PHASE-TRANSFER CATALYSTS

Optimizing Efficiency in Biphasic Organic Reactions

Sigma-Aldrich®
Lab & Production Materials

Phase-transfer catalysts (PTCs) are molecules that enable chemical reactions between reagents in immiscible phases, typically aqueous and organic, by transferring reactive ions across the phase boundary.

They act as molecular shuttles, transporting reactive ions across phase boundaries and dramatically enhancing reaction rates and yields. By eliminating the need for strictly anhydrous conditions or highly polar solvents, PTCs simplify reaction setups while improving operational efficiency.

PTCs offer several advantages that make them indispensable in modern synthesis:

- Enhanced reaction rates under mild conditions
- Improved selectivity and reproducibility
- Reduced solvent and energy requirements
- Compatibility with green chemistry principles
- Excellent scalability from lab to production

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1. General Principles

In a typical biphasic system, inorganic salts or bases remain confined to the aqueous phase, limiting reactivity. A PTC forms a lipophilic ion pair with the reactive species, allowing it to migrate into the organic phase where the reaction occurs. This ion-pair shuttle mechanism enables efficient transformations without requiring homogeneous reaction media.

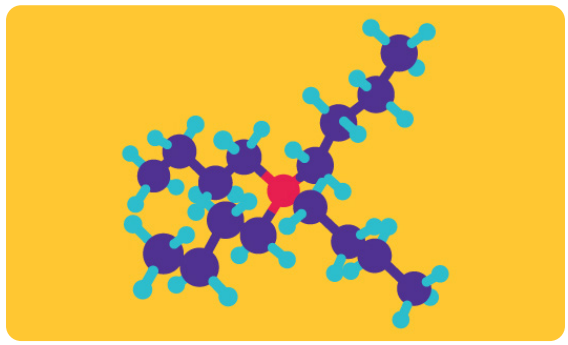
Common Reaction Types Enabled by PTCs:

- S_N2 nucleophilic substitutions
- Alkylation and arylation reactions
- Oxidations using inorganic oxidants
- Olefination and C–C bond formation
- Polymerization and functional materials synthesis

2. Classification

2.1 Ammonium-Based Phase-Transfer Catalysts

Ammonium-based phase-transfer catalysts remain the most widely used PTCs due to their structural versatility, broad solvent compatibility, and predictable performance. Their tuneable alkyl substituents allow chemists to adjust lipophilicity, thermal stability, and ion pairing strength to fit a wide range of nucleophilic displacement, alkylation, and condensation reactions.

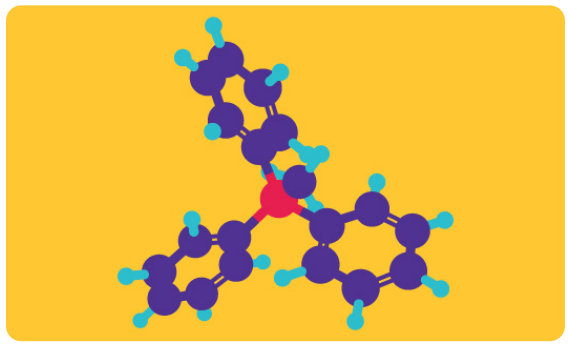


Recent advances emphasize their role in green and sustainable chemistry, including water-based synthesis, reduced solvent usage, and lower energy input. We offer a comprehensive portfolio of ammonium PTCs to support reaction optimization from discovery through scale-up.

Explore Products

2.2 Phosphonium-Based Phase-Transfer Catalysts

Phosphonium salts offer enhanced thermal stability and often superior solubility in organic phases, making them ideal for demanding chemical transformations. They are widely utilized in key applications such as Wittig and related olefination reactions, carbon-carbon bond formation, and the synthesis of polymers and specialty materials.

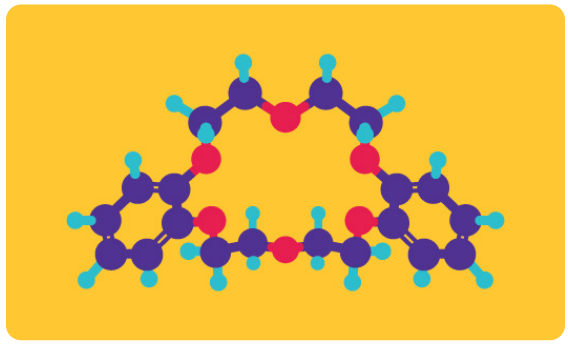


These catalysts deliver excellent performance at elevated temperatures, exhibit high relevance in industrial and process chemistry, and provide improved stability compared to their ammonium counterparts. Products in this category are particularly valuable for process development and scale-up applications, ensuring robust and reliable outcomes in complex synthetic workflows.

Explore Products

2.3 Crown Ethers and Cryptands

Macrocyclic phase-transfer catalysts (PTCs), such as crown ethers and cryptands, offer exceptional ion selectivity, particularly for alkali metal cations. Representative examples include 18-Crown-6, Dibenzo-24-crown-8, and Kryptofix® cryptands.



These specialized catalysts are widely employed in reactions involving poorly soluble inorganic salts, the generation of "naked" anions, nucleophilic substitutions and oxidations, as well as polymerization and electrochemical processes. Their unique cavity-based binding mechanism enables highly controlled and selective transformations, making them indispensable for advanced synthetic applications. This is reflected in our comprehensive product range.

Explore Products

3. Choosing the Right Phase-Transfer Catalyst

Selecting an appropriate PTC depends on several factors:

- Nature of the nucleophile (hard vs. soft)
- Desired reaction temperature and conditions
- Solvent compatibility
- Required selectivity, including enantioselectivity
- Reaction scale (laboratory vs. production)

Our diverse PTC portfolio allows chemists to optimize performance without compromising sustainability or scalability.

4. Applications Across Industries

PTCs play a central role in modern organic synthesis, enabling faster, higher yielding transformations in biphasic reaction systems. By enhancing ion transfer between aqueous and organic phases, PTCs streamline C-C bond formation, nucleophilic substitution, polymer synthesis, oxidations, fluorination, and green chemistry workflows. Their versatility makes them a core enabling technology across research and manufacturing environments.

This section helps chemists quickly find PTC strategies relevant to their reaction type, substrate class, and scalability needs, improving method selection, optimization, and productivity in both research and process development.

C–C and C–X Bond Formation

PTCs accelerate C–C and C–X bond forming reactions by enabling rapid nucleophile transfer across phases, improving yields under mild, scalable conditions. This section highlights key PTC enabled alkylations, couplings, and enolate based transformations essential for organic synthesis.

Phase transfer catalysts enable efficient, stereoselective alkylation of protected glycine derivatives to produce optically enriched α amino acids. Using chiral cinchona derived PTC catalysts, the method achieves high enantioselectivity, broad substrate scope, and practical reaction conditions, providing a general, scalable route to valuable chiral amino acid building blocks. ***N*-benzylcinchoninium chloride** as a chiral PTC has been successfully utilized for the asymmetric alkylation of glycine Schiff base by O'Donnell and co-workers (**Figure 1**).[1]

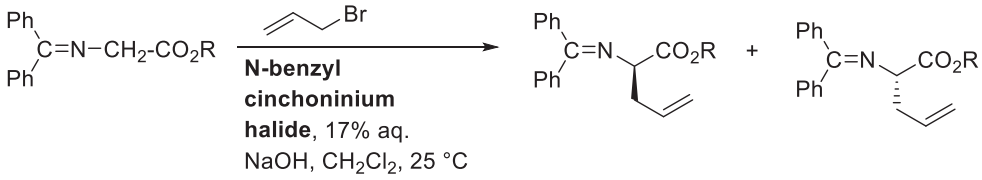


Figure 1. Asymmetric alkylation of glycine derivative using ***N*-benzylcinchoninium chloride**.

Tetraalkylammonium salts (**NEt$_4$Br**, **NPr$_4$Br** and **NBu$_4$Br**) act as solid, easy to handle olefin surrogates for C-H alkylation via Hofmann elimination, generating short chain alkenes *in situ* (**Figure 2**).[2] These ammonium PTCs enable direct C-H alkylation across multiple substrates, improve handling over gaseous olefins, support two chamber setups, and help identify active Rh-OH catalytic species.

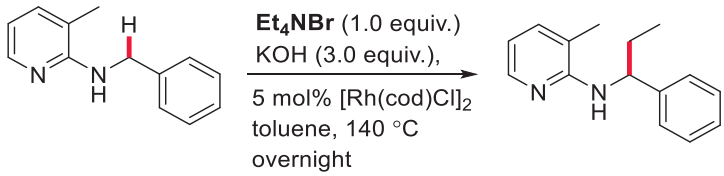


Figure 2. Methylation of benzylic amines using **tetraethylammonium bromide**.[2]

While **tetramethylammonium chloride** and **trimethylphenylammonium chloride** primarily yielded 1:1 mixtures of α-C- and *O*-methylated species, changing the methylating agent to **PhMe$_3$NBr** and finally to PhMe$_3$NI significantly favored the desired α-C-methylated product (**Figure 3**).[3]

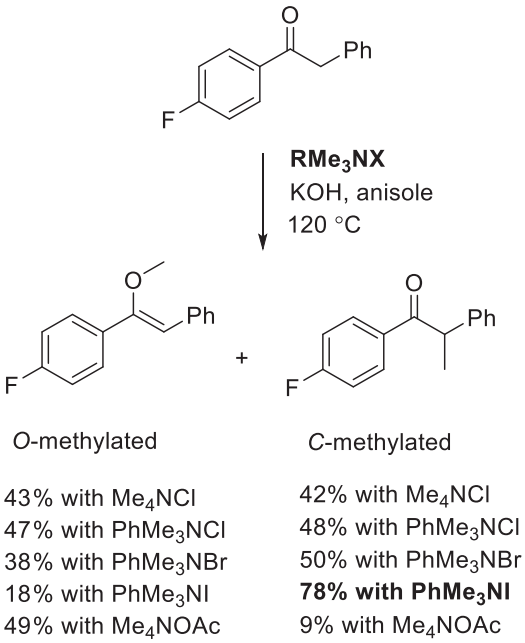


Figure 3. α-methylation of 1,2-diphenylethan-1-one derivatives with **tetramethylammonium chloride** and **trimethylphenylammonium chloride**.[3]

The Heck reaction sometimes also uses quaternary ammonium salts (**tetraethylammonium bromide**) as solid olefin precursors under ambient conditions, eliminating the need for ethylene gas (**Figure 4**). These salts enable a safe, convenient, one-pot process with broad applicability for research and discovery, offering improved practicality over traditional gas-based protocols.[4]

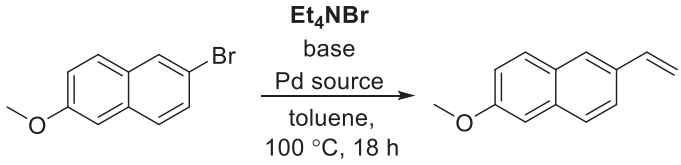


Figure 4. Heck reaction to generate 2-methoxy-6-vinylnaphthalene using **tetraethylammonium bromide** as a pseudo-ethylene source.[4]

Methylation of C(sp²)−H bonds was achieved through the Ni(II)-catalyzed reaction of benzamides with **phenyltrimethylammonium bromide** or phenyl trimethylammonium iodide as the source of the methyl group. The reaction has a broad scope and shows high functional-group compatibility. The reaction is also applicable to the methylation of C(sp³)-H bonds in aliphatic amides (**Figure 5**).[5]

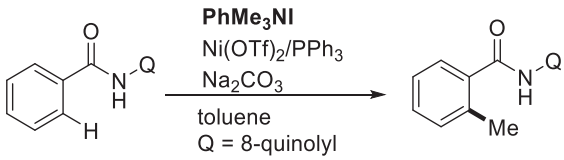


Figure 5. α-C methylation using **trimethylphenylammonium bromide**.[5]

A simple, efficient and eco-friendly procedure has been developed using **tetrabutylammonium bromide (TBAB)** as catalyst for the synthesis of biscoumarin and dihydropyrano[*c*]chromene derivatives in water and solvent-free/ neat conditions. This methodology offers several advantages over conventional methods such as excellent yields, short reaction time and environmentally benign milder reaction conditions (**Figure 6**).[6]

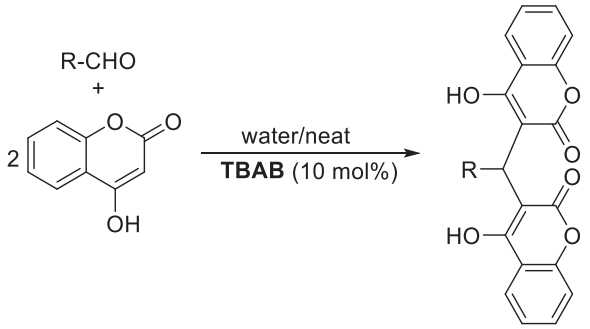


Figure 6. Synthesis of biscoumarin derivatives using **tetrabutylammonium bromide**.[6]

Recent work by Keenan and co-workers presents an efficient, scalable phase transfer catalyzed C5 alkylation of hydantoins using **tetrabutylammonium bromide (TBAB)** as the catalyst. TBAB enables high yields under mild, sustainable conditions and broad electrophile scope. Its simplicity, low cost, and adaptability, including potential enantioselective variants, underscore its utility in phase transfer catalyzed hydantoin functionalization (**Figure 7**).[7]

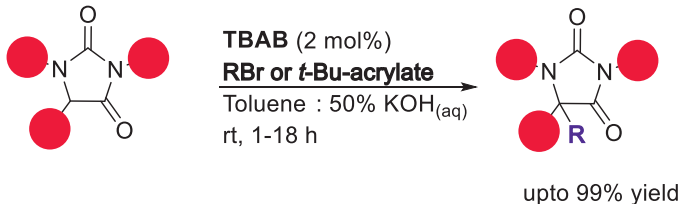


Figure 7. C5 alkylation of hydantoins using **tetrabutylammonium bromide** in biphasic conditions.[7]

Tetrabutylammonium bromide (TBAB) enhances Sonogashira-coupling of *N*-tosyl aryltriazenes by acting as a dual activator for both the palladium catalyst and aryltriazene substrate. **TBAB** improves oxidative addition, broadens functional group tolerance, and delivers high yield arylalkyne formation under efficient, operationally simple conditions (**Figure 8**).[8] *N*-tosyl aryltriazenes by acting as a dual activator for both the palladium catalyst and aryltriazene substrate. **TBAB** improves oxidative addition, broadens functional group tolerance, and delivers high yield arylalkyne formation under efficient, operationally simple conditions.

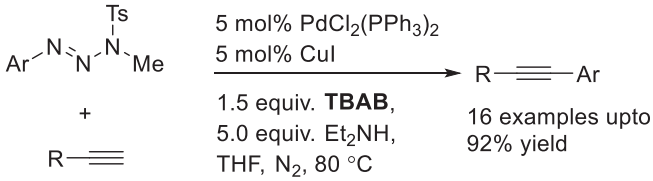


Figure 8. Highly efficient Sonogashira-coupling of an aryltriazene using **tetrabutylammonium bromide** as a PTC.[8]

Benzyltriethylammonium chloride (BTEAC) has been shown to be extremely effective in the reaction of α-halocarbanions with aldehydes and ketones to produce oxiranes (the Darzens reaction **Figure 9**).[9]

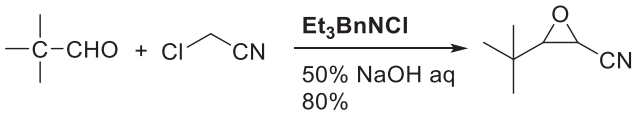


Figure 9. Synthesis of cyano-substituted oxiranes using **benzyltriethylammonium chloride**.[9]

Quaternary ammonium salts (**Tetraethylammonium bromide**) can also be used as practical phase transfer alkylating reagents in Rh- or Ru-catalyzed C–H activation (**Figure 10**).[10] Through *in situ* Hofmann elimination, these solid PTCs generate olefins, enabling efficient alkylation without gaseous reagents and broad applicability across directing groups and catalysts.

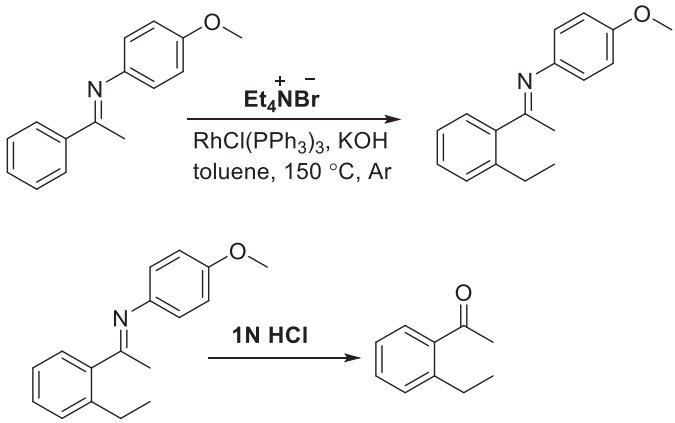


Figure 10. Imine-directed C–H alkylation reaction with **tetraethylammonium bromide** as an alkyl source.[10]

Phase-transfer catalysis accelerates the biphasic Wittig reaction by enhancing interphase ion transfer and mass transport. The study employs **benzyltriphenylphosphonium bromide** as the PTC to drive faster, more efficient two-phase conversions (**Figure 11**).[11]

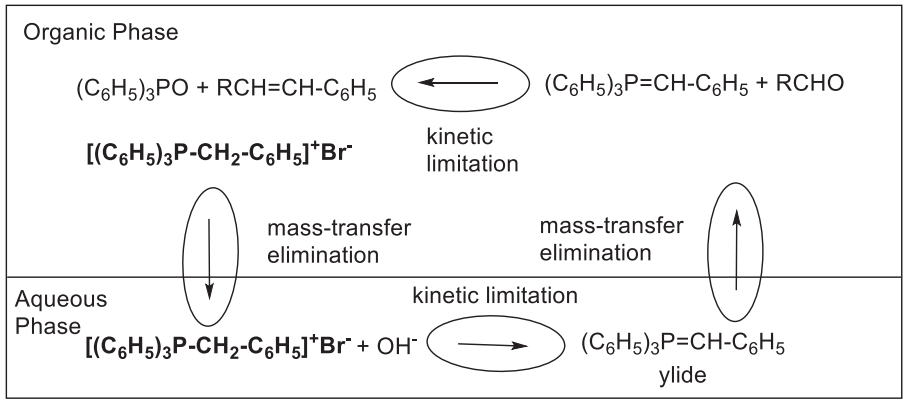


Figure 11. Wittig reaction of **benzyltriphenylphosphonium bromide** and benzaldehyde (mass transfer and kinetic steps).[11]

Nucleophilic Substitution & Alkylation Reactions

PTCs enhance the reactivity of anionic nucleophiles, making O-, N-, S- and halide substitutions faster, cleaner, and more selective. Explore how crown ethers and quaternary ammonium salts unlock efficient S_N2, alkylation, and heterocycle functionalization pathways across diverse substrates.

Quaternary ammonium salts can serve as safer alkylating agents that enable *O*, *N* and *C* alkylation reactions under phase transfer conditions. They support late-stage functionalization, introduce methyl or alkenyl groups, and facilitate downstream transformations such as cyclopropanation, epoxidation, and radical processes, expanding PTC applications in synthesis and materials chemistry (**Figure 12**).[12]

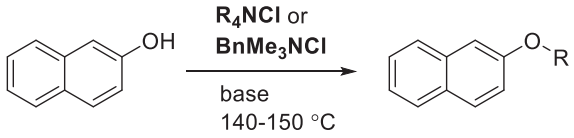


Figure 12. *O*-alkylation of naphthenol using **Benzyltrimethylammonium chloride**.[12]

González-González et al. utilized **Tetradecyltrimethylammonium bromide** to methylate various *N*-heterocycles in toluene under basic conditions at reflux temperatures, obtaining the *N*-methylated products in 43 to 97% yield (**Figure 13**).[13]

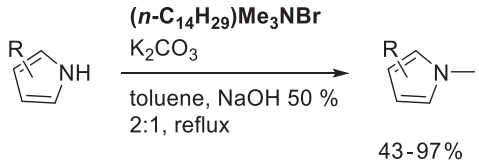


Figure 13. Methylation of *N*-heterocycles including pyroles using **Tetradecyltrimethylammonium bromide**.[13]

A pioneering work on *N*-methylation using ammonium salts was published in 2022 by the group of Schönebeck. They employed **tetramethylammonium fluoride** (Me_4NF) in toluene at 100 °C to methylate various nucleophiles including amides, indoles, alcohols, thiophenols, pyrroles, and imidazoles, with a focus on the first two compound classes (**Figure 14**).[14]

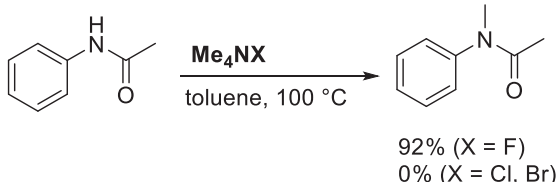


Figure 14. *N*-methylation of *N*-phenylacetamide with **tetramethylammonium fluoride**.[14]

Benzyltriethylammonium chloride (BTEAC) acts as a PTC to enable a rapid, ultrasonic assisted *S*-alkylation of bromobenzofuran oxadiazoles, delivering high yields (75–88%). BTEAC significantly accelerates thiol-alkyl halide coupling under mild conditions, providing efficient access to bioactive scaffolds (**Figure 15**).[15]

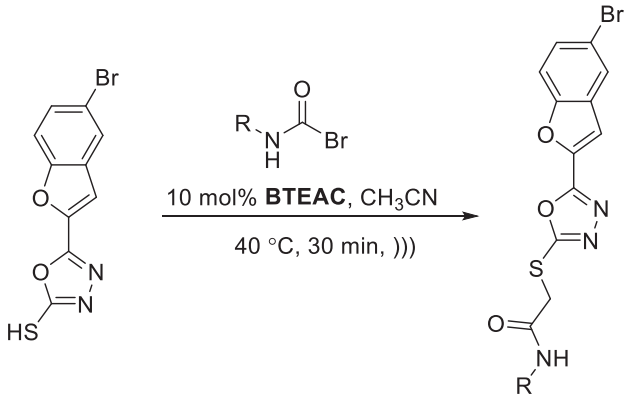


Figure 15. Ultrasonic assisted synthesis of *S*-alkylated bromobenzofuran-oxadiazole structural hybrids catalyzed by **benzyltriethylammonium chloride**.[15]

This method employs **tetramethylammonium bromide** or **tetraethylammonium bromide** as PTCs for efficient *S*-alkylation of arylthioureas, producing 68 *S*-substituted aryl isothioureas in good to excellent yields under metal-free conditions. It offers broad functional group tolerance, simple execution, and uses readily available starting materials, enabling synthesis of biologically and pharmaceutically relevant compounds (**Figure 16**).[16]

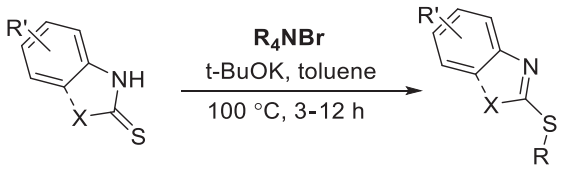


Figure 16. *S*-alkylation of arylthiourea using **tetraethylammonium bromide** or **tetramethylammonium bromide**.[16]

Research has shown that **18-crown-6** enables the solubilization of potassium fluoride in aprotic solvents, generating highly reactive "naked" fluoride. This crown activated fluoride acts as a strong nucleophile and base, efficiently promoting S_N2, elimination, and aromatic substitution reactions to form organic fluorides in high yields under mild conditions.

Recent study demonstrates that **18-crown-6** activates potassium fluoride by enhancing its solubility and nucleophilicity, enabling more efficient S_N2 fluorination of alkyl halides. When combined with bulky diols, **18-crown-6** significantly increases reaction rates and selectivity, offering an improved approach to KF based nucleophilic fluorination with minimal elimination byproducts (**Figures 17** and **18**).[17]

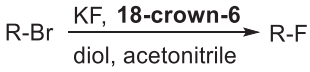


Figure 17. Nucleophilic fluorination using **18-crown-6**.[17]

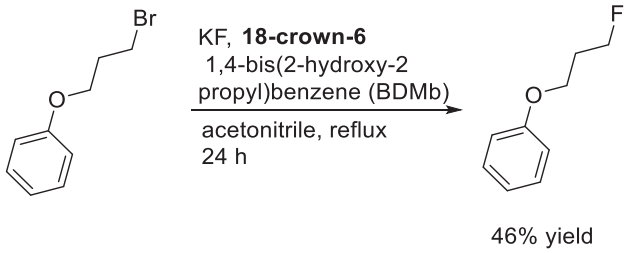


Figure 18. Synthesis of (3-fluoropropoxy)benzene using **18-crown-6**.[17]

PTCs can often increase reaction rates significantly. In the displacement reaction of 1-chlorooctane with aqueous sodium cyanide is accelerated many thousand-fold by the addition of **tributylhexadecylphosphonium bromide** as a PTC (**Figure 19**).[18]

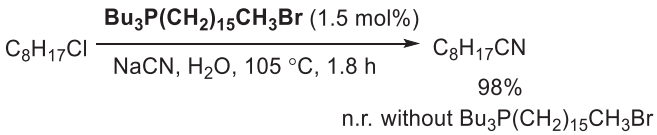


Figure 19. Substitution reaction of chlorooctane using **tributylhexadecylphosphonium bromide** as a PTC. No reaction occurs without the presence of PTC.[18]

Quaternary ammonium salts as high boiling, green phase transfer alkylating agents enabling rapid, solvent free *N*-alkylation of azaheterocycles under microwave irradiation. In the presence of K_2CO_3, these PTCs provide excellent yields within minutes, offering an efficient, sustainable alternative to traditional alkyl halides (**Figure 20**).[19]

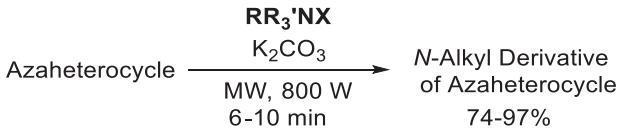


Figure 20. *N*-Alkylation of azaheterocycles by quaternary ammonium salts in the presence of K_2CO_3 under MW irradiation.[19]

Tetramethylammonium fluoride (TMAF) can act as an efficient phase transfer type methylating reagent that selectively methylates amides, *N*-heterocycles, thiols, and alcohols (**Figure 21**).[20] Acting through a fluoride assisted concerted deprotonation–methyl transfer pathway, TMAF enables metal free, chemoselective methylation with broad substrate scope and simple purification.

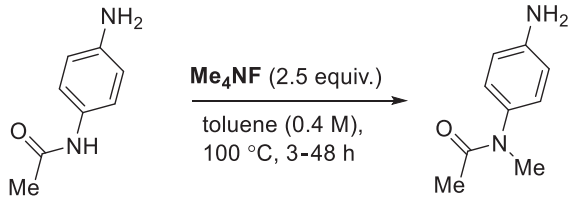


Figure 21. Chemoselective *N*-methylation of amides using **tetramethylammonium fluoride**.[20]

Tetramethylammonium hydroxide can act as an efficient, green phase transfer methylating agent for rapid, selective *O*-methylation of phenolic compounds (**Figure 22**).[21] Under microwave conditions in ethanol, TMAH enables high yield aryl methyl ether formation without strong bases, minimizing byproducts and offering broad substrate compatibility under environmentally benign reaction conditions.

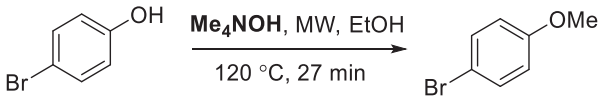


Figure 22. *O*-methylation of *p*-bromophenol using **tetramethylammonium hydroxide solution** under MW irradiation.[21]

Quaternary ammonium salts, especially **tetramethylammonium chloride** and **benzyltrimethylammonium chloride**, acts as phase transfer alkylating reagents for phenols, enabling efficient *O*-methylation and *O*-benzylation (**Figure 23**).[22] Under high temperature PEG or diglyme conditions with base, these PTCs promote selective ether formation and even double bond isomerization in allyl substituted phenols.

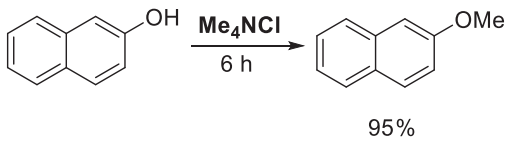


Figure 23. O-methylation of β-napthol using **tetramethylammonium chloride** reagent under MW irradiation.[22]

18-crown-6 acts as an efficient PTC, forming "naked" cyanide ions by solubilizing KCN in aprotic solvents (**Figure 24**).[23] This dramatically enhances nucleophilicity, enabling rapid, high-yield substitution, elimination, and hydrocyanation reactions of organic halides under mild conditions, outperforming traditional PTC and DMSO-based methods.

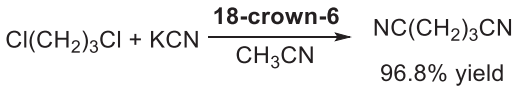


Figure 24. Cyanation of 1,3-dichloropropane in presence of **18-crown-6**.[23]

Kryptofix® 222 enables efficient nucleophilic ^{18}F radiolabeling during PET radiotracer synthesis, enhancing fluoride reactivity and FDG (fludeoxyglucose) yield. It is essential for producing PET tracers (**Figure 25**).[24]

Figure 25. Synthesis of ^{18}F-FDG by nucleophilic substitution in the presence of **Kryptofix® 222**.[24]

Redox & Radical Chemistry

Phase-transfer catalysis streamlines oxidation and radical processes by improving the movement of oxidants and reactive intermediates into organic media. This category covers TBAI-driven oxidative couplings, peroxide activation, carbene chemistry, and other high-efficiency PTC-enabled transformations.

Tetrabutylammonium iodide (TBAI) has also been shown to be an efficient, inexpensive, metal free catalyst for oxidative coupling of enol acetates with sodium sulfinates, enabling mild, greener synthesis of β-keto sulfones. **TBAI** promotes *tert*-butyl hydroperoxide (TBHP) driven radical generation, delivering high yields, broad substrate scope, and environmentally benign reaction conditions (**Figure 26**).[25]

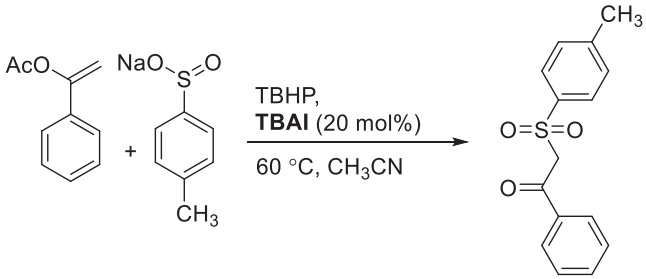


Figure 26. Synthesis of 1-phenyl-2-tosylethan-1-one using **tetrabutylammonium iodide** as a PTC.[25]

TBAI enables an efficient, metal free one pot synthesis of β-keto sulfones via oxidative sulfonylation of enol acetates with sodium sulfinates using TBHP at 60 °C. This mild, inexpensive, and environmentally friendly protocol delivers diverse β-keto sulfones with operational simplicity (**Figure 27**).[25]

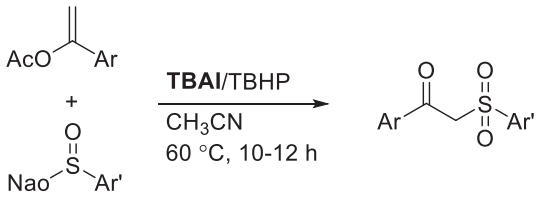


Figure 27. One-pot synthesis of β-keto sulfones using **tetrabutylammonium iodide**.[25]

Tetrabutylammonium iodide (TBAI) enables efficient, mild, and regioselective dioxygenation of 1,3 butadienes by activating hydroperoxides without dry conditions. As a versatile phase transfer catalyst, **TBAI** enhances peroxide transfer, broadens substrate compatibility, and delivers high yield hydroxyperoxidate formation for streamlined synthetic workflows (**Figure 28**).[26]

Figure 28. Synthesis of hydroxyperoxidates using **tetrabutylammonium iodide** as a PTC.[26]

Quaternary ammonium phase transfer catalysts, like, **Benzyltriethylammonium chloride (BTEAC)** enable highly efficient generation of dichlorocarbene from chloroform and aqueous NaOH, delivering significantly higher yields than conventional base-solvent systems (**Figure 29**).[27] Under PTC conditions, DCC decomposition by NaOH is minimal, making the process cleaner and more productive.

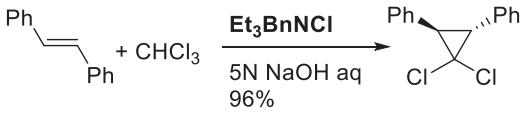


Figure 29. Synthesis of ((1*R*,2*R*)-3,3-dichlorocyclopropane-1,2-diyl)dibenzene using **benzyltriethylammonium chloride**.[27]

Methyltrioctylammonium chloride act as highly effective PTCs, enabling rapid anion transfer from aqueous to organic phases (**Figure 30**).[28] PTC accelerates permanganate oxidation by shuttling MnO_4^- into the organic phase, eliminating phase separation limitations and enabling fast, high yield conversion of olefins to carboxylic acids.

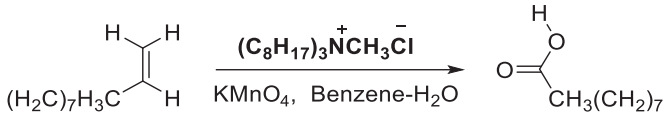


Figure 30. Oxidation of 1-decene to nonanoic acid using **methyltrioctylammonium chloride**.[28]

Polymer, Materials & Specialty Systems

PTCs support polymer growth, hydrogel structuring, and specialty material synthesis by enhancing ion transport and microenvironment control in multiphase systems. These applications demonstrate how PTCs enable higher molecular weights, tunable network properties, and efficient biphasic materials processing.

Phase transfer catalysis enables efficient two phase polycondensation of cyclotriphosphazene acid chlorides with bisphenol A, producing high molecular weight polyesters. Using **benzyltriethylammonium chloride** facilitates polymer growth, especially from the trans isomer, giving polymers with improved structural incorporation and thermal stability compared to other polycondensation methods (**Figure 31**).[29]

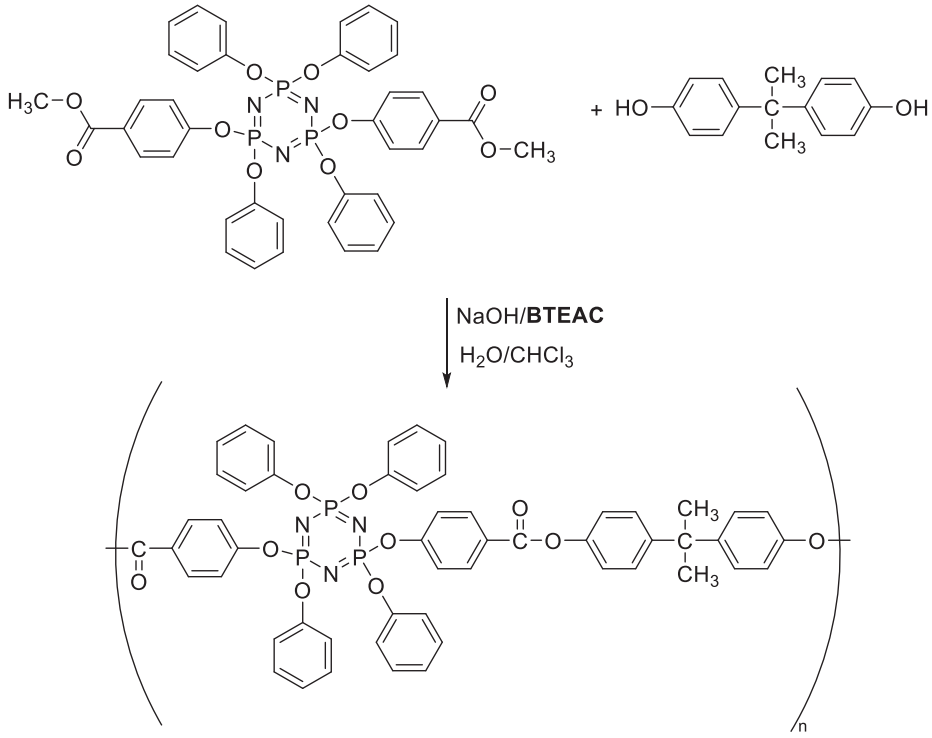


Figure 31. Production of high-molecular-weight polyester using **benzyltriethylammonium chloride**.[29]

Recent studies demonstrated that **Hexadecyltrimethylammonium chloride (CTAC)** creates denser hydrogel networks via enhanced counterion dissociation. Surfactant–polymer systems like CTAC/HPMC can be used as tuneable media for organic reactions, controlled release, gel supported catalysis, and encapsulation of hydrophobic organic molecules (**Figure 32**).[30]

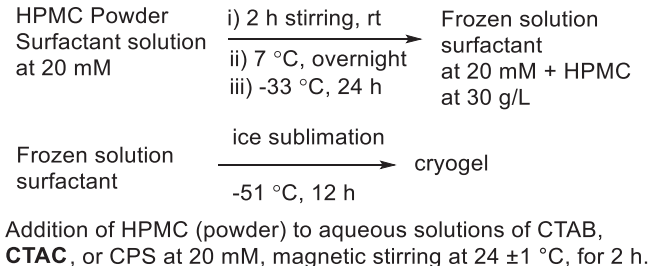


Figure 32. Synthesis of hydrogel networks using **hexadecyltrimethylammonium chloride**.[30]

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