

technology !index 2007

Koei Chemical Company Limited



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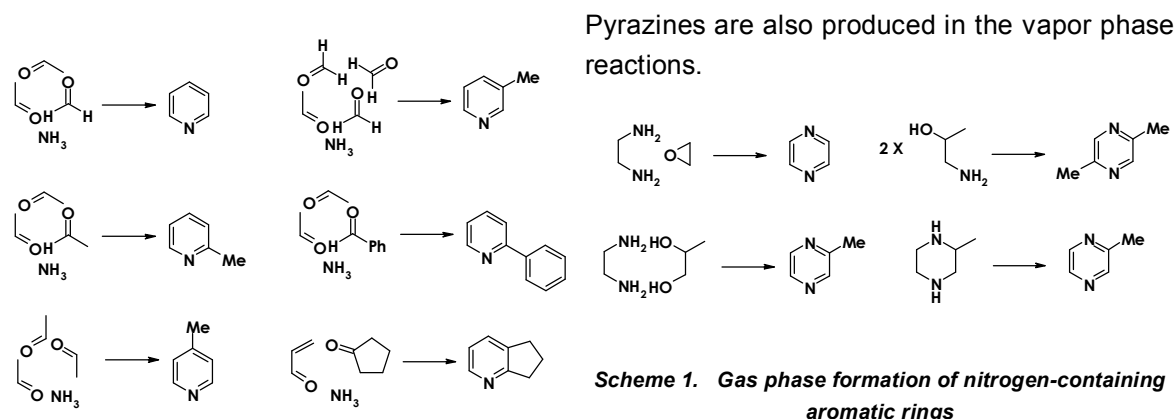
Koei's Core Technologies

Koei produces a wide variety of fine chemical products containing nitrogen, such as pyridines, pyrazines, piperidines piperazine and amine derivatives.

1. Vapor Phase Technologies

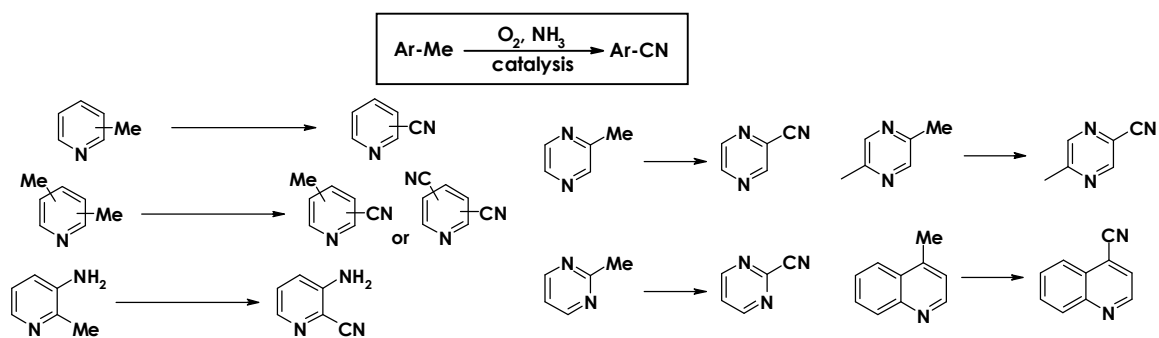
(1) Syntheses of Pyridines and Pyrazines

We produce pyridines in the vapor phase reactions from acetaldehyde, formaldehyde and ammonia. These processes put our company in a very competitive position in pyridine production internationally.



(2) Syntheses of Cyanopyridines and Cyanopyrazines by Ammoxidation

Ammoxidation is one of the most important vapor phase technologies. A simple methyl group is transferred into a nitrile group under oxygen and ammonia atmosphere at high temperature in the presence of catalysts. Cyanopyridines and cyanopyrazines are produced by this reaction.



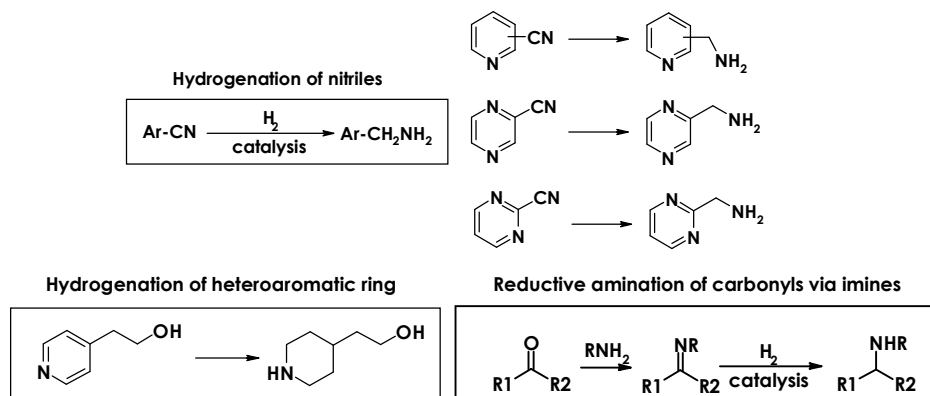
Scheme 2. Ammoxidation of cyanopyridines and cyanopyrazines



2. Liquid Phase Technologies

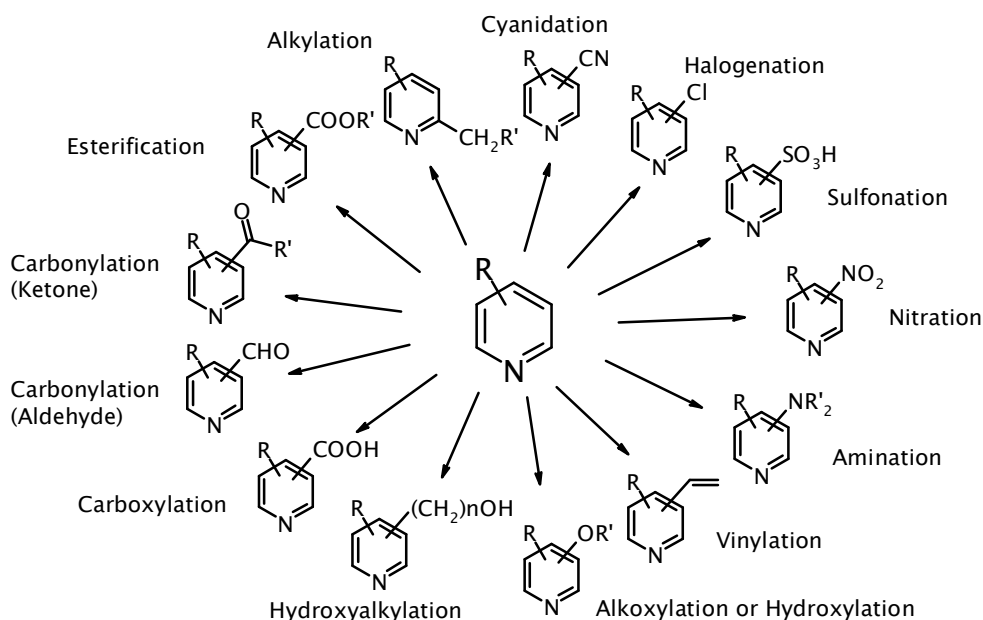
Syntheses of Amines

Hydrogenation of nitriles, reductive amination and hydrogenation of heteroaromatic rings are our expertise. Various amines are manufactured by catalytic hydrogenation under high pressure.



3. Concept of Pyridine Derivative Syntheses

We produce pyridines by vapor phase reactions. As you can see in the picture below, in one case, the pyridines produced are hydrogenated under high pressure to provide piperidines. In the other case, the pyridines are transformed to other pyridine derivatives by liquid phase reactions. As a result, we produce fine chemicals by combining vapor phase reactions and liquid phase reactions.

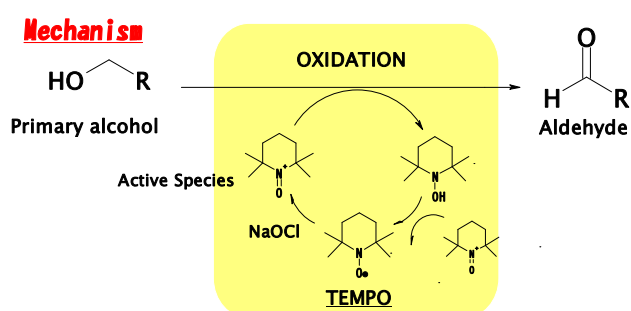


Koei's Recent New Products

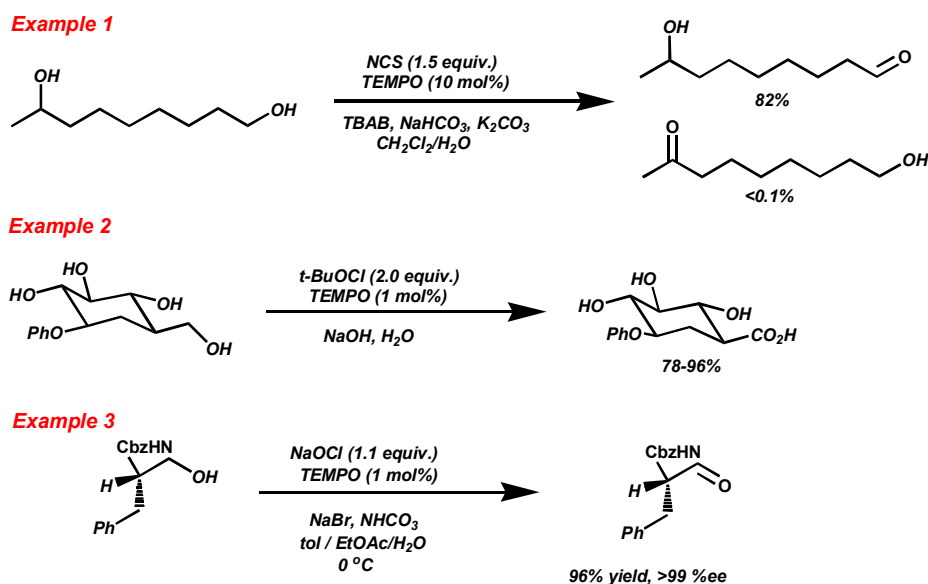
1. TEMPO

TEMPO is not only used as a stabilizer and as a polymerization controller, but also used as an oxidant. TEMPO-mediated oxidation can be carried out under mild conditions. The reactions proceed with high selectivity.

Three examples of selective oxidations are shown here. The first example is chemoselective oxidation. The second example is stereoselective oxidation. The third example is also stereo-controlled oxidation. The optically pure aldehyde is obtained without racemization.



Scheme 5. TEMPO-mediated oxidation process



Scheme 6. Examples of TEMPO-mediated oxidation of various alcohols



2. Ionic Liquids

We synthesize ionic liquid samples from our amines. Ionic liquids have thermostability, nonflammability, nonvolatility, high ionic conductivity, large electrochemical potential window, low viscosity and no corrosiveness.

Since these properties, ionic liquids are used for electronic devices such as batteries, capacitors and solar cells.

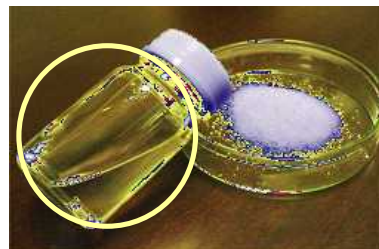


Figure 1. Ionic liquid and ionic solid

Koei's Recent New Technologies

Koei's nitrogen compounds

quarternarization



Feigure 2.

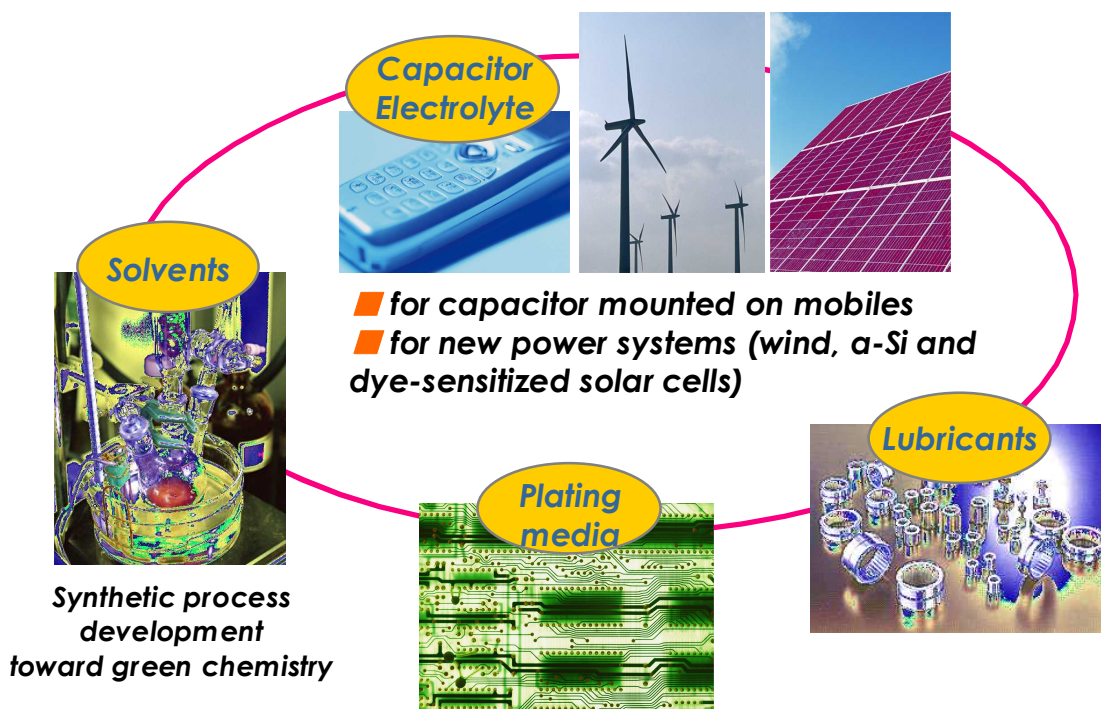


Figure 3. Examples of Ionic Liquids' application

1. Organometallics

We manufacture organometallic compounds, which are highly sensitive to moisture and oxygen. In 2007, a new facility for filtering, drying and packing organometallic compounds under nitrogen will be introduced.

(1) Organoboron Compounds

Aryl and heteroarylboron compounds are versatile synthons in the Suzuki-Miyaura coupling that is a powerful procedure for the synthesis of biaryl compounds. We produce a variety of heteroarylboron compounds by the borylation of aryllithium or arylmagnesium intermediates as well as the direct C-H borylation of heteroaromatic compounds.

1) Borylation of Lithium or Magnesium Intermediates

We provide boronic acids as well as esters from lab scale to industrial scale at the customers' request. We have the cryogenic reactor which can control the reaction temperature from -70 °C to 150 °C¹.

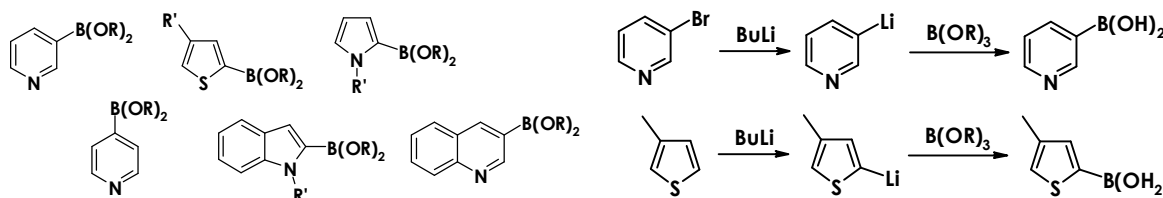
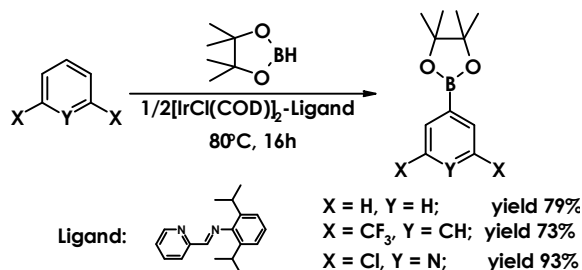


Figure 3. Examples of heteroaromatic boronic acid derivatives and their preparation

2) Aromatic C-H Borylation

The direct C-H borylation of aromatic compounds has high atom efficiency and productivity. An advantage to this reaction is that arylhalides are not required as a raw material. We have developed our original diimine ligand for this reaction².



Scheme 7. C-H Activation of pyridine derivatives

(2) Metallocenes

We manufacture a certain metallocene (Figure 6), which is a catalyst of olefin polymerization, in multiple kg scale. In 2007, as a new facility for filtering, drying and packing organometallic compounds is introduced, 1T scale production will be started.

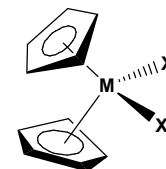


Figure 6



2. Cross-Coupling Reactions

We use our organometallic compounds in the reactions of transition metal-catalyzed cross-coupling reactions. For example, Grignard reagents are used in Kumada coupling and organoboron compounds in Suzuki-Miyaura coupling. We also use Sonogashira coupling and Pd-catalyzed amination for the syntheses of OLED.

(1) Pd/C-Catalyzed C-C Bond Formations

We found that Pd/C catalyzed the Suzuki-Miyaura coupling and the Sonogashira coupling²⁾. The main advantages of these processes are as follows. The palladium charcoal containing water is safe to handle and easy to remove from the reaction mixture by simple filtration. The recovered palladium charcoal can be purified and reused as palladium metal. In case we carry out Suzuki-Miyaura coupling utilizing Pd/C, we can obtain less-colored crude products as shown in Figure 7. This difference is due to palladium contamination. When we measured the Pd content in the recovered Pd/C, we found that 80% of the Pd in the original Pd/C was recovered.



Figure 7. Crude products produced by Pd/C (left) and by Pd(OAc)₂ (right)

1) Suzuki-Miyaura Coupling

There are two types of Pd/C, which differ with regard to the degree of the reduction of palladium. One has a high degree of palladium reduction [Pd(0)/C]. The other has a low degree of palladium reduction [Pd(II)/C]. In the reactions of halopyridines and haloquinolines (Table 1), the product was obtained in a high yield in the presence of Pd(II)/C with PPh₃³⁾.

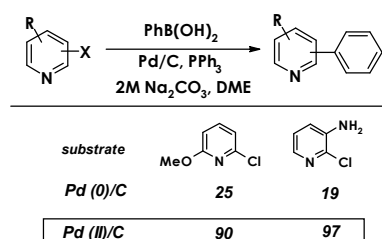
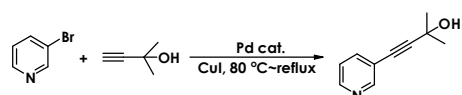


Table 1.

2) Sonogashira Coupling

In the Sonogashira coupling of bromopyridine in the presence of PdCl₂(PPh₃)₄ in the air, the dimerization of the acetylenic compound took place to give the desired product in 34% yield. However, the Pd/C-catalyzed reaction improved the yield remarkably even in the aerobic conditions. Water-DME can be used as a solvent system (Table 2)⁴⁾.



Run	Pd cat.	solvent	Time (h)	Yield (%)
1	PdCl ₂ (PPh ₃) ₄	iPr ₂ NH	1	34
2	Pd/C+ PPh ₃	DME/H ₂ O/K ₂ CO ₃	2	87
3	Pd/C+ PPh ₃	iPr ₂ NH	3	93

Table 2.

(2) Hydroxyapatite-Supported Pd-Catalyzed Suzuki-Miyaura Coupling

We have jointly applied for the patent for the hydroxyapatite-supported Pd-catalyzed Suzuki-Miyaura Coupling developed by Kaneda at Osaka University (Figure 3). Hydroxyapatites, the main component of bones and teeth, are synthesized from $\text{Ca}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$ and $(\text{NH}_4)_2\text{HPO}_4$ in the lab. When the Ca/P ratio is 1.5, nonstoichiometric Ca-deficient hydroxyapatite $\text{Ca}_9(\text{HPO}_4)(\text{PO}_4)_5(\text{OH})$ is produced. Pd(II) phosphate complex can be generated in a Ca-deficient site by the treatment of $\text{Ca}_9(\text{HPO}_4)(\text{PO}_4)_5(\text{OH})$ with $\text{PdCl}_2(\text{PhCN})_2$, which acts as an efficient catalyst for the Suzuki-Miyaura coupling⁵.

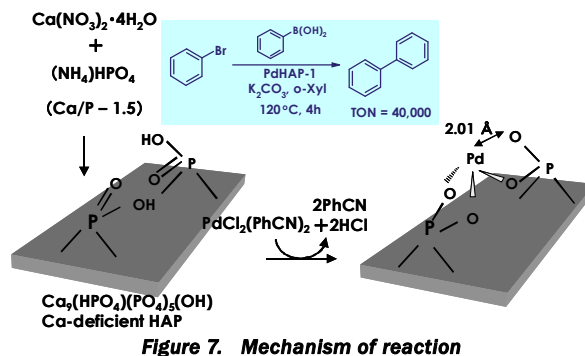
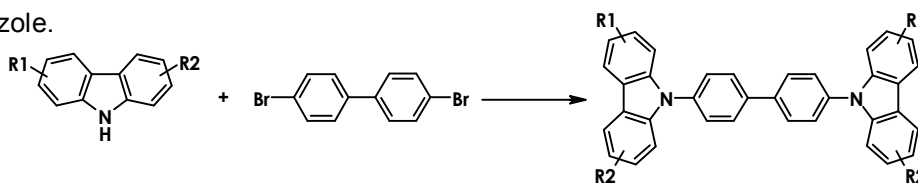


Figure 7. Mechanism of reaction

(3) Pd-Catalyzed Amination

We synthesize samples of OLED materials. In particular, bis(alkylcabazole-9-yl)biphenyl derivatives are synthesized by Pd-catalyzed coupling of dibromobiphenyl with carbazole. This amination proceeds at a lower temperature and gives a higher yield, compared to the Ullmann reaction of diiodobiphenyl and carbazole.



Scheme 8. Example of palladium-catalyzed amination

(4) References

- 1) P2003-160586A; P2004-189705A; P2004-238298A; P2004-238341A; P2006-096714.
- 2) Nishida, M. *Advanced Synthesis & Catalysis* **2004**, 346, 1660-1665; P2004-238298A; P2005-298432A.
- 3) Tagata, T. & Nishida, M. *J. Org. Chem.* **2003**, 68, 9412-9415; P2003-128641A; 2003-300940A; P2004-083530A; P2005-298432A; P2006-219395A.
- 4) P2001-342176A.
- 5) Kaneda, et al., *J. Am. Chem. Soc.* **2002**, 124 (39), 11572-11573; Kaneda, et al., *New Journal of Chemistry* **2005**, 29 (9), 1174-1181; P2004-57898A.



Koei's New Facilities

Outline of New Pilot Plant

In 2006 our new pilot plant began working. This five-story structure was designed for API production.

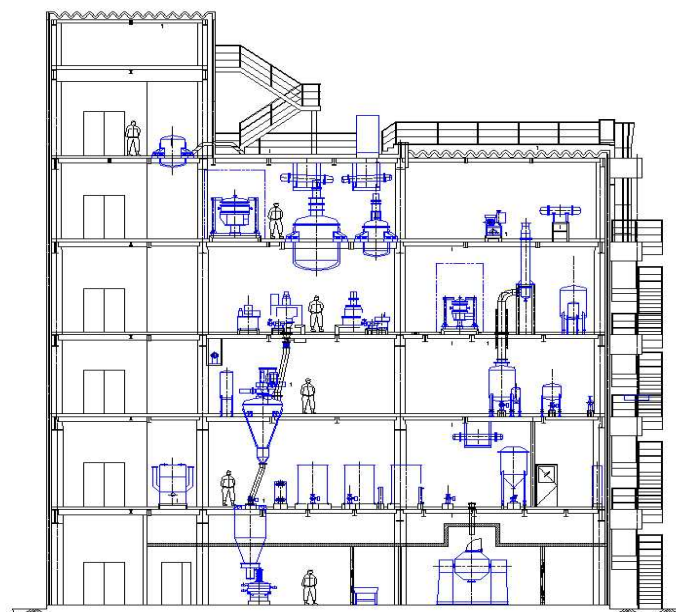


Figure 8. Whole view of New Pilot Plant

Koei's Cryogenic Synthesizing Reactor

As a powerful equipment to realize manufacturing various functional chemicals, we introduced a 20L cryogenic synthesizing reactor. This reactor has a remote controlling system to bring effective operation with safety in wide range temperatures from -70°C to 150°C .

In case that using the air-sensitive reagents; i.e. alkyllithiums, Grignard reagents, inert gas keeps



Figure 9. Glass reactor

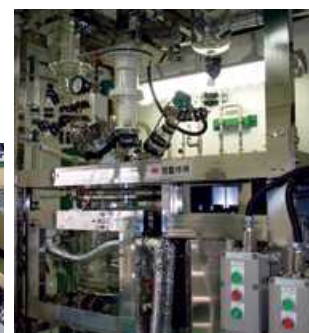


Figure 10. Front view