Chiral Phase-Transfer Catalysis

*Brief History & Recent Advances*

Summary: Chiral Phase-Transfer Catalysis is in its “4th generation” of development. Enantiomeric excess of >99% has been achieved for C-alkylation and Michael addition; >90% ee is achieved routinely for other reactions. This article reviews the progress from the early ephedra quats to benzyl cinchona quats to anthracenylmethyl cinchona quats and finally the new “Maruoka” catalysts which are thermally stable, can be used at 1mole% and achieve 98% ee in > 90% isolated yield.

Chloromethylation

*An Outstanding PTC Platform*

Summary: New PTC chloromethylation technology affords ready access to benzyl chloride derivatives, which also happen to be among the best reactants in all of phase-transfer catalysis. As a result, great advantage can be achieved by commercially performing consecutive PTC reactions in one pot, avoiding isolation of intermediates, which start with chloromethylation and are followed by numerous other outstanding PTC reactions to form benzyl esters, ethers, nitriles, alkylated nitriles, alcohols, aldehydes, acids and more.

Effective Process R&D Management Needs

**Effective PTC Process Screening**

As every process R&D manager knows, the decisions made in the early stages of process screening have a significant impact on the downstream stages of process development and scale-up. The challenge of the process R&D manager is to identify the technology most likely to be successful for a given process in the shortest period of time while investing the minimum amount of R&D resources. Often, phase-transfer catalysis is the technology most likely to be successful. If PTC really does excel in thousands of reactions in over 40 reaction categories, why isn't PTC screened more often?
Chiral Phase-Transfer Catalysis
A Brief History of the Development and Recent Advances in Asymmetric PTC Reactions

Darrell Crick and Marc Halpern
PTC Organics, Inc., 900 Briggs Road, Suite 145, Mt. Laurel, New Jersey 08054 USA
tel 609-835-0200; E-mail dcrick@ptcorganics.com

The growing importance of enantiometrically pure compounds for life-science applications has fueled a wealth of research in asymmetric synthesis. The importance of the field was underscored in 2001 when the Nobel Prize in Chemistry was awarded to W. S. Knowles (an industrial chemist!), K. B. Sharpless, and R. Noyori for their work in asymmetric synthesis. Numerous commercial processes involving asymmetric synthesis are now practiced.

Given that Phase-Transfer Catalysis can increase yields, reduce cycle times, eliminate hazardous or expensive reagents and solvents, and provide numerous other benefits to organic chemical manufacturers, it is not surprising that much effort has been directed toward the coupling of Phase-Transfer Catalysis with asymmetric synthesis. Examination of asymmetric PTC reactions began in the mid-1970's and has continued at an accelerating pace, along with asymmetric catalysis in general, to become the most active area of academic PTC research. Excellent reviews exist on the subject of chiral PTC, and these may be consulted for additional information.1,2,3,4,5 In particular, the recent review by O'Donnell is exceptionally comprehensive through 1999.4 This article will provide a brief overview of the history of Chiral Phase-Transfer Catalysis, highlighting key results from the first low enantiomeric excess reaction, through the development of catalysts based on cinchona alkaloids (breakthroughs in 1984, 1990 and 1997), to the most impressive breakthrough in stable catalysts (1999-2002) which provides > 90% isolated yield with 98% ee using only 1 mole% catalyst. A wide variety of reactions have been examined, but the bulk of the publications have dealt with alkylations, epoxidations, and Michael additions.

First Results (Generation 1) and the Occasional Misstep

Beginning in 19756 and continuing through the early 1980's, early investigators examined a wide variety of reactions with numerous catalyst structures, primarily those based on ephedrine (Figure 1).

Figure 1: Typical Ephedrinium Salt

Figure 2: Optically Active Catalyst Decomposition Product

Rapid Screening of Breakthrough Processes
by the Industrial Phase-Transfer Catalysis Experts

PTC Contract Research

PTC Process Screening

- “proof-of-concept” in ~ 3 weeks
- Resource-efficient breakthrough PTC process innovation

PTC Process Development

- Define PTC process parameters to achieve a high-performance PTC process ready for scale-up.

PTC Consulting

PTC Consulting

- Effectively screen PTC process options in YOUR lab saving 50-90% of internal R&D resources

PTC Organics, Inc.

You already know that Phase-Transfer Catalysis excels in 40 reaction categories
Use PTC Organics’ highly specialized PTC expertise to assure high R&D productivity and quality in the early crucial screening stages of your new projects

Contact PTC Organics
tel (+1) 856-222-1146 fax (+1) 856-222-1124 E-mail mhalpern@ptcorganics.com

© 2003 PTC Communications, Inc. www.phasetransfer.com
Chloromethylation
An Outstanding PTC Platform

Phase-transfer catalysis excels in nucleophilic substitution. The title “King of PTC S_N2 Substrates” belongs to benzyl chloride and benzyl chloride derivatives which react cleanly, rapidly and in high yield under PTC conditions. Nucleophilic substitution of the chloride of benzyl chloride derivatives provides a broad array of useful products and intermediates such as benzyl esters, ethers, nitriles, alkylated nitriles, alcohols, aldehydes, acids and much more (see Figure CM-1). Benzyl chloride derivatives are used commercially in the manufacture of pharmaceuticals, agrochemicals, dyes, flavors & fragrances, monomers, additives, modification of polymers and a wide range of specialty and fine organic chemicals.

PTC Organics developed PTC chloromethylation technology which provides access to these benzyl chloride derivatives and can be directly converted into valuable downstream products using other outstanding PTC reactions. This technology offers multiple advantages. The new PTC chloromethylation is emulsion-free, resulting in easy workup (separation achieved in < 1 min) and avoids the use, isolation and transfer of chloromethyl methyl ether or its regulated byproduct, bis-(chloromethyl)ether. Interestingly, careful choice of chloromethylation conditions leads to higher selectivity and higher reactivity simultaneously. **A great advantage of the new PTC chloromethylation is that it provides the first step for a variety of versatile multi-step high-yield PTC reaction sequences performed without isolation of intermediates.** The actual chloromethylation can be performed and treated in a sealed reactor system and the chloromethylated intermediate can be further reacted without isolation or handling. This reduces cycle time and reduces loss of intermediates and catalyst. The system can be designed to be performed using a single catalyst and either solvent-free PTC conditions or a single solvent PTC system.

Figure CM-1: Consecutive High-Yield PTC Reactions Starting with Chloromethylation
*Avoiding Isolation of Intermediates*

---

X = almost any nucleophile, such as

- carbanions from substrates with pKa up to 23 (e.g., from malonate, cyclopentadiene, sulfones, ketones, esters, imines)
- N-anions from heterocycles (e.g., triazole, indole, pyrimidine), benzamide, sulfonamide
- mercaptans
- inorganic: F, Br, I, N_3, SCN
Given these advantages and the broad scope of utility of benzyl chloride derivatives and downstream products, PTC Organics and Single Site Catalysts (Chester, PA) are commercializing the chloromethylation and subsequent PTC reactions. SST Corporation (Clifton, NJ) is promoting chloromethylation sequences in the pharmaceutical industry.

Figure CM-2 shows some of the reactions in the benzyl chloride tree which have been successfully developed by PTC Organics. Figure CM-3 shows reaction sequences which may be able to benefit from consecutive PTC reactions in the chloromethylation platform. PTC Organics is aware of other reaction sequences (not shown) beginning with chloromethylation which have significant potential for improvement using PTC for pharmaceutical, agrochemical and monomer applications. Contact PTC Organics (tel: +1 856-222-1146) to inquire about your potential application.

Figure CM-2: PTC Applications Using Benzyl Chloride Derivatives Developed by PTC Organics

Figure CM-3: Potential Consecutive PTC Reaction Sequences
Highly Effective Process R&D Management

Simply put, without highly specialized expertise in PTC, it is likely to take too much valuable time during the busy and crucial process screening program to determine if PTC is a reasonable process option. Effective process screening can be achieved by applying the highly specialized PTC expertise of PTC Organics at the pivotal screening stage to achieve resource-efficient proof-of-concept.

Good news...PTC can often be screened effectively in 1-2 weeks

During the first two weeks of screening, PTC Organics’ PTC experts identify the most crucial process parameters and specialized PTC techniques for the specific process, which are most likely to lead to success. The PTC screening program designed by PTC Organics typically achieves the following progress:

PTC Process Screening
- Weeks 1-2: Achieve promising results or determine proof-of-concept
- Week 3: Define the identities and limits of the parameters for Design of Experiments or other process development program

PTC Process Development
- Weeks 4-6: Definition of PTC process parameters ready for scale-up

If promising PTC conditions are not discovered rapidly, PTC is often abandoned as a viable route. Scale-up then occurs with a non-optimal, non-PTC process and retrofit is, in certain cases, not possible due to registration constraints (e.g., pharmaceuticals). Even high-throughput screening or Design of Experiments can lead to an incorrect conclusion about the potential feasibility of a PTC process option when specialized PTC expertise is not available to identify key non-obvious parameters and set the proper limits.

PTC Organics has helped customers overcome many common challenges and pitfalls which are specific to PTC Process Screening. These include:
- Address the most important PTC process parameters first (catalyst is usually NOT first).
- Plan for catalyst separation method at the outset to assure high product assay.
- Broaden the scope of process options using water-sensitive reactants/products.
- Achieve promising reactivity, volume efficiency and raw material efficiency by choosing surprisingly low levels of water, solvent and agitation at the outset.
- Integrate other highly specialized PTC techniques (“tricks”) not commonly known, without which the PTC process option would simply not be feasible.

In summary, integration of your process chemistry department with the expertise of PTC Organics is a highly efficient way to achieve peak performance from your process R&D program in the most cost-effective manner. Contact Marc Halpern (tel +1 856-222-1146 or mhalpern@ptcorganics.com) to integrate PTC Contract Research or PTC Consulting into your process screening and development programs.
Highly Effective Process Screening

needs

PTC Process Screening or PTC Consulting

Benefits

• rapid proof-of-concept
• best PTC expertise available
• cost-effective use of R&D resources
• assures high process R&D productivity & quality during early crucial stages of process screening

PTC Organics, Inc.
The Industrial Phase-Transfer Catalysis Experts

O-Alkylation (Etherification), Esterification & Transesterification, N-Alkylation, C-Alkylation & Chiral Alkylation, S-Alkylation, Dehydrohalogenation, Displacements with Cyanide, Fluoride, Iodide, Bromide, Azide, Thiocyanate/Cyanate, Sulfide, Hydroxide/Hydrolysis, Alkyl, Acyl or Sulfonyl Halides, Other Nucleophilic Aliphatic & Aromatic Substitutions, Oxidation, Epoxidation & Chiral Epoxidation, Borohydride Reduction, Hydrogenation, Michael Addition, Aldol Condensation, Wittig, Darzens Condensation, Carbene Reactions, Carbylation, Chloromethylation, HCl/HBr Reactions and more

PTC Organics now provides PTC Contract Research and PTC Consulting for effective process screening

Contact PTC Organics
Tel (+1) 856-222-1146 fax (+1) 856-222-1124 E-mail mhalpern@ptcorganics.com

© 2003 PTC Communications, Inc. www.phasetransfer.com
Chiral PTC — continued from page 2

In those early days, reported enantiomeric excesses (ee’s) ranged from only a few percent to approximately 50%.7,8,9,10 While encouraging from a proof-of-concept standpoint, such ee’s are not synthetically useful on a commercial scale. Complicating the situation was the discovery that many of the reported ee's were actually due, at least in large part, to optically active catalyst decomposition products11 such as that shown in Figure 2 (see page 2). Nonetheless, not all reports were discredited and the events highlighted both the importance of understanding catalyst stability and of using other analytical techniques in addition to optical rotation to measure the success of a reaction. In general, higher, more reproducible ee's were obtained with catalysts based on cinchona alkaloids (much more on those in a moment) although they too can decompose during the reaction.

The most remarkable achievement to be found in the early literature is that of Donald Cram's group at UCLA.12 The crown ether shown in Figure 3 gave 99% ee in the Michael addition of an indanone to methyl vinyl ketone. Potassium t-butoxide was used as the base. Although much additional work has been done with a variety of crown ethers, none has surpassed this early success. A disadvantage of catalysts such as these that must be considered is their cost. The high cost of crown ethers in general, and in particular highly specialized ones such as that used in Cram's work, is prohibitive with all but the very highest value added products. Also of note is that lower temperature, not surprisingly, was found to increase the optical purity of the products. The best results were obtained at -78°C.

**Generation 2: Cinchona alkaloids**

The most intensely studied group of catalysts has been those prepared by quaternization of cinchona alkaloids (Figure 4 and Table 1 – see p. 10). Cinchona alkaloids are readily available and relatively inexpensive, they are easily quaternized and they exist in diastereomeric pairs. N-Benzyl quininium chloride (“QUIBEC”) was prepared very easily by mixing quinine and benzyl chloride in benzene-ethanol at room temperature for 26 hours.8 Quinine has long been used as a chiral resolving agent and has been used as a catalyst itself for asymmetric reactions as long ago as 1912.13

The "first generation" of cinchona quats, as O'Donnell terms them,3 had a free -OH at C-9 and were quaternized with benzyl chloride derivatives. As mentioned earlier, ee's rarely exceeded 50% although decomposition appeared to be less of a problem than with the ephedra quats and few challenges were made to the reported results.

Chiral PTC performance changed significantly in 1984, when researchers from Merck reported an efficient asymmetric methylation of the indanone shown in Figure 5 using N-[p-(trifluoromethyl)benzyl] cinchoninium bromide as the phase transfer catalyst.14 A yield of 95% with 92% ee was obtained. Based on molecular modeling and X-ray crystal structures, it was proposed that the quinoline ring, the C9-O bond and the benzyl group all lie in a single plane and provide a multipoint interaction with the indanone ring, the oxygen of the enolate and the phenyl group (π, H-bond, π), respectively. continued on p. 10

---

13 Bredig, G.; Fiske, P.S. *Biochim. Z.* 1912, 46, 7.
PTC Organics, Inc.

The Industrial Phase-Transfer Catalysis Experts

O-Alkylation (Etherification), Esterification & Transesterification, N-Alkylation, C-Alkylation & Chiral Alkylation, S-Alkylation, Dehydrohalogenation, Displacements with Cyanide, Fluoride, Iodide, Bromide, Azide, Thiocyanate/Cyanate, Sulfide, Hydroxide/Hydrolysis, Alkyl, Acyl or Sulfonyl Halides, Other Nucleophilic Aliphatic & Aromatic Substitutions, Oxidation, Epoxidation & Chiral Epoxidation, Borohydride Reduction, Hydrogenation, Michael Addition, Aldol Condensation, Wittig, Darzens Condensation, Carbene Reactions, Carbonylation, Chloromethylation, HCl/HBr Reactions and more

To learn more about how PTC can help you improve synthesis, process R&D and production

Contact PTC Organics
Tel (+1) 856-222-1146 fax (+1) 856-222-1124 E-mail mhalpern@ptcorganics.com

Ask about our new PTC Contract Research and PTC Consulting
Chiral PTC – continued from p. 8

This was, by far, the most impressive, well-studied and practical example of chiral PTC at the time and would set the stage for future development with cinchona alkaloids. Alas, the drug substance apparently did not make it all the way through the pipeline, else this would have likely been the first commercial use of chiral PTC.

A great deal of research has been conducted on the asymmetric synthesis of \( \alpha \)-amino acids via alkylation of esters of benzophenone-imine protected glycine. In 1989, Professor Martin O'Donnell reported the synthesis of \( \alpha \)-amino acids with ee's as high as 99% using either benzyl cinchoninium or benzyl cinchonidinium quats (Figure 6).\(^\text{15}\) It is important to note that either enantiomer of the amino acid could be prepared simply by switching the catalyst to the other diastereomer!

2-Day PTC Course
“Practical Phase-Transfer Catalysis”
May 6-7, 2003 in New Jersey

O-Alkylation (Etherification), Esterification & Transesterification, N-Alkylation, C-Alkylation & Chiral Alkylation, S-Alkylation, Dehydrohalogenation, Displacements with Cyanide, Fluoride, Iodide, Bromide, Azide, Thiocyanate/Cyanate, Sulfide, Hydroxide/Hydrolysis, Alkyl, Acyl or Sulfonyl Halides, Other Nucleophilic Aliphatic & Aromatic Substitutions, Oxidation, Epoxidation & Chiral Epoxidation, Borohydride Reduction, Hydrogenation, Michael Addition, Aldol Condensation, Wittig, Darzens Condensation, Carbone Reactions, Carbonylation, Chloromethylation, HCl/HBr Reactions and more

Find agenda, registration, hotel information at
www.phasetransfer.com
click on 2-Day PTC Course
or call (+1) 856-222-1146

A senior scientist at a major pharmaceutical company who attended the April 2002 PTC course reported a new PTC process in scale-up by November 2002. "It was the best training I had in 18 years in industry!" he wrote at the end of the training.

Just one great idea from this course will return your investment many times!
Chiral PTC – continued from p. 10

O'Donnell also reported studies that indicate that the active catalyst species is one in which the C-9 oxygen has been alkylated.¹⁶ This contradicts earlier conclusions which emphasized the necessity of having an -OH β to the onium.¹⁰ N-benzyl and N,O-dibenzyl cinchonidinium bromide were equally effective as chiral catalysts. In addition, alkylation of the C-9 oxygen could prevent racemization of the α-amino acid by preventing the C-9 alkoxide from behaving as a lipophilic base. O'Donnell's "second generation" catalysts (R = benzyl) were quite successful.¹⁷

Generation 3: The Anthracenylmethyl Cinchona Alkaloid Quats

A major advance was independently reported in 1997 by both Corey and Lygo.¹⁸,¹⁹ Enhanced ee's were obtained by quaternizing cinchonidine with 9-chloromethylanthracene (see Figure 7). Corey's group reported ee's from 92 to 99.5% with yields ranging from 67-91% for the alkylation of benzophenone imine of t-butyl glycine with various alkyl bromides and iodides (reaction in Figure 6). Catalyst design was based on the general idea that only one of the four tetrahedral faces of the quaternary nitrogen should be open enough to allow close approach of the anion. One face is inherently blocked by the bicyclic ring structure and another is blocked by alkylation of the oxygen on C-9. The bulky anthracenylmethyl group was used to provide enhanced steric hindrance of the remaining face relative to previously prepared benzyl and naphthyl derivatives. Crystal structures of the catalyst supported the proposed structure.

Figure 7: Anthracenylmethyl Cinchona Alkaloid Quat

Figure 8: The “Maruoka”
Chiral Phase-Transfer Catalyst
Ar = β-Naphthyl, 3,4,5-trifluorophenyl

There has been some debate over which group was the first to discover the anthracenylmethyl catalysts. The landmark publications from each group were received at the publishing journal in the same week and both groups had prior publications indicating work along the same lines.

However, it appears that neither Corey nor Lygo was the first to describe cinchona alkaloids quaternized with 9-chloromethylanthracene. To our knowledge, the first description was reported in the 1993 Ph.D. dissertation of Patricia Stone,²⁰ who was working with Professor Thomas Pochapsky at Brandeis University. This document and subsequent publications²¹ describe an elegant series of 2-D Nuclear Overhauser Effect NMR experiments which characterized the borohydride salt of cinchona quats. Based on the structure as determined by NMR, Pochapsky's group proposed that the additional steric bulk which

would be provided by the anthracenylmethyl group should enhance the enantioselectivity. Indeed, a
catalyst prepared from quinine and 9-chloromethylanthracene showed enhanced enantioselectivity relative
to the benzyl and naphthyl derivatives.\textsuperscript{20} Ee's were not as high, however, as those obtained by Corey and
Lygo using the cinchonine and cinchonidine-based catalysts.

Even though most of the work with anthracenylmethyl cinchona quats has focused on chiral C-alkylation,
other reactions are being investigated also. Lygo performed epoxidation using 11\% bleach and observed the
same ee with opposite configuration using two diastereomeric anthracenylmethyl cinchona quats.\textsuperscript{22}

**Figure 9: Chiral PTC Epoxidation**

![Chemical structure](image)

**PRACTICAL TIP:** A particularly useful tip is that when Lygo et al used the anthracenylmethyl cinchona
quat with toluene as the solvent, the catalyst could be \textit{easily recovered} by filtering through a short column
of MgSO\textsubscript{4}, then washing the MgSO\textsubscript{4} with chloroform.\textsuperscript{23}

**Generation 4: The Maruoka Chiral Phase-Transfer Catalysts**

The latest breakthrough in chiral phase-transfer catalysis, and perhaps the most exciting development in
phase-transfer catalysis in twenty years, came in 1999 from Professor Maruoka's group at Kyoto University.
Quaternary ammonium catalysts with C\textsubscript{2} symmetry, such as that shown in Figure 8, were synthesized and
found to give high enantioselectivity in the formation of \(\alpha\)-amino acids with only 1 mole\% catalyst
loading.\textsuperscript{24,25,26,27}

Reaction conditions were mild (toluene solvent, 50\% KOH as base, 0\(^\circ\)C) and the catalysts possess enhanced
stability due in large part to the lack of a \(\beta\)-hydrogen that could promote Hofmann Elimination. Granted,
the catalysts are inherently more expensive than cinchona quats due to their more elaborate synthesis.
However, their enhanced activity and the potential for recycle afforded by higher stability offers the
possibility of offsetting some of the increased cost. Work has been reported on simpler versions,\textsuperscript{28} and it is
likely that more efficient syntheses as well as less elaborate catalyst molecules will both be developed in the
future.

Despite the advantages offered by the cinchona quats with respect to cost and availability of raw materials
and ease of syntheses, it must be noted that the highest activity highest ee catalysts have been those
prepared by Maruoka's group and Cram's similar crown ether.\textsuperscript{12} The development of new classes of
catalysts with similar symmetry elements is an exciting possibility.

---

\textsuperscript{22} Lygo, B.; Wainwright, P. \textit{Tetrahedron Lett.}, \textbf{1998}, \textit{1599}
\textsuperscript{23} Lygo, B.; Crosby, J.; Lowdon, T.; Peterson, J.; Wainwright, P. \textit{Tetrahedron}, \textbf{2001}, \textit{57}, 2403
\textsuperscript{27} Ooi, T.; Takeuchi, M.; Maruoka, K. \textit{Synthesis} \textbf{2001}, \textit{1716}.
\textsuperscript{28} Ooi, T.; Uematsu, Y.; Kameda, M.; Maruoka, K. \textit{Angew. Chem.} \textbf{2002}, \textit{114}, 1621-1624

© 2003 PTC Communications, Inc. www.phasetransfer.com
**The Most Recent Novel Applications**

The scope of chiral PTC is constantly being expanded. Though much of the research has been concerned with alkylations using alkyl halides, Michael additions and epoxidations, other reactions such as Darzen's condensation, Horner-Wadsworth-Emmons reactions, oxidations and reductions have been explored. Below are two recent examples that demonstrate high yield and enantioselectivity with newer types of chemistry.

D. Y. Kim's group reported the enantioselective fluorination of an indanone as shown in Figure 10.29 Mild conditions (rt, toluene, K₂CO₃) were employed using N-fluorobenzenesulfonimide as the fluorinating agent. Many combinations of N- and O- groups on cinchona were examined and it was found that the O-propargyl, N-3,5-di-t-butyl-4-methoxybenzylcinchonine was most effective. Yields of 92% with 69% ee were obtained. These results exceed even those of the O-allyl-N-anthracenylmethyl catalyst developed by Corey.

Figure 10: Novel Chiral PTC Fluorination

![Fluorination Reaction](image)

Yoshiji Takemoto's group at Kyoto University has used cinchona quats to catalyze the Pd-assisted allylation of glycine imino ester using allyl acetate as the alkylating agent.30 The chiral phase-transfer catalyst gave 94% ee in the absence of a chiral Pd complex. Thus, triphenylphosphite was used as the Pd ligand to conduct the reaction at 0°C in the presence of 50% KOH. O-methyl N-anthracenylmethyl cinchonidinium iodide was used as the catalyst.

Figure 11: Chiral PTC C-Alkylation Using Allyl Acetate (not Allyl Halide)

![Alkylation Reaction](image)

Work also continues on the design of more effective cinchona catalysts. Lygo's group reports a study designed to identify the key elements responsible for stereocontrol.31 Planar substituents (such as 9-anthracenylmethyl) on the nitrogen proved to be important as did the 1-quinolyl group from the parent alkaloid.

---

Future Directions in Chiral PTC

Despite the great advancements made over the years, chiral phase-transfer catalysis is, to our knowledge, still not used in a commercial process of significant scale. One primary reason is that chiral PTC catalysts are significantly more expensive than conventional ones and are not yet available in “large” commercial quantities. Both Aldrich and Tyger Scientific offer several of the cinchona quats. Two of the Maruoka catalysts (Ar = β-Naphthyl and 3,4,5-trifluorophenyl) are now available through Aldrich, though only in very small lab quantities. The need to optimize the catalyst for each substrate has also slowed commercial implementation. As with all asymmetric reactions, the cost-benefit of the catalyst system must be determined vs. the cost of chiral resolution. With ever-increasingly valuable molecules in the pipeline, the cost barrier is perhaps eroding somewhat. A familiar quandary is left. The cost of catalyst will not decrease until large scale manufacture is undertaken and that awaits use in a commercial process.

Academic work is sure to continue on many new fronts. A few well-established groups have made most of the major contributions to the modern era of chiral PTC. Since 1990, these include the groups of M.J. O'Donnell, B. Lygo, E.J. Corey, K. Maruoka, T. Shioiri and D.Y. Kim among others. The field has now matured to the point where not only are these pioneering groups making further contributions, but new groups are entering the field. Additional breakthroughs are certain to happen and the elusive commercial application awaits the right conditions to materialize.
Send your E-mail address

___________________________  @  ____________________________

and we will send you

“The Best of Industrial Phase-Transfer Catalysis”
a CD-ROM which contains > 80 pages of valuable industrial PTC articles from 1996-2002

“The PTC Tip of the Month”
E-mail newsletter

Register at: www.phasetransfer.com (click on Register for “PTC Tip of the Month”)
by telephone (+1) 856-222-1146
or fax this page to (+1) 856-222-1124

Notice:
The list of E-mail addresses for the “PTC Tip of the Month” and “Industrial Phase-Transfer Catalysis” will NOT be sold or transferred to any entity and will be used only by PTC Communications, Inc. and PTC Organics, Inc. to provide information related to Phase-Transfer Catalysis.

IMPORTANT – HARD COPY SUBSCRIBERS READ THIS!

PTC Communications is converting to web-based publication of “Industrial Phase-Transfer Catalysis.” Selected subscribers at each location will continue to receive the hard copy of the journal. Check the box to continue to receive the hard copy of this journal and fax this entire page to (+1) 856-222-1124.

PTC Communications, Inc.

Suite 145, 900 Briggs Road, Mt. Laurel, New Jersey 08054 USA