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**IIT Jodhpur**

**DESIGN CREDIT COURSE**

(Semester 1 AY 2022-2023)

# TOPIC

- TECHNO-ECONOMIC ANALYSIS FOR SMALL AND MEDIUM SCALE CHEMICAL INDUSTRIES

Under the guidance by- Sumit Kamal Sir

Name - Utkarsh Gupta

Roll number - B21CH034

# What is fine chemicals, its type and examples

- Fine chemicals are single, pure and complex chemicals that are only produced in small amounts by multipurpose plants. They are produced by a limited number of companies. The chemicals are never sold in their natural state.
- TYPES- They are divided into three main forms:
- Active pharmaceutical ingredients – They are then produced in varying doses as medical drugs.
- Biocides are chemicals used to kill weeds and pests. They include pesticides and herbicides.
- Specialty chemicals are used in various processes such as making ceramics, additive in plastics, glass and disinfectants or antioxidants.

# Different sectors of chemical industries

- 1)Construction chemicals-Construction chemicals are chemical formulations used with cement concrete or other constructions materials at the time of construction to hold the construction material together.
- Chemicals -Concrete admixtures, concrete curing compound, polymer bonding agents, protective and decorative agents, water repellents, adhesives, sealants and caulks, epoxy grouts.
- Global Companies- Apple Chemie, Ardex Endura, ATPL Group, Carborumdum Universal, Cryso India, Elkay Chemicals, Kunal Conchem, Mapie Construction Products, MCON Rasayan, Polygon Chemicals.

- 2)Pesticides Industries - Pesticides are defined as the substance or mixture of substances used to prevent, destroy, repel, attract, sterilise, mitigate, any insects. Generally pesticides are used in three sectors agriculture, public health and consumer use.
- Chemicals used- Chlorpyrifos, Malathion, Molluscicide, DDT, Glyphosate, Organophosphate, Lindane, Atrazine, Carbaryl, Fipronil.
- Top Global Companies- Syngenta, Bayer Crop Science, BASF, Dow AgroScience, FMC, ADAMA, Nufarm, Sumitomo Chemicals, UPL, Huapant life.

- 3)Dye and Pigment Based industries-Dying is the application of dyes or pigments on textiles materials such as fibers, yarns, and fabrics with the goal of achieving color with desired color fastness. Dying is normally done in a special solution containing dyes and particular chemical material.
- Chemical used – Caustic Potash, Lye(Sodium hydroxide), Bleach(Sodium Hypochlorite), Thiox(Thiourea Dioxide), Urea, RIT Dyes, Fiber reactive dyes, Vat.
- Top Global Companies – Asahi Sangwon Colors, Bhageria Industries, Dynemic Products, ITDL, Kiri Industries, Micas Organic limited, Riverside industries, Shree pushkar Chemicals and Fertilizers, Sudarsham Chemicals, Vidhi Speciality food Ingridients.

- 4) Fertilizer industries – Fertilizer manufacturing plants means a plant that manufactures a substance that contains one or more compounds of nitrogen, phosphorous, potassium or other plant food and is sold or represented for use as a plant nutrient.
- Chemical used – Urea, phosphorous, ammonium nitrate, potassium chloride, Ammonium sulfate, Potassium nitrate, Ammonia, Sodium nitrate, nitrogen, phosphoric acid, Ammonium phosphate.
- Top companies – National Fertilizers, coromandel industries, madras fertilizers limited, Rashtriya chemical and fertilizers, GNFC, Nutrien, CF Industries, The Mosaic Company, Israel Chemicals, Wesfarmers.

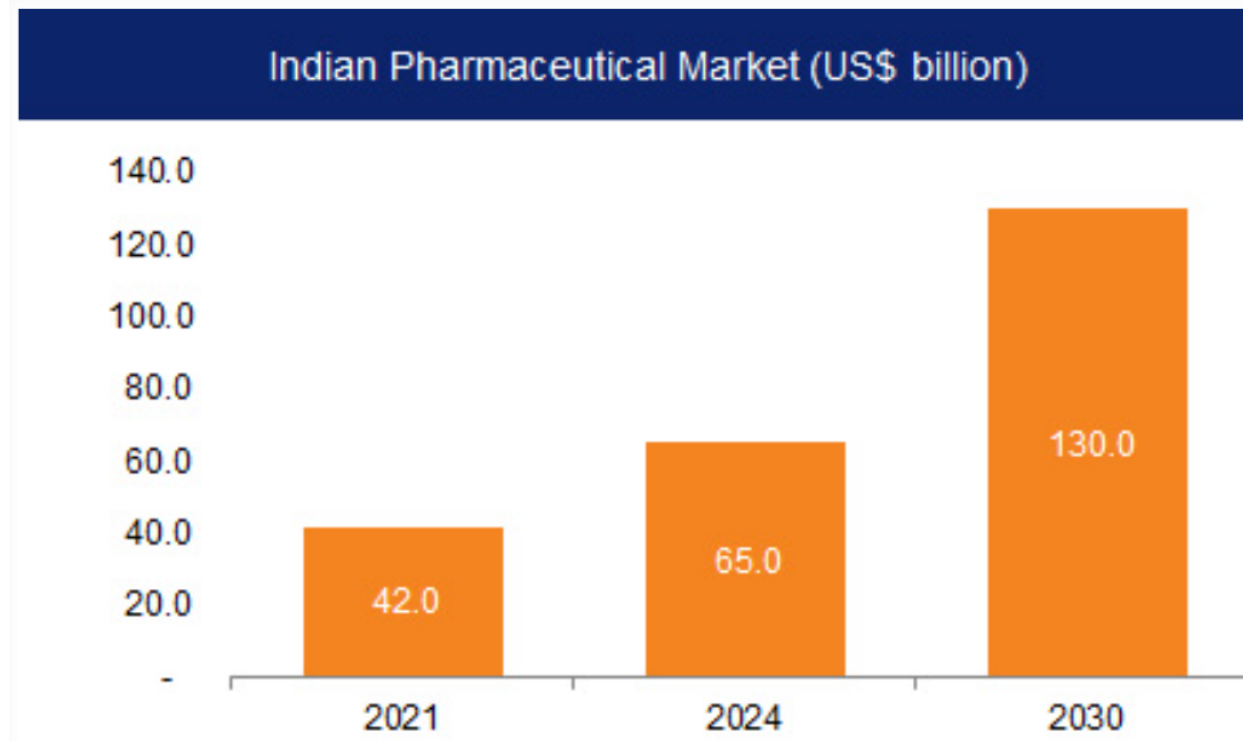
- 5) Soap and cleaning compound manufacturing industries -This industry produces substances that loosen and remove soil from a surface for personal hygiene, sanitization or cleaning clothes, linens and furnishings.
- Chemical used – Sodium silicate, sodium carbonate, sodium perborate, sodium hydroxides, potassium hydroxide, hydroxyethyl cellulose, sodium tripolyphosphate, zeolites, linear alkyl benzene, sulphonic acid.
- Top companies – Dove, Olay, Dial, Irish spring, Aveeno, Ivory, BASF SE, Evonik Industries, Lion corporation, Solvay.



- 6)Pharmaceutical Industries – This industry is defined as the discovery, development, and manufacture of drugs and medicines.
- Chemical used – Ibuprofen, Menthol, Celecoxib, Etoposide, Tinidazole, Nimusulide, Carboplatin, Raloxifene, Diclofinac.
- Top Companies- Johnson and johnson, F Hoffman la roche, Pfizer, Bayer, Navortis, Merch and co, GlaxoSmithKline, Sanofi, AbbVie, Abbott Laboratories.

# Market data of pharmaceutical industries.

- According to the Indian Economic Survey 2021, the domestic market is expected to grow 3x in the next decade. India's domestic pharmaceutical market stood at US\$ 42 billion in 2021 and is likely to reach US\$ 65 billion by 2024 and further expand to reach US\$ 120-130 billion by 2030



# Active Pharmaceutical Ingredients (APIs)

- It is that part of the medicine that produces the intended therapeutic effects.
- For example, in a painkiller, the active ingredient relieves pain. In the OTC drug Crocin, the API is paracetamol.
- Only a small amount of the API is required to produce the effect and so the medicine contains only the required amount of the API.
- Some drugs contain multiple APIs to treat varied symptoms.
- API is the most important raw material in the production of medicines.

# Components of Drugs

- All drugs contain two parts:
- 1. API
- 2. Excipient – These are chemically inactive substances that help deliver the API to the system. Eg. lactose, mineral oil, etc. Intermediate is the chemical substance that is in the process of becoming an API from a raw material. Sometimes, many intermediates are produced before the final API is manufactured.
- How are api's made?
- An API manufacturer first develops the chemical compound in a laboratory. Later, the production department manufactures high quantity of APIs using large reactors. It is then checked for purity before selling it to drug-makers. “If an API is not ultra-pure, medicine cannot meet the strict quality criteria.

# Major companies operating in the Indian Active Pharmaceutical Ingredients Market are

- BASF ltd
- Dr. Reddy's Laboratories Ltd.
- Sun Pharmaceutical Industries Limited
- Cipla Limited
- Atul chemicals.
- Aarti Drugs Ltd.

# Intermediates of API:

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Companies are-

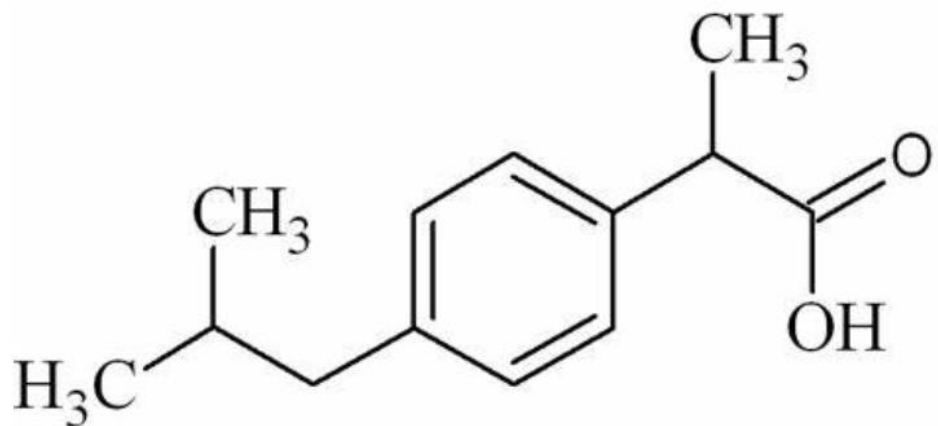
- Atul Chemicals
- Aarti drugs

# Companies which make API and some examples

- APIs by Sun Pharma
  - Gemcitabine, Oxaliplatin, Tramadol, hydrochloride, Mesalazine, Bicalutamide, Capecitabine, Carboplatin
- APIs by Cipla
  - Celecoxib, Risedronate sodium, Amlodipine besylate, Etoposide, Abacavir sulfate, Alendronate Sodium, Budesonide, Efinaconazole, Escitalopram Oxalate.
- APIs by Aarti private limited
  - Aceclofenac , Celecoxib , Diclofenac Sodium , Diclofenac Potassium , Diclofenac Diethylamine , Diclofenac Resinate , Diclofenac Epolamine , Nimesulide , Clopidogrel Bisulphate , Cardioprotectant Ticlopidine HC

# IBUPROFEN

- Ibuprofen is a monocarboxylic acid that is propionic acid in which one of the hydrogens at position 2 is substituted by a 4-(2-methylpropyl)phenyl group. It has a role as a non-steroidal anti-inflammatory drug, a non-narcotic analgesic, a cyclooxygenase 2 inhibitor, a cyclooxygenase 1 inhibitor, an antipyretic, a xenobiotic, an environmental contaminant, a radical scavenger, a drug allergen and a geroprotector. It is functionally related to a propionic acid. It is a conjugate acid of an ibuprofen(1-).
- Molecular Formula C<sub>13</sub>H<sub>18</sub>O<sub>2</sub>
- Structure





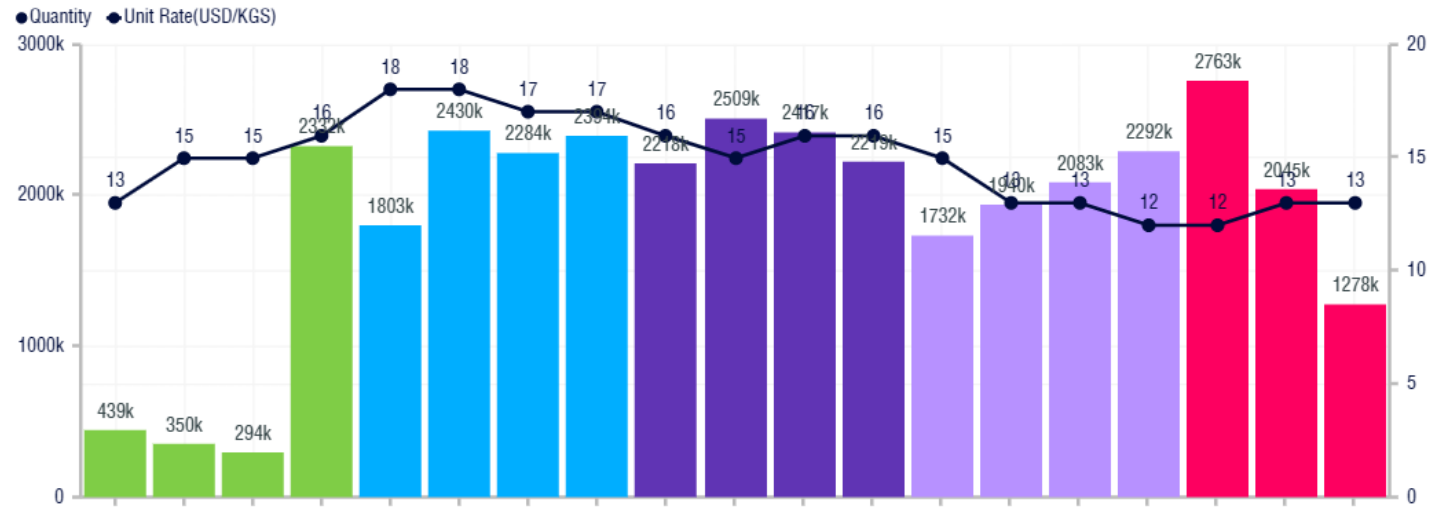
# PROPERTIES

- IUPAC NAMES 2-[4-(2-methylpropyl)phenyl]propanoic acid
- MOLECULAR WEIGHT 206.28
- PHYSICAL DESCRIPTION Solid
- COLOUR/FORM Colorless, crystalline stable solid
- ODOUR Characteristic odor
- BOILING POINT 157 °C
- MELTING POINT 75-77.5 °C
- SOLUBILITY 21 mg/L (at 25 °C)
- VAPOUR PRESSURE  $4.74 \times 10^{-5}$  mm Hg @ 25 °C

## PRICES AND MARKET DEMAND OF IBUPROFEN

The total ibuprofen market size is estimated about 43000 MT as of 2017 and growing at a CAGR of 2 percent.

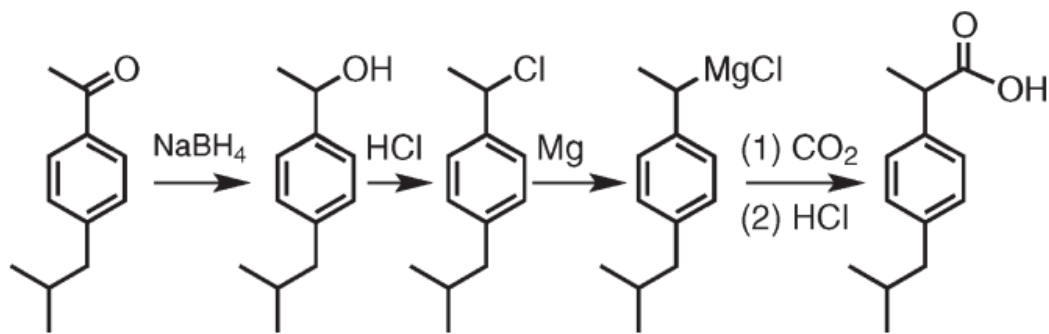
Quantity (KGS) & Unit rate (USD/KGS) over time



Importing Country	Total Quantity (KGS)	Average Price (USD/KGS)	Number of Transactions
UNITED KINGDOM	25,28,227.20	15.1	>200
INDIA	55,93,240.63	15.0	>200
INDIA	18,30,330.26	10.5	>200
NETHERLANDS	25,23,440.00	14.6	>200
GERMANY	12,84,869.54	17.6	>200
KOREA,REPUBLIC OF	4,51,072.30	34.3	>200
SPAIN	15,85,035.25	14.4	>200

# Some production methods, analysis methods and catalyst details for the production of ibuprofen

- Production of ibuprofen in introductory organic laboratory

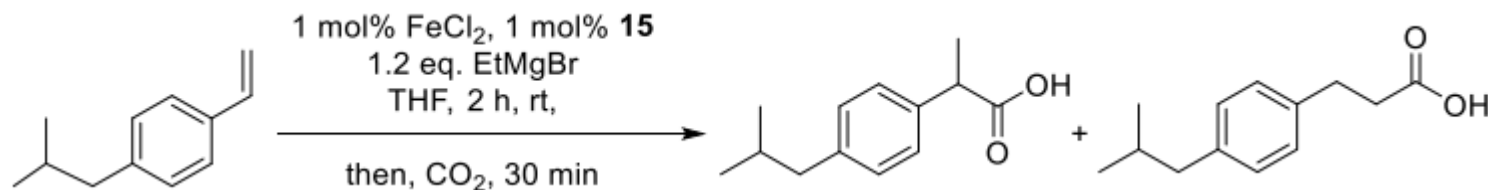


This experiment requires two 3-h lab sessions. In the first lab session, reduce p isobutylacetophenone to an alcohol and then convert this alcohol to the corresponding chloride. In the second session, convert this chloride to a Grignard reagent, which is then carboxylated and protonated to give ibuprofen.

- Sodium borohydride to reduce p-isobutylacetophenone in methanol. After characterization of the resulting alcohol by  $^1\text{H}$  NMR, they convert it to the corresponding chloride by shaking with concentrated hydrochloric acid in a separatory funnel. The chloride samples are handed in to the instructor who combines and dries the material prior to the next meeting. On the second day, a sample of the alkyl chloride that was made on the first day is converted to a Grignard reagent by heating under reflux with tetrahydrofuran (THF), oven-dried magnesium turnings, and a small amount of 1,2-dibromoethane. After cooling, carbon dioxide gas is bubbled into the reaction mixture by way of a balloon equipped with a stopcock and a disposable pipet. Aqueous workup, including extraction of the product into aqueous sodium hydroxide followed by protonation, another extraction, and then rotary evaporation, gives a clean sample of ibuprofen.
- Catalyst details –
- The reason for the extraction with sodium hydroxide is that the ibuprofen must be separated, as the sodium salt, from a dimer and any other water-insoluble impurities produced during Grignard formation.
- Dimerization could be minimized by using specially activated magnesium or carrying out the reaction at a lower temperature.

# Recent advanced methods in the production of ibuprofen

## 1) Iron-catalyzed hydrocarboxylation for ibuprofen synthesis

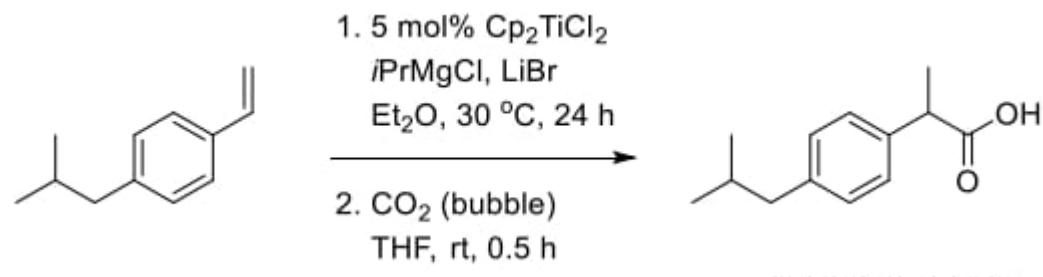


Iron-catalyzed hydrocarboxylation, as reported by Thomas et. Although hydrocarboxylation of styrene was expected to introduce the ibuprofen skeleton, the regioselectivity hampered it. However, the highly selective addition of CO<sub>2</sub> was possible by employing an iron catalyst and pyridine ligand **15**. It showed that the transmetallation and hydrometallation of iron and styrene moieties are important for regioselective addition.

### Catalyst details

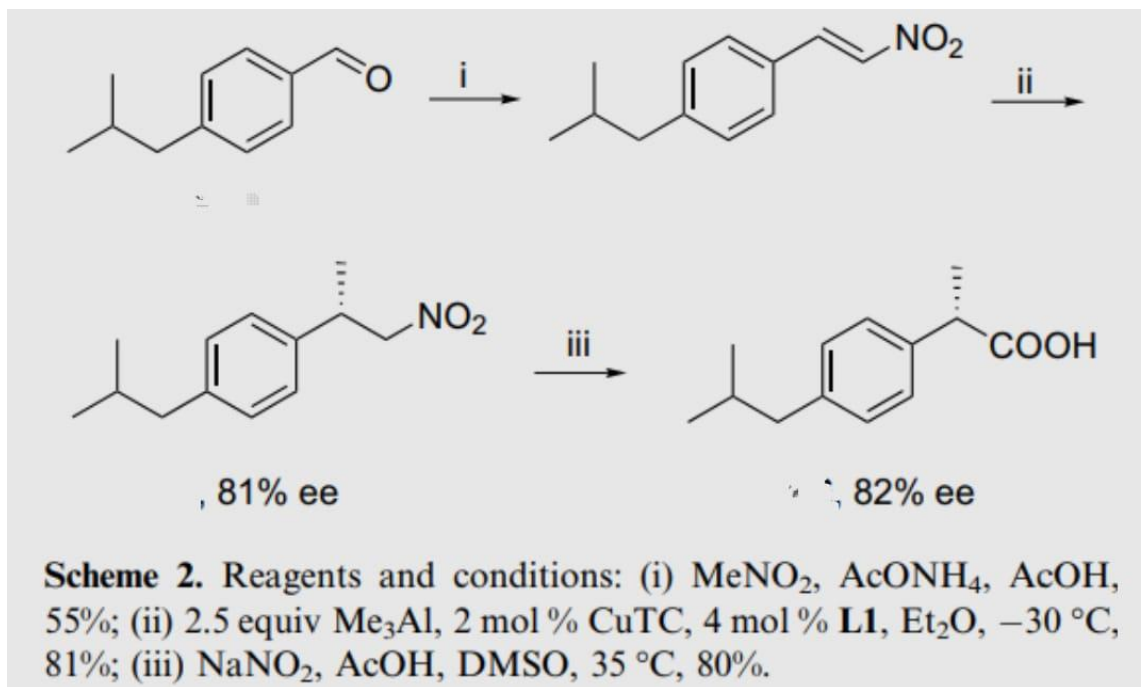
The industry uses iron catalysts to improve or increase the rate of reaction in chemical processes.

- 2) Titanium-mediated hydrocarboxylation for ibuprofen synthesis



- Hydrocarboxylation of styrene using  $\text{Cp}_2\text{TiCl}_2$  catalyst, reported by the Xi group in 2016. For this approach, the regioselectivity of the styrene moiety was screened using various Grignard reagents and additives. When this reaction was applied to alkyl-substituted alkenes, reversed regioselectivity was observed to have resulted in a linear product, nonanoic acid.
- Catalyst details
- $\text{Cp}_2\text{TiCl}_2$  is more stable in air and can reach maximum catalytic activity at low catalyst amount.

- Cu-catalysed asymmetric 1,4-addition of  $\text{Me}_3\text{Al}$  to nitroalkenes For Synthesis of (+)-ibuprofen



- t trimethylaluminium could advantageously replace dimethylzinc in the copper-catalysed conjugate addition to a wide variety of nitroalkenes. Yields and enantioselectivities are generally good to excellent (up to 93%). Coupled with the oxidative transformation of the nitro group, the sequence could provide with an excellent entry to the family of aryl propionic acid derivatives.
- We had first to synthesize the corresponding nitroolefin from the commercially available 4- isobutylbenzaldehyde. The one-pot Henry condensation followed by dehydration afforded 4 in 55% yield after distillation. We then proceeded to the copper-catalysed 1,4-addition of trimethylaluminium onto 4 affording 5 in good yield (81%) as well as with acceptable enantioselectivity (ee 82%). The transformation of the primary nitroalkane 5 to (+)-ibuprofen 6 (80%, ee 82%) was then achieved following the elegant literature procedure.
- Catalyst Details
- Cu catalysed reaction- During the reaction, the monovalent copper salt catalyst reacts with the ligand and base to produce an active compound that activates the C-H bond



- <https://www.globenewswire.com/news-release/2021/09/28/2304140/28124/en/India-11-Billion-Active-Pharmaceutical-Ingredients-API-Markets-2017-2020-2021-2023-2027.html>
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