Refrigeration Trends in Chiral Synthesis Reactions

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Dr Alan Cheng of **Praxair** argues the case for cryogenic over mechanical cooling systems in chiral chemistry*

The global demand for chiral chemicals is projected to increase by over 13%/year from 2005 to 2012, according to a recent study.[1] This demand is in part fuelled by increasing reliance on optically pure compounds as opposed to using racemic mixtures for the preparation of new APIs.

The importance of evaluating the behaviour of stereoisomers is highlighted in an FDA regulatory document of 2005.[2] As a result of this release, many companies are developing manufacturing processes that produce a finished product comprised of the desired isomeric compound as opposed to a racemic mixture.

This article focuses on ultra-low temperature organic synthesis reactions and the importance of refrigeration design relative to robust performance in the manufacture of optically pure chemical compounds. With proper reaction and system design, low temperature chiral synthesis using suitable reagents can enhance the stereoselectivity and yield of enantiomeric processes while also providing the reliable system performance which is critical to the production of high value pharmaceutical ingredients.

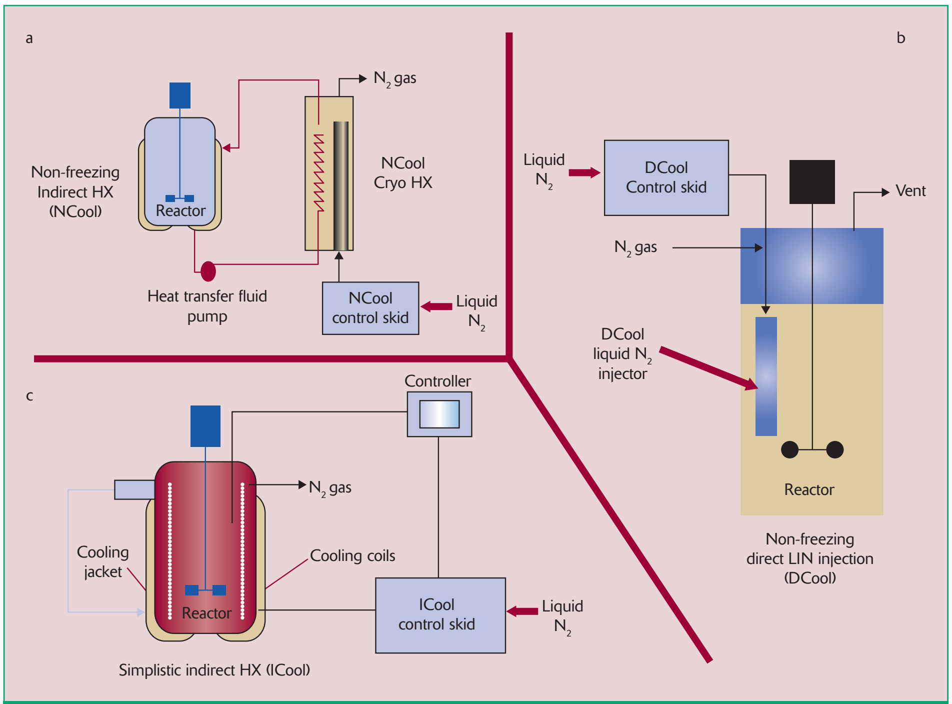

Figure 1 - Praxair's LN2 reactor cooling systems

Reactions using low temperatures

A broad range of chemical reactions either use low temperatures steps to obtain the desired stereoisomer or have a need to control reaction exotherms or heat releases adequately. A few of the more common reactions and unit operations exhibiting these requirements are:

- Grignard synthesis of alkanes, alcohols & carboxylic acids
- Wittig reactions
- Catalytic reactions with n-butyl lithium
- Birch reduction in hormone synthesis
- Crystallisation
- Purification
- Low temperature condensation

For each of these processes, tight control of the kinematic and thermal conditions associated with the reaction will influence the outcome and productivity.[3]

Refrigeration requirements

The careful selection and design of the refrigeration system is vital to establishing a robust manufacturing process. There are two key considerations in providing refrigeration to a process: the refrigeration temperature required and the maximum cooling rate associated with the process.

The refrigeration temperature and cooling profile associated with the chemical reaction in many cases dictate the type of refrigeration system employed. Commercially available refrigeration technologies possess different thermodynamic limitations in terms of operating temperature, cooling rate capability, thermal efficiency and cooling power. The peak and turn-down cooling capacities for the selected refrigeration system are determined by the cooling load profile over time.

Some forms of chiral synthesis are unique from the refrigeration point of view. Not only do the reactions require ultra-low temperatures (-50 to -120°C) but also, because the load is extremely variable, they require significant turn down capabilities. Both of these requirements impact the design and selection of the refrigeration for the process.

There are two dominant choices in refrigeration available when performing low temperature processing. The first, which is gaining favour, involves using liquid or gaseous nitrogen and a specially designed injector or heat exchanger to provide the required refrigeration. The second involves the use of a mechanical refrigeration system to achieve the required cooling. These systems are explained below.

Cryogenic systems

Cryogenic refrigeration systems typically fall into one of three categories (Figure 1a-c). These variously use the cryogenic liquid or gaseous nitrogen for direct contact cooling of the reactants or fluids, employ indirect contact cooling in which the cryogen indirectly cools a heat transfer fluid which in turn cools the reactants, or (the least sophisticated method) involve injecting the cryogen directly into the internal coils or jacket of the reactor.

Interest in cryogenic cooling is expanding as a result of the broader operating requirements for reactions, as well as the improved operating economics associated with cryogenic refrigerated systems. Modern systems provide up to 98% liquid nitrogen thermal efficiency, as they use both the latent heat of vapourisation for the liquid nitrogen and the sensible heat of the gaseous nitrogen.

This can reduce nitrogen consumption and generate cost savings of up to 35% versus older style, less efficient cryogenic designs.[3] Additionally, as the systems have minimal moving parts, they also provide high reliability and unit availability to the end user, with significantly reduced maintenance and repair (M&R) performance interruptions or expenses as opposed to the M&R associated with the more complex mechanical systems.

In the past, companies adopting cryogenic refrigeration tended to experience freezing and ice build-up, which negatively impacted system availability and production duration. This situation has been rectified in newer units using the non-freezing direct or indirect contact cooling design similar to those

Table 1 - Properties of various low temperature heat transfer fluids

HTF	Density (kg/m³) at -80˚C	Viscosity at -80˚C (cps)	Flash point (˚C)	Reported freezing point (˚C)	Boiling point (˚C)	Temp. at which kinematic visc. >10 cSt (˚C)
d-Limonene	NA	NA	43	-96	176	-80
Dynalene HF	870	60	>60	<-112	186	NA
Dynalene MV	>920	10	53	-118	176-179	NA
Ethanol	810	6.3 at -50˚C	12	-117	78	-60
Novec HFE 7000	1700	1.2	Not Flammable	-122	34	<-110
Novec HFE 7100	1800	1.9	Not Flammable	-135	61	<-95
Methanol	867	6.1	12	-98	65	-90
Polydimethylsiloxane	965 at 25°C	NA	>110	-50	<200	NA
Syltherm XLT	968	33.7	42	-111	NA	NA

Source: Manufacturers' websites, MSDS publications and public sources

illustrated in Figures 1a and 1b respectively. Systems similar to 1c are still widely used but are subject to non-homogeneous cooling within the reactor and heightened risk of icing on the internal cooling coils or jacket walls.

Typical direct contact cooling systems are available with refrigeration capacities of up to 1,000,000 Btu/hour or 283 kW of cooling, depending on the operating temperatures. These systems feature stainless steel, Hastelloy and other corrosion-resistant alloy injectors with proprietary non-freezing nozzles and a PLC-controlled flow control skid which delivers carefully controlled amounts of the cryogenic fluid to the reactor in response to output signals from thermocouples located within the reactor.

For this system, a reactor can be cooled rapidly to any cryogenic temperature. The lowest temperature limit is the boiling point of cryogenic nitrogen at -196°C. As such, reaction temperatures are chosen to meet the needs of the specific reaction while also ensuring that the reactants or solvents are not frozen solid and the temperature is kept within the operating range for the given reactor. Thermal efficiencies of up to 98% can be obtained with this technology.

Alternatively, indirect contact cooling systems can provide comparable refrigeration capacities, depending on the reactor temperatures. These systems provide on-demand cooling capabilities using the refrigeration available from gaseous and liquid nitrogen to control and remove the heat from the recirculating heat transfer fluids. Current leading system designs offer up to 95% thermal utilisation efficiency in addition to the non-freezing design.

Figure 2 shows a typical indirect contact cooling systems. The cryogenic nitrogen is distributed from the storage tank to the heat exchanger which in turn provides on demand cooling to the recirculating heat-transfer fluid. Advanced PLC controls help adjust the nitrogen feed rate to offset the heat gain in the circulating heat transfer fluid.

This allows very high thermal utilisation efficiency and tight process controls, while meeting the cooling needs specific to each phase of the reaction. Additionally, appropriately designed systems enable the use of lower pressure nitrogen which increases the enthalpy available for the cooling process increasing nitrogen utilisation efficiency.

Another important consideration when designing an indirect contact cooling system involves specifying the lowest required temperature for the given chemical reaction. Whereas a mechanical refrigeration system may limit the lowest achievable temperature, a cryogenic system's temperature is only limited by the design characteristics of the reactor or the properties of the heat transfer fluid (HTF), not by the temperatures associated with the cryogen.

Table 1 provides information on properties associated with a variety of low temperature heat transfer fluids. As noted, HTF selection must consider such properties as the flash and fire point of the fluid, viscosity at both ambient and desired cooling temperatures, and the freezing point and boiling point of the fluid, as each property may impact the suitability of the HTF for a specific synthesis operation.[4,5]

Mechanical systems

In mechanical systems, compressors driven by electric power provide the required refrigeration. Ultra-low temperature mechanical refrigeration systems generally have a multi-stage, cascading design, which uses two or more refrigerants with descending boiling points, a vapour compressor, a condenser and several heat exchangers.[4]

Necessary auxiliary systems include a cooling water loop, an oil lubrication system and power

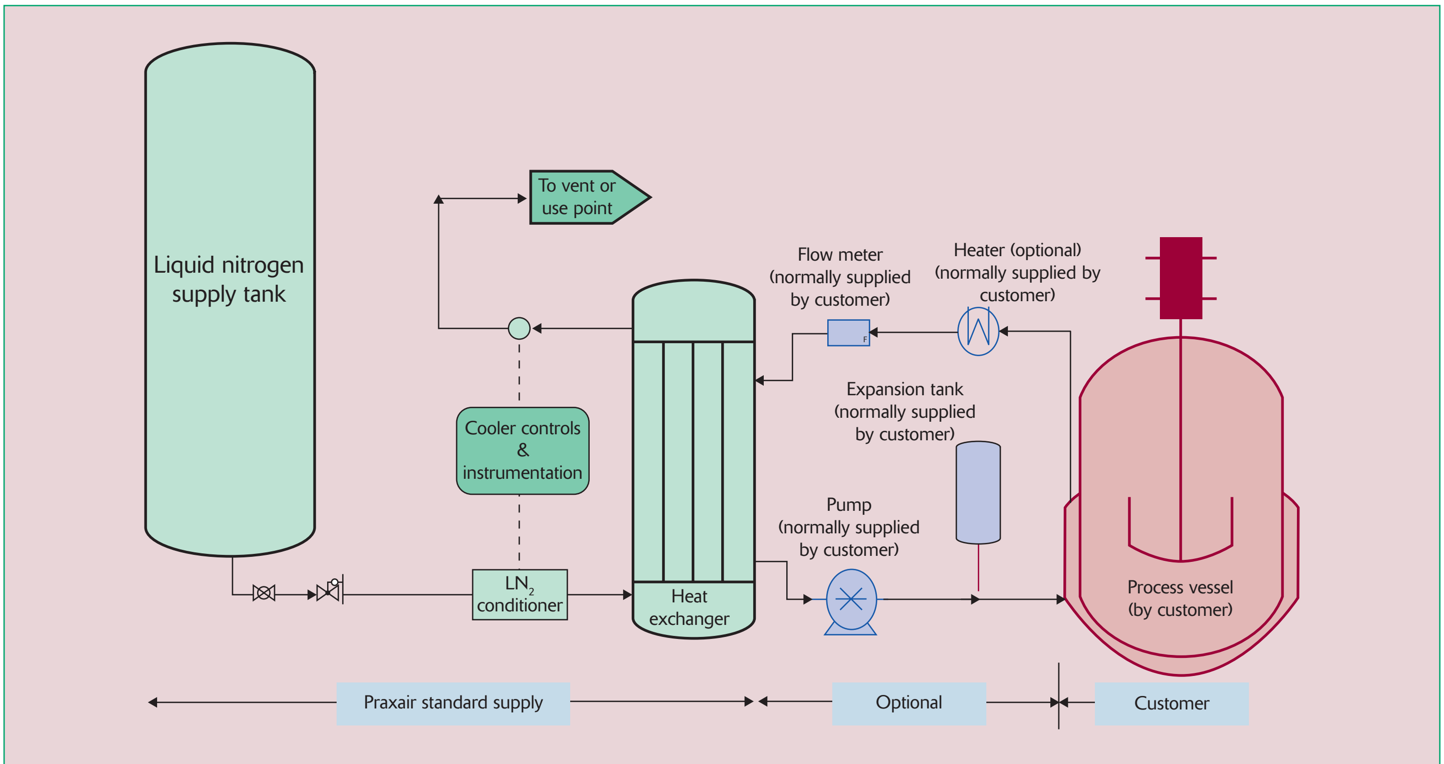

Figure 2 - Typical scope of NCool cryogenic indirect contact cooling system

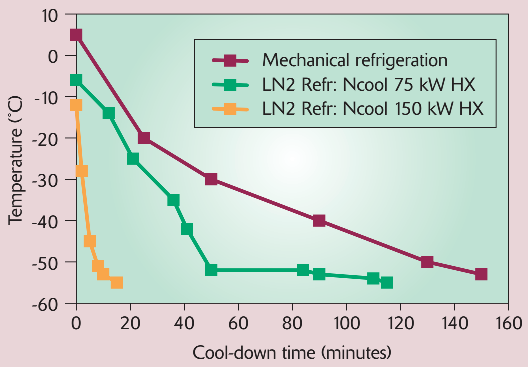

Figure 3 - Cryogenic versus mechanical cooling capabilities

infrastructure (including an extra supply and backup system) to support the significant power demand associated with the compressors. Generally, the rotating compression equipment is comprised of either reciprocating or screw type compressors. Recently, screw compressors have gained favour, due to their greater reliability.[5,6,7]

The refrigeration is obtained by using appropriately selected refrigerants, such as R-23, R-404a, R-507 and R-508b (an azeotropic mixture of R-23 and R-116).[4] The refrigerants are first vapour-compressed, then condensed, adiabatically expanded and evaporated in the heat exchanger to cool the HTF. Refrigerants are typically comprised of multiple component mixtures of hydrofluorocarbons (HFCs), which are often toxic or flammable.

Mechanical refrigeration systems are generally self-contained and require a large footprint, due to the design considerations associated with compressor capacity and heat exchanger requirements. In general, due to the rigorous refrigeration cycle, ultra-low temperature mechanical refrigeration systems are quite complex and require significant maintenance throughout the useful life cycle of the equipment.

Their cooling rates are also limited, since they rely on indirect heat transfer and use refrigerants which themselves have to be cooled (system latency). The cooling capacity, cooling rate and achievable temperature range of mechanical refrigeration systems depends on the system design, selection of refrigerants and equipment sizing

Comparison

Operating temperatures below -50°C negatively impact the performance, efficiency, and reliability of mechanical systems. However, such operating temperatures have no impact on cryogenic systems driven by liquid nitrogen (which has a normal boiling point of -196°C). The cooling rate and efficiency of a mechanical compressor-based system starts to deteriorate at below -20°C.[6,8]

Figure 3 shows the typical cool-down profile of mechanical compressors versus cryogenic heat exchangers when employed as part of a lyophilisation process. As illustrated, cryogenic systems are capable of providing a rapid, sustained cool-down rate throughout the entire ultra-low temperature range. Mechanical refrigeration systems on the other hand, cannot maintain their initial rate throughout the entire cooling process.

Cryogenic systems have reliably maintained tightly controlled cool-down rates of up to 5°C/minute for the duration of the cooling portion of a synthesis reaction. This rapid cooling capability is especially critical when dealing with highly exothermic reactions where insufficient cooling can lead to the risk of fire or explosion.

In addition to the considerations mentioned above, the refrigeration system must also provide favourable economics. In the advent of rising power costs and mounting environmental limits on the use of refrigerants such as CHCs, CFCs, etc., cryogenic systems not only reduce or eliminate reliance on such refrigerants, they also represent a cost-effective alternative to mechanical refrigeration systems.

As illustrated in Table 2, the capital and operating costs, including the costs associated with auxiliary systems and the maintenance of the refrigeration system, should be considered. In many cases, cryogenic systems prove to be less expensive. Liu drew the same conclusion following many years of experience with mechanical refrigeration systems.[4]

Conclusion

Whether your process requires cryogenic operating temperatures (-50 to -120°C) to provide the proper reaction kinetics to produce the desired chemical intermediates or rapid cooling to control the exotherm associated with the reaction, the cooling system must be capable of reliably providing the cooling at the rates and degree needed for normal and extraordinary operating conditions.

Care must be exercised in selecting the refrigeration design so that your system not only can meet your cooling needs today but also provide operating flexibility to meet the requirements for future product lines that might be produced at your facility. Cryogenic refrigeration can provide the operating flexibility, reliability, competitive costs and control needed for advanced low temperature synthesis reactions.

* - Also contributing were Ranko Bursac, Balazs Hunek and Barb Jordan, all of Praxair

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Table 2 -

Relative Capital Expense	Mechanical	Cryogenic
Refrigeration skid	Comparable	Comparable
Cooling water systems	Moderate	None
Upgrade power	Low	None
LN_2 VJ piping	None	Low
UPS battery	Low	Low
Operating Cost Factors	**Mechanical**	**Cryogenic**
Cooling water/treatment	Low	None
Power	Moderate	Low
Liquid nitrogen	Not applicable	Moderate-High*
M&R parts	Moderate	Low
M&R labour	High	Low

* - Depending on system design and N2 utilisation efficiency

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