Article

Using Phase-Transfer Catalysis to Compete Effectively With Low-Cost Producers in Highly Competitive Organic Chemical Markets

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There is no denying that the organic chemical markets have become exceedingly competitive in the past five years and that this trend is likely irreversible. The impact on investment in process improvement efforts has been profound at chemical companies of all sizes especially in the US, Europe and Japan. Despite the great achievements of continuous improvement programs, Six Sigma and corporate edicts of many kinds, the reductions in production costs are not always sufficient to retain attractively profitable business. As a result, many companies in pharma, agchem, monomers, specialty and fine chemicals, have severely cut back on process improvement programs and indeed some have reduced process R&D headcount by as much as 50-75% in the past 5-8 years (yes, even in big pharma!).

Strategy – Focus on Raw Material Usage Efficiency

As each company faces the "fight or flight" decision for investing in process improvement, is there hope for effectively competing with low cost producers? Of course there is! If the primary factor of the competitor's low cost is *low labor cost* then a strategy for competing effectively may be based on leveraging process cost vulnerabilities which are not related to labor cost. Accordingly, one strategy could be to shift the battleground to ***raw material usage efficiency*** to offset the effect of low labor cost.

The point is that even Chinese producers have to pay for raw materials. If a Chinese producer has, for example, an 80% yield for a challenging reaction/workup, there is opportunity for a US, European or Japanese facility to be competitive if they can develop a 95% yield process using advantageous (and possibly less obvious) technology. PTC Organics is aware of a process being performed in India for a pharmaceutical intermediate at a volume of > 100 tons/year which suffers from a 65% yield due to a selectivity challenge which can likely be overcome with non-obvious technology. Do you think that in this case, if a 90% yield could be achieved by a Western producer, it would make a competitive difference?

Phase-transfer catalysis, "PTC", technology provides seven categories of process improvement for significantly increasing raw material usage efficiency for thousands of reactions in > 30 reaction categories (see table on p.6). The 7 process parameters which PTC routinely provides advantage for raw material usage are increasing yield, reducing excess reactants, replacing expensive strong base with inexpensive base, increasing selectivity, avoiding isolation of intermediates to minimize handling losses, flexible choice of solvent for easy workup to minimize handling losses and reduction of energy requirements. Examples will be discussed below.

Due to the extra degrees of freedom which PTC systems enjoy for choosing process parameters, PTC reactions are generally driven to completion with less side reactions and under milder conditions. PTC applications typically achieve % yields in the high 90's for most nucleophilic substitutions, most strong base reactions and some oxidations and reductions. In fact, since 2000, most PTC retrofit of non-PTC processes have been initiated to increase yield, increase selectivity or otherwise improve raw material usage efficiency.

Phase-transfer catalysis also provides other process cost reductions and process benefits such as a dramatic reductions in reaction times (50-90% cycle time reduction is not uncommon!!!), enhanced environmental performance (reduced waste, lower emissions) and improved safety (better controlled exotherms, use of alternate less hazardous raw materials). The author has been directly involved in developing PTC technology which has been responsible for > $100 million in cost reductions due to shorter reaction time. However, most of those savings were calculated based on the fully absorbed cost of reactor-hours eliminated which relate back to high labor cost and high overhead in chemical companies in the US, Europe and Japan. The costs of both constructing and operating reactors in countries such as China and India is currently so low that often low productivity processes in these countries can be overcome by simple inexpensive physical plant expansion, which is further often subsidized by the government.

So, even though PTC technology definitely delivers dramatic cycle time reductions (shorter reaction times, streamlined processes with single solvents for multiple steps, avoiding isolation of intermediates), these often represent “catch-up” accomplishments to match the overall plant productivity of a low labor cost producer. This reinforces the strategy of focusing on raw material usage efficiency, because ***companies in China and India still have to pay for raw materials***.

Likewise, the cost of safety and environmental compliance is much lower in China and India than in the US, Europe and Japan. Thus, even though these are important benefits which PTC provides and for which successful arguments are made for their impact on cost, they often do not provide great cost advantage relative to low cost producers in developing countries, rather they help level the playing field.

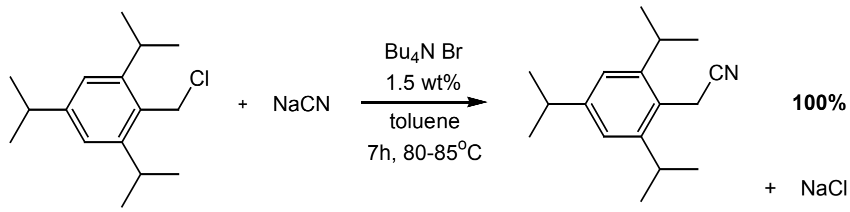
Examples – PTC Provides Dramatic Increase in Raw Material Usage Efficiency

Following are selected examples from the hundreds of documented reports of using phase-transfer catalysis to improve raw material usage efficiency.

Chemists at the former Parke-Davis reported a cyanide/chloride exchange on a 40 kg scale in which they replaced a non-PTC DMSO process with a PTC-toluene process (Figure 1) .[1] The yield of the PTC-toluene process was 100% versus 81% for the DMSO process. The quantitative yield of the PTC-toluene process was achieved using only a 2 mole% excess of cyanide (5 mole% reported) versus a 70 mole% excess of cyanide in the DMSO process. The volume of toluene used in the PTC process was 40% of the volume of the DMSO and the toluene in the PTC process was fully recoverable after the next step whereas the cyanide-laden DMSO was not recoverable after extensive aqueous workup. The PTC-toluene process generated 85% less aqueous waste than the DMSO process and eliminated three workup unit operations. Overall, chemical usage was greatly improved by the 19% yield increase, full recovery of the solvent and high atomic efficiency of the cyanide at low excess. Such results are typical when using PTC for a wide variety of nucleophilic substitutions to replace solvents such as DMSO, NMP, DMF and DMAC.

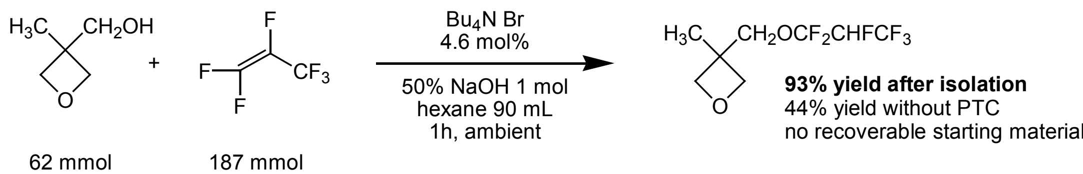
[1] Dozeman, G.; Fiore, P.; Puls, T.; Walker, J., *Org. Proc. Res. Dev.*, **1997**, *1*, 137

Figure 1: High Raw Material Usage Efficiency – PTC Cyanation



An example of leveraging PTC to achieve high selectivity and crucial raw material usage efficiency is shown in Figure 2.[2] The lower energy of activation typically associated with phase-transfer catalyzed reactions allowed performing the Michael addition of the alkoxide to the fluorinated alkene at ambient temperature and short time. This prevented extensive decomposition of the reactive starting material. PTC afforded a 93% while non-PTC conditions gave only a 44% yield and no recoverable starting material. Obviously, such substantial improvement in chemical usage cannot be offset simply by low labor cost.

Figure 2: High Raw Material Usage Efficiency – PTC Addition



PTC-NaOH can replace the use of expensive hazardous strong bases such as sodium methylate, sodium hydride, sodium metal, sodium amide, potassium t-butoxide and sometimes lithium diisopropyl amide at cost savings of thousands of dollars per ton of base used.[3] In one case, LDA was replaced with NaOH in a Michael addition with a simultaneous yield increase from 65% to 84%. This represents very substantial savings in cost, safety and operability.[4] In another case, PTC Organics developed successful PTC technology to replace many tons of sodium metal in an existing process with NaOH while simultaneously achieving a 92% reduction in reaction time, a 10% yield increase and a 20°C reduction in reaction temperature. This represents huge savings in cost as well as greatly enhanced safety.

PTC has been used to avoid isolation of intermediates to provide many practical advantages. In one case, shown in Figure 3 (see page 6), the solvent for a step 3 thiolation using PTC was chosen to be the same for the previous two steps.[5] o-Xylene was used as the solvent for displacing the two chlorine atoms from trichlorotriazine by amines. Before retrofit with PTC, the xylene was replaced by acetone in order to dissolve and react the polar $NaSCH_3$ salt. Replacing a higher boiling solvent with a low boiling solvent is costly and results in significant emissions. This patent is just one example of the ability of PTC to transfer just about any anion in just about any organic liquid and achieve high reactivity.

In fact, PTC can be used to perform multiple consecutive PTC strong base reactions and PTC nucleophilic substitutions to achieve high yield and short cycle time in a single solvent while avoiding isolation of intermediates and handling losses.[6] For example, one agricultural chemical with an annual volume greater than 200 tons/year which is made in three steps has reported yields of 90% (cyanation), 65% (strong base C-alkylation) and 88% (a second strong base C-alkylation). All three of these reactions are classical PTC applications which *con't on p. 6*

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[2] Yamamoto; A. (Daikin Industries) **2004**, US 6,777,563
[3] Halpern, M., *Ind. Phase Trans. Catal.*, **2001**, 1
[4] Gestmann, D.; Laurent, A.; Laurent, E.; *J. Fluor. Chem.*,**1996**, *80*, 27
[5] Grace, H.; Wood, M.; (Ciba-Geigy) **1994**, EP 0 648 755
[6] Halpern, M., *Ind. Phase Trans. Catal.*, **2005**, 1

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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Figure 3: High Raw Material Usage Efficiency – PTC Nucleophilic Aromatic Substitution Avoiding Isolation of Intermediate

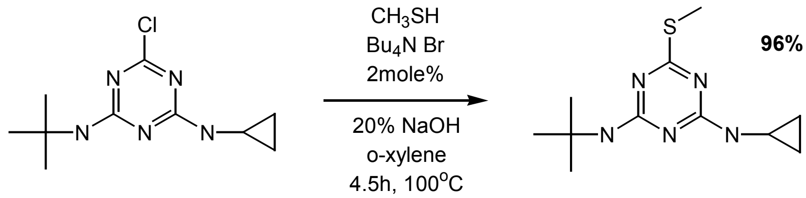


Table: **Reactions In Which Phase Transfer Catalysis Excels**

- Etherification
- Esterification
- Transesterification
- N-Alkylation
- C-Alkylation
- S-Alkylation
- Other Mercaptan Reactions
- Dehydrohalogenation
- Michael Addition
- Aldol Condensation
- Oxidation
- Epoxidation
- Chloromethylation
- Hydrohalogenation
- Hydrogenation
- Borohydride Reduction
- Chiral Reactions
- Darzens Condensation
- Carbene Reactions
- Condensation
- Polymerization
- Polymer Modification

Displacements Using:
- cyanide
- fluoride, bromide, iodide
- azide
- thiocyanate, cyanate
- sulfide
- inorganic nucleophiles

Displacements Using:
- benzyl chloride
- allyl chloride
- many alkyl halides
- benzoyl chloride
- other acyl halides
- methanesulfonyl chloride
- other sulfonyl halides
- epichlorohydrin
- PCl_3, $POCl_3$
- other phosphoro halides
- anhydrides

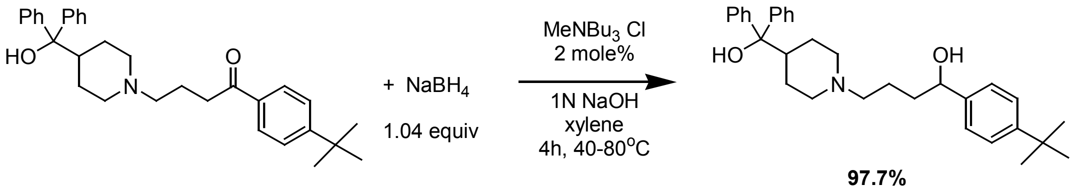
Other reactions involving anions or anionic metal complexes

con't from page 4 can easily attain 90-95% yield for each of the three steps and be performed in a single solvent to avoid handling losses associated with isolation of intermediates. The cost difference in yield alone is 42%! Granted, highly specialized expertise in industrial PTC is required to achieve such a high-performance low-cost process. However the investment in specialized breakthrough PTC process R&D can be justified when considering that more than 80 tons/year of product are obtained for free (in a growing market) using the advantageous PTC sequence.

An innovative example of problem solving using PTC resulted in a significant reduction in excess borohydride, an expensive reducing agent. In the original process, ethanolic borohydride was used to reduce the ketone to the secondary alcohol of terfenadine (Figure 4).[9] The yield of the non-PTC process was high, but a 30 mole% excess of borohydride was required and a low melting polymorph was produced which needed to be recrystallized from xylene to obtain the desired high melting polymorph. After retrofit with PTC, the borohydride excess was reduced to only 4 mole% achieving a 97.7% yield. This can be accomplished because borohydride is more stable in basic water than in ethanol and PTC affords the opportunity to use aqueous borohydride. The solvent used for the reduction was the same nonpolar xylene used for the recrystallization, since again, almost any anion can be transferred into any almost organic liquid and reacted effectively using PTC.

[9] Magni, A. (Gruppo Lepetit) **1989,** Eur. Pat. EP 0 346 765

Figure 4: High Raw Material Usage Efficiency – Reducing Expensive Reducing Agent with PTC-Borohydride



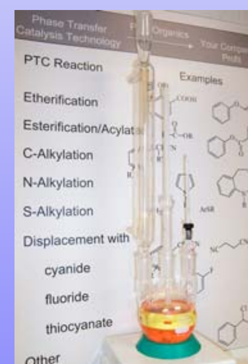
A recent patent by PTC Organics[10] leverages the ability of PTC to reduce the energy of activation of a high temperature transesterification to reduce the temperature of a 50,000 ton/year process from 250°C to 100°C!!! In this reaction, catalytic potassium carbonate is used to deprotonate a small amount of glycerol to the glycerol mononanion which is transferred into vegetable oil in a highly active form by an organophilic phase-transfer catalyst. The energy savings can be enormous, especially after the recent (irreversible?) rise in energy prices.

After reviewing the patent literature, PTC Organics believes that significant improvements can be made using PTC for multiple steps in the production of generic pharmaceuticals and agrochemicals such as myclobutanil, fenvalerate, chlorpheniramine, ibuprofen, verapamil, guaifenesin and others. Some of these processes are already reported to use PTC, but PTC Organics believes that many of these processes are far from optimal. Occasionally over-confident non-PTC experts think they have developed the best processes and this over confidence is leaving their companies open to competition. Such opportunities are waiting to be recognized by open minded process chemists and managers at manufacturing companies looking for commercial development opportunities. These kind of opportunities cannot be overemphasized in today's market, especially when they relate to processes for existing products and intermediates which do not require re-registration of the process.

One can make the valid argument that producers in China and India can use PTC to reduce their cost as well. In fact, Chinese and Indian producers do use phase-transfer catalysis. However, the reality is that chemists around the world do not use PTC when they should due to a variety of reasons which range from lack of expertise/awareness of PTC to simple resistance to change.[11] Based on visits to discuss PTC at over 200 industrial process R&D sites in the US, Europe, Asia and Africa, the author estimates that PTC is used in less than 10% of the applications which it should be used to achieve advantageous processes and competitive advantage. Thus, for any given process there is usually a low likelihood that a company will actually be using phase-transfer catalysis to achieve the lowest cost of manufacture.

Perhaps ***your company should be the low cost producer by using phase-transfer catalysis*** when the competitor is relying simply on low labor cost and for one reason or another is not using PTC.

[10] Halpern, M.; Crick, D. (PTC Organics) **2004**, US Patent 6,833,463
[11] Halpern, M., *Ind. Phase Trans. Catal.*, **1996**, 33



.Process Improvement Opportunity Evaluation Form

FREE Evaluation from PTC Organics
The Industrial Phase-Transfer Catalysis Experts

Do not disclose proprietary information unless a secrecy agreement has been properly executed between your company and PTC Organics

Step 1: **Draw the reaction you want to improve or develop**
Include reactants, molar ratios, solvent, catalyst (if any), time, temperature, yield and key impurities (if important)

Reaction to be improved:

Step 2: **Describe the performance parameter(s) you want to improve**

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add additional pages if necessary

Step 3: **Fill out your name, company, address, phone, fax**

Name ____

Company ____

Address ____

____

Phone ____________________ Fax ____________________

E-mail ____

Step 4: **Fax this form to Dr. Marc Halpern at PTC Organics: +1 856 222 1124**