

Phase-Transfer Catalysis Communications

PTC Cost Savings: Reduce Excess Expensive Reactants Reduce Excess Hazardous Reactants

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Summary: Phase Transfer Catalysis increases the efficiency of organic chemical reactions so much that it is often possible to significantly reduce the excess reactants used and achieve significant cost savings, enhanced safety/environmental and selectivity. This article will discuss reducing the excess of expensive reducing agents such as borohydride, hazardous nucleophiles such as cyanide, hazardous electrophiles such as phosgene and excess reactants in high dilution systems. Reducing excess reactants is a compelling driving force for using PTC in industry which is sometimes overlooked during initial process development but may well be recognized when cost saving are sought.

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FMC Agricultural Products Signs Cost Savings Agreement with PTC Organics

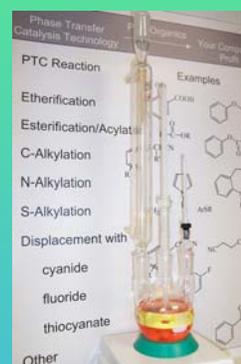
FMC Corporation's Agricultural Products Group entered into a development agreement with PTC Organics to develop and apply phase transfer catalysis technology to enhance existing FMC manufacturing processes. FMC is implementing the "PTC Cost Savings Program" as part of their Agricultural Products Group's Six Sigma Program. FMC is one of the world's leading producers of chemicals and machinery for industry and agriculture, and participates on a worldwide basis in five broad markets: Energy Systems, Food and Transportation Systems, Agricultural Products, Specialty Chemicals and Industrial Chemicals. FMC operates 90 manufacturing facilities and mines in 25 countries. PTC Organics is the only company dedicated exclusively to developing and commercializing advantageous high performance processes for the manufacture of organic chemicals using phase-transfer catalysis. PTC Organics offers the performance-based PTC Cost Savings Program to chemical companies, which have opportunities to achieve cost savings using phase transfer catalysis.

Top 10 PTC Opportunities!
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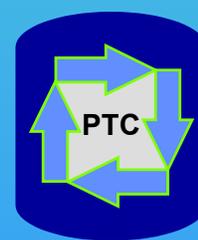
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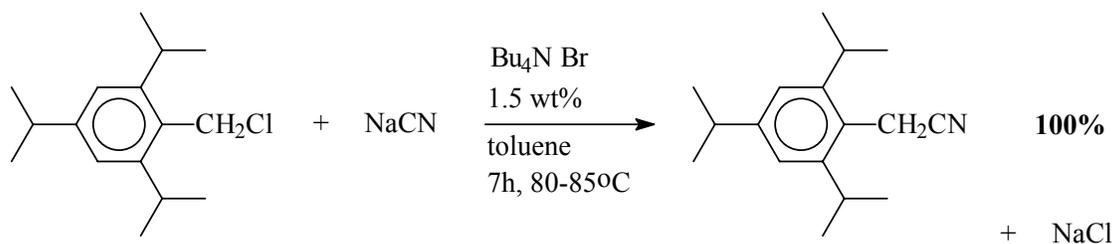
What are the first five cost savings categories of Phase Transfer Catalysis you would probably think of, assuming you are a connoisseur of PTC? You would probably include [1] increasing yield, [2] reducing cycle time, [3] replacing expensive strong base with inexpensive inorganic base, [4] eliminating/reducing/replacing solvent and [5] increasing selectivity. All of these benefits can be attributed in one way or another to the unique ability of PTC systems to control the transfer and reaction of reactants in a two (or more) phase system.

One of the subsets of increasing selectivity in PTC systems, by controlling transfer and reaction of reactants, is to increase efficiency of reactant usage and avoid decomposition of reactants, in particular, that of the reactant that is used in excess. When we start process scouting, we usually push the reaction being screened by using a significant excess of the more expendable reactant, just to be sure. Later, during process optimization, when we become more cost conscious and seek to enhance safety and environmental performance, we eventually take a harder look at minimizing the excess of the excess reactant. During process optimization of PTC processes, we are very often pleasantly surprised to learn that we can obtain very high yields with relatively low excess of reactant. This article will cite examples of PTC systems which use advantageously low excess of reactant. Depending on the system, the benefits of reducing excess reactant usually include one or more of the following: lower reactant cost, increased safety, enhanced environmental performance, and other selectivity benefits.

Reducing Excess Cyanide Achieving Higher Yield, Easier workup and Much Less Waste

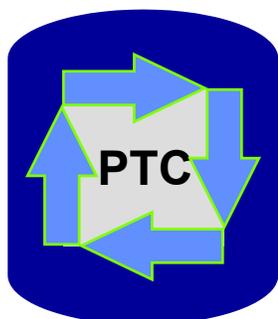
When performing nucleophilic substitutions with cyanide, you basically have two practical choices: [1] use PTC or [2] use polar aprotic solvents like DMSO. This is the choice faced by process chemists at (then) Parke Davis. Both PTC and DMSO act by solubilizing the cyanide in the organic phase in which the substrate is located. A big difference between the two is in the ease of the workup. In the case shown below, Parke Davis chemists not only achieved easier workup, but they also **reduced the cyanide excess by 95%**, **increased yield by 19%**, **reduced aqueous waste by 85%**, replaced the non-recoverable DMSO solvent (containing much water and cyanide) with fully recoverable toluene and eliminated three workup unit operations. PTC is very effective in transferring cyanide to most organic solvents and efficient reaction can be obtained in high yield with very low excess of cyanide. Dozeman, G.; Fiore, P.; Puls, T.; Walker, J. *Org. Proc. Res. Dev.*, **1997**, *1*, 137

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BREAKTHROUGH PROCESS IMPROVEMENT

using Phase Transfer Catalysis



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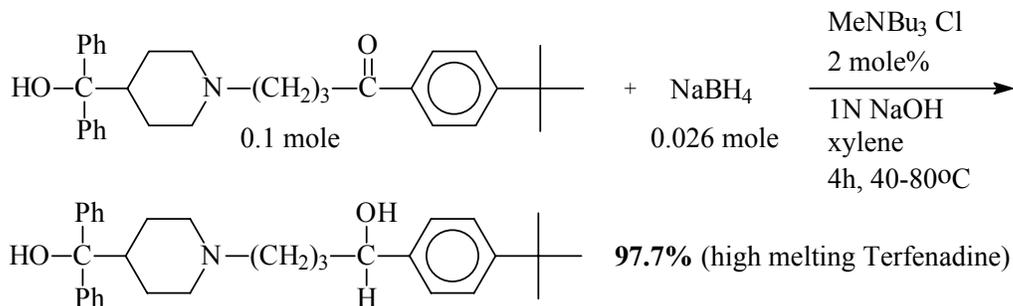
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Reducing Excess Borohydride - Cost Savings & Flexible Solvent Choice

Sodium borohydride is an excellent reducing agent but it is expensive enough to be a concern to your purchasing manager, so it is a good idea to reduce excess borohydride used as much as possible. Borohydride reductions are usually performed on high value added reactants, so typically a significant excess of the borohydride is used to assure complete conversion. Excess borohydride usage of 25-100 mole% is common. Why is so much excess borohydride used? Obviously, the excess borohydride is used to drive the reaction, especially at higher conversion (assume 2nd order kinetics). However, a good deal of the excess borohydride is required because, not surprisingly, the borohydride reacts with the alcohol to form hydrogen gas and alcoholysis products. It turns out that borohydride is actually more stable in the presence of water than in the presence of alcohol. However, many or most organic reactants are not soluble in water, they are soluble in ethanol (hence ethanolic borohydride). The solution is to use PTC to transfer borohydride from water into just about any organic liquid, even into nonpolar solvents such as xylene. Then you may be able to get away with using less borohydride and save some serious money. You can even choose the solvent based on all kinds of benefits, such as using the same solvent you used to prepare the value added reactant and maybe even avoid an isolation of that reactant before the borohydride reduction!

An excellent example of using PTC to reduce excess borohydride while maintaining high yield and achieving an elegant choice of solvent is shown in the following patent. Magni, A. (Gruppo Lepetit) **1989** Eur. Pat. EP 0 346 765.



The original driving force for this patent was to eliminate a solvent exchange before recrystallization. The reduced borohydride excess with high yield was icing on the cake. The reduction of the ketone (Terfenadone) to the alcohol (Terfenadine) proceeds very well with ethanolic borohydride. However, when the product is isolated from ethanol, the wrong polymorph is obtained. As a result, the product must be recrystallized from xylene to obtain the required higher melting polymorph. Dr. Magni reasoned that since PTC can be used to transfer borohydride into almost any organic solvent, then why not simply use PTC with xylene as the solvent? He was right! The reaction was performed in xylene with aqueous borohydride and methyl tributyl ammonium chloride as the catalyst (for easy washing of this catalyst into water – see Halpern, M.; Grinstein, R., *PTC Comm.* **1998**, 4, 17). At the end of the reaction, the xylene solution is concentrated and the desired polymorph is obtained. During process optimization, it became clear that the borohydride could be reduced from 30 mole% to 4 mole% while obtaining a desirable yield of 97.7%. Thus, this patent is an excellent example of process chemistry problem solving to achieve desirable solvent selection, reduced excess of expensive borohydride and high yield.

Frankly, PTC is usually not considered early in borohydride process development because ethanolic borohydride reactions are so easy to perform with high yield and easy workup. In light of the higher stability of borohydride in water and the ability of PTC to transfer borohydride into just about any organic solvent of your choice, PTC should really be seriously considered for borohydride reductions. Reducing the borohydride excess will make your purchasing manager and safety manager happy. *continued on page 6*

Customer-defined criteria for success

**YOUR NEED TO REDUCE
PROCESS COST**

PTC Organics' highly specialized expertise

**PHASE TRANSFER
CATALYSIS EXPERTISE**



The PTC Cost Savings Program

*process improvement/development performed by PTC Organics
process commercialization by customer*



Better Process Performance

Cost Savings



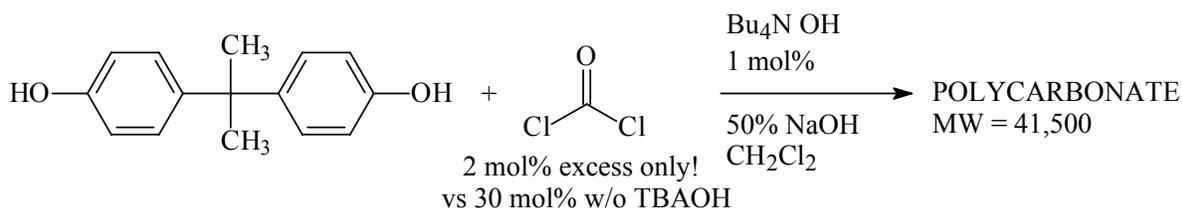
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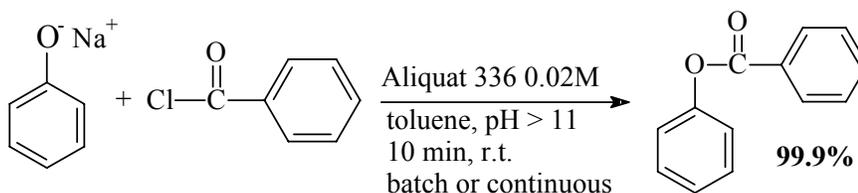
Reducing Excess Phosgene

Would you be crazy enough to perform a reaction that mixes a phenolic with phosgene and 50% NaOH and expect to REDUCE the excess phosgene required for complete reaction?!? The following GE patent is a good example of reducing the excess of a reactant, phosgene, which is sensitive to aqueous base by using PTC. The patent notes that before PTC was considered, the catalyst was triethylamine. The triethylamine would activate the C-Cl bond in phosgene or the chloroformate intermediate so the phenoxide anion could attack. At the same time, the C-Cl bond was open to attack by water and hydroxide, thereby hydrolyzing some of the phosgene and chloroformate. The patent states that, using triethylamine as the catalyst, a 30 mole% excess of phosgene is used to compensate for hydrolysis. The patent notes that hydrolysis is reduced 200-fold by the removal of the triethylamine and replacement by PTC. The role of the phase transfer catalyst is to selectively transfer the phenoxide to the organic phase (methylene chloride in this case) where the phosgene or chloroformate are located, while suppressing hydroxide transfer. In addition, as long as extreme agitation is avoided, the interfacial hydrolysis of phosgene and chloroformate can be minimized because the phosgene and chloroformate are “protected” from the aqueous phase by being soluble in the bulk organic phase. Boden, E.; Phelps, P.; Ramsey, D.; Sybert, P.; Flowers, L.; Odle, R.; (General Electric) **1995**, US Patent 5,391,692



Reducing Excess Benzoyl Chloride

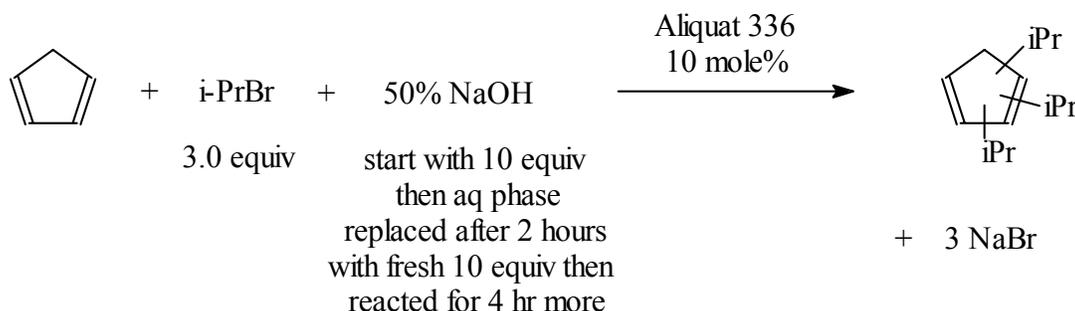
Similar to the reduction of excess phosgene shown above, other acyl halides may be reacted in the presence of basic water using PTC while avoiding significant hydrolysis and reducing excess acyl halide. An interesting application shown below uses PTC to extract phenol as phenoxide from a basic aqueous waste stream and react it with benzoyl chloride to form phenyl benzoate. An intriguing aspect of this report is that the authors report using NO excess of benzoyl chloride, but they still obtain 99.9% conversion of the phenol. The reaction time is short and the reaction is performed at room temperature, which undoubtedly contribute to the ability to utilize all of the benzoyl chloride, despite the aqueous phase which is at pH > 11. Krishnakumar, V.; Sharma, M.; *Ind. Eng. Chem. Proc. Des. Dev.*, **1984**, 23, 410 Economic & technical analysis: Dutta, N.; Borthakur, S.; Baruah, R. *Water Environ. Res.*, **1998**, 70, 4



Reducing Alkylating Agent in C-Alkylation

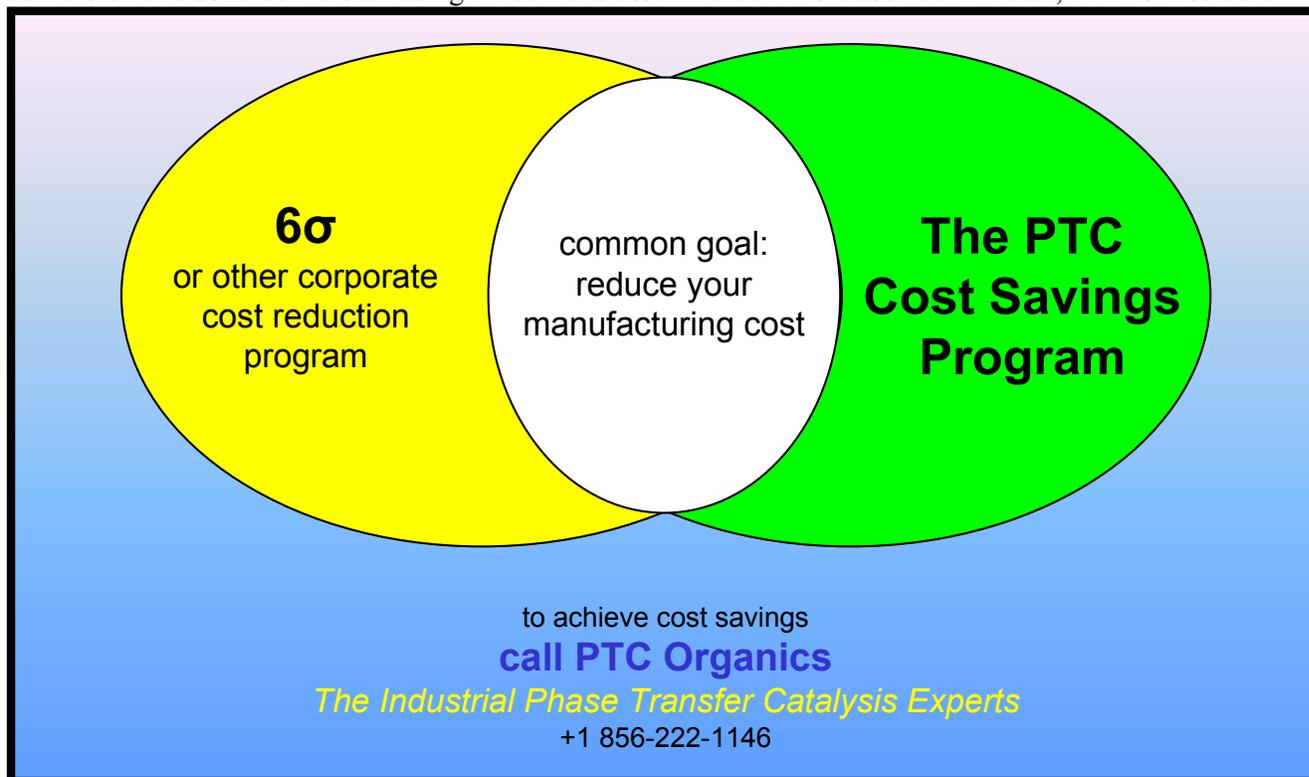
Cyclopentadiene derivatives are useful for metallocenes. According to EP 0 805 133 A (van Beek, J.; Gruter, G.; Green, R., **1997** to DSM) it is challenging to obtain multi-alkylated cyclopentadienes with good selectivity. For example, in order to obtain tri-isopropyl cyclopentadiene one must use 5 equivalents of isopropyl bromide under classical non-PTC basic conditions, and then a mixture of tri- and tetra-substituted

cyclopentadienes are obtained. The inventors of this patent use only three equivalents of iso-propyl bromide and obtain 93% tri-isopropyl cyclopentadiene and 4% di-isopropyl cyclopentadiene. PTC provides high selectivity with minimal excess alkylating agent.



Simulating High Electrophile-Nucleophile Ratio In A Near Stoichiometric System

Here is some PTC magic. The goal of the following long explanation is to simulate very high dilution of a nucleophile using only 10 mole% excess electrophile. Let's say you want to react a nucleophilic anion, A^- , with an electrophile (e.g., alkylating agent R-X), but for selectivity or stability reasons you need A^- to "think" it is swimming in a large excess of R-X. Under classical conditions, say using DMSO, you would probably need to use an A^- to R-X ratio of 100:1. By using PTC, you can use an A^- to R-X ratio of about 1.1 to 1 to achieve the same result. To understand this let's examine the reaction at 0% conversion, 50% conversion and 99% conversion using PTC. Let's assume that A^- is dissolved in water, R-X is insoluble



in water and we are using 1 mole% phase transfer catalyst (Q^+). If we use 1 mole% catalyst, then we can have a maximum of *only* 1 mole% Q^+A^- in the organic phase at any given time (assuming that Na^+A^- is not soluble in the organic phase). At the beginning of the reaction, we have 110 mole% R-X, so the 1 mole% Q^+A^- sees a 110-fold excess of R-X in the organic phase and a reaction occurs producing R-A. At 50% conversion, we still only have 1 mole% Q^+A^- and it sees 60 mole% R-X, because 50 mole% has been consumed (we started with 110 mole% R-X). So, Q^+A^- sees a 60-fold excess of R-X at 50% conversion. At 99% conversion, we still have only 1 mole% Q^+A^- and it sees 11 mole% R-X, because 99 out of 110 mole% R-X has been consumed. So, even at 99% conversion, Q^+A^- sees an 11-fold excess of R-X. Thus, at no time will A^- see less than a 10-fold excess of R-X, despite the fact that we charge only 1.1 equivalents of R-X relative to A^- . Overall, we can achieve the effect of high dilution using only a small excess of the electrophilic reactant.

Summary

The efficiency of phase transfer catalysis and its ability to transfer anions into the organic phase in a controlled manner, provides the opportunity to minimize the excess reactant used in many PTC applications. These applications include reducing the excess of nucleophilic anions, water-sensitive alkylating and acylating agents, expensive oxidizing agents and reducing agents. Always ask yourself the following question: "Am I using more than a 10 mole% excess of an expensive and/or hazardous anionic nucleophile, alkylating agent, acylating agent, oxidant or reducing agent?" If the answer is yes, then you should think about using PTC. Your application may or may not be applicable to PTC. To find out, go to www.ptcorganics.com/60sec.htm to take the "60-Second PTC Test." Some say that in today's modern society, we live with too much excesses. Well, if you use PTC, that doesn't have to be true.

Questions about this article? Contact Marc Halpern at PTC Organics at telephone +1-856-222-1146 or E-mail mhalpern@ptcorganics.com

Breakthrough Process Improvement Using Phase Transfer Catalysis

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PTC Cost Savings Program

Pre-Screening

PTC Organics' Scientific Advisory Board determines the technical probability of success of potential customer process improvements using Phase Transfer Catalysis (under secrecy agreement). If "high," proceed to Development Agreement. Pre-screening is free of charge.



Development Agreement

Reach development agreement based on "Criteria For Success" defined by the customer and upon which process performance is measured during development and commercialization. Agreement is designed for alignment of interest.



Laboratory Development

PTC Organics commits its best efforts to develop a process in the laboratory with the goal of meeting the Criteria For Success. A commitment fee is paid by the customer at the outset of laboratory development. PTC Organics invests laboratory resources and expertise of leading PTC scientists.



Process Verification

After submission of a written report by PTC Organics describing a detailed procedure for meeting the Criteria For Success, the customer verifies the performance of the written procedure in its own laboratory. A Successful Laboratory Development Fee is paid after verification. The customer incurs no additional financial obligation if the Criteria For Success are not met.



Scale Up & Commercialization

At its discretion, the customer performs scale up and commercialization of the advantageous process. Technical support is provided by PTC Organics. The Commercialization Fee is typically 25% of the cost savings achieved.



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