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IIT Jodhpur

DESIGN CREDIT COURSE

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

Under the guidance by- Sumit Kamal Sir

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Name- Utkarsh Gupta

Roll Number- B21CH034

TECHNO-ECONOMIC ANALYSIS FOR SMALL AND MEDIUM SCALE CHEMICAL INDUSTRIES

What are fine and specialities chemicals.

Firstly we should know about commodity chemicals.

They are chemicals produced in large quantities and in general their applications can be traced back to their chemical structures. They are produced by continuous plant and in general their cost is relatively low such as ammonia and ethylene oxide.

Specialities Chemicals

These are constituted by a mixture of different chemical substances that is designed and produced in order to be applied to a specific application. Each formulation and associated properties are unique and for this reason in the majority of the cases it is not possible to easily interchange two different specialities produced by two different suppliers; examples of applications of speciality chemicals are pharmaceutical industry and agriculture; they are produced by batch plant and in general their cost is higher if compared with commodity chemicals.

Fine chemicals

As the commodity chemicals, they are chemical substances characterized by their chemical structure, but, on the contrary of commodity chemicals, they are produced in a small quantity. Fine chemicals can be used as components in the formulation of speciality chemicals. for example active ingredients of pharmaceutical drugs are fine chemicals, but the pharmaceutical drug is a speciality chemical; examples of applications of fine chemicals are: pharmaceuticals industry, agriculture, photography chemicals and electronic chemicals; they are produced by batch plant and in general their cost is relatively high.

Different types of chemical industries, Chemicals used and Top companies of that industry

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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.

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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 sectorsagriculture, 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.

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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.

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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 nutritient.

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 Cmpany, Israel Chemicals, Wesfarmers.

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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.

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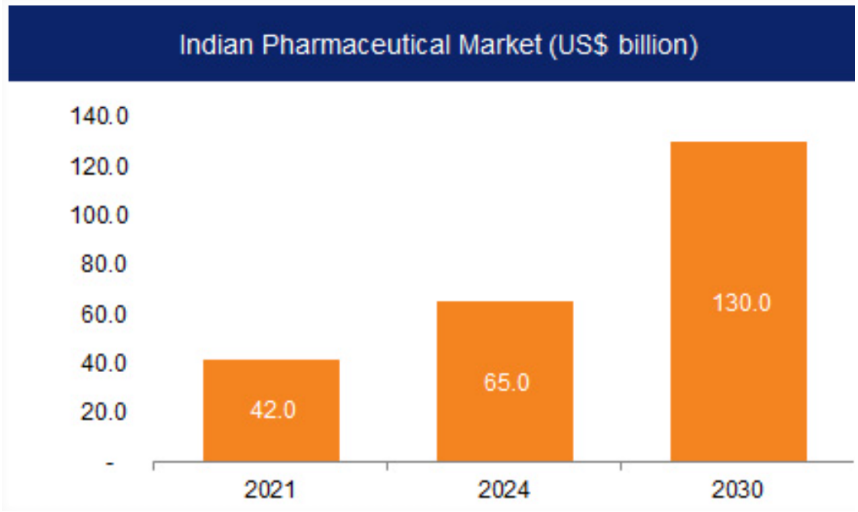
6)Pharmaceutical Industries – This industry is defined as the discovery, development, and manufacture of drugs and medicines.

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)

Active Pharmaceutical Ingredients are the active ingredients contained in a medicine.

- 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:

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.

Intermediates of API made by Atul chemicals

(-)(1R)-Menthyl chloroformate

A clear, colourless to pale yellow liquid used as an intermediate for APIs.

(-)(1R)-Menthyl chloroformate

A clear, colourless to pale yellow liquid used as an intermediate for APIs.

(2R)-2-[(4-Ethyl-2,3-dioxopiperazinyl)carbonylamino]-2-phenylacetic acid

A white to off white powder that is used as an intermediate in Piperacillin, an API.

(S)-1-(2-Chloroacetyl)pyrrolidine-2-carbonitrile

A white to light brown powder used as an intermediate for APIs such as Vildagliptin and Anagliptin.

1-[2-Amino-1-(4-methoxyphenyl)ethyl] cyclohexanol HCl

A white to off white solid used as an intermediate for APIs such as Venlafaxine and Desvenlafaxine.

1-[Cyano-(4-methoxyphenyl)methyl] cyclohexanol

A white to off white powder used as an intermediate for APIs such as Venlafaxine and Desvenlafaxine.

1-Chloro-2-methylpropyl chloroformate

A clear, colourless to light yellow liquid used as an intermediate in APIs.

1-Chloroethyl chloroformate

A clear, colourless liquid used as an intermediate for APIs such as Cefpodoxime, Ampiroxicam, Candesartan, Gabapentin and Ropinirole.

1-Chloroethyl cyclohexyl carbonate

A clear, colourless to pale yellow or brownish liquid used as an intermediate for APIs such as Cefotiam and Candesartan.

1-Chloroethyl isopropyl carbonate

A clear, colourless to pale yellow liquid used as an intermediate in Cefpodoxime, an API.

1-Chloroethyl-4-nitrophenyl carbonate

A clear, colourless to pale yellow liquid used as an intermediate in Gabapentin, an API.

Intermediates of API made by aarti drugs

Product	**Chemical Name**
Tinidazole	2-Methyl-5-Nitro lmidazole
	4(5)-Nitrolmidazole
Celecoxib	4-Sulfonamidophenylhydrazine. HCI
	4,4, 4-Trifl uoro-l-[4-(methyl)phenyl]-butane- 1 3dione
Ciprofloxacin	Methyl 3-(cyclopropylamino)-2-(2,4-dichloro-5-fluorobenzoyl)acrylate
	7-chloro-l-cycloproply-6-fluoro-1,4-dihydro-4-0x0quinoline-3-carboylic acid(
	1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-quinoline-3-carboxylic acic Base)
Clopidogrel	D-(+)-Methyl-alpha-{2-thienylethamino)(2-chlorophenyl)acetate
Diclofenac	2,6-Dichloro Diphenl Amine
	N-Chloro Acetyl-2,6-Dichloro Diphenyl Amine
	1-(2,6-Dichlorophenyl)-2-indolinone
Ketoconazole	N-Acetyl-4-(4-hydroxypheny) Piperazine(AHPP)
	4-methylbenzenesulphonate (Cis – Tosylate
Nimesulide	N-(2-phenoxyphenyl) methanesulphonamide
Raloxifene	4-Methoxy-a-[(3-Methoxyphenyl)Thio]Acetophenone
	6-Methoxy-2-(4-methoxyphenyl) benzo[b]ithiophene
	6-Hydroxy-2-(4-hydroxyphenyl) benzo[b]thiophene
	4-(2-(l-piperidyl)ethoxy)benzoic acid. HCL

API by sun-pharma

APIs	Prize(USD/Kg)	API Market Place
Gemcitabine	4086	13
Oxaliplatin	6998	3
Tramadol hydrocholride	56	44
Mesalazine	57	16
Bicalutamide	761	8
Capecitabine	333	8
Carboplatin	27404	7
Desloratadine	798	20
Divalproex	34	18
Fluvoxamine	446	13
Isotretinoin	1882	13
Iansroprazole	47	13
Ietrozole	8906	14
Ieuprolide acct	84073	5

APIs BY CIPLA

APIs	PRZIE (USD/KG)	MARKET PLACE
Celecoxib	61	10
Risedronate sodium	1039	3
Amlodipine besylate	106	30
Etoposide	959	4
Abacavir sulfate	408	1
Alendronate Sodium	214	10
Budesonide	1759	14
Efinaconazole	8868	9
Escitalopram Oxalate	567	8

APIs by Aarti pvt ltd

Product	Specification	Therapeutic Category
Aceclofenac	BP/EP/IP	Anti-inflammatory
Celecoxib	EP/USP	Anti-inflammatory
Diclofenac Sodium	BP/EP/USP/IP	Anti-inflammatory
Diclofenac Potassium	BP/EP/USP	Anti-inflammatory
Diclofenac Diethylamine	BP	Anti-inflammatory
Diclofenac Resinate	PN	Anti-inflammatory
Diclofenac Epolamine	PN	Anti-inflammatory
Nimesulide	BP/EP/IP	Anti-inflammatory
Clopidogrel Bisulphate	USP/IP	Cardioprotectant
Ticlopidine HCL	BP/EP/USP/IP	Cardioprotectant

API By BASF pharma

Azelaic Acid 99% (Dermaz® 99)

API for dermatology and acne treatments

Dexpanthenol Ph. Eur.

Dexpanthenol for various therapeutic efficacy

Ibuprofen 25

Fine grade Ibuprofen

Ibuprofen 38

Powder grade ibuprofen with controlled particle size

L-Menthol (Flakes)

Menthol for fresh and minty taste

Omega-3-Acid Ethyl Esters for Italian Market

Omega-3-acid ethyl esters as an Active Pharmaceutical Ingredient (API), specified for the Italian Market

APIs By Atul chemicals

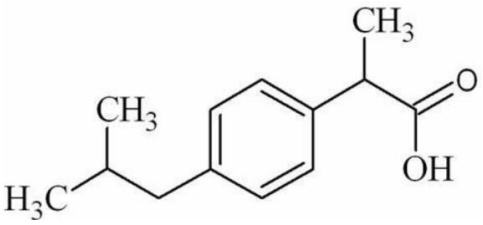
Product name	Therapeutic class
Acyclovir	Antiviral
Chlorobutanol hemihydrate	Antibacterial | antifungal
Chlorobutanol anhydrous	Antibacterial | antifungal
Dapsone	Antibacterial
Desvenlafaxine succinate	Antidepressant
Fluconazole	Antifungal
Losartan potassium	Antihypertensive
Metoprolol succinate	Antihypertensive
(S)-Metoprolol succinate	Antihypertensive
Metoprolol tartrate	Antihypertensive
Valacyclovir hydrochloride	Antiviral
Venlafaxine hydrochloride	Antidepressant

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 C13H18O2

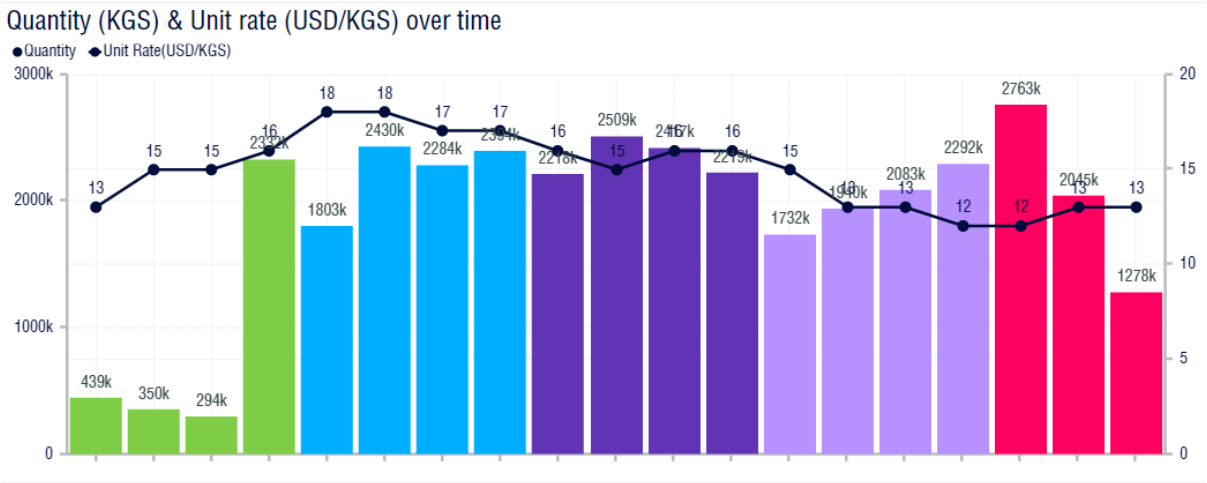
Structure:



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 ºC
MELTING POINT	75-77.5 ºC
SOLUBILITY	21 mg/L (at 25 °C)
VAPOUR PRESSURE	4.74X10-5 mm Hg @ 25 °C

PRICES AND MARKET DEMAND OF IBUPROFEN

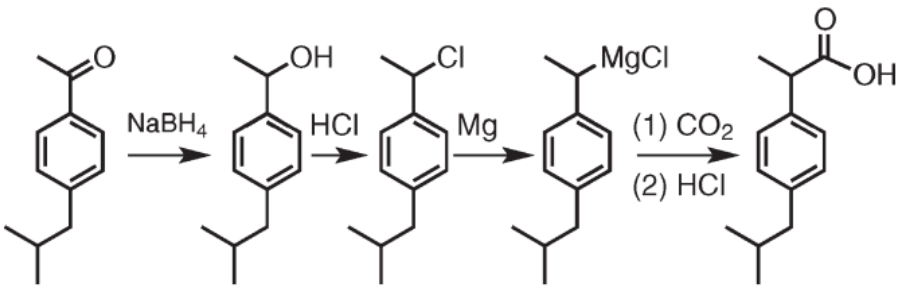
What is the total market size of ibuprofen? The total ibuprofen market size is estimated about 43000 MT as of 2017 and growing at a CAGR of 2 percent.



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 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.

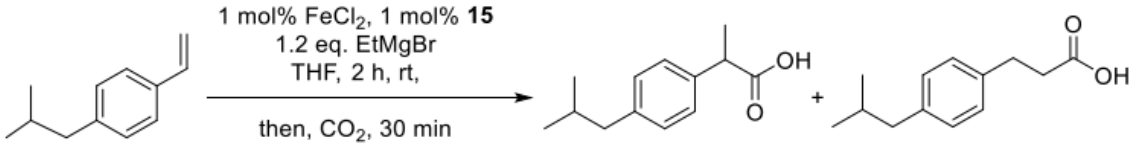
Catalyst details –

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

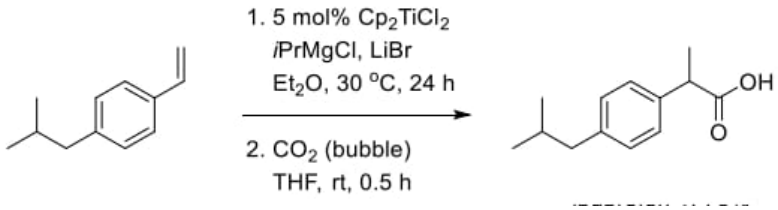


Iron-catalyzed hydrocarboxylation, as reported by Thomas et. Although hydrocarboxylation of styrene was expected to introduce the ibuprofen skeleton, the regioselectivity hampered it. However, the highly selective addition of CO_2 was possible by employing an iron catalyst and pyridine ligand 15. It 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



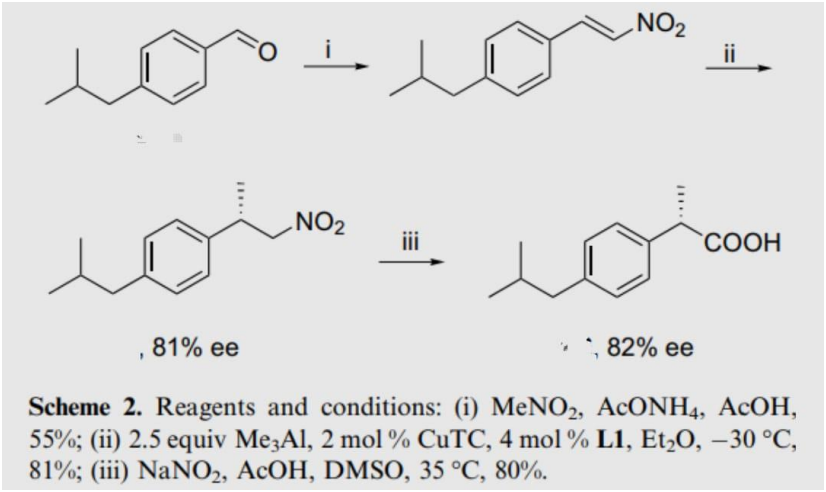
Hydrocarboxylation of styrene using Cp_2TiCl_2 catalyst, reported by the Xi group in 2016. For this approach, the regioselectivity of the styrene moiety was screened using various Grignard reagents and additives. When this reaction was applied to alkyl-substituted alkenes, reversed regioselectivity was observed to have resulted in a linear product, nonanoic acid.

Catalyst details

Cp_2TiCl_2 is more stable in air and can reach maximum catalytic activity at low catalyst amount.

Cu-catalysed asymmetric 1,4-addition of Me3Al 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.



Scheme 2. Reagents and conditions: (i) $MeNO_2$, $AcONH_4$, AcOH, 55%; (ii) 2.5 equiv Me_3Al, 2 mol % CuTC, 4 mol % **L1**, Et_2O, −30 °C, 81%; (iii) $NaNO_2$, AcOH, DMSO, 35 °C, 80%.

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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