FINE CHEMICALS: TECHNOLOGY AND PRODUCTS

1. Fine Chemicals Industry

Global fine chemicals market is expected to witness a steady growth during the next decade driven by growth of pharmaceuticals, agrochemicals, polymer additives, food and feed, electronics, perfumes and fragrances, and others. Pharmaceuticals (45%) and agrochemicals (25%) have been the major consuming sectors. In the next 5 year period, ie, 2018–2023, growing demand from developing countries, especially those in Asia Pacific, is expected to result in growth of global fine chemicals market.

The pharmaceutical industry has always been the largest market for the fine chemicals industry. Agrochemical intermediates representing the second largest category among fine chemicals (after APIs) are focused on pesticides, herbicides, insecticides, fungicides, and fumigates. The global fine chemicals market is led by majors like Lonza, Sumitomo Chemicals, BASF SE, Boehringer-Ingelheim, Sigma-Aldrich Corporation, Chemada fine chemicals, Albemarle Corporation, and China Sanjiang Fine Chemicals Company Limited.

Some of the key trends that are shaping the fine chemicals industry are:

Outsourcing:
Fueled by the growing importance of biopharmaceutical and pharmaceutical companies in low cost destinations such as Asia.

Increasing demand for high potency active pharmaceutical ingredients (HPAPIs):
Many companies are differentiating their products from their competitors through specialized technologies and demonstrated expertise. The growth in demand for HPAPIs, primarily in cancer therapies, is expected to drive the markets in the near future.

Relocation to emerging and fast growing markets:
Managing and rationalizing existing assets in the European Union and investing in new facilities in emerging markets has been a key focus. Growth in Western Europe started to slow in recent years, making Asia (mainly China and India) and Latin American countries the new growth markets for the fine chemicals industry.

Advanced technologies:
Recently, many of the leading pharmaceutical and fine chemicals manufacturers have started to focus on small-scale complex products, an area where advanced technologies are required.

Global fine chemical majors have adopted diverse strategies for growth but innovating across business operations has been the mainstay. BASF, The Dow Chemical Company, E.I. DuPont de Nemours, Evonik Industries AG, and Syngenta have their strategies aligned toward new technology innovations that create new opportunities for sustainable value creation. To this end, they leveraged their capabilities to address global mega trends such as sustainability, food, and water shortage.

Increased use of digitization has also enabled new innovations in operations, supply chain, manufacturing, and customer delivery systems. Many fine chemicals firms have leveraged digitization to enhance operational efficiencies.

DOI: 10.1002/0471238961.1618150416151212.a01.pub4

Fine chemicals manufacturers are now busy in rationalization of their businesses, spinning off assets to achieve cost savings, realize economies of scale, and pursue new growth opportunities. In this pursuit, they have adopted inorganic growth to enhance their competitive positioning. Mergers and acquisitions are expected to dominate the next 2 years and many of these will center on digital technologies and innovative technology platforms and portfolios.

Technology acquisition transactions proved to be major focus in recent years. Some of these were Diana Food's acquisition of Nutra Canada and Brenntag's acquisition of ACU Pharma und Chemie GmB where each acquirer gained specific technological platforms or intellectual property rights. In coming year, this trend will dominate the fine chemicals industry.

According to Deloitte Touche Tohmatsu Limited, 2017 Global chemical industry mergers and acquisitions outlook report, mega deals have become the norm with 41 deals valued above US$1 billion over the past 3 years, as compared to 30 deals between 2011 and 2013. Many companies continue to pursue M&A as a strategy to achieve growth and spur innovation.

1.1. Understanding Fine Chemicals. Fine chemicals are low volume, high priced, chemical intermediates, and bulk active ingredients, which are used primarily in the preparation of pharmaceuticals, agrochemicals, and other specialties, eg, household and personal care ingredients, electronic chemicals, and flavors and fragrances. These complex, pure chemicals are manufactured in limited quantities and according to exacting specifications for their intended application. Manufacture of fine chemicals involves conversion of basic chemicals into complexes that serve as building blocks.

Custom manufacturing is very integral to fine chemicals business and it has its own characteristics with regard to R&D, production, marketing, and finance. Product innovation absorbs considerable resources in the fine chemicals industry, mostly because of the shorter life cycles of fine chemicals compared to commodities. Consequently, research and development (R&D) plays an important role.

Fine chemicals are manufactured in batch multipurpose plants and of late advances in new technologies continuous plants have come into play. Fine chemicals are categorized into non-cGMP products such as advanced intermediates and active ingredients for pesticides, adhesives, biocides, catalysts, colorants, electronic chemicals, fragrances, personal care products, etc.

The cGMP products are substances like key starting materials and advanced intermediates for APIs – sterile and nonsterile APIs – which are manufactured via chemical synthesis, biotechnology, extraction, and recovery from natural sources.

Veterinary drugs, vitamins, food and feed additives, flavors, etc, and their advanced intermediates are produced through the cGMP regime (1).

There are more than 1000 odd key companies worldwide involved in fine chemicals production, R&D, and sales. Their evolution has been through diverse approaches.

- Through forward integration: BASF (Germany) and Lonza (Switzerland) from fertilizers
- From commodity organic chemicals: Daicel (Japan) and Jubilant Organosys (India)

- From diversifications: DSM (the Netherlands) and UBE (Japan) from coal mining; Evonik (Germany) from noble metals; and Dottikon Exclusive Synthesis (Switzerland) and SNPE (France) from explosives.
- From pharmaceutical companies: Fermion (Finland), Nicholas Piramal (India), Siegfried (Switzerland), Abbott (USA), Boehringer-Ingelheim (Germany), Johnson & Johnson (USA), Merck KGaA (Germany), and Pfizer (formerly Upjohn) (1).
- From acquisitions: Clariant, Evonik-Degussa, DSM, and SAFC

The small fine chemicals companies have only limited capabilities and often specialize in niche technologies, eg, reactions with hazardous gases (ammonia–amines, diazomethane, ethylene oxide, halogens, hydrogen cyanide, hydrogen sulfide, mercaptans, ozone, nitrous oxides, phosgene). Their small size, however, is not necessarily a disadvantage. As most fine chemicals are produced in quantities of not >10 tons/year in multipurpose plants, there is little or no economy of size (2).

From a commercial perspective, fine chemicals can be classified either as standard, resp. catalogue, or as exclusive products. In terms of the molecular structure, one first distinguishes between low molecular weight (LMW) and high molecular weight (HMW) products. The small molecules (LMW products) are produced by traditional chemical synthesis and/or enzymatic fermentation; the big molecules are obtained by biotechnology processes (1).

In the fine chemicals industry, some of the major commercial products are based on heterocyclic molecules containing 1,3,4,5 nitrogen incorporated in them. Five-membered N-hetrocycles like vitamins biotin (H), niacin (PP), pyridoxine HCl (B_6), riboflavin (B_2), thiamine (B_1), and folic acid are the most important. Some of the major variations are as follows:

- Five-membered ring having one N atom: Lipitor.
- Five-membered with two nitrogen atoms: Imidazolinones (eg, Imazapyr); drugs like antimycotics (Isoconazole, Ketoconazole, and Miconazole); anticancers (eg, Temodar), and antiulcerants (Cimetidine and Omeprazole).
- Five-membered rings with three nitrogen atoms: Triazoles or triazolones are found in other antimyotics (eg, Fluconazole and Itraconazole); antivirals (eg, Ribavirin), and antidepressants (eg, Nefazodone hydrochloride)
- Five-membered rings with four nitrogen atoms: Tetrazoles and tetrazolines as antihypertensives ("Sartans", like Candesartan, Irbesartan, Losartan, and Valsartan)
- Antibiotics (Cefotetan and Cefazolin); Antiallergics (Pemirolast and Pranlukast), and analgesics (eg, Alfentanil).
- Four-membered N-heterocycles like β-lactam moiety: Penicillin and cephalosporin antibiotics.
- Six-membered rings with one nitrogen atom: Diquat and Chlorpyrifos herbicides, as in modern chlornicotenyl insecticides, eg, Imidacloprid.

A vast array of pharmaceuticals and agrochemicals are built around a pyrimidine (two nitrogen atoms in the 1,3-position) ring structure. An important class is the antiviral compound like zidovudine. Chiral-based fine chemicals are a major focus for advanced APIs. Other fine chemicals are peptides like calcitonin and epoetin alfa, produced via microbial biotechnology.

2. Sustainable Fine Chemical Technologies

The global fine chemicals business is a knowledge-intensive component of the chemical value chain, catering to a multitude of societal and industrial needs. Regulatory, sustainability, and consumer forces have been constantly shaping the business fundamentals of this industry in diverse ways.

Sustainability practices have brought about shifts in structures, procedures, and systems to manage strategic sustainability goals within the fine chemicals industry. In its endeavor to create sustainable value, the fine chemicals industry adopted multiple strategies internally and externally (3).

Through the last two decades the pharmaceutical fine chemicals industry witnessed complex challenges in development of sustainable products and processes. Tackling these call for innovative initiatives in development of eco-efficient products, design of safer products, synthetic redesign, enhancing energy efficiency models, to name a few (4).

Regulations have contributed significantly in eliminating hazardous products and processes and integrating sustainable approaches in production technologies. In the last decade, the industry made significant progress in addressing the critical needs in sectors where a high level of chemical intensity and negative impacts were present. The industry also developed enhanced capabilities in meeting regulatory standards with REACH posing new challenges.

The regulatory forces led to the development of environment-friendly programs and green technologies in every sector of the industry – pharmaceuticals, polymers, food, and consumer products. Integration of green chemistry and engineering (GCE) tools led to advanced products and processes; CO_2 as a raw material for chemical synthesis, microwave, electrochemical and ultrasound synthetic methods; solvent free reactions (or water as a solvent); phytoremediation, waste management; catalysis and biocatalysis, biopolymer technology, renewable materials, renewable energy sources, etc (5).

There is a strong emphasis on adopting renewable resources and fuels to complement traditional sources. Increasing emphasis on waste valorization and recycling tools have allowed for far reaching developments in the last decade.

Biocatalysis has been a prime mover of novel fine chemicals by biotransformation processes. This was complemented by advances in directed evolution (new enzymes for organic synthesis), multicomponent reactions, new separation technologies, flow chemistry and continuous processes in chemical industry, and solvent selection guides in industrial synthesis.

In the last decade there have been far reaching developments in the development of tools and methodologies, such as the following:

- Product differentiation and customization as key business strategy tools
- Improved information and communication technology (ICT) tools that have enabled distributed manufacturing networks

- New product and process reliability tools
- Advanced process and product reliability tools

2.1. Sustainability Models. Typically four models were adopted by the industry. These were based on energy efficiency, waste valorization, innovative GCE platforms, bio-based products, and adoption of green metrics and tools (3).

Energy Efficiency. Investing in energy efficiency is the first choice for most companies seeking to lower their carbon footprint. This was driven by advances in process intensification, novel feedstocks, and materials, all of which led to numerous innovations targeted at improving energy management in the industry.

Green Chemistry and Technology Platforms. Investing in green chemistry and engineering tools has been one of the widely adopted models within the fine chemicals industry and contributed to commercially sustainable products and process. Some of the well known commercial examples are paracetamol, naproxen, (s)-metolachlor, aprepitant, ibuprofen, citral, lazabemide, to name a few. New advances in phase transfer catalysis, asymmetric catalysis, and biocatalysis led to improved process economics and minimal environmental impact.

Biocatalysis led to blockbuster drugs Atorvastatin, Simvastatin, Pregabalin etc being made by ecoefficient models at low costs. Process intensification, process integration, resource optimization, and green tools and guides have complemented computational and combinatorial tools to enable ecoefficient products and processes. New tools and metrics have led to accurate measurements of many products and processes while advances in reaction media and process design have opened up immense scope for rationalizing and improving economics of various processes.

Waste Valorization: From Wastes to High Value Products. Waste valorization is one of the most active areas within the fine chemicals industry where waste by-products are converted to high value chemicals. There are numerous examples of both solid and gaseous wastes being converted to high value products using diverse techniques. Conversion of agricultural, food, and fruit processing wastes to high value fine chemicals offered companies significant opportunities to generate revenues while pursuing their sustainability agenda.

Bio-Based Product Platforms. Bio-based product development based on synergies between chemical and synthetic biology has been a major landmark in the industry. Bio-based chemicals based on synthetic biology, thermochemical conversion, and algae platforms have been the key focus for several companies. Some examples of products compiled where synthetic biology has been a key facilitator are given in Figure 1.

Adoption of Green Metrics and Tools. The need for validated and reliable green metrics has become very critical in design and development of greener product and processes. It has been the active pharmaceutical ingredient (API) segment where a large number of green tools and metrics were developed and deployed till date. Development of green chemistry metrics poses challenges as newer and complex chemistries continue to dominate new product development.

GSK developed many metrics that were focused on solvents: solvent intensity = (mass of all solvent used excluding water/mass of product) kg/kg of product, and water intensity = (mass of all water used/mass of product) kg/kg of product. This led to the development of methodologies for measuring the relative greenness of common solvents used in the pharmaceutical industry to aid chemists in their

Chemicals	Materials	Medicine	Food	Fuels
D-Lactic acid (Myriant)	**Farnesene** (Amyris/Kuraray)	**Sitagliptin** (Merck/Codexis)	**Valencene/Nooktatone** (Isobionics/DSM, Allylix)	**Isobutanol** (Gevo)
Biofene (Amyris)	**PIIA** (Metabolix)	**Cephalexin** (DSM)	**Vanillin/Resveratrol** (Evolva)	**Algal oils** (Solazyme)
Butanediol (BioAmber, Genomatica)	**Isoprene** (Amyris, Genencor etc.)	**Antitrypsin** (Intrexon)	**Vetivone** (Allylix)	**Butanol** (Butamax/DuPont)
Adipic acid (Verdezyne)	**PBS** (BioAmber)	**Artemisnin** (Amyris)	**Corn-enzyme** (Syngenta/Verenium)	**Algal biofuels** (Syn. Genom)
Succinic acid (BioAmber, etc.)				**Ethanol** (Mascoma/Qteros)

Fig. 1. Syn–bio products. (http://www.synbioproject.org/cpi/companies/.)

understanding of the environment, health, and safety issues associated with choosing any particular solvent (6).

Besides, several green metrics are reported such as life cycle metrics; energy metrics, renewability metrics, recyclability metrics, and degradation potential metrics. Today, pharmaceutical industry has developed a series of green chemistry metrics of different categories (mass, energy, safety, ecotoxicity, etc) to evaluate efficiency and potential environmental impact of various chemical processes.

One of the most significant developments toward building a comprehensive green metric tool kit was undertaken by the CHEM21 project (Chemical Manufacturing Methods for the 21st Century Pharmaceutical Industries), a consortium of academics, pharmaceutical companies, and SMEs (7). The basic focus of this initiative was to develop sustainable alternatives for a number of key transformations (eg, amidation, C—X bond formation, and C—H activation) utilizing a wide range of chemical catalysis and synthetic methods, biocatalysis, and synthetic biology techniques.

Some of key manufacturing directions that are likely to shape sustainable manufacturing of fine chemicals are as follows: (8).

New catalysts: Nanostructured catalysts, enzymatic and biocatalysts, and catalytic distillations

New process technology: Reconfigurable design, distributed computing, and process intensification

New chemical processes: New membrane technology, microreaction technology, high throughput technology, bioprocesses, and stereoselective (chiral) chemistry

New product and process design technology: New product architecture (platforms, modules, services), distributed production, smaller and local final assembly sites, new processes for visualization, and modular design for products and production.

3. Catalysis in Fine Chemicals Manufacturing

The global chemical industry faces a variety of challenges in creating alternative fuels, reducing harmful by-products in manufacturing, design and development of safer and cleaner products and processes, developing tools for waste valorization, and other pressing issues. A common thread underlying the resolution of these challenges lies at the heart of catalysis and catalytic technologies. The progress in the industry has been led by a host of catalytic technologies that enabled synthesis of ecoefficient designer products with customized specifications.

New developments in catalytic systems combined with advances in electronics, nanoprocessing, and automation have allowed for a shift in manufacturing from a large to more elegant and sustainable flexible manufacturing platform. The fine chemical production will change beyond the present systems to highly elegant models aided by new generation catalysis.

One of the new developments in catalysis is etching small, moving structures onto a chip. The tiny scale of devices will improve regulation and control. The micro-scale helps in precise heat application, prevents the formation of by-products, and avoids incomplete reactions. The technology is very promising for the fine chemicals and pharmaceuticals industry, which are sectors where precision is crucial and output is often measured in small quantities (9).

3.1. New Generation Catalytic Technologies: Fine Chemicals Perspective. Fine chemicals manufacture leads to complex mixture of products that often need high cost isolation, separation, and purification. Selectivity is the most important criteria in fine chemicals manufacturing since it eliminates high cost isolation and purification processes. Selectivity is often controlled by choice of chemical route, solvent, catalyst, and operating conditions, but most often it depends on improved catalytic technologies. New catalytic systems have enabled elegant and highly selective routes to complex fine chemicals. The emergence of newer catalytic process besides biocatalytic techniques have opened up new synthetic possibilities that were so far not possible (3,4).

Heterogeneous and homogenous phase transfer catalysis, single-site catalysis, and selective oxidation catalysis are well established catalytic platforms where several commercially successful and greener products have been developed.

Enzymatic catalysis, enantiomeric and biocatalysis have led to several innovative greener routes to fine chemicals. Transition metal, metal oxide, and chiral metal complexes have been increasingly used as potential alternative catalysis. In recent years, advances in nanocatalysis, fluorous catalysis, and solvent free catalysis have led to new pathways for complex products. The use of combinatorial catalysis for discovery and optimization of catalytic performance are significantly impacting the speed at which new catalysts are developed.

Advances in Catalysis. Advances in catalysis and catalytic systems have transformed the fine chemical manufacture in radical ways. New catalysts are being continuously explored for various reactions where existing systems have been found to be limiting. Catalytic conversions in water have also enabled to obviate the need for elaborate methods to separate the expensive catalyst from the reaction mixture. Advances in heteroployacids, nanocatalysis, solvent-free catalysis, olefin metathesis catalysis, and fluorous catalysis have led to vastly improved fine chemical processes. Solvent-free catalysis has been used effectively in a one-step Knoevenegal condensation of aliphatic and heteroaromatic derivatives with malononitrile in liquid phase.

Olefin metathesis is finding increasing use in synthesis of fine chemicals. Development of ruthenium-based catalysts enabled wider avenue for the use of olefin metathesis for synthesis of fine chemicals. Ruhrchemie/Rhône–Poulenc process for the hydroformylation of propylene to *n*-butanal is a classic example of rhodium catalysis for a vitamin A intermediate.

Fluorous biphasic catalysis for greener synthesis of a variety of organic molecules has been gaining importance due its high catalyst recovery capability, catalyst recycling, and low solvent usage. Fluorous catalysis has been used in Diels-Alder, Michael addition, and enatioselective aldol condensations.

Biologically inspired catalysis, ie, biomimetic catalysts have been used in several oxidation reactions. Catalytic antibodies have also been explored for their high selectivity and stereospecificity in chemical transformations.

Over the last two decades, there has been an intense focus on enzymes as industrial catalysts; numerous examples of biological catalysis, including fermentations, whole-cell biotransformations, and the use of isolated enzymes have been reported. In the future, new technologies such as protein engineering, directed evolution and metabolic engineering are likely to open up further opportunities for biocatalytic routes, provided they can meet the stringent productivity and cost criteria.

Biocatalytic technologies are still on a learning curve and issues related to validation, productivity, selectivity, and more importantly consistency in formulation and limited substrate options are in need of resolution (3).

Development of biocatalytic tool box for a host of industrially important reactions like nitrile hydrolysis, ketone reduction, hydrocyanation, hydroxylation, and amidation and epoxidation etc, will be crucial. Design and development of newer enzymes for fine chemical manufacture offers immense scope for chemists in the near future.

Several novel avenues are opening up for research pursuits in catalysis in diverse segments like fine chemicals, renewables, materials, carbon dioxide usage, fuels, health ingredients, bio-based chemicals, multifunctional hybrid reactions, microreactors, chiral molecules, etc (10).

In fine chemicals synthesis, new approaches for direct regioselective and (in part) diastereoselective or enantioselective functionalization of aromatic compounds (hydroxy, amino, carbonyl, and carboxyl groups) and avoidance of (or at least reduction of) by-products in conventional reactions (eg, Friedel-Crafts reactions) will be key. In chirally active ingredients, key focus is on development of highly selective and active catalysts that enable cost-effective production of enantiomerically pure compounds. New generation catalysts are expected to offer high selectivity, flexibility on feedstocks use, process intensification, and energy reduction.

4. Next-Generation Fine Chemical Manufacturing

Since 2000, the fine chemical manufacturing technologies have gone through rapid transformations driven by sustainability mandates, rationalization of business models and structures, shifts in product portfolio strategies, emergence of new manufacturing models, emergence of stringent regulations, energy efficiency models, and complex supply chains.

New digital technologies promise to usher in a new era of manufacturing driven by data analytics and mining tools. Digital technologies encompass wireless tracking, global positioning system (GPS) mobile equipment, sensors, analytics, the cloud, and the Internet of Things (IoT) – that is, the connection of sensors, devices, and equipment to the network. This is expected to revolutionize sustainable manufacturing practices in the future in synergies with novel physical manufacturing technologies (4).

Enhancing reaction efficiency, product reliability, and process safety have been the three pillars of the fine chemical industry as the industry began to focus on the following:

- Higher product selectivity and yield by minimizing side reactions
- Tailored high quality materials through precisely controlled process conditions
- Accelerated development and optimization of new chemical processes
- Opening novel process windows for processes that are not feasible hitherto
- Increasing productivity through higher reaction rates and improved process control

An analysis by American Chemical Society (ACS) has marked six technology directions poised that are projected to alter manufacturing of chemicals in the future (11). These are as follows:

- Process intensification (PI), which is projected to rationalize material, energy, and capital requirements while incorporating enhanced safety parameters in the plant. Flow reactors are now leading to wider use of PI approaches and will have profound positive impact in the future.
- Active analytical devices that assure reliability of inputs, conditions, and outputs to match engineering and operating specification and lead to better productivity, profitability, safety, and product quality.
- Advanced separation processes where novel innovations in materials (eg, membranes) and processes (eg, membrane reactors) are enabling efficiency of operations.
- New energy activations like photochemical, microwave, and ultrasonic and electron beam energy for high value fine chemicals production.
- Computational modeling power to analyze massive data sets, provide visualization, and integrate finite element analysis with biological, chemical, thermal, and mechanical modeling.
- Automation, robotics, computing, and intelligent systems for new manufacturing systems that will lead to sustainable fine chemical manufacturing.

4.1. Digital Technology Revolution in Chemical Manufacturing. In the last decade, chemical industry invested billions in automation and information technology to rationalize energy efficiency, reduce overhead, and increase reliability. In this and coming years, major investments are likely to be made in digitally assisted machines, tools, and parts to enable real-time performance indicators and analytics.

In a new initiative, the World Economic Forum's Meta-Council on Emerging Technologies explored many new technologies that are most likely to radically change and transform manufacturing models in an attempt to address the emerging challenges driven by global mega trends (12).

In this context 3D printing has made a major foray in the fine chemicals manufacturing field with the possibility of a 3D printer being able to systematically synthesize thousands of different molecules. It promises flexibility in manufacturing and is a low cost option to build custom-built reactors. Distributed manufacturing models are poised to radicalize the way the industry practices supply chain management. In this model, the raw materials and methods of manufacturing will be more decentralized with final product manufacturing close to the customer. It is expected to lead to sustainable manufacturing and supply chains using digital platforms while leading to efficient resource management.

The new developments in neuromorphic technology contribute to immense energy optimization allowing for faster data processing and machine learning capacity. Real-time data analysis in chemical processing tools are leading to new knowledge mobility in manufacturing sites to access analytics and data to keep track of production, spot quality issues, and minimize delays and downtime.

Robotics has high level of relevance in fine chemicals manufacturing where high levels of precision, product integrity, and safety are called for. New advances in robotics technology have led to new applications in sensors, biological structures, patient handling, surgeries, and also in cloud computing technologies. They have brought in precision, reliability, and work place safety in fine chemical manufacturing plants.

4.2. Future Production Technologies for Fine Chemicals. The most profound shift in the chemical and allied industry came from the emergence of biology as a key tool for fine chemicals production. Future regulatory domains will demand more attention for molecular engineering and molecular probes. Molecular engineering to develop new materials and new molecules and molecular probes that track and control the path of each molecule are on the anvil. Development of solid-state chemicals for APIs and computational tools for smart manufacturing plants are being explored with fervor. In addition, molecular transformations, multiscale analysis and systems analysis, and synthesis have attracted significant research dollars (3).

Flexible Manufacturing Models. With ever increasing focus on sustainability in chemical manufacturing diverse options were explored by the industry in its efforts to rationalize manufacturing infrastructure and ensure safer, resource efficient, sustainable, and flexible output. One of the primary approaches involve shifting from batch to continuous-flow and modularized production to ensure competitive, sustainable, and faster to market products.

There is a need for flexibility in fine chemicals production to make it adaptable to product diversity and short product life cycles. The continuous-flow and modularized process model is emerging as a competitive alternative to batch process to ensure simultaneous energy and resource efficiency (13). Competitive manufacturing in the future will have to leverage the promise of intensified processes and new production concepts, to enable process efficiency, improve sustainability, and speed up market launch.

Modularized plant systems operating in a continuous mode permit faster response to increasing or decreasing market demands. These modules have to be integrated into a planning tool that supports the entire design process from early process development in the laboratory up to the 3-D plant model. Such modularization enables increased efficiency and reduced time to markets. This leads to competitive production by enabling optimal balance between investments and operating costs.

Innovative Flexible Production Projects. *Co*mbining *P*rocess *I*ntensification-driven Manufacture of Microstructured *R*eactors and Process Design regarding to *I*ndustrial *D*imensions and *E*nvironment (CoPIRIDE) and Flexible, Fast, Future (the F^3 Factory) are two of the projects that have focused on innovative technologies to support the shift toward the design and operation of innovative chemical plants. CoPIRIDE is an EU-project that focuses on developing new technologies, processes, and manufacturing concepts for the designing of future chemical plants (14).

The F^3 Factory Project. F^3 Factory is a €30 million collaborative research program that was initiated for flexible production methods. Some of the key applications targeted within the F^3 Factory project include solvent-free polymers, innovative surfactants, compounds for the health care industry, and materials from renewable resources (15). The unique aspect of this modular and container-based platform is that it can use any type of feedstock in contrast to conventional bulk processing that is tailored to a specific feedstock. Some of the commercially relevant examples are given below.

- Demonstration of a new "transformation methodology" for increasing throughput of early phase pharmaceutical materials (AstraZeneca)

  It involved the development of a proof of principle concept for a flexible, continuous production of pharmaceutical fine chemicals for toxicological and clinical studies. A new generic transformation methodology for the formation of pharmaceutical intermediates was developed and validated.
- Development and validation of modular, continuous production concept on medium scale plant level (20–30 kilotonnes p.a.) for decentralized production based on renewable resources (Arkema)

  It involved technical and economic viability for the production of high volume intermediate chemicals in a modular, medium scale plant. The target was the production process of acrylic acid and its derivatives from biomass-based glycerol.
- Transfer of a multistep synthetic batch process for pharma intermediates to a fully continuous manufacturing process (Bayer)

  The focus was to develop a modular, flexible continuous production of active pharmaceutical intermediates. The shift of a multistep synthetic batch process for pharmaceutical intermediates to a fully continuous manufacturing process in a modular, flexible infrastructure, including downstream processing, was investigated and demonstrated.

Some of the primary drivers for flexible plants are shortened time to market, fast response to market demands, enabling quick market entry, and reducing CAPEX risks. Fine chemical production can be flexible in multiple ways: in capacity, product type, innovation, location, and feedstock. At present, advances in tools and systems have enabled the implementation of flexible plants as the modular design offers the needed flexibility to increase or decrease capacity.

In the near future, manufacturing technologies will have to integrate with new approaches in supply chains as time to market will decrease significantly. To this end, virtual, flexible, and shared production models are being explored (8). The chemical industry and in particular the fine chemicals industry is opting for decentralized and flexible production capacities.

In the high value fine chemicals domains, manufacturing will shift toward customer-tailored and service-intensive models and these will need innovative supply chain integration. With increasing sustainability pressure the move toward integrated products-services model will emerge as a key trend.

4.3. Enabling Tools in Fine Chemical Processes. Development of advanced fine chemicals has been due to several enabling tools and technologies and some of these are discussed here.

Process Intensification. PI has emerged as a key enabler of sustainability across the fine chemical industry. Large plants with high environmental and energy footprints are being replaced with miniature continuous process plant with minimal energy and environmental impact. In modern fine chemical plants, classical unit operations are being rapidly replaced or complemented by novel multifunctional systems.

Developments like spinning disc reactor and rotating packed bed systems enabled the application of PI in the manufacturing of several fine chemicals. Several commercial operations deploy multifunctional reactors like membrane reactors, trickle bed reactors, reverse flow reactors, monolith reactors, microreactors, rotating packed bed reactors, and biocatalytic reactors. Process intensification approach also enables manufacturing of products that are not possible by conventional routes.

A very important development is Phoenix's concept of VRT "variable residence time" reactors that are currently used to produce the hydroxynitrile intermediate for Lipitor (16).

Microreactor Technology (MRT) for Fine Chemical Synthesis. The fine and specialty chemical industry has rapidly integrated the concept of process intensification through microreactions. Microreactions have now emerged as one of the most significant tools for process intensification programs in the fine chemicals industry. Microreactors enable miniaturization of reactor dimensions to microscales and control, selectivity, and productivity are ensured.

Transition from conventional batch processes to continuous processing has been gaining momentum in fine chemical industry. Continuous processing is a key element of process intensification approach in fine chemical manufacture and several commercially important products have been made in continuous flow reactors.

Since early 1990s, chemical industry has extended the principles of MRT to an array of traditional unit processes such as nitrations, lithiations, reduction, and oxidation transacetalizations. A large number of reactions like aldol/carbanion chemistry, amides from amines and acid chlorides, brominations of toluene, 3-nitro-toluene, thiophene, cumene hydroperoxide rearrangement, diazomethane conversion, diazotization and diazo coupling, Diels-Alder reaction, to name a few, have been attempted in microreactor systems (3).

Some of the notable reactions are as follows:

- Solvent-free zero hazard process for thiophene bromination was effectively done in microreactor. In batch reactors, these type of brominations often lead to thermal runaways, a phenomena which is avoided by running such bromination in microreactors.

- Gemifloxacin is a quinolone antibiotic and classically five different steps were used for its intermediate synthesis are now done in microstructured reactors.

Sustainable Innovations: Processes and Operations. To remain competitive in the future, the fine chemicals industry will have to explore options for competitive, sustainable, and market-oriented product development. This will call for increased focus on customized products, designer specifications, lower costs, and flexible and efficient manufacturing systems. The industry faces more challenges from those segments that demand tailored products and services like specialty chemicals, materials, consumer chemicals, and wellness products. Process design and computational tools are very important strategic tools to meet these needs of the society in a sustainable manner.

Many unit processes and operations are now fully centered on innovative sustainability platforms. One of the most significant innovations is in hydrogenation technology due to advances in developments in equipment, process intensification, and catalysis. Novel developments in chiral catalysis, new mixing technology, high throughput screening, etc, have expanded the scope of hydrogenation technology. The continuous advances in hydrogenation technology will drive further innovation in equipment design, process monitoring, process engineering, and catalysis (17).

Sustainable reactive separation is yet another area where new innovations are deployed. For a chemical separation process to be sustainable, it must be much less energy intensive than incumbent technologies like distillation and evaporation and the supply and use of the separation process must be inherently safe and resource efficient (eg, low energy and water intensities). In reactive distillation, optimal heat integration can be achieved in equilibrium-limited reactions where one of the products is continuously removed *in situ*. Some of the commercially important reactive separations are reactive distillation, membrane-based separations, adsorptions, extraction, and crystallization (18).

The importance of design of novel reactors and reactor engineering in process economics, energy integration, safety, and environmental compatibility is now recognized as a key factor in fine chemicals manufacturing (19).

5. Biotransformations in Fine Chemicals Manufacturing

Biotransformation in fine chemicals manufacturing is now one of the rapidly growing areas of investment, as it has emerged as a vital platforms for complex multifunctional molecules. Industrial biotransformation for fine chemicals using biocatalysis is well advanced with remarkable instances of several products being made in elegant and environmentally benign ways (20).

New enzymes capable of facilitating synthetic transformations of complex molecules that were hitherto not possible have changed the fine chemical manufacturing. Advances in recombinant DNA techniques, protein engineering, and *in vitro* evolution coupled with directed evolution technologies have been some of the primary movers behind the rapid pace of integrating biocatalytic technologies across fine chemicals industry. Besides, effective immobilization techniques have paved the way for optimizing the process efficiency and also enable recovery and recycling of expensive enzymes (3).

Biotransformations have also emerged as a synthetic tool for a wide range of high value amino acids, beta-lactams, peptides, chirals, steroids, nucelotides, etc. A large number of commercially important pharmaceutical fine chemicals have been possible through enzyme-catalyzed biotransformations. Aromatic and halogenated aromatic compounds have also been converted to a range of homochiral diene diols, a key intermediate for a wide array of fine chemicals and natural products. Biocatalytic technologies differ from conventional platforms both in feedstocks and technology base. Some of the key concerns related to wider acceptance of biocatalysis were the substrate specificities, enzyme stability, and availability and need for cosubstrates. Lonza's process for nictotinamide (vitamin B3) is a classical example of biotransformation involving chemo and biocatalytic systems from 2-methylglutaronitrile.

Industrially a variety of enzymes like transferases, hydrolases, isomerases, lyases, oxidoreductase etc, have been deployed for many biotransformations (21). Advanced examples of industrial processes based on immobilized biocatalysts include isomerization of glucose to fructose, production of various amino acids, and hydrolysis of penicillin to 6-aminopenicillanic acid.

Metabolic engineering creates efficient microbial cell factories for producing chemicals at higher yields. Molecular genetic techniques are then used to optimize metabolic pathways of genetically and metabolically well-characterized hosts. Synthetic bioengineering represents a novel approach to employ a combination of computer simulation and metabolic analysis to design artificial metabolic pathways suitable for mass production of target chemicals in host strains (22). Recent advances in protein discovery and enzymatic process have ushered in an era of new biocatalytic platforms for pharmaceutical intermediates, fine chemicals, agrochemicals, and novel materials.

Enzymatic processes have emerged as a key alternative to chemical synthesis for diverse commercially important reactions like esterification, transesterification, interesterification, lactonization, thiotransesterification, and aminolysis. Use of a lipase enzyme along with a nickel catalyst can increase reaction speed and product yield in the production of γ-aminobutyric acid (GABA) (23).

DSM's process for cephalosporins, vitamin B2 (riboflavin) by fermentation at BASF and Hoffman La Roche, vitamin C (ascorbic acid), chloro-2 propionic (Avecia) using a dehalogenase enzyme, and L-DOPA from catechol, pyruvate, and ammonia are some of the commercially important products. Pfizer synthesized the antiparasitic drug doramectin (Dectomax) and antimalarial drug artemisinin through biocatalaytic routes (24).

Some of the commercially important products through biocatalysis are oselravimit, pelitrexol, gemifloxacin, taranabant, paclitaxel by BMS, lamivudine by Glaxo, LY300164 by Eli Lilly, to name a few. Atenolol, propanolol, metoprolol, penbuterol, etc, belong to the group of beta blockers that are now made by biocatalytic route.

Statins are one of the biggest anticholesterol groups containing related chiral 3,5-hydroxy side chains. The key statins, atorvastatin, simvastatin, and rosuvastatin are all made by biocatalytic routes in high selectivity and elegance as reported further.

Atorvastatin. Atorvastatin is one of the key intermediates for Lipitor®, an anticholesterol drug of Pfizer. The manufacturing process for atorvastatin has undergone several improvizations. The key chiral building block in the synthesis of atorvastatin is hydroxynitrile, HN, ethyl (R)-4-cyano-3-hydroxybutyrate. Formation of the nitrile requires hydrogen bromide and a cyanide substitution that had poor selectivity and involved expensive purification.

Codexis developed a two-step as against the multistep process for making HN at room temperature without any metal catalyst or chemical methods. The new process was based on three specific enzymes that involved recombinant-based, directed evolution technologies to provide the activity, selectivity, and stability. The first step involved the enantioselective reduction of a prochiral chloroketone (ethyl 4-chloroacetoacetate) by glucose catalyzed by two enzymes to form an enantiopure chlorohydrin. This was followed by biocatalytic cyanation of the chlorohydrin under mild conditions using a third enzyme (25). Figure 2 illustrates the process sequence of atorvastatin.

Pregabalin. Pregabalin is the active ingredient in Pfizer's Lyrica, an anticonvulsant drug used to treat neuropathic pain. High enantioselectivities are required of the active (S)-enantiomer. The first-generation process based on knoevenagal condensation followed by cyanation and nickel catalysis led to high amounts of unwanted (R)-CNDE. The second-generation process through biocatalysis of racemic-CNDE was a vastly improved process but led to the undesired enantiomer that had to be incinerated. The third-generation biocatalytic process was an improved process than the second-generation process and needed low protein loading, increased recycling possibilities of the unwanted isomer, and reduced solvent usage, and enabled high throughput process and use of water as a reaction medium (26). The process sequence is illustrated in Figure 3.

Biocatalytic technologies are poised to open up novel pathways for a variety of fine chemicals. Advances in enzymatic reactions, bioreactors design, and new enzymes will increase the process options. Directed evolution processes and

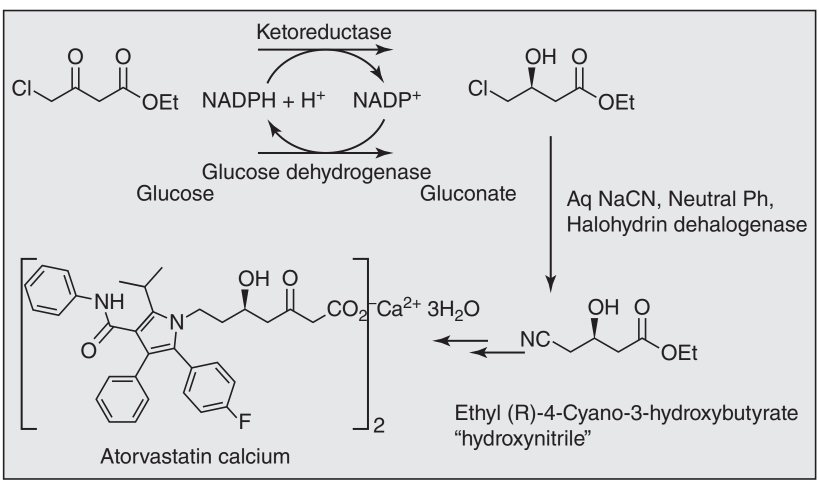

Fig. 2. Atorvastatin.

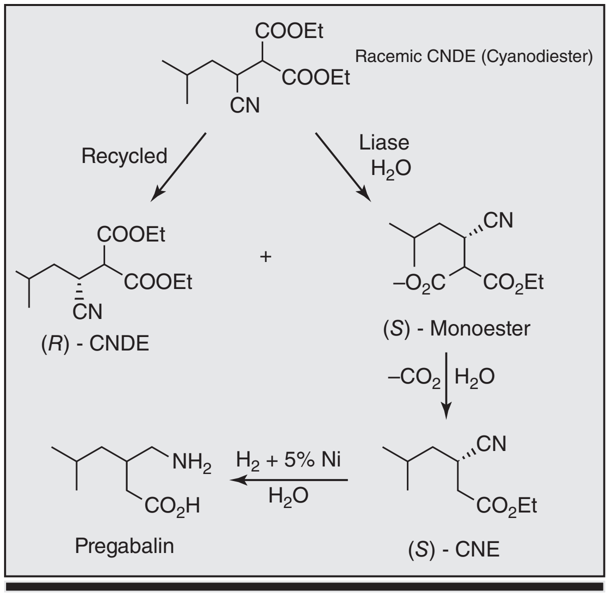

Fig. 3. Pregabalin.

genetically engineered modification of microorganisms for tailor made enzymes will form the basis of several high value fine chemicals manufacturing.

6. Bio-Based Fine Chemicals

Early 1990s witnessed a slow and steady transition from a fossil-based economy to a bio-based economy. This was driven by three key factors. The first driver came not only from new advances in biotechnology, molecular engineering, synthetic biology, and chemical and agricultural sciences but also from the convergence of these disciplines. The second one was the rapid advances in design and development of biorefinery models that operated with multiple feedstocks to produce chemicals and fuels in a sustainable manner. The third significant driver was the impending supply risks and price volatilities from fossil sources and the need for nonfossil-based energy security (3).

Bio-based product development has been largely based on carbohydrates, oil and fats, and lignin platforms. Bio-based companies explored diverse C-chemistries aligned with their capabilities.

Carbohydrates: Sugars can be transformed into chemicals with multiple functional groups that have a high transformation potential into new families of useful molecules. Examples of sugar-based platform chemicals are ethanol (C2), glycerol (C3), succinic acid (C4), xylitol (C5), and sorbitol (C6).

Oils and fats: Oil and fats are a key source of high value chemicals. A variety of chemical and enzymatic reactions are used to transform oils and fats into basic oleochemical substances like fatty acids, fatty acid methyl esters (FAME), fatty alcohols, fatty amines and glycerols, which can be further converted into fine chemical intermediates.

Lignin: Lignin platform offers key routes to several fine chemicals led by developments in microbial conversions, enzymatic oxidations, and pyrolysis.

Bio-based fine chemicals are expected to make a major penetration into traditional chemicals. Several products such as levulinic acid (Segetis), isosorbide (Roquette and Mitsubishi/PTT), glucarates (Rivertop chemicals), etc are all key developments.

Biosuccinic acid is one of the major platform chemical for high value downstream products such as butyrolactone, tetrahydrofuran (THF), 2-pyrrolidone, *N*-methyl pyrrolidone (NMP), succindiamide, 1,4-diaminobutane, succinonitrile, and 1,4-butanediol. Acrylic acid is a key building block for several value chains such as acrylates, acrylonitriles, and acrylamide. Hydroxymethylfurfural (HMF) is a very good source for a high value furan derivative based on carbohydrates. Sorbitol, a key raw material for a wide range of building blocks, traditionally made from petrochemical route, is also made by fermentation route. Commercial production of sorbitol derivatives like ascorbic acid, sorbitan, isosorbide, and 1,2-propanediol is underway. Levulinic acid is a very important building block for a variety of fine chemicals like gamma valerolactone, 2-methyl THF, and acrylic acid.

7. Oleochemical-Based Fine Chemicals

Oleochemicals from biofeedstocks are a new trend in the development of novel high value fine chemicals. The fundamental reactions are saponification, hydrolysis, polymerization, interesterification, and hydrogenation. Nitrogen-containing fatty acids derivatives and esters are two of the most important classes of derivatives consuming more than 50% of fatty acids. Oleochemicals also include those chemicals derived from subsequent modification of the carboxylic acid group of the fatty acids by chemical or biological means, and other compounds obtained from further reactions of these derivatives.

Development of eco-friendly oleochemicals has gained special momentum in the oleochemistry. New classes of fatty acid derivatives containing heterocyclic systems such as benzimidazole, pyrazole, triazole, and oxazole derivatives find huge commercial potential.

Advances in biological and industrial potentialities of oleochemicals have resulted in the development of various synthetic heterocyclic moieties that are incorporated in the fatty acid chain. Therapeutic properties and industrial applications of heterocyclic moieties have opened up new avenues for fatty acid chain containing heterocyclic systems such as oleopyrazoles, oleobenzimidazoles, oleotriazoles, and oleooxazoles.

The development of highly selective catalysts improves the economic competitiveness of basic oleochemicals. Many oleochemicals are manufactured starting with fatty acids, the most important being nitrogen derivatives: esters, metallic soaps, alcohols, dimeric acids, and ozonolysis products such as pelargonic and azelaic acids.

New opportunities from second-generation technologies laid emphasis on new reactive functions at unsaturated sites. These involved biotechnology, thermal and chemical technologies synergizing to produce a variety of high value products for high end use. These open up an entire range of newer chemicals: 9-octodecenoic acid, pelargonic acid, azelaic acid, caproleic acid. Caproleic acid is a key platform for a range of high value derivatives like amino decanoic acid, sebacic acid, N-decanol, capric acid, etc (3).

Recent developments in olefin metathesis offer new opportunities for converting crop-based feedstocks, especially vegetable oils, into a wide range of high value products required for niche market applications. Metathesis of unsaturated fatty acid esters offers a very elegant pathway to unsaturated diesters, key raw materials for a range of fine chemicals.

Advances in technology are redefining the oleochemical space. Among several technologies that radicalized chemical manufacturing, olefin metathesis is one of the most profound due to its game changing dimensions. Metathesis technology is being leveraged to convert vegetable oils to value-added products. Metathesis technology offers a breakthrough in plant oil modifications to arrive at unique functionalities via branching, chain extension or termination and oligomerization/polymerization.

Perhaps the most significant deployment of metathesis is in the synthesis of fine chemicals, due to the development of well-defined and functional group tolerant catalysts. In the drug industry, one of the most exciting areas is use of enantioselective catalysts for olefin metathesis. Molybdenum (Mo)- and ruthenium (Ru)-based complexes have made significant inroads in fine chemicals manufacturing. Some of the important ones include Mevinolin (drug used to lower cholesterol rates), Ambruticin (antifungal antibiotic), and Nonenolide (antimalarial).

Ketorolac is an anti-inflammatory drug used as a racemic mixture. The key intermediate for this is a pyrrole prepared from an alpha, beta unsaturated aldehyde produced by cross-metathesis between crotonaldehyde and allyl benzoate. The key intermediate for Paxil, GlaxoSmithKline's blockbuster antidepressant is *p*-fluorocinnamaldehyde, which is now prepared efficiently through cross-metathesis of *p*-fluorostyrene and crotonaldehyde. Metathesis chemistry is also now widely used to develop greener alternatives to agrochemicals and flavor and fragrance chemicals.

8. Waste Valorization: Biowastes to New Generation Fine Chemicals

Biowaste valorization is embedded in the sustainability protocols for the agricultural and food production, and defined by complex societal, scientific, and commercial issues. It is a key focus for governments to establish sound resource management models and for the industry to align their business and revenue models with sustainability mandates. New technologies and biowaste sources have made it possible to tap the potential of diverse biowastes into value-added chemicals for a host of functional applications (3).

Vegetable and fruit processing by-products, waste, and effluents typically consist of high amounts of proteins, sugars, and lipids. Following physical and biological pretreatments and recovery procedures these biowastes provide value-added natural antioxidants, antimicrobial agents, vitamins, etc, along with macromolecules (such as cellulose, starch, lipids, proteins, plant enzymes, and pigments), which find use in the pharmaceutical, cosmetic, and food industries.

Biowastes are broadly categorized into cereals, roots and tubers, oil seeds, fruits, and pulses. In recent years, wastes from agri biomass, dairies, oil extraction, and food and fruit processing industries have been researched, scaled up, and commercialized with varying levels of success. R&D programs in high value chemicals from biowastes have been driven by advances in chemical and biotransformations. High value ingredients from orange peels (D-limonene), tomato wastes (lycopene), and tea wastes (caffeine) are now in commercial domains. Market prospects for natural antioxidants, antimicrobial agents, vitamins, cellulose, starch, lipids, proteins, plant enzymes, flavors, monomers, biopolymers, and pigments have been driving the growth of this segment.

8.1. Biowastes to Fine Chemicals. In recent years, wastes from agri biomass dairies, oil extractions, and food and fruit processing industries have been studied in depth. Production of high end fine chemicals from food and fruit processing wastes through chemical and biotechnological transformations is a fast developing area worldwide.

These wastes are rich in natural antioxidants, antimicrobial agents, vitamins, etc, as also macromolecules like cellulose, starch, lipids, proteins, plant enzymes, and pigments, and find wide usage in the pharmaceutical, cosmetic, and food industries. There is immense scope for additional value-added products like flavors, biopolymers, and enzymes from waste streams. Figure 4 highlights the high value fine chemicals from biowastes (3).

The processing of fruits results in high amounts of waste materials such as peels, seeds, stones, and oilseed meals. These by-products represent an important source of sugars, minerals, organic acid, dietary fiber, and phenolics that find use in diverse therapies. Phenolics are a much diversified group of secondary plant metabolites, which include simple phenolic, phenolic acids (benzoic and cinnamic acid derivatives), lignans, lignins, coumarins, flavonoids, stilbenes, flavonolignans, and tannins.

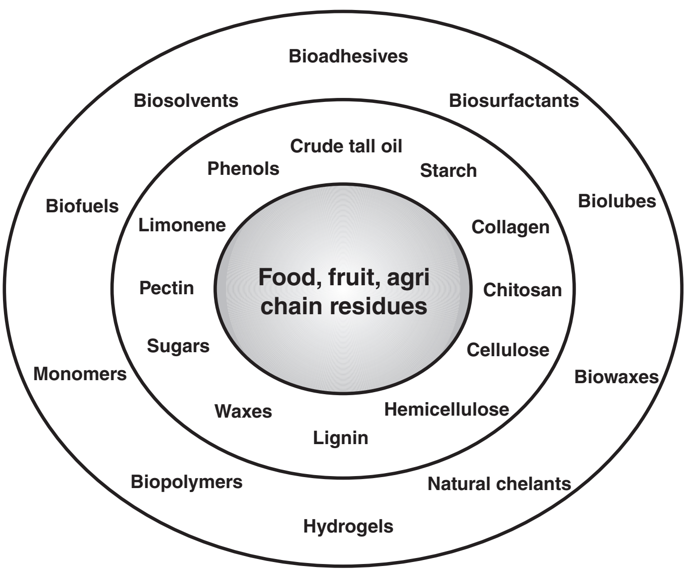

Fig. 4. Biowaste valorization.

Microwave technology is the most preferred one in extraction of fine chemicals from waste streams due its cost efficiency. It is used in extraction of hesperidin and limonene. A novel cascade-type valorization technology using a single-step, low-temperature hydrothermal microwave treatment is being developed for D-limonene, pectin, an unusual form of mesoporous cellulose, and also for *in situ* conversion of D-limonene into α-terpineol. *N*-methyltyramine, flavones, synephrine, carotenoids, and octaopamine from orange peels offer new avenues for high value fine chemicals.

8.2. Lignin-Based Fine Chemicals. Lignin has gained prominence in the last decade as an emerging platform for diverse high value fine chemicals. The perception that lignin is regarded as a waste by-product has changed radically to one where lignin is being heralded as one of the most important building blocks for a host of high value products. Lignin undergoes depolymerization to monomers through diverse reactions like alkaline oxidation, pyrolysis, or enzymatic decomposition to yield complex aromatic compounds having diverse functionalities (27). Figure 5 illustrates the chemistries and products from lignin (3).

Many of these molecules themselves possess biological activity or can be used as raw material for the production of pharmaceuticals, perfumes, food additives, etc. A typical value chain begins from sources like wood or lignin types to intermediates to value-added products like carbon fibers, adhesives, plastics, active carbon and dispersants, etc.

With recent advances in biocatalysis and its commercial potential, the move toward processes with high chemo-, regio-, and stereoselectivity has accelerated.

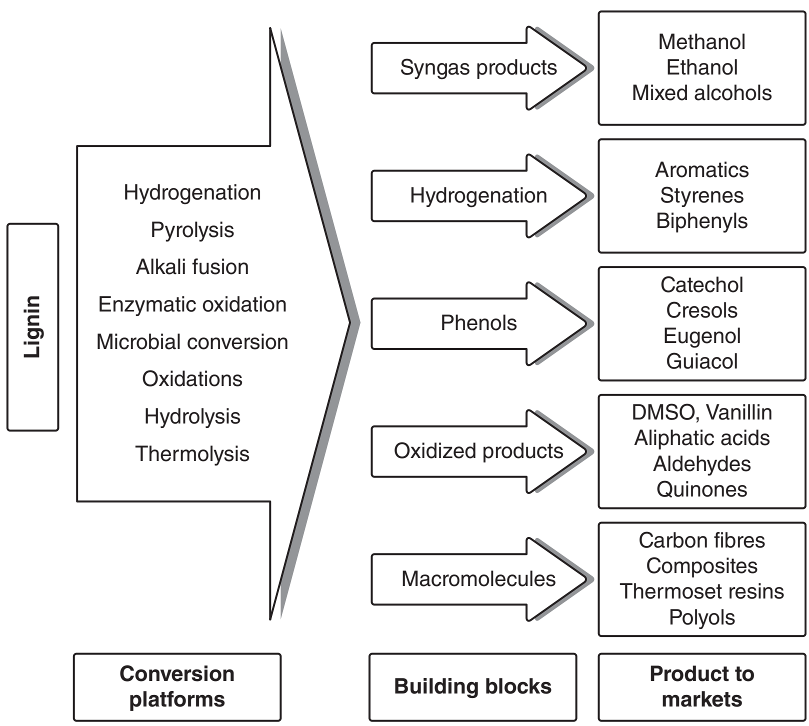

Fig. 5. Lignin chemistries and products.

These are key parameters for synthesizing the desired products at high purity and high selectivity. Biocatalytic processes obviates the need for protecting groups and in the process reduces the number of steps and optimizes water usage.

The valorization of lignin represents a crucial step in the development of modern biorefinery processes. Its complex structure offers unique routes to produce fine chemicals using new catalytic technologies for specific functionalization of lignin molecule.

Oxidative enzymes, biomimetic catalysts, and inorganic catalysts that undergo concerted oxidation pathways are vital tools for selective functionalization and depolymerization of lignin. Of late, inorganic oxidative catalysts capable of undergoing radical species formations have found favor for lignin oxidation to monomeric phenols and aliphatic acids.

At present, extensive research is being undertaken to convert lignocellulosic biomass to value-added chemicals and polymers at high selectivities and yields at economical costs. Future developments in the valorization of lignocellulosic biomass are directly correlated to improvements in the fields of chemical and microbial synthesis.

Lignol, Verenium, and Mascoma are some of the companies who have undertaken the development of biorefining technologies for the production of advanced biofuels, biochemicals, and biomaterials from non-food cellulosic biomass feedstocks. DuPont, BASF, SABIC, The Dow Chemical Company, LyondellBasell, and Mitsubishi Chemical have also been actively engaged in valorization of lignocellulosic biomass.

Development of an economically viable lignin valorization route for the production of aromatic chemicals or carbon fiber demands further research and high purity lignin.

A detailed assessment of high value opportunities have been discussed in a report (28).

8.3. Valorization of Carbon Dioxide. The immense opportunity to valorize carbon dioxide and carbon monoxide emissions from industrial operations into high value fuels and fine chemicals will make a major impact in lowering carbon footprint of many industries that have high carbon dioxide emission levels. The increasing focus on carbon dioxide to chemicals as an approach to mitigate climate change pressures has led to investments in R&D in carbon dioxide valorization. A recent and classical example of carbon monoxide valorization is that of Lanzatech's technology where steel industry flue gases rich in carbon monooxide was converted through a microbial process to high value ethanol-based chemicals (29).

9. Future Direction in Fine Chemicals Manufacturing

The fine chemicals industry faces challenges related to innovations, remaining competitive and choosing the appropriate business model. Leveraging innovations at the market place has proved to be most challenging for many companies. Low and slow pace of return on innovation investments has led to shift in approaches within organizations.

Despite the progress, there exists a vast scope for new approaches to feedstock generation, R&D management, technology development, manufacturing, and supply chains. Differentiated products and services, customer engagement models, and real-time analysis of market dynamics will be crucial as the industry strives to create sustainable value. Besides, innovation in plant engineering, material efficiency, resource optimization, supply chain, and facility management will be critical inside manufacturing facilities. ICT-led process optimization combined with flexible production partnerships will be key in the future.

In the future, the industry will be shaped by game changers like synthetic biology, third-generation biorefining technologies, biologically derived molecules, improved carbon dioxide conversion processes, and metathesis technology. Firms pioneering innovative feedstock generation, process optimization tools, and product redesign approaches around sustainability protocols will develop leadership position. However, this will need investments in innovations in design of eco-efficient products, energy efficiency programs, and emission reduction systems. This will have to be complemented by improved design and development of sustainability tools, metrics, and methodologies.

On the renewables front, increasing emphasis on bio-based chemical economy will have to be supported by better knowledge of the underlying technological, feedstock, and market complexities of the bioproducts business (3).

The fine chemicals industry has positioned strategic cost management and sustainability management at apex of its growth plans. Innovative production processes will change the scope and scale of manufacturing, and increasing convergence of physical, chemical, and biological sciences and a host of other engineering disciplines will lead to a novel range of products and processes. Such progress will also need new multidisciplinary skill sets for chemists and chemical engineers.

Digital technologies will enable development of novel working architectures in manufacturing making it possible to network with widely distributed manufacturing facilities. Data analytics and network organizations working on real-time data exchange are already making it possible for intelligent manufacturing. With increasing sustainability pressure the move toward integrated products-services model will emerge as a key trend.

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