

Carbonylation using carbon monoxide: Novasep's shortcut to complex structures

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The rising complexity of active pharmaceutical ingredients (APIs), combined with the need to curb costs, calls for creative solutions. The use of highly reactive reagents in the synthesis routes offers an important extension of the existing traditional chemical processes for pharmaceutical, agrochemical and specialty chemical companies. These potentially hazardous reactions often substantially shorten the synthesis routes while at the same time affording highly selective individual reactions.

However, such high reactivity also involves a certain hazard potential, leading to certain reservations regarding their use, in spite of the technical and commercial benefits they offer. But, when handled and controlled by experts, hazardous chemistry represents an indispensable supplement to synthesis technology.

Novasep ranks among the world's leading experts in the handling of hazardous reagents for the synthesis of active ingredients and advanced intermediates for its life science and specialty chemistry customers. Novasep's Leverkusen site, founded by Alfred Nobel in 1871 is the group's competence center for hazardous chemistry.

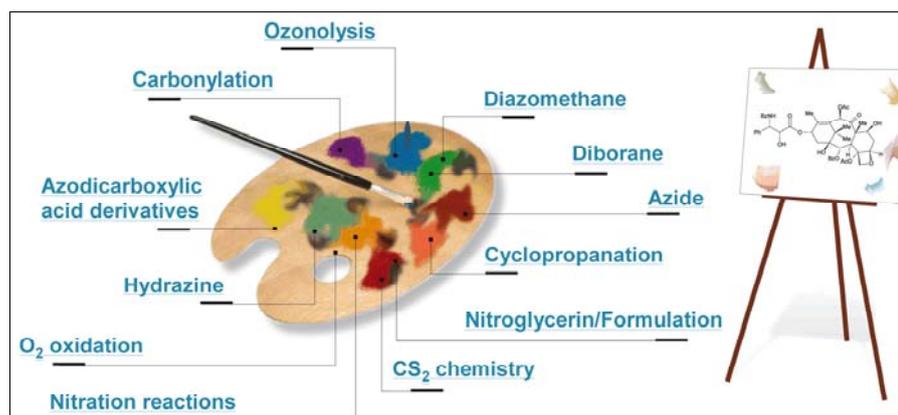


Fig. 1: Novasep's unique palette of energetic reactions

Novasep masters a unique palette of energetic reactions (Fig. 1) that helps to considerably reduce the number of steps of a synthesis as well as the amount of impurities and by-products generated, leading to cost-effective, short and elegant synthetic routes.



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Carbonylation reactions using carbon monoxide

Carbon monoxide can be used to transform a wide range of substrates. In the process, the carbon chain is extended and an attractive functionality, a carbonyl group, is added. In many cases, instead of a multi-step synthesis, the targeted product can be obtained in a single selective catalytic step, resulting in a substantially higher overall yield.^[1a] This is particularly important for long synthesis sequences.

In a recent project, Novasep succeeded in shortening by two steps the traditional synthesis route via the Grignard compound using the carbonylation of an aromatic compound (Fig. 2).

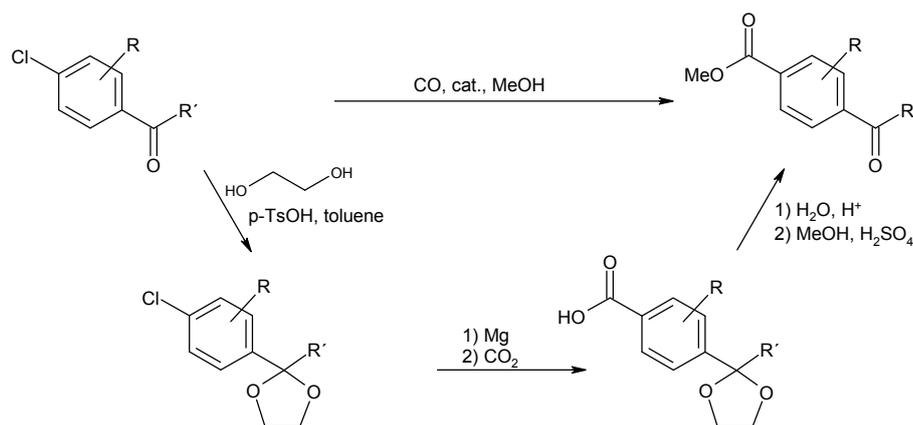


Fig. 2: Recent synthesis performed by Novasep: Shortening the reaction route with carbonylation using carbon monoxide

In the traditional variant, first the carbonyl group has to be protected otherwise it would react under the conditions prevailing during the subsequent Grignard synthesis. In a second step, the realization of the Grignard compound and the subsequent reaction with carbon dioxide follow. Finally, in a third synthesis step, the protection group is removed and the acid esterified.

This route is shortened to one single synthesis step using direct carbonylation and esterification. For the production of 100 kg of the carbonyl compound this means:

- saving around 4,000 liters of solvents;
- saving the equivalent amount of waste solvent and the resulting disposal costs;
- reducing by around 90 kg the additional raw materials required (such as ethylene glycol, p-toluenesulfonic acid, magnesium, etc.);
- reducing the reactor occupancy time by around 48 hours including the related costs for manpower;
- reducing time and the costs incurred in cleaning the reactors between the different production steps;
- reducing energy costs;
- reducing costs in the analytical monitoring of reaction steps and intermediate products.

Even more important in this context is the reduction of the volume of the precursor by 126 kg, which means savings up to 52% as compared to carbonylation with carbon dioxide.

Further cost drivers are the specific tasks that need to be performed for each reaction step ahead of a production campaign. These can be cut down by carbonylation. The development of two synthesis steps can be removed together with the accompanying analytical development and safety evaluations (e.g. only 1 instead of 3 reaction calorimetry analyses).

Moreover, the applications for the 2 steps required pursuant to REACH (Registration, Evaluation, Authorization and Restriction of Chemical Substances), the related fees and time expenditure can be saved.

If a molecule is to be produced under cGMP standards (good manufacturing practice), each production step requires the mandatory qualification of the process in the lab, the validation of the process in production and of most analytical methods (for isolated intermediates and critical process steps). Consequently, any reduction of synthesis steps directly saves the corresponding time of intensive GMP work.

Last but not least, mention should be made that the product generated via the shorter synthesis route, i.e. the direct carbonylation, can be supplied to the customers faster and in appreciably higher amounts in relation to the raw material provided.

This example clearly demonstrates that carbonylation with carbon monoxide represents an attractive and cost-efficient synthesis alternative for customers of the life science industries.

Fig. 3 shows a selection of some key carbonylation reactions.

A well-known reaction in this context is the Pauson-Khand reaction where the 2+2+1 cycloaddition of an alkene, alkyne and carbon monoxide in the presence of a $\text{Co}(\text{CO})_8$ catalyst yields substituted cyclopentenones (Fig. 3, a). Recent studies focus on the stereospecific control of this reaction type by adjusting the catalyst design and using additives.^[2]

In the carbonylation of aromatics with carbon monoxide both aryl^[3] and benzylic^[4] leaving groups can be substituted by CO. Depending on the consecutive reaction of nucleophiles either acids, esters, amides or ketones can be obtained (Figs. 3, b and c). In this context, it is worth noting that the reactivity between iodine and chlorine drops appreciably when substituting a halogen. By contrast, a heteroatom in the aromatic substance, e.g. in the case of pyridines, will distinctly accelerate a substitution in the 2- and 4-position so that carbonylation with carbon monoxide is facilitated even in the case of chloroaromatic compounds. Moreover, a substrate-specific catalyst design and specific reaction conditions will allow carbonylation of specific substituents of the reactant, even in the presence of other reactive positions on the molecule. It is thus possible to cause *meta*-iodo benzyl bromide to react with carbon monoxide to give *meta*-iodobenzoic acid. For this reaction, a bimetallic catalyst made of palladium and rhodium is used. In this reaction, the normally highly reactive aryl iodine is not substituted.^[4a]

Also α -halogen ketones can be reacted with CO ^[5] (Fig. 3, d). The β -keto esters that form have proven to be useful intermediates for the synthesis of heterocycles.

The stereospecific synthesis of β -hydroxy esters by the ring-opening reaction of terminal chiral epoxides with carbon monoxide^[6] (Fig. 3, e) was used by AstraZeneca for the synthesis of Rosuvastatin, a drug to reduce cholesterol levels^[6] (Fig. 4).

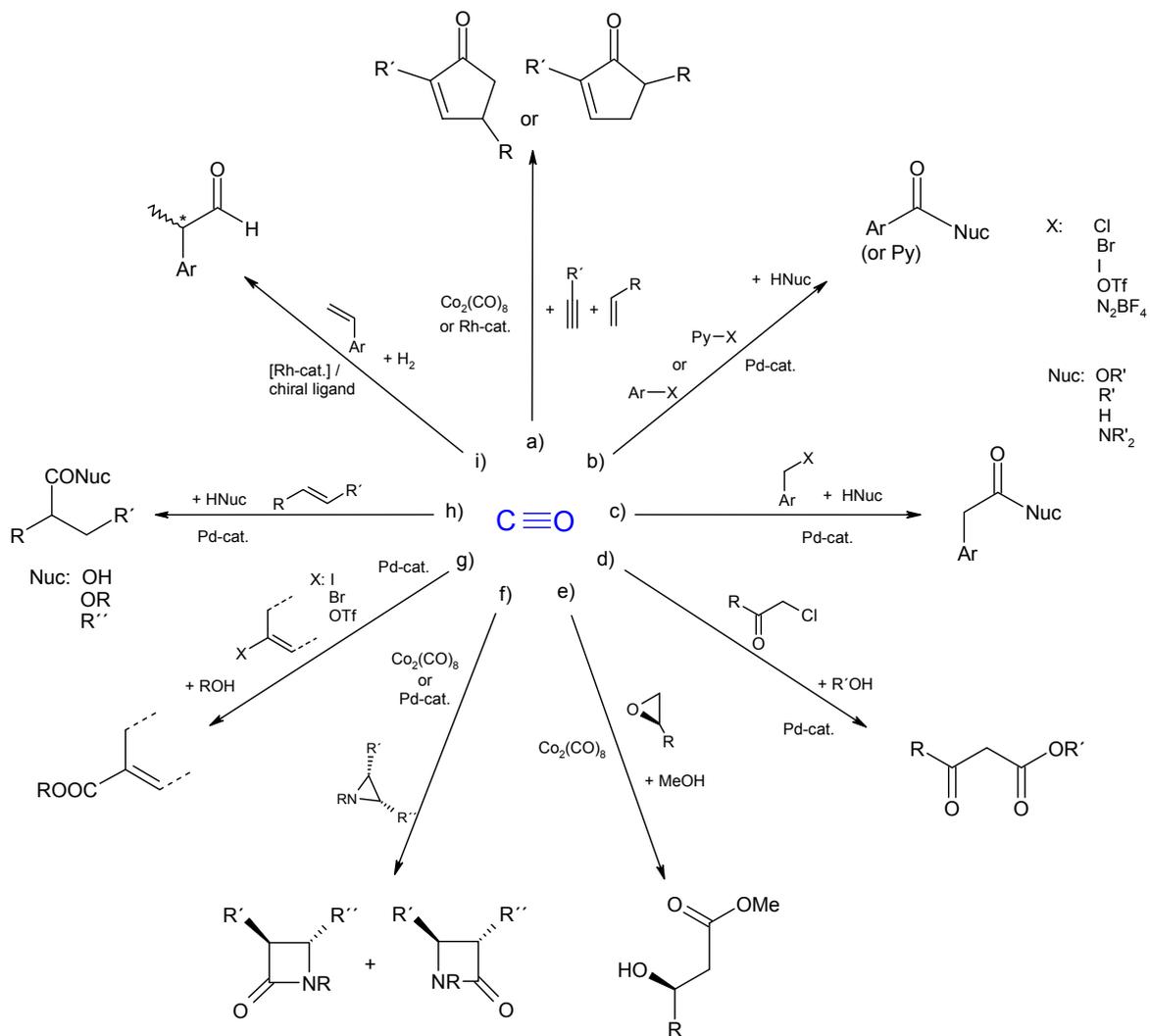


Fig. 3: Carbonylation reactions.^[1-9]

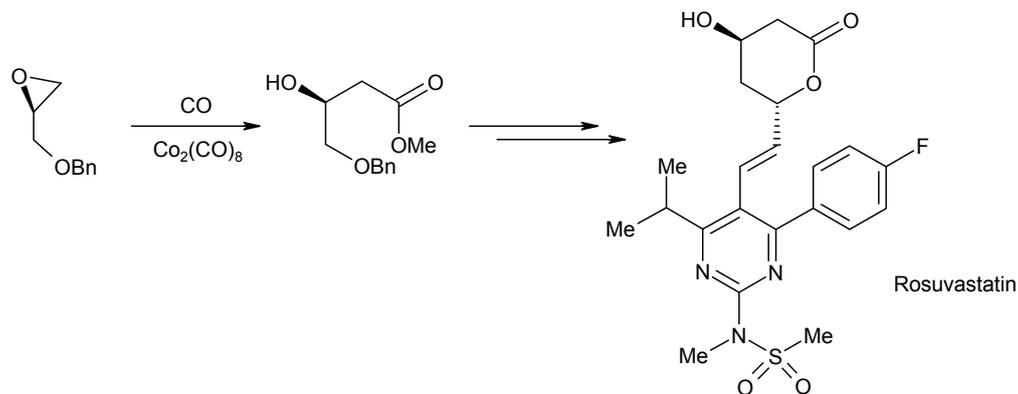


Fig. 4: Detail of the synthesis to generate Rosuvastatin

Unlike the carbonylation of terminal epoxides which takes place by opening the epoxide ring, the synthesis of aziridines with carbon monoxide does not involve ring opening but a ring extension^[7] (Fig. 3, f). This has proven to be a useful reaction to generate β -lactam rings for carbapenem antibiotics (e.g. (+)-Thienamycin or (+)-PS-5).^[7]

Vinyl iodides, bromides and triflates can also be substituted using CO^[8, 9] (Fig. 3, g). This reaction is used, for example, in the synthesis of Triptolide (immunosuppressant drug used for cancer treatment) in order to generate a 5-membered lactone ring^[9] (Fig. 5) by substituting the triflate group, followed by a cyclization involving a reaction with a β -stable hydroxy function.

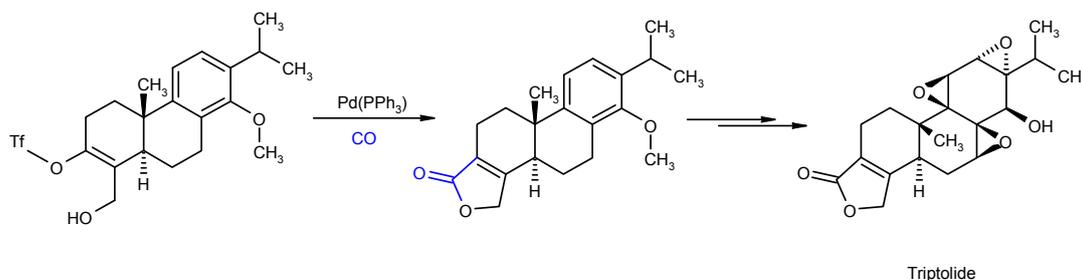


Fig. 5: Detail from the synthesis of Triptolide

Multiple bonds are not only easy to substitute in the presence of a leaving group but, depending on the reaction conditions, they can easily react with the addition of carbon monoxide. Depending on the catalyst used, the reaction conditions and the co-reagent, they afford acids, esters, ketones (Fig. 3, h) or aldehydes (Fig. 3, i; hydroformylation).^[1]

In this context, the possibility of a cascade reaction (or domino reaction) must be mentioned where more than one of the afore-mentioned reactions can occur before isolating an intermediate (Fig. 6). In addition to the savings which result in terms of materials and energy in particular, a substantial amount of time can be saved.^[10]

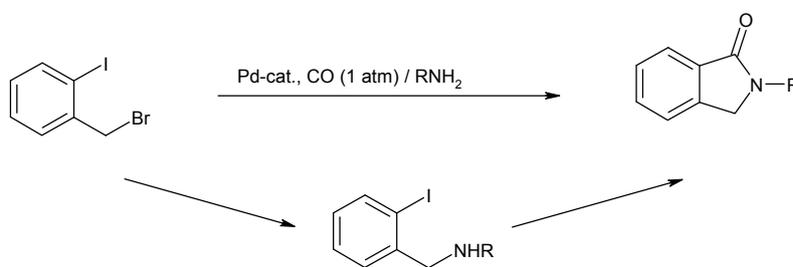


Fig. 6: Palladium-catalyzed cascade reaction (substitution, carbonylation, amination)^[10 a)]

One important aspect in the reaction scale-up, from laboratory to commercial-scale production, is the pressure required. Arylic, benzylic and vinylic halogens or halogen analogs can frequently be substituted at a 1 bar pressure. A carbon monoxide pressure of 1 bar is also sufficient for a ring-opening reaction of terminal epoxides.

Generally, cobalt-catalyzed reactions mostly require a higher pressure than those involving rhodium or palladium catalysts. *Trans*-aziridines can be reacted to form *cis*-lactams in the presence of a cobalt catalyst at 34 bar while the reaction of *trans*-aziridines to *trans*-lactams in vinylic position on a palladium catalyst only requires a carbon monoxide pressure of 1 bar.^[19] If double bonds are added, it was shown that the carbon monoxide pressure required depends to a large extent on the substrate, catalyst or further additives. Most reactions take place at elevated pressure but there are

also palladium-phosphine complexes that enable carbonylation at 20 °C with 1 bar carbon monoxide, for example.^[1]

Carbonylation under oxidative conditions

Besides the reactions with carbon monoxide just described (Fig. 3), a series of other promising reactions also exist. In this context, mention should be made of the reactions with carbon monoxide under oxidative conditions which mostly occur in the presence of a palladium catalyst^[11] (Fig. 7).

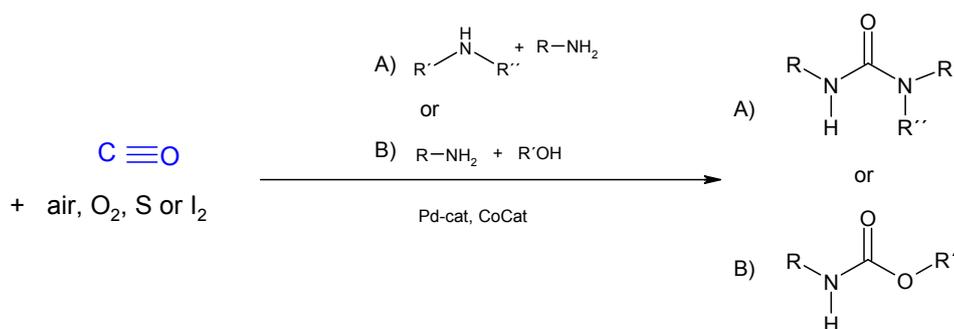


Fig. 7: Oxidative carbonylation^[12]

In this context, amines can be reacted with carbon monoxide under oxidative conditions using a palladium catalyst, for example. Depending on the consecutively reacting nucleophile, symmetrical^[12] or selectively also asymmetrical^[12, 13] urea derivatives can be generated, that constitute valuable functionalities in various agrochemical and also in some active pharmaceutical ingredients^[14, 15] (HIV inhibitors, e.g. Ritonavir, Emtricitabine or DMP-323).

So far, urea derivatives had been synthesized by reaction of amines with isocyanates, which in turn were generated from phosgene or phosgene derivatives, and a second amine. The direct reaction of carbon monoxide with the corresponding amines to yield urea derivatives thus allows saving both, the synthesis with isocyanates and the previous phosgene synthesis as well as the related production time and waste streams. It is atom-economical and more cost-efficient than the traditional, longer synthesis routes. Moreover the second amine can be replaced with an alcohol to afford cyclic or open-chain carbamates^[12a)] (Fig. 7).

The challenge in this type of reactions lies in the handling of the carbon monoxide / oxygen mix required for the reaction. In this context it is imperative that the reaction conditions be selected so that the synthesis is not conducted in an explosion-critical pressure, temperature and gas composition range.

Hazards involved in the handling of carbon monoxide^[16, 17]

Special protective measures have to be taken to handle carbon monoxide. It is a highly flammable, toxic and teratogenic gas which, in addition, is colorless, tasteless and odorless. Carbon monoxide leakage from reactors or piping cannot be detected without special equipment. With excessive exposure no reactions or only very unspecific reactions can be observed before very serious symptoms set in. The effect of carbon monoxide on humans is that it blocks or stops the oxygen intake by the blood because carbon monoxide binds to the iron contained in the hemoglobin; this, in the worst case, will lead to asphyxiation. Furthermore, carbon monoxide can form explosive mixes with oxygen (explosion limits: 12.5 - 74 vol.-%) (Fig. 8). For the above reasons any commercial scale reactions with CO should only be handled by experienced specialists such as Novasep's.

Carbon monoxide ^[17]		
- CAS No.	630-08-0	
- Colorless, odorless and tasteless gas (no warning mechanism in case of gas leakage)		
- Teratogenic		
- AVI:	30 ml/m ³ 33 mg/m ³	
- Combinations of concentration and exposure time that are considered potentially lethal for humans ^[16] :		
	40,000 ppm·2 min	(4 vol.-%)
	16,000 ppm·5 min	(1.6 vol.-%)
	8,000 ppm·10 min	(0.8 vol.-%)
	3,000 ppm·30 min	(0.3 vol.-%)
	1,500 ppm·60 min	(0.15 vol.-%)
- Ignition temperature:	620 °C	
- Explosion limits (vol.-%)		
	in air:	12.5 - 74
	in O ₂ at standard pressure, 18 °C ^[12b] :	16.7 - 93.5
	in O ₂ at standard pressure, 200 °C ^[12b] :	14.2 - 95.3
- Oxidation enthalpy:	- 283.17 kJ/mol	

Fig. 8: Physical and chemical data of carbon monoxide

Novasep's Leverkusen facility: Competence Center for Hazardous Chemistry

Novasep's Leverkusen facility is precisely specialized in handling reactions such as these, that would pose safety problems in standard chemical plants. Owing to its history as an explosives-producing plant and the resulting specific infrastructures, coupled with the longstanding expertise of working in the limits of chemical and physical ranges, the site is equipped to handle such hazardous reactions. It has been continuously modernized to cope with and exceed the most stringent quality, safety and environmental regulations (FDA, ISO9001, ISO14001). A stable core of very experienced personnel, long and specific training and a comprehensive system of drastic quality and safety procedures enable us to safely operate hazardous chemistry at all scales.

At the time explosives were produced, a network of underground bunkers for storage and for testing was created. Today, they are used to perform comprehensive safety tests on educts, intermediates and end products, as well as synthesis reactions to ensure a maximum level of safety in production. As a rule, the specific explosion conditions in potentially explosive reactions are determined before transferring the process to its commercial scale. A large number of stability analyses can be performed on site, therefore close to the R&D and production facilities. DSC (Differential Scanning Calorimetry), TGA (Thermal Gravimetric Analysis), SEDEX (Sensitive Detector of Exothermic Processes), Koenen test and many other analyses to determine the dust explosion risk, form part of the standard safety testing capability of Novasep.

Since the mid-2008, the R&D department also features an autoclave facility used to optimize reactions that is installed in a separate building. Reactions involving pressures of up to 60 bar are optimized and adapted to the production facilities available at the site where pressures up to 10 bar can be achieved.

A pilot facility annexed to the R&D department comprising 4 reactors with a volume in the range of 100-500 liters is the link to the technical scale and production scale operations.

This is where scale-up tests and small-scale productions can be realized under cGMP conditions if required. Like the subsequent production plants, this pilot facility is suited for pressures of up to 10

bar. The close cooperation between R&D and the production team allows early identification and remedy problems associated with scaling-up.

Currently, the facility offers 10 reactors in one building for non-GMP production with a total volume of approximately 30 m³ as well as 31 reactors in 4 buildings for cGMP production with a total volume of around 110 m³, where reactions with carbon monoxide can be performed. The latest cGMP unit with 3 reactors installed by Novasep in 1999 and extended by 6 reactors is currently being extended by an additional 26 m³. Excess carbon monoxide from all these units will soon be treated by combustion. This combustion facility has been in place for years allowing for the cost-efficient and environmentally friendly disposal of effluents and solvents.

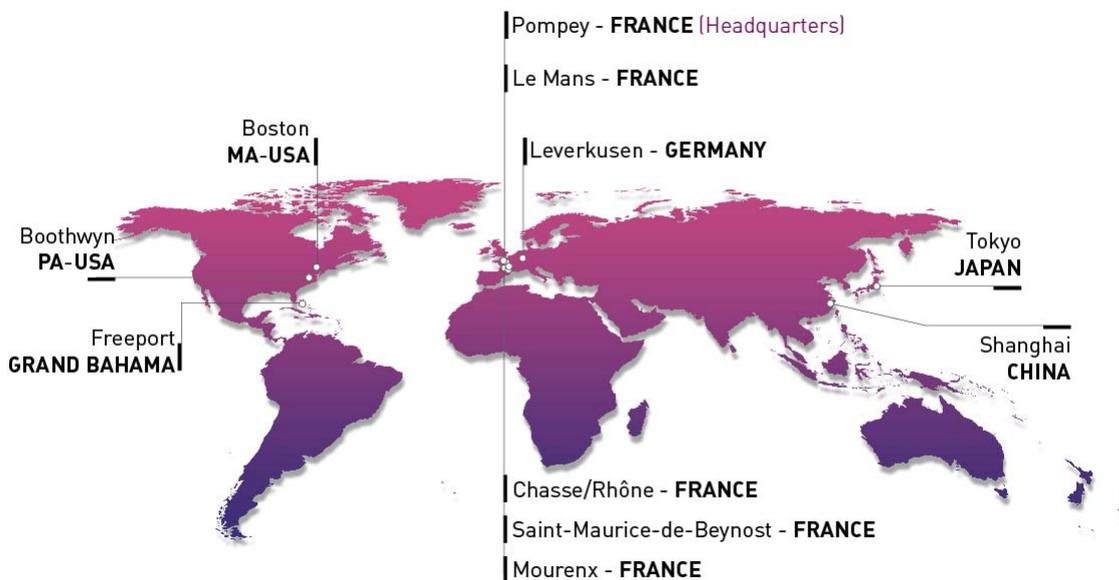
The plant is located on a 80 hectares land, 10% of which is used for the production plants and surrounded by a forest. Wide spacing between the production buildings allows operating all plants in complete isolation from each other. Carbonylation reactions can be performed in the most diverse as well as redundant plants with production volumes in the range of grams to tons.

Conclusion

Rising cost pressure on all markets, in particular in the pharmaceuticals industry, call for a selection of the most efficient production methods. In this framework, the synthesis routes via hazardous reactions frequently offer clear advantages over the standard routes. With more than 130 years of experience in the safe handling of hazardous reactions, Novasep is one of the world's leading solution providers in this field. The carbonylation presented here supplements the diborane, diazomethane and ozone reactions introduced at multi-ton scale in prior years, and our much longer experience with large-scale utilization of azide and hydrazine chemistries. With its consistent extension of its technological portfolio, Novasep offers its customers an ever larger range of instruments that open up new and more efficient synthesis routes.

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