Phase-Transfer Catalysis Communications

Industrial Phase-Transfer Catalysis: Classic PTC Patents.

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The use of Phase-Transfer Catalysis, "PTC," in industry is increasing at more than 10% per year. This growth is driven by the capabilities of PTC technology[1] which meet the demands of the current trends in the chemical industry to reduce manufacturing costs of existing processes and new processes in development (increasing yield, reducing cycle time, using alternate raw materials), reduce pollution (solvent and waste) and expand plant capacity with minimum capital. In parallel, patents which are easily identifiable as PTC patents are growing at a rate of approximately 11% year. These patents cover a wide range of applications, some of which are brilliantly clever and others which simply provide advantageous process conditions for "mundane" high volume reactions. Some of these patents required man-years of development time (e.g., chiral PTC) and others have been commercialized rapidly due to their simplicity in achieving great benefit (e.g., certain dehydrohalogenations and etherifications). In contrast to some other technologies, many onstream PTC plant processes are actually patented and run as reported. PTC processes are generally not kept as trade secrets. As usual for patents, most of the PTC patents issued are not commercialized.

This article is the first in a series which will highlight selected PTC patents, chosen on the basis of either their commercial importance, their elegance or their ability to provide learning value.

The Foundation PTC Patent

The discussion of PTC patents must begin with Starks' classic US Patent 3,992,432 (1976)[2] which provides 43 examples that describe enhancing the reaction rates of a wide variety of nucleophilic displacements, oxidations, reductions, carbene reactions and hydrolysis. In addition, the patent describes the fundamental principles of the now-classic phase-transfer catalysis extraction mechanism, including rate expression and supporting evidence using radioactive tracer labels (such discussions are rarely included in issued patents). The broad scope of application and the discussion of fundamentals renders this patent a "must-have" in your PTC library.

The nucleophilic displacements reported in this patent which use "inorganic" salts are shown in Table 1. The Starks patent explicitly highlights the advantages of not needing to use DMSO or DMF (expensive, difficult to recover, need to keep anhydrous) commonly used for substitution reactions. This is one of the key triggers for PTC Retrofit[1].

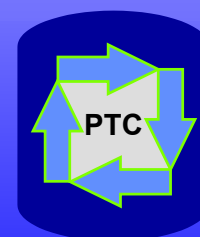[1] Halpern, M.; Phase Trans. Cat. Comm., **1996**, *2*, 1
[2] Napier, D.; Starks, C.; (Continental Oil) US Patent 3,992,432 (1976)
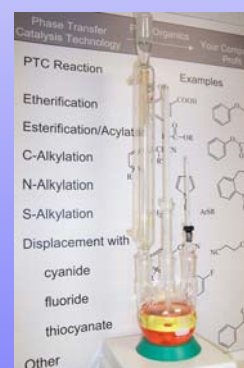
Hydrolysis of various esters (Examples 9, 10, 14; 95-100% yield) was included because PTC can reduce the temperature of hydrolysis to 30-50°C compared to 100°C for conventional saponification.

Table 1: **Nucleophilic Substitutions ("Inorganic" Salts)**

Nucleophile	Yield & Comments	Example #
cyanide	reaction progress described	1, 2, 43
halides	100% or equilibrium	3-5
acetate	100% (pseudo-1st kinetics reported)	6
thiocyanate	100%	7
cyanate		8

Examples 11-13 describe the PTC carbene reaction (extensive references to Makosza's landmark work may be found in the prior art section of the patent). In this section, Starks highlights another classical PTC trigger, namely replacement of anhydrous alkoxides and lithium alkyls with aqueous alkali metal hydroxide.

Examples 15-40 describe a wide variety of oxidations using KMnO$_4$, OsO$_4$, H$_2$O$_2$, RuO$_2$, and HIO$_4$. Starks notes that PTC enhances reactivity but does not change selectivity. Furthermore, the PTC conditions stabilize H$_2$O$_2$ relative to non-PTC conditions, which results in less waste of peroxide. Again, anhydrous conditions required in many conventional oxidations are not required using PTC. One borohydride reduction of a ketone was described (Example 41). PTC catalyzed the reduction at least 20-fold relative to the non-catalyzed system. It should be noted that it is sometimes preferred to use PTC/borohydride or ethanolic borohydride for the reduction of ketones and aldehydes, depending on which is more effective (not noted in the patent). Borohydride reductions using PTC will be the focus of an article in a future issue of this journal. PTC borohydride can be advantageous in certain other reductions (such as for esters). Lastly, C-Alkylation of malononitrile was described (Example 42).

Obviously, this patent covers a lot of ground and has great historical significance as a patent which widened the perspectives of PTC application. It is interesting to note that this patent may be traced back through several filings to 1967 (three Continuations In Part which were abandoned) while background publications cite Makosza's work during the period 1965-1968.

The chief catalyst used in this foundation patent was methyl tricaprylyl ammonium chloride, Aliquat 336^R (trademark of Henkel now Cognis). Together with the similar methyl tridecyl ammonium chloride these two catalysts were used in 21 examples. The remainder of the examples used ditallow dimethyl ammonium chloride, tributyl stearyl phosphonium bromide and hexadecyl tributyl ammonium bromide.

PTC Provides Great True Advantage for Commodity Scale Dehydrochlorination

Ideally, a chemical process should give high yield and low waste (of any kind; including raw materials, solvents and by-products) in a short cycle time and high utilization of reactor volume with the minimum number of unit operations. PTC dehydrochlorination patents describe meeting almost all of these criteria.
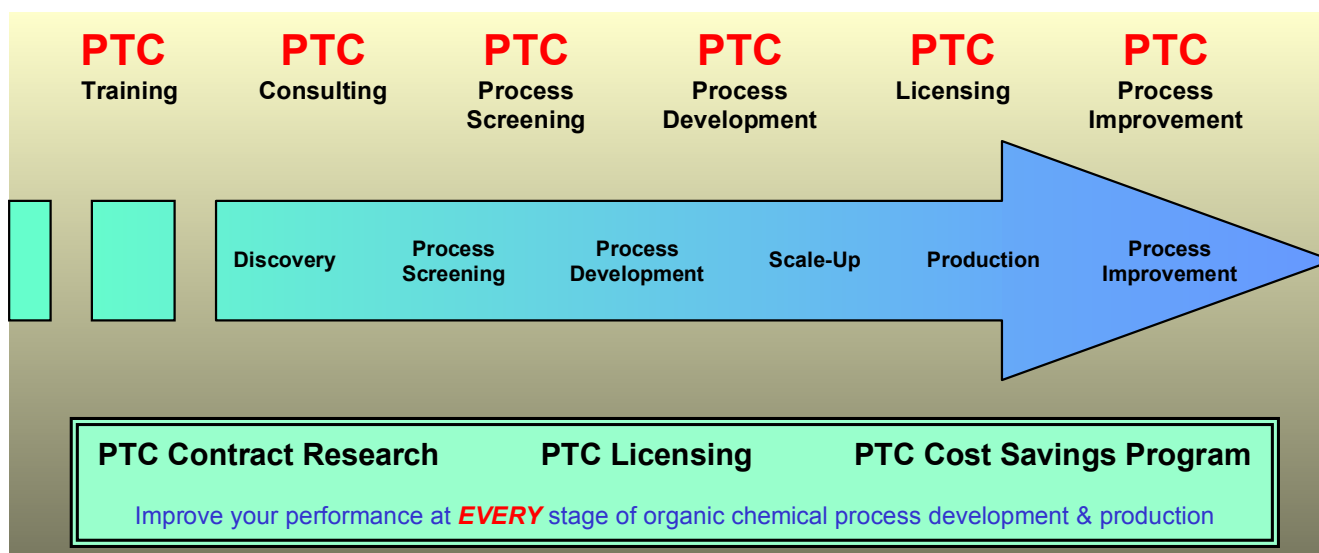
The reaction (shown in Figure 1) is the dehydrochlorination of 1,1,2-trichloroethane (TCE) to vinylidene chloride (VC).[3] The key advantages of this dehydrochlorination are: (1) The VC product flashes off during the reaction, (2) a phase-transfer catalyst provides high reaction rate, (3) the catalyst is recovered by a 1-4 minute extraction using the TCE starting material as the extraction solvent and the resulting TCE/catalyst phase is simply recycled into the next reaction. When using 5000 ppm benzyl tributyl ammonium chloride, 93-99% of the catalyst could be recycled (depending on the ratio of TCE to aqueous phase used in the extraction, which would be determined by the economics of the process). (4) Reactor volume is utilized efficiently (no added solvent). (5) The aqueous effluent which contains NaOH and NaCl can be

Figure 1: **Dehydrochlorination**
Emphasis on Catalyst Recycle

$$Cl_2CH\!-\!CH_2Cl \ + \ NaOH \ \xrightarrow{\ PTC\ } \ Cl_2C\!=\!CH_2 \ + \ NaCl$$

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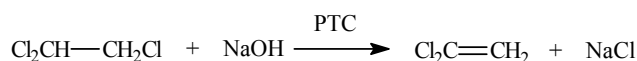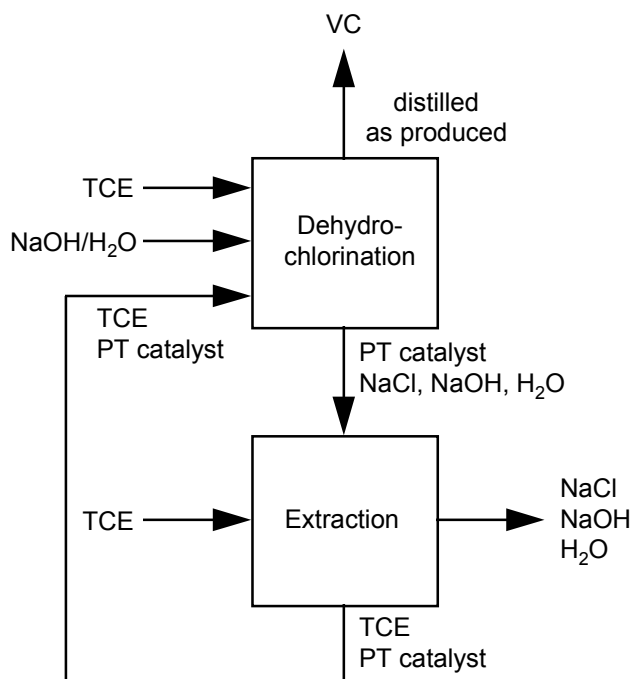
[3] Reed, D.; Snedecor, T.; (Dow Chemical) WO 95/05352 (1995)

used as part of the feed to the dehydrochlorinator. The patent does not describe in detail the recycle of the aqueous phase but describes the aqueous feed to the dehydrochlorinator as

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follows "An aqueous sodium hydroxide solution was prepared that had a composition similar to that of spent solution from a commercial process used to make vinylidene chloride." The only known disadvantage of the process is the generation of one mole of salt which is inherent to all base-promoted dehydrochlorinations. The actual yield or throughput of product is <u>not</u> disclosed in the patent (only if the throughput is high enough will this patent be truly advantageous).

The classic PTC dehydrochlorination patent describes the production of chloroprene[4] and predates the patent described above. This patent focuses on (1) the highest possible yield, (2) optimization of NaOH usage and (3) plant scale operations (an "actual plant run" is described in Example 3 with a reactant feed rate of 4310 kg/hr; Example 2 describes a reactant feed rate of 16,589 kg/hr!). Figure 2 shows the dehydrochlorination of 3,4-dichlorobut-1-ene (DCB) to chloroprene.

Figure 2: **Dehydrochlorination**
Emphasis on Yield and NaOH Usage
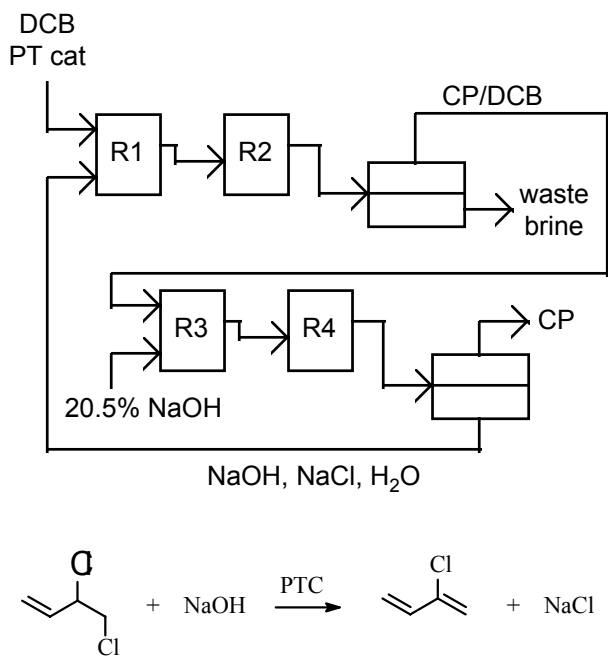
The key in this patent was to arrange the reactors and feed points in such a manner to allow the lowest possible mole ratios of reactants and catalyst, while maximizing yield. The cascade reactor configuration shown in Figure 2 gave optimal results. The system consists of four liquid full dehydrochlorinators, R1, R2, R3, R4, two separators and various feed points as follows: (1) fresh 20.5% NaOH is fed into dehydrochlorinator R3, together with the organic phase described in step 6 below, (2) the effluent (both aqueous and organic phases) from R3 (already at 97.3% conversion) is fed into R4 to complete the reaction (to 99.78% conversion), (3) the effluent from R4 is separated into a product stream (99.2% actual yield recovered) and an aqueous stream which contains

4 Maurin, L.; (DuPont) US Patent 4,418,232 (1983)

enough NaOH to promote dehydrochlorination in R1 and R2 plus the NaCl by product from R3 and R4, (4) this aqueous stream is recycled into R1 together with fresh DCB and phase-transfer catalyst, (5) the effluent (both phases) from R1 (at 56.0% conversion) is fed into R2, (6) the effluent from R2 is separated into a waste brine stream and an organic phase (at 62.3% conversion) which is fed into R3 together with the fresh 20.5 % NaOH in step 2 above. This process achieves an **actual yield of 99.2% using only 1.008 moles of NaOH per mole of DCB fed!** Only 0.22% of the DCB remains unconverted and only 1115 ppm of the catalyst, coco benzyl bis(2-hydroxypropyl) ammonium chloride, is used. The catalyst is most likely lost in the aqueous brine purge (unless some may be carried through and accumulate in the process).

The choice of catalyst for this particular reaction was also studied extensively by a Russian group.[5] It is clear that the phase-transfer catalyst is needed to achieve the desired productivity for this reaction. Overall, the DuPont patent is an excellent example of application of PTC to achieve a highly desirable commercial process with great profit implications.

O-Alkylation: Why Etherify ArO⁻/RO⁻ by Anything But PTC?

The Williamson ether synthesis was forever revolutionized by PTC when McKillop et al[6] published the etherification of phenols and Freedman and DuBois[7] published the etherification of alcohols. PTC drives these reactions to completion at much shorter times and milder reaction conditions than the classical Williamson conditions, mostly due to altered solvation of the alkoxide or phenoxide. In conventional etherifications, an abundance of H-bonding species (such as the alcohols themselves) in the reaction phase, solvate the alkoxide or phenoxide and reduces nucleophilicity. Solvation is greatly reduced in PTC systems.

Freedman patented[8] the O-alkylation of chloropyridinates with methyl ∝-chloroacetate (useful as herbicides) in toluene using benzyl triethyl ammonium chloride as the phase-transfer catalyst, achieving 90-95% yield. The inventor notes that under various (non-PTC) conditions this reaction is "plagued by the low reaction rates, concurrent formation of N-alkylated by-products, and so forth." PTC enhances the rate and gives high yield.

A decade later, this same reaction was patented using a "solvent-free" process.[9] <u>The ability to perform PTC reactions without added solvent is one of the greatest driving forces for considering PTC for industrial processes.</u>[1,10] This etherification is shown in Figure 3. The catalyst used was tetrabutyl ammonium bromide.

The solvent free patent cites as advantages: (1) eliminating the need to separate the solvent by multiple steps with high energy

5 Kurginyan, K.; Mendeleev Chem. J. (Eng), **1986**, *31*, 74
6 McKillop, A.; Fiaud, J.; Hug, R.; Tetrahedron, **1974**, *30*, 1379
7 Freedman, H.; DuBois, R.; Tetrahedron Lett., **1975**, 3251
8 Freedman, H.; (Dow Chemical) US Patent 3,969,360 (1976)
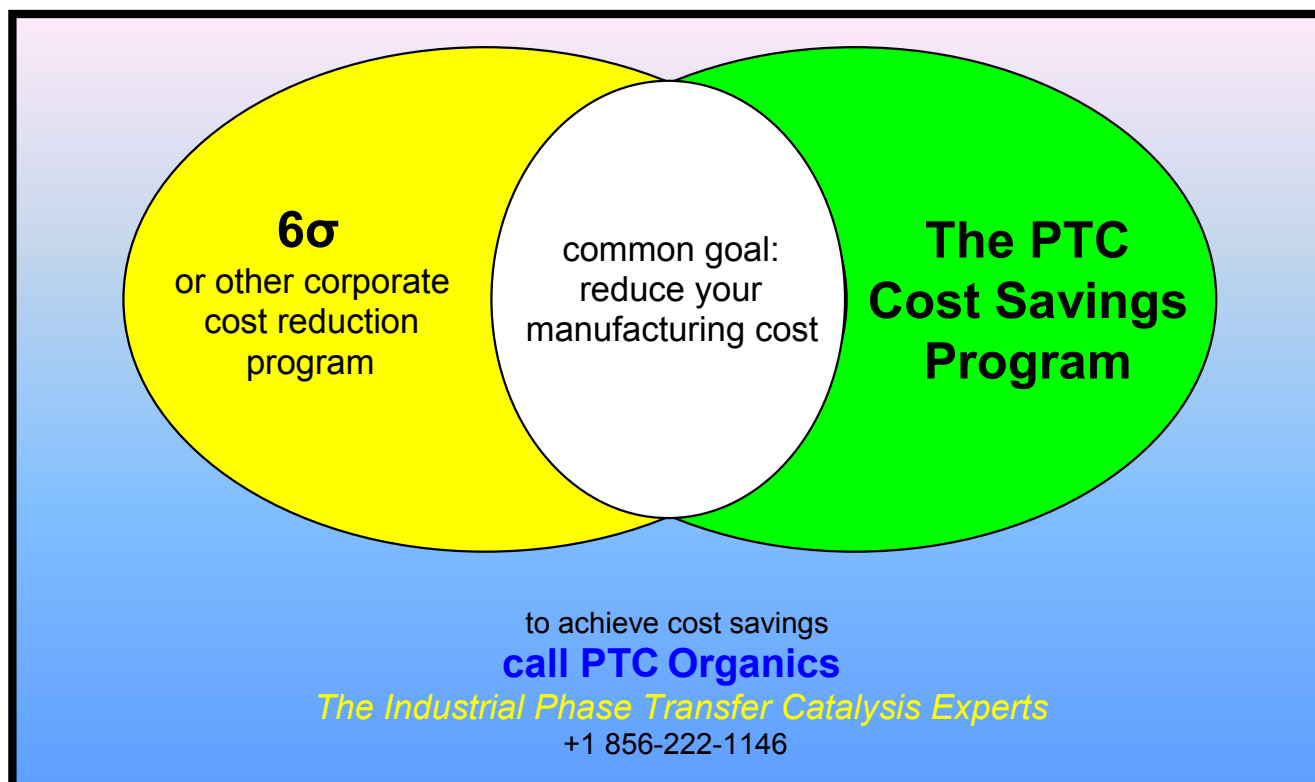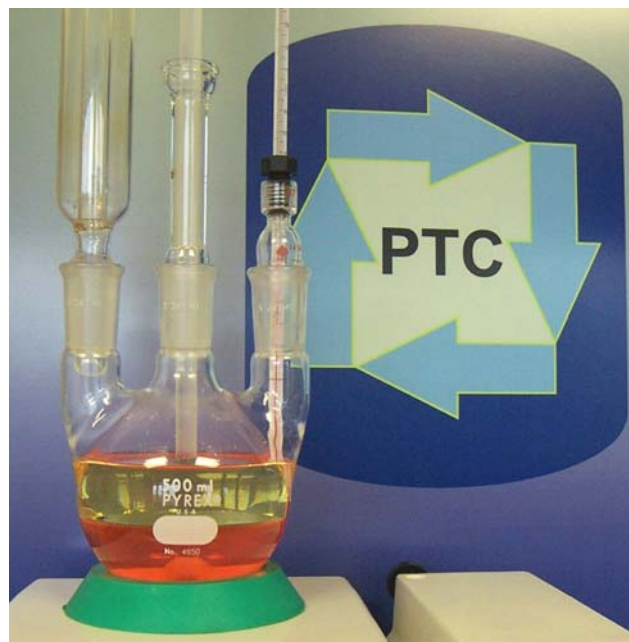9 Adaway, T.; (Dow Chemical) US Patent 4,701,531 (1987)
10 Halpern, M.; Phase Trans. Cat. Comm., **1994**, Preview Issue

requirements, (2) eliminating the need for waste disposal and/or recycling of the solvent, (3) ability to reduce the amount of water in the system. Water, in fact, causes yield loss by hydrolysis of the haloester alkylating agent.

Figure 3: **Solvent -Free Etherification**
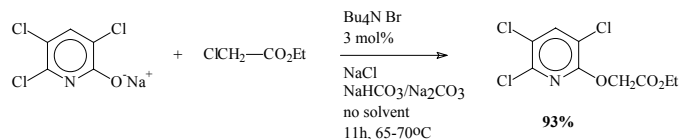
Other benefits may be gained by the solvent free process such as greater utilization of reactor volume and possibly higher reaction rates. In the original Freedman patent an unspecified quantity of toluene was used as the solvent and no salts were added. In the solvent free patent, a 17 mole% excess of the alkylating agent was used and salts were added. Without knowing the actual quantities of solvent, salt and alkylating agent used in the two patents we cannot determine the relative utilizations of reactor volume. In addition, if the reaction is intrinsic reaction rate limited[1] and if the kinetics are first order in each of the reactants then it would be reasonable to assume that the overall reaction rate would be greater for the solvent free process due to increased concentration of the alkylating agent/solvent. Since there were differences in both time and temperature between the two patents it is difficult to compare the kinetics of the two processes in this case.

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PTC Oxidation - Simple, Convenient, Inexpensive, High Yield, Selective and Short Cycle Time

Successful process chemists follow the "KISS" guideline ("Keep It Simple Stupid"). Usually simpler reaction conditions are easier to scale up. The following Lee and Freedman patent[11] is simple to perform and the special PTC system provides the added bonus of excellent selectivity in the oxidation of a primary alcohol to an aldehyde without the over-oxidation to the carboxylic acid.

Figure 4: **Simple and Selective Oxidation**
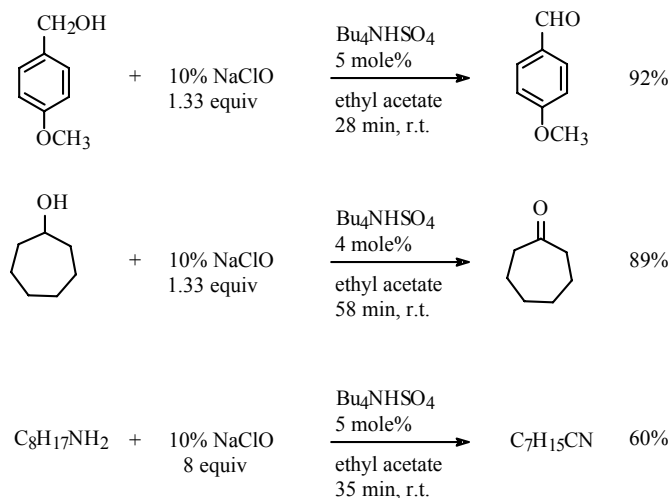
The process consists of charging the reactor with four components (substrate, bleach, solvent, catalyst), stirring (no heat) for under an hour and isolation (presumably solvent separation, wash and distillation). The oxidizing agent is the inexpensive and readily available 10% NaClO. The key to high yield in short reaction time is choosing ethyl acetate as the solvent (which forms a complex with the hypochlorite). The catalyst is 4-5 mole % Bu_4N HSO_4. The selectivity of the PTC oxidation of benzyl alcohol to benzaldehyde was emphasized by showing that without the catalyst, benzaldehyde itself can be further oxidized to benzoic acid (Example 6). Oxidation of the 2° alcohol to the ketone proceeded well. Even an aliphatic amine could be oxidized to the nitrile, but the yield was low and a very large excess of hypochlorite was required. This patent, which already expired, is highly useful for oxidation of alcohols. Chemists should consider PTC/ClO⁻ for oxidation of alcohols (use proper safety precautions for all oxidations!).

**Reducing Hazardous Raw Materials**

Chemists are often amazed at the ability of PTC to reduce the excess moles of labile reactants required to achieve complete reaction. Sensitive compounds such as benzoyl chloride and dimethyl sulfate can often be used with only a small excess (or no excess at all) in high yield benzoylations or methylations usually in the presence of basic aqueous phase. The following

General Electric patent[12] describes the advantageous PTC preparation of polycarbonate from bis-phenol A and phosgene, which does **not** need PTC to proceed in high yield and short cycle time. Conventional preparation of polycarbonate includes the use of 3° amines, such as Et_3N, as the condensation catalyst in a basic aqueous reaction medium. Replacing Et_3N with a phase-transfer catalyst reduces the hydrolysis of the phosgene and the chloroformate intermediate by approximately two orders of magnitude. As a result, the amount of excess phosgene can be reduced to only 1-2 mole%. In a similar patent for the preparation of flame retardant polycarbonate,[13] Boden and Phelps were able to reduce the excess phosgene from 30 mole% to 2 mole%! Thus, chemists should consider PTC when forced to work with base-sensitive compounds under basic aqueous conditions.

High Temperature PTC (Nitrogen-Based Salts)

Brunelle at General Electric changed the way we think about nitrogen-based salts useful for PTC at "high" temperature. N,N-Dialkylaminopyridine can be quaternized to form ammonium salts which have high temperature stability,[14,15,16] presumably due to added resonance structures which can be drawn for the conjugated di-nitrogen system and by properly choosing a minimum of β-hydrogens. The catalysts shown below have half lives from 8 to 12 h in toluene at 110^oC in the presence of sodium phenoxide, whereas Bu_4N Br has a half life of 7 min under the same conditions. Brunelle used these and similar catalysts[17] for a variety of nucleophilic aromatic substitutions, using primarily phenoxides (bisphenol type) as the nucleophiles.
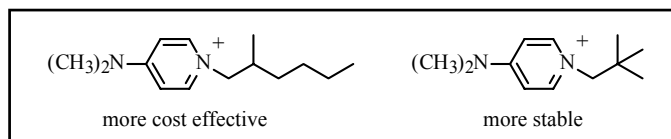
Although the dimethylaminopyridine-based quats are not stable in the presence of NaOH, they can be used for high temperature fluoride displacements.[18]

More recently, Brunelle prepared guanidinium salts which can also be used as high temperature phase-transfer catalysts.[19] Interestingly, Bu_4N Br (2 mole%) was used as the phase-transfer catalyst to prepare dihexyl tetramethyl guanidinium bromide in 98% yield from tetramethyl guanidine and hexyl bromide (acetonitrile reflux, 15h, K_2CO_3).

[11] Lee, G.; Freedman, H.; (Dow Chemical) US Patent 4,079,075 (1978)

[12] Boden, E.; Phelps, P.; Ramsey, D.; Sybert, P.; Flowers, L.; Odle, R.; (General Electric) US Patent 5,391,692 (1995)

[13] Boden, E.; Phelps, P. (General Electric) US Patent 5,300,624 (1994)

[14] Brunelle, D.; (General Electric) US Patent 4,460,778 (1984)
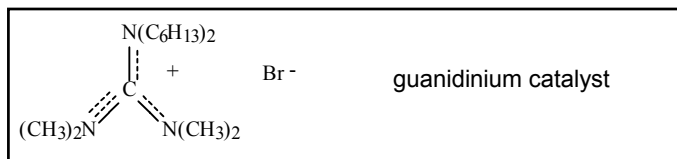
[15] Brunelle, D.; Singleton, D.; Tetrahedron Lett., **1984**, 3383

[16] Brunelle, D.; ACS Symposium Series 326, 38 (1987); Starks, C. editor; Washington DC

[17] Brunelle, D.; (General Electric) US Patent 4,595,760 (1986) and US Patent 4,535,143 (1985)

[18] Cantrell, G.; (Mallinckrodt) US Patent 4,973,772 (1990)

[19] Brunelle, D.; (General Electric) US Patent 5,082,968 (1992)

guanidinium catalyst

ephedrinium salts as the chiral catalysts, with the former showing higher activity. All chiral PTC candidate reactions need to be evaluated on a case-by-case basis and are usually resource intensive in development.

Chiral PTC

Much has been written about the classic Merck patent describing the use of substituted N-benzyl cinchonidinium halides for the chiral alkylation of an indanone (Figure 5).[20,21,22] This patent and JOC article constitutes the foundation for most subsequent attempts to perform chiral PTC. This patent required very significant R&D resource to develop, the documentation of which illustrates that industrial laboratories can produce outstanding applied fundamentals. The major findings of the research to elucidate the fundamentals include: (1) the three point interactions between the quat and substrate responsible for asymmetric induction were identified (two π-π and one H-bond) (2) electron withdrawing substituents on the N-benzyl group enhanced ee by strengthening one of the π-π interactions, (3) deprotonation of the indanone to form the enolate was interfacial and not rate determining, (4) the chiral quat is soluble in toluene as a dimer. Many other intriguing and well studied parameters and conclusions were reported. An adequate description of this patent and related articles is beyond the scope of this review and the reader is referred to the original publications for in-depth analysis and guidelines.

To date, most chiral PTC has used cinchona alkaloids and

Figure 5: **Chiral Alkylation**

95% yield
92% ee

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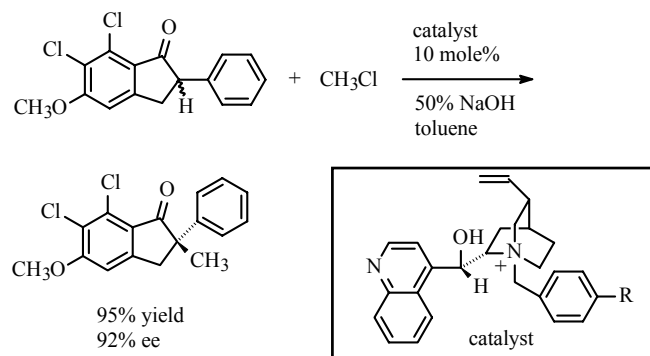
[20] Dolling, U.; Grabowski, E.; Pines, S.; (Merck Sharpe and Dohme) US Patent 4,605,761 (1986)
[21] Hughes, D.; Dolling, U.; Ryan, K.; Schoenewaldt, Grabowski, E.; J. Org. Chem., **1987**, *52*, 4745
[22] Dolling, U.; Davis, P.; Grabowski, E.; J. Amer. Chem. Soc., **1984**, *106*, 446

Thiolates Are Easily Transferred and Are Very Good Nucleophiles

Deprotonated thiols are polarizable anions and as such are readily transferred to organic phases in the presence of a phase-transfer catalyst. Once in the organic phase, thiolate can effectively perform nucleophilic aliphatic or aromatic substitution. Thiolates and iodides are among the best PTC anions when needed in synthesis because they are polarizable (easily transferable) and nucleophilic.

S-Alkylation of triazines are important for certain agricultural chemicals. Figure 6 shows such a nucleophilic aromatic substitution. Forty alkylthiotriazines were reported to be prepared by this process.[23] Grace and Wood of Ciba-Geigy note that the use of the phase-transfer catalyst in the alkylthiolation "reduces cycle times, reduces environmental emissions by the elimination of the number of solvents used for production and makes facile the removal of sodium chloride from the final product." Again, we see that PTC is useful not only for improving the chemical aspects of a reaction, PTC also provides the opportunity to improve the process aspects as well.

One of Brunelle's first patents used alkylthiolation to reduce trace PCB levels from transformer oil by two orders of magnitude, using PEG-400 as the catalyst and dodecylmercaptan as the thiol (better than either phenylmercaptan or benzylmercaptan).[24]

Figure 6: **Thiolation**
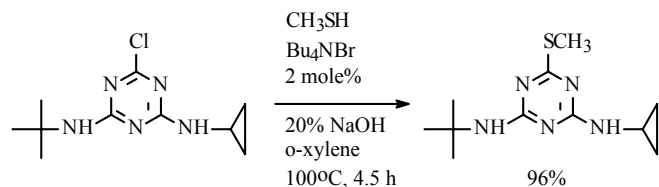
### A Very Clever Application of PTC

PTC excels at transferring and reacting dozens of inorganic anions. Wright at Eli Lilly recognized the ability of Aliquat 336[R] to effectively transfer and react azide and cyanide and to combine these in a single novel application.[25] The beauty of this patent lies in the visualization of the tetrazole ring (4 nitrogens, 1 carbon) as a combination of azide (3 nitrogens) and cyanide (1 nitrogen, 1 carbon) using PTC to prepare the cyanoformate and azidoacetate used to construct the ring. To further streamline the process, Wright prepared the azidoacetate intermediate in methylene chloride and, without further isolation, simply added the cyanide and chloroformate. The cyclization was performed after adding additional cyanoformate (in excess, nearly all of which was recovered by distillation). The yield was 80.6% in the first cycle and 93.1% after recycle of the mother liquors.

Figure 7: **Combining PTC Strengths in Cyanide and Azide**
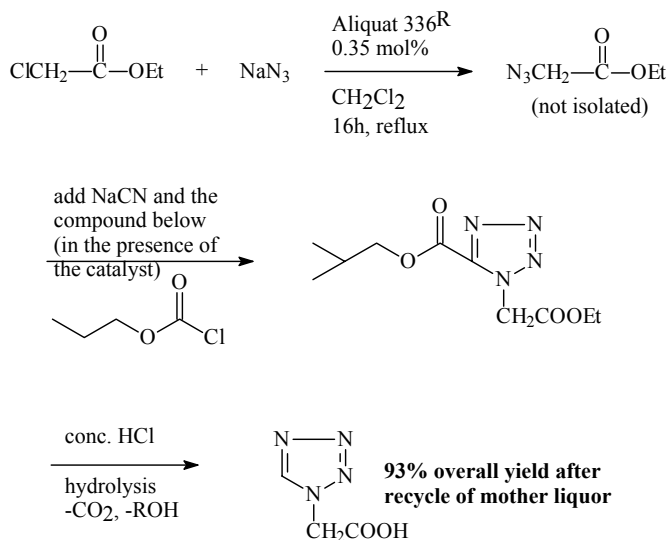
This patent makes no claims regarding the azidoacetate nor the formation of the tetrazole (useful as an intermediate for cephalosporins). The patent notes "The present process has been found to economically produce large quantities of C_3-C_8 alkyl cyanoformate derivatives in very high yields and to provide the product consistently with high purity without the need for additional expensive purification steps." This patent illustrates creativity in the application of PTC and the principles of process chemistry to problem solving.

Summary

Phase-Transfer Catalysis graduated from the infancy of lab curiosity to adolescent growth with high volume commercial manufacturing processes. PTC has yet to reach life cycle maturity as a process technology. Many PTC process patents have yet to be innovated and filed, maybe by you. Apply PTC to increase yield, reduce cycle time, eliminate solvent, improve selectivity, enhance safety, perform new chemistry to which there are no alternatives, streamline processes and innovate other creative applications which the rest of us have not yet thought of. Combine your expertise as a process chemist/engineer with the commercial needs of your company and with the unique highly desirable attributes which PTC offers for improving processes. You will then enhance the profits of your company and add to the enjoyment of your career.

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[23]Grace, H.; Wood, M.; (Ciba-Geigy) EP 0 648 755 A1 (1994)
[24] Brunelle, D.; (General Electric) US Patent 4,410,422 (1983)
[25] Wright, I.; (Eli Lilly) US Patent 4,539,422 (1985)