest in metabolites of known drugs as well as in their enantiomers as potential drugs themseves. This is because drugs can compete with one another for the same enzyme to metabolize them. Such competition can lead to unfavorable drug interactions if the one drug ties up the available enzyme and the other drug builds up to excess blood levels.

Fang reported that Sepracor's technology for (*S*)-bupropion begins with*m* -chloropropiophenone. The company converts that to a silyl enol, which undergoes asymmetric dihydroxylation to (*R)-m*-chloro- β -hydroxypropiophenone. The trifluoromethanesulfonate ester of that intermediate undergoes displacement

by *tert*-butylamine to yield (*S*)-bupropion. Fang also reported a commercial synthesis of single-enantiomer (*S*)-hydroxybupropion metabolite.

[DiCicco, 2nd R, and other TCI staff. Photo by Stephen Stinson]

Hong described two methods for making (*S*)-desmethylzopiclone on a large scale. In one method, the company uses d-malic acid to resolve zopiclone by classical diastereoisomeric crystallization to the (S)-isomer, which is demethylated with 1-chloroethyl chloroformate. In the second method, racemic desmethylzopiclone, made by demethylation of zopiclone or other syntheses, is resolved with *N*- benzyloxycarbonyl-l-phenylalanine.

Sepracor's experiences with zopiclone and desmethylzopiclone point out a salient feature of modern production of single-enantiomer drugs: Classical diastereoisomeric crystallization of salts with resolving agents is still the most prevalent method of separating enantiomers.

Sepracor announced in September that it is in Phase III clinical testing of (*S*)-zopiclone in the U.S. Phase III is the final, large-scale test of a drug on humans before approval to market.

Marketing drug combinations

In addition to extending patent protection on a racemic drug by later patenting its single active enantiomer, drug companies can "enhance its status," as DiCicco puts it, by combining an old drug with a newer, patented one that treats the same disease condition but by a different mechanism. For example, Whitehouse Station, N.J.-based Merck markets a combination of Merck's simvastatin and Schering's ezetimibe, both single enantiomers, to lower serum cholesterol. Simvastatin inhibits the enzyme β-hydroxy- β -methylglutarylcoenzyme A reductase, which mediates a step in the biosynthesis of cholesterol, while ezetimibe inhibits the absorption of dietary cholesterol.

A second example of enhancing an older single-enantiomer drug is the marketing by Schering of a combination of Merck's montelukast with Schering's loratidine for asthma. Both are single-enantiomer compounds. Loratidine is a nonsedating antihistamine, while montelukast is a selective leukotriene D_4 receptor antagonist. Both histamine and leukotriene are mediators of inflammation.

One advantage to marketing such combinations is that a newer agent with a longer patent life adds its independent effectiveness to a drug whose patent is closer to expiration. Ezetimibe is newer than simvastatin, while the patent on montelukast expires after the patent on loratidine.

Marketing such combinations can also fend off competition from newer agents. For example, AstraZeneca is bringing along enantiomeric rosuvastatin as a cholesterol-lowering drug. The industry has dubbed this a "superstatin" because it is more effective than simvastatin. Schering is hoping that the combination of simvastatin plus ezetimibe will trump a superstatin.

Innovator drug companies have always faced stiff competition from one another as each strives to bring out the next member of a certain class of compounds for treatment of a disease. Today, however, the pace of that competition has dramatically accelerated, as Sandra Erb, assistant to the president at TCI, explained at the International Symposium on Chirotechnology in Seoul, South Korea, in June.

She noted the introduction of propranolol by American Home Products in 1965 as a β-adrenergic blocking agent for treatment of high blood pressure. It was 13 years later, in 1978, that what is now AstraZeneca

followed with metoprolol. By contrast, when Hoffmann-La Roche brought saquinavir on the market as an AIDS virus protease inhibitor in late 1995, it was only three months until Abbott Laboratories started marketing ritonavir.

And the second company to market need not be at a disadvantage. Sometimes companies can maneuver their compounds into blockbuster status by carefully crafting the protocols of clinical trials. A good example, according to DeCicco, is Warner-Lambert's second-to-market drug of the statin class, the single-isomer atorvastatin. In designing clinical studies to gain FDA approval, Warner-Lambert tested atorvastatin head-to-head with Merck's simvastatin and set the endpoints not only as lowering cholesterol, but also as lowering low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), triglyceride, and apolipoprotein B.

Lipoproteins are the substances that actually carry cholesterol in blood. LDL and VLDL are the particular lipoproteins most apt to deposit cholesterol on arterial walls. High triglyceride and apolipoprotein B levels are also risk factors for heart disease. So by showing that atorvastatin outperformed simvastatin in a broader test of endpoints that physicians desire, Warner-Lambert, now owned by New York City-based Pfizer, could leapfrog their second-to-market drug into blockbuster status.

But chiral drugs can also suffer setbacks. To DiCicco, the most emblematic such stumble is omapatrilat, in development at Bristol-Myers Squibb, New York City. The compound is a vasopeptidase inhibitor, which means that it treats high blood pressure by inhibiting both angiotensin-converting enzyme (ACE) and neutral endopeptidase.

The company withdrew its New Drug Application from FDA after the occurrence of severe facial swelling in a few of the 25,000 patients studied. But the drug may yet be saved. Bristol-Myers Squibb has already started another study on 25,000 patients at a lower dosage, and there are signs that the drug may be useful to treat certain cancers.

To DiCicco, the omapatrilat story is a replay of Bristol-Myers Squibb's ACE-inhibiting drug captopril. During initial tests, there was alarm over the incidence of cough and a metallic taste in the mouth. Theories abounded about how the sulfur atom was at fault. Eventually, captopril was approved at a lower dose and has great success today.

Chiral intermediates

All of this activity in chiral drugs leads fine chemicals producers to develop new enantiomeric intermediates for the industry and new enantioselective technology to produce intermediates and bulk active drugs to special order. These new wares will be on display at CPhI next month in Milan.

For example, BASF is adding to its ChiPros line of chiral products. The line began three years ago with some three dozen amines made by enzyme-catalyzed resolution. The company treats racemic amine with ethyl methoxyacetate and a lipase. The reaction product is a mixture of (R)-methoxyacetamide and (S)-amine, which are then separated by distillation. BASF plans to build a 5.5 million-lb-per-year chiral amines plant in Geismar, La., slated to come onstream in the first half of 2001, and a 2.2 million-lb-per-year plant in Ludwigshafen, Germany, to come onstream later in that year.

In addition, the company has a line of enantiomeric alcohols, also resolved by lipase-catalyzed acylation. For example, reaction of racemic α-phenethyl alcohol with vinyl propionate, mediated by a lipase from *Burkholderia plantarii*, yields (S)-alcohol and (R)-propionate, separated by distillation. The reaction is irreversible because of tautomerization of coproduct vinyl alcohol to acetaldehyde.

Also, reaction of styrene with hydrogen peroxide and hydrogen chloride yields racemic 2-chloro-1-phenylethanol. Treatment of the racemate with succinic anhydride and *B. plantarii* lipase gives a mixture

of (R)-alcohol and (S)-succinate half ester. Reaction of each product with sodium hydroxide leads to either (*R*)- or (*S*)-styrene oxide.

According to Gisela Hieber, product manager for life sciences intermediates, the latest additions to the BASF ChiPros stable are (*R*)- and (*S*)-mandelic acid. Benzaldehyde and hydrogen cyanide react to give racemic mandelonitrile, kinetically resolved via a nitrilase to a mixture of (*R*)-mandelic acid and (*S*)-mandelonitrile.

Synthon Chiragenics, Monmouth Junction, N.J., has also added to its line of single-isomer intermediates. Founded by organ-ic chemistry professor Rawle I. Hollingsworth of Michigan State University, East Lansing, the company's key technology is conversion of lactose to (*S*)-3-hydroxy-γ-butyrolactone and l-arabinose to the (R)-lactone. Lactose and l-arabinose are cheaply available as a by-product of cheese making and from sugar beet processing waste, respectively. Now Hollingsworth has invented a conversion of the two lactones to either isomer of 5-hydroxymethyl-2-oxazolidinone. That heterocycle is a component of several drug types, including novel antibacterials.

A third company with new enantiomeric intermediates is K-Genix Group of Mumbai, India. In addition to dosage-form drugs and bulk active drugs, the company has a line of intermediates based on amino acids and carbohydrates. These include phenylglycinols and phenylalaninols, 4-benzyl-2-oxazolidinones, and γ,δ-dihydroxyvaleric acid γ-lactone. K-Genix is represented in the U.S. by Technology Catalysts International.

Yet a fourth company with new enantiomeric intermediates is Onyx Scientific, which started up this past June in Sunderland, England. Principal founders are Chief Executive Officer Tony Flinn and research director Steve Bone, who was previously research director at ChiRex, Stamford, Conn. The firm will develop processes and analytical methods for clients as well as produce to special orders.

Onyx has licensed technology to make enantiomeric amines from the University of Durham, England. The technology's inventor is organic chemistry professor David O'Hagan, who is now at the University of St. Andrews, in Scotland. The amines are useful as resolving agents, asymmetric catalysts, and chiral auxiliaries.

In O'Hagan's method, a natural or nonnatural amino acid such as l-valine ethyl ester hydrochloride reacts with phenylmagnesium bromide to give (2*S*)-amino-3-methyl-1,1-diphenylbutanol. Treatment of that amino alcohol with diphosgene (trichloromethyl chloroformate) yields 5,5-diphenyl-(4*S*)-isopropyl-2-oxazolidinone. The heterocycle in this molecule can either be hydrogenated to (2*S*)-amino-1,1-diphenyl-3-methylbutane or treated with hydrogen fluoride to yield (2*S*)-amino-1-fluoro-1,1-diphenyl-3-methylbutane. The method needs work before it is scaled up, because 3 moles of phenylmagnesium bromide are sacrificed to blow away the amine salt protons before the last 2 moles add to the substrate.

One of O'Hagan's compounds, (2*S*)-diphenylmethylpyrrolidine, made from l-proline, has already been put to work as a catalyst by organic chemistry professor Varinder K. Aggarwal of St. Andrews University. Working with graduate student Mauro F. A. Adamo and postdoctoral fellow Matthew A. Sage, Aggarwal epoxidized 1-phenylcyclohexene with potassium monopersulfate to the (S,S)- isomer in 96% yield and 57% enantiomeric excess (ee) [*J. Am. Chem. Soc.*, **122**, 8317 (2000)].

Although the enantioselectivity of the reaction is poor, the work is exciting because the catalyst is a nonmetal. Thus there is no metal waste to treat and no concern about trace metal turning up in a drug compound. If other diphenyl amines push the enantioselectivity to 90% or better, the method could be a great commercial success.

ChiRex will also be showing new chiral intermediates in Milan. The company has long had a license on the hydrolytic resolution technology of epoxides invented by organic chemistry professor Eric N. Jacobsen of Harvard University.

ChiRex is expected to announce in Milan that it has modified its plant in Dudley, England, to produce ton quantities of intermediates such as either isomer of epichlorohydrin, 3-chloro-1,2-propanediol, propylene oxide, propylene glycol, propylene carbonate, styrene oxide, methyl glycidate, and glycidyl *p*-toluenesulfonate and *m*-nitrobenzenesulfonate. Aldrich Chemical Co., Milwaukee, will market ChiRex's intermediates in gram to kilogram amounts, while ChiRex will service customer needs from multikilos to tons.

In the Jacobsen technology, an asymmetric catalyst based on chelation of a transition metal by a ligand derived from either isomer of *trans*-1,2-diaminocyclohexane mediates hydrolysis of one enantiomer of an epoxide preferentially. The process either makes the product diol or leaves the unreacted epoxide in high enantiomeric purity.

New technologies

In addition to chiral intermediates, enantioselective technologies will also be on display at CPhI from such companies as DSM, Lonza, ISP, and Johnson Matthey. Q. B. (Rinus) Broxterman, a research fellow at DSM's laboratories in Geleen, the Netherlands, tells C&EN that the company will show off a low-cost asymmetric hydrogenation catalyst and production technology for substituted pipecolic acids that combine DSM's expertise in biocatalytic and synthetic organic methods. Pipecolic acids are rigid, cyclic amino acids that can be used to restrict conformations of polypeptides. They may also serve as polyfunctional scaffolds in synthesizing libraries of diverse compounds.

Development of the two technologies also points up DSM's collaboration with academicians. Senior research fellow Hans Schoemaker at DSM, who is also adjunct professor of organic chemistry at the University of Amsterdam, teamed with organic chemistry professors Henk Hiemstra , also at Amsterdam, and Floris Rutjes at the University of Nijmegen, the Netherlands, to invent the pipecolic acid process.

In the biocatalytic part, the collaborators resolve a nonnatural amino acid using an aminopeptidase from the bacterium *Pseudomonas putida*. Thus racemic 2-amino-4-pentenoamide is hydrolyzed to a mixture of (S)-acid and (R)-amide.

The team next treats the N-protected methyl ester of the (S)-acid with allenyl benzyl ether and a palladium(II) catalyst, which adds NH of the amino group across one allene double bond. They use a ruthenium carbene olefin metathesis catalyst to cyclize that adduct to a benzyloxypipecolic acid. Reaction of that with allyltrimethylsilane displaces the benzyl group by allyl, resulting in the desired allyl pipecolic acid derivative.

The collaboration that led to the asymmetric catalyst began with DSM research fellow Hans de Vries, who is also adjunct professor of organic chemistry at the University of Groningen, the Netherlands. Working with organic chemistry professors Ben Feringa and Adri Minnaard and graduate student Michel van den Berg, de Vries invented and demonstrated the catalyst.

In one form, (*R*)-1,1'-bi-2-naphthol reacts with hexamethylphosphoramide (HMPA) to produce the cyclic amido phosphate ester. This phosphorus compound serves as a ligand for rhodium(I) in asymmetric hydrogenation, as in that of methyl α-acetamidocinnamate to (*S*)-phenylalanine methyl ester. The ligand is cheaper than those based on phenyl phosphines because of the lower price for HMPA.

Asymmetric hydrogenation is also an area of expertise at Lonza of Basel, Switzerland, and Fair Lawn, N.J. The company's key catalyst is a diphosphino ferrocene. Lonza recently demonstrated its enantioselective prowess in both hydrogenation and hydroamination. In a process to make piperazinecarboxylic acids, for example, the company begins with partial hydrogenation of methyl 2-pyrazinecarboxylate to the Δ^2-tetrahydro derivative. After further transformations of that to the *N,N'*-diacetyl *tert*-butylamide, Lonza hydrogenates asymmetrically with a rhodium-ligand catalyst to get the protected (*S*)-piperazine acid in 95% ee.

The same ligand functions with iridium(I) to catalyze asymmetric hydroamination. For example, reaction of norbornene with aniline yields (2*S*)-*exo*-phenylaminonorbornane in 92% ee.

Among capabilities at ISP, Wayne, N.J., are reactions at low temperature. Paul D. Taylor, vice president for technical development and quality assurance, says that the company has a total 6,850 gal of low-temperature reactor capacity. The largest vessel is 3,500 gal, cooled by direct injection of liquid nitrogen into the jacket coils. Direct injection means the company can theoretically achieve -160ºC, and Taylor says they have actually been down to -110ºC.

He points out that such low temperatures are really cost-effective once a company has made the initial investment to install the capacity. The reason for going to such low temperatures is usually not to control exotherms of highly reactive chemicals, Taylor notes, but to achieve high enantioselectivity.

He cites the example of one project to make *tert*-butyl (*S,S*)- β,δ-dihydroxycaproate. The key step was reduction of (*S*)-δ-hydroxy-β-ketocaproate with sodium borohydride. In order to ensure asymmetric induction from the (S)-hydroxyl group, ISP chemists added triethylborane. The borane formed a six-membered ring complex with the keto and hydroxyl oxygen atoms, holding the molecule rigid for approach of the hydride reductant. But the complex was only stable at -80ºC. Warming even to -60ºC began to degrade the complex.

Other capabilities of ISP are Grignard reactions and boronic acid production. Boronic acids are useful in the Suzuki coupling reaction, in which the acid couples with an aryl or alkenyl halide. The company makes them by lithiating aromatic compounds and treating the organolithiums with triisopropyl borate. It comes by its Grignard expertise from the longstanding production of insect pheromones at its plant in Columbus, Ohio.

In addition to its Columbus plant, which operates under FDA's current good manufacturing practices (cGMP) regulations, ISP has a plant in Freetown, Mass., that it is bringing up to cGMP. Taylor says the Freetown plant will produce its first bulk active drug in the first quarter of 2001.

Like Onyx Scientific, Johnson Matthey, West Deptford, N.J., got an entrée into enantioselective chemistry by licensing academic technology. The company licensed the patents for asymmetric diazo chemistry invented by Michael P. Doyle , an organic chemistry professor at the University of Arizona, Tucson.

The reactions covered include cyclopropanations and insertion into carbon-hydrogen bonds. The catalysts consist of two rhodium(I) ions complexed by four molecules of enantiomeric five-membered heterocyclic carboxylates.

A recent application of the Doyle catalysts is that of organic chemistry professor Stephen F. Martin of the University of Texas, Austin. Martin makes a phenylcyclopropanated butyrolactone in which the phenyl group is trans to the lactone carbon atoms. This product can then be converted to a diaminophenylcyclopropane that has the right stereochemistry to fit into a peptide as an analog of an enkephalin. In particular, internal cyclization of *trans*-cinnamyl diazoacetate with a Doyle catalyst using (*S*)-pyroglutamic acid as a ligand gives the product with the needed stereochemistry.

Rather than license technology off the shelf, Dow Contract Manufacturing Services (CMS) , Midland, Mich., has reached out to industrial and academic partners to develop proprietary enantioselective technology. Two recent agreements are with the Center for Applied Catalysis at Seton Hall University , South Orange, N.J., and Diazem Corp. , Midland, Mich. The agreement with Seton Hall is to develop heterogeneous asymmetric catalysts. Diazem will invent proprietary, enantioselective, liquid-chromatographic column-packing material.

The virtue of heterogeneous catalysts is that they are insoluble in reaction mixtures, and the user can filter them off. Robert L. Augustine, catalysis center executive director and emeritus organic chemistry

professor, explained the Seton Hall approach to the Chiral USA 2000 conference in Boston last May. The heart of the approach is to incorporate homogeneous catalysts into an insoluble support substance.

In one version, the investigators use montmorillonite clay as the solid support. They treat a stirred methanol slurry of the alkaline clay first with phosphotungstic acid, then with a chelate of rhodium(I) fluoborate with cyclooctadiene and DIPAMP, which is (*R,R*)-(-)-1,2-bis-[(*o*-methoxyphenyl)(phenyl)phosphino]ethane. Phosphotungstic acid is a complex of a central phosphorus atom linked through a network of 52 oxygen atoms to 12 outer tungsten atoms. The heteropoly acid binds to the outer surfaces of the clay particles, and the asymmetrically chelated rhodium ions become part of the outer tungstic acid structure. The Seton Hall workers demonstrate the heterogeneous catalyst by hydrogenating α-acetamidoacrylic acid to *N*-acetyl-l-alanine in 92% ee. Rhodium does not leach from the catalyst on reuse, and the enantioselectivity of the product actually increases with reuse.

Diazem's technology for chiral and other liquid chromatography column packings comes from 12 patents that the company licenses from Dow Corning, Midland, Mich. The key step is the reaction of specially treated silica gel with 3-aminopropyltrimethoxysilane, which binds 3-aminopropyl groups covalently to the silanol surfaces in the interiors of the pores. The amino groups are then acylated by such enantiomeric discriminator compounds as l-leucine and d-phenylglycine.

Multicomponent reactions

Further technology is also under development in universities. One reaction type of interest is the multicomponent reaction. The interest lies in use of such reactions in combinatorial syntheses of libraries of varied compounds for drug screening. The more components that react simultaneously, the more bonds can be formed in a single reaction. By changing the substituents on the component molecules, it is possible to multiply the number of different compounds rapidly. Thus, if any of the components of a multicomponent reaction are single enantiomers, then such components would contribute their own asymmetry to the resulting library compounds as well as induce further asymmetry in newly formed chiral centers. And by synthesizing single-enantiomer libraries, investigators would know the particular chirality of any hits in the ensuing screen.

The prototypes for such multicomponent reactions are the Ugi and Passerini reactions. In the Ugi reaction, a carboxylic acid, primary amine, aldehyde, and isonitrile react in one pot to form an α-acylamino carboxamide. In the Passerini, a carboxylic acid, aldehyde or ketone, and isonitrile react all at once to yield an α-hydroxy carboxamide.

Most recently, organic chemistry professor Barry M. Trost of Stanford University has invented a four-component reaction of an acetylene, an α,β-unsaturated carbonyl compound, an aldehyde, and the anion of a metal salt [*J. Am. Chem. Soc.*, **122**, 8081 (2000)]. In one example, 1-octyne, methyl vinyl ketone, cyclohexanecarboxaldehyde, and tin tetrachloride react to yield 6-chloro-3-(cyclohexyl)(hydroxy)methyldodec-(5*E*)-en-2-one. The catalyst is a ruthenocene isonitrile complex. Although Trost has not reported work with asymmetric catalysts or enantiomeric starting materials, the geometry of the product is racemic syn-diastereoisomer. Thus, if the reaction were carried out with single-enantiomer components, chances are high that the product would have a single stereochemistry at that syn disubstituted center.

Elsewhere, University of Southern California organic chemistry professors George A. Olah, Nicos A. Petasis , and G. K. Surya Prakash have devised a three-component chirally selective reaction of an amine, boronic acid, and aldehyde to yield an amino alcohol [*Org. Lett* ., **2**, 3173 (2000)]. For example, dibenzylamine, α-bromostyrene-β-boronic acid, and β,β,β-trifluoro-l-lactaldehyde react to form 5-bromo-(3*S*)-dibenzylamino-5-phenyl-1,1,1-trifluoro-(4*Z*)-penten-(2*S*)-ol in 92% ee. The trifluoromethyl group is interesting from a drug development point of view, because this group often confers enhanced pharmacological activity.

Petasis reported another three-component reaction that forms benzodiazepines at Chiral USA 2000 in Boston. The reaction is likely to be of great interest to drug companies because large numbers of successful drugs have phenylated and benzo annulated heterocyclic structures. Such ring systems as benzodiazepines serve as scaffolds on which chemists can build molecules that interact strongly with different kinds of enzymes, messenger substances, and cell surface receptors to treat disease.

In Petasis' reaction, β-styreneboronic acid, glyoxylic acid, and *o*-aminobenzylamine protected at the benzylamine nitrogen by *tert*-butoxycarbonyl react to form an extended chain amino alcohol, which can be cyclized to the benzodiazepine product.

Thus as the drug industry and its fine chemicals suppliers prepare for CPhI next month in Milan, both sides have their eyes on a chiral drug industry that appears to be enjoying healthy growth. Drug companies routinely use racemic switches now to manage the life cycles of their racemic chiral drugs coming off patent. And drug firms are tending to choose one enantiomer of a chiral drug to develop when applying for marketing approval the first time.

For their part, fine chemicals suppliers come to CPhI with new entries in their catalogs of single-isomer intermediates and in their portfolios of enantioselective technology. Academic chemists also create enantioselective chemistry for license to industry. Some of the new academic chemistry is based on three- and four-component reactions, where varying the substituents on the components makes possible fast combinatorial syntheses of libraries of compounds for screening.