ORGANIC PROCESS RESEARCH & DEVELOPMENT
OPR&D
Review
pubs.acs.org/OPRD

Sustainable Oxidations under Phase-Transfer Catalysis Conditions

Domenico C. M. Albanese,*[,†] Francesca Foschi,[‡] and Michele Penso[‡]

[†]Department of Chemistry, Università degli Studi di Milano, via Golgi 19, 20133 Milano, Italy
[‡]Institute of Molecular Science and Technologies (ISTM-CNR), via Golgi 19, 20133 Milano, Italy

ABSTRACT: Phase-transfer catalysis (PTC) is a well-known useful tool to develop sustainable processes. Benefits deriving from using PTC are particularly evident in oxidation chemistry where it has been possible to replace many toxic, aggressive reagents with harmless and milder oxidants such as bleach or hydrogen peroxide.

1. INTRODUCTION

Phase-transfer catalysis (PTC) is nowadays a well-established methodology to perform reactions using environmentally benign reagents and solvents. Reactions are carried out in a heterogeneous, mutually immiscible two-phase system, in which one phase provides anions or a base for their generation, whereas the second phase contains the organic reactant and the PT catalyst, usually a lipophilic quaternary ammonium or phosphonium salt. The reacting anion can thus be brought to the organic phase where the reaction occurs.[1]

Mild reaction conditions, safety, operational simplicity, and high selectivity are widely accepted typical features of PTC processes that allow an easy scale-up of reactions. Indeed, numerous industrial applications,[2] e.g., in pharmaceutical and agrochemical industry, as well as in monomer synthesis and polymer modification[3] have been developed. More than four decades have passed since the landmark paper of Starks describing PTC was published.[4] Nevertheless, many new applications, both academic and industrial, show that this methodology is continuously appreciated as a valuable tool for organic synthesis. Moreover, the great development in asymmetric PTC reactions has enormously increased the synthetic potential of this methodology.

This microreview will focus on oxidative transformations carried out under PTC conditions. The oxidation will be considered in a broad sense. Since oxidation is defined as a chemical reaction which causes carbon to decrease electron density, reactions that break bonds between carbon atoms and less electronegative atoms (hydrogen), forming bonds with more electronegative atoms (i.e., oxygen, halogen) will be described. Therefore, not only classical oxidation reactions, but halogenations and C−H activation will also be covered.

This review does not intend to be exhaustive, but it will present selected subjects in order to illustrate the great potentiality of PTC in the field of oxidation.

2. OXIDATION

In spite of the paramount importance of oxidation processes in converting hydrocarbons to useful chemicals, they have been mostly exploited by using toxic metal oxidants such as the hexavalent chromium salts. Furthermore, not environmentally friendly and expensive stoichiometric organic oxidants have been employed, thus generating the desired product along with huge amounts of byproducts to be disposed of.[5] The choice of the oxidant is undoubtedly the main factor that defines the sustainability of an oxidation reaction. Although molecular oxygen is an ideal oxidant, it also often exhibits poor selectivity due to competitive combustion. Moreover, conversions should be kept low to control overoxidation and heat generation.

On the other hand, sodium hypochlorite and hydrogen peroxide have emerged as useful reagents to perform oxidations under mild reaction conditions and without metallic waste. Bleach is particularly inexpensive as witnessed by its use to inhibit microbial growth in swimming pools, whereas H_2O_2 has recently been used in the manufacture of bulk chemicals such as propylene oxide.[6] Indeed, the progress of process technology and the increasing economies of scale allowed the manufacturing cost of H_2O_2 to decrease. Moreover, new promising methods will probably make this reagent still cheaper.[7]

2.1. Hydrogen Peroxide.

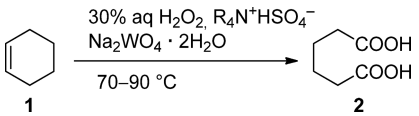
Excluding oxygen, H_2O_2 is the most valuable oxidant with an atom efficiency of 47%, generating water as the only byproduct. Lipophilic quaternary ammonium salts such as Aliquat 336 or $Hex_4N^+Br^-$ are capable to efficiently extract H_2O_2 from the aqueous to the organic phase, allowing fast oxidation reactions under PTC conditions. In some cases the H_2O_2 oxidation processes are accelerated by the addition of molybdates or wolframates as cocatalysts.[8]

For example, a halide and organic solvent free oxidation of primary and secondary alcohols with H_2O_2 under liquid−liquid (LL) PTC conditions afforded the corresponding carboxylic acids and ketones with high yields in short reaction times.[9]

The direct oxidation of cyclohexene **1** to adipic acid **2** is one of the most remarkable oxidation reactions under PTC conditions (Scheme 1).[10]

In fact, adipic acid is manufactured as much as 3.5 million tons, mainly for nylon-6.6 production. However, the classical commercial process relies on a hazardous cyclohexane air oxidation providing a mixture of cyclohexanol and cyclo-

Scheme 1. Cyclohexene Route to Adipic Acid



Received: November 20, 2015

DOI: 10.1021/acs.oprd.5b00385
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

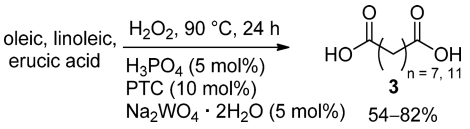
hexanone, followed by nitric acid oxidation that generates large amounts of the greenhouse gas N_2O as byproduct.[11] The cyclohexene route, originated from the development of selective hydrogenation of benzene to cyclohexene, enables a more efficient approach requiring less hydrogen and generating lower amounts of byproducts.

The cyclohexene oxidation proceeds through extraction in the organic phase of a bisperoxotungstate species, initially formed in the aqueous phase by $Na_2WO_4{\cdot}2H_2O$ and 30% H_2O_2, by the quaternary ammonium salt. After releasing oxygen, the reduced monoperoxo tungstate ion is reoxidized by H_2O_2 to initiate a new cycle.[12]

Although the cyclohexene pathway can solve environmental and safety problems related to the current commercial process, it still does not appear to be competitive due to the low selling price of adipic acid.[13] Several other approaches have been investigated by using organic ligands or acidic promoters, instead of PT catalysts, even in flow processes.[14]

Unsaturated fatty acids have been oxidized under acidic PTC conditions by reaction with 30% H_2O_2, in the absence of organic solvents, affording moderate to good yields of the related dicarboxylic acids **3** (Scheme 2).[15]

Scheme 2. Oxidation of Unsaturated Fatty Acids



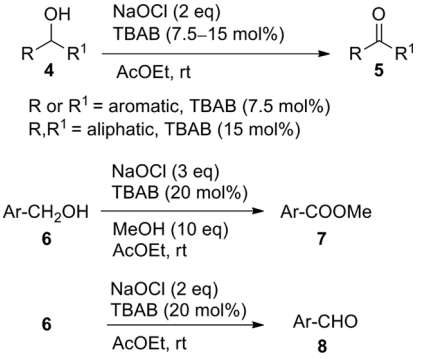
This protocol allows the synthesis of carboxylic acids from renewable feedstocks and constitutes a more sustainable approach to this class of compounds currently generated by oleic acid ozonolysis that suffers from huge energy demand, toxicity of ozone, and safety risks.[16]

Hydrogen peroxide has also been used for the one-pot conversion of cyclohexanol to ε-caprolactam in the presence of ammonium tungstophosphoric salt (n-$C_{16}H_{33}NMe_3$)-$H_2PW_{12}O_{40}$.[17]

Although an ammonium sulfate free technology has been developed, based on ENI TS-1 ammoximation followed by catalytic rearrangement,[18] caprolactam is manufactured mainly by the cyclohexanone oxime process generating huge amounts of ammonium sulfate and suffering from corrosion caused by fuming sulfuric acid. Therefore, this approach may results in a simple and practical approach to the synthesis of ε-caprolactam.

2.2. Sodium Hypochlorite. Oxidations of alcohols to aldehydes/ketones or carboxylic acids with aqueous NaClO under PTC conditions have been previously reported.[19] More recently the same reactions have been investigated under continuous flow conditions at room temperature (rt) by mixing an organic solution of the substrate and $Bu_4N^+Br^-$ (TBAB) with 12.6% sodium hypochlorite.[20] Biphasic reactions in flow benefit from high surface area to volume ratio providing better mass and heat transfer. Secondary aliphatic and benzylic alcohols **4** can be oxidized to ketones **5**, whereas benzylic alcohols **6** can be selectively oxidized to esters **7** or aldehydes **8**, depending on the reaction conditions (Scheme 3). In fact, when the same reactions have been carried out in the presence of excess MeOH, the methyl esters were obtained, likely through the oxidation of a hemiacetal formed in situ. Complete conversions can be obtained in short reaction times (5−30 min).

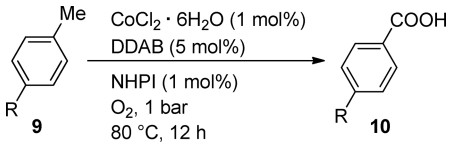
Scheme 3. Oxidation of Alcohols in Flow under PTC Conditions



The production rate of these reactions has been increased up to 700 times by the proper choice of the microreactor.[21]

2.3. Oxygen. The solvent free autoxidation of methylbenzenes **9** to benzoic acids **10** has been obtained with high conversion in the presence of $CoCl_2{\cdot}6H_2O$, *N*-hydroxyphthalimide (NHPI), and didecyl dimethylammonium bromide (DDAB) by sparging oxygen through the solution at 80 °C (Scheme 4).[22]

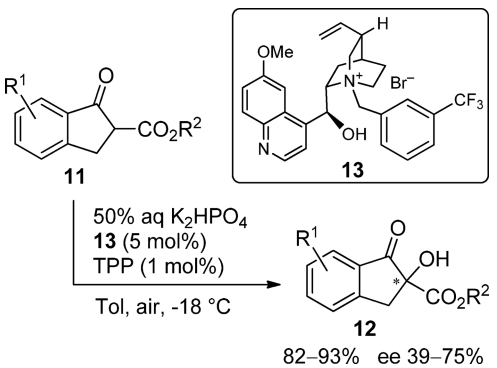
Scheme 4. Solvent-Free Autoxidation of Methylbenzenes



This ternary catalytic system outperformed previous results in NHPI promoted autoxidation of hydrocarbons since the PT catalyst allows the solubilization of NHPI (otherwise poorly soluble in apolar media), at the same time preventing its degradation.[23] Indeed, after complete conversion, the reaction started again at the same rate when a second batch of the starting material was added.

Photooxygenation of β-keto esters **11** through air oxidation in the presence of tetraphenyl porphine (TPP) as a sensitizer afforded hydroxylated compounds **12** in high yields and good ee's under LL-PTC conditions, with a cinchonine based ammonium salt **13** (Scheme 5).[24] The authors provided evidence for the involvement of $^1O_2$ in the hydroxylation reaction.

Scheme 5. Hydroxylation of β-Keto Esters

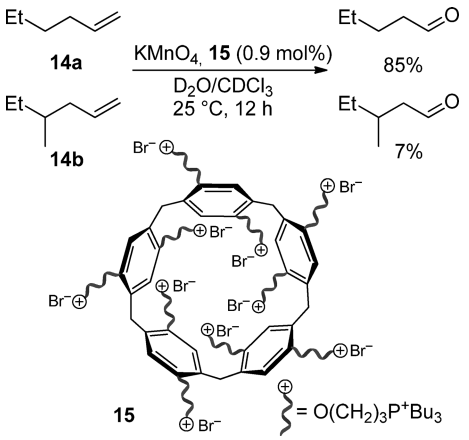


DOI: 10.1021/acs.oprd.5b00385
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

The same authors had previously described the hydroxylation of β-keto esters with a cinchonine based ammonium salt and commercially available cumyl hydroperoxide as oxidant.[25]

2.4. Potassium Permanganate. Potassium permanganate oxidation of alkenes has been an established reaction since the dawn of PTC. A new pillar[5]arene macrocyclic PT catalyst **15** has recently shown high substrate selectivity in the oxidative cleavage of linear short alkenes in the presence of branched alkenes (Scheme 6).[26] The authors ascribed the selectivity

Scheme 6. Substrate Selective Oxidation of Alkenes



observed in the competitive oxidation of 1-hexene to 1-pentanal and 4-methyl-1-hexene to 3-methyl-1-pentanal (85/7) to the host–guest complexation between the catalyst and the olefin.

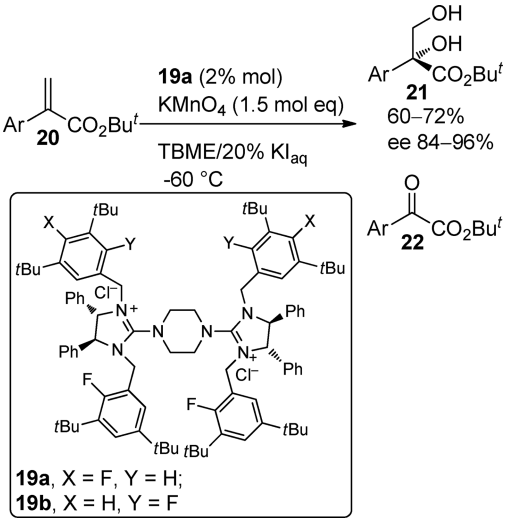
A new approach to asymmetric dihydroxylation has been explored through the permanganate promoted oxidative cyclization of achiral 1,5-dienes **16a** in the presence of a chiral PT catalyst **17** that could generate tetrahydrofuran diols **18** in a single step (Scheme 7).[27]

The same approach proved less fruitful when applied to the dihydroxylation of enones **16b** since stoichiometric amounts of the PT catalyst were required to obtain good ee's.[28]

A novel dicationic bisguanidinium salt **19** has been successfully used in the enantioselective oxidation of α-aryl acrylates **20** and trisubstituted enoates **23**.[29] The catalyst has been proved to be stable under permanganate oxidation conditions, at the same time facilitating cation–anion interactions due to the highly charge localized dicationic moiety.

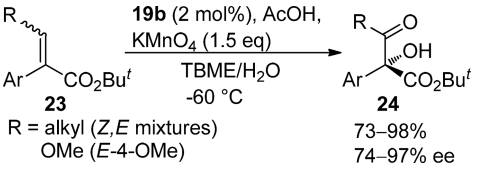
Dihydroxylation of α-aryl acrylates **20** could give access to diols **21** in moderate yields (60–72%) and high enantioselectivity (84–94%) along with *tert*-butyl 2-oxo-2-arylacetates **22** derived from the C–C oxidative cleavage (Scheme 8).

Scheme 8. Dihydroxylation of α-Arylacrylates



In the case of trisubstituted enoates **23** (*Z,E* mixture), it was found that the best results could be obtained under acidic conditions affording 2-hydroxy-3-oxo derivatives **24** in good to excellent yields and ee's (Scheme 9). The stereoselectivity obtained points out that both *Z*- and *E*- substrates were transformed to the same enantiomer.

Scheme 9. PTC Route to 2-Hydroxy-3-oxoesters

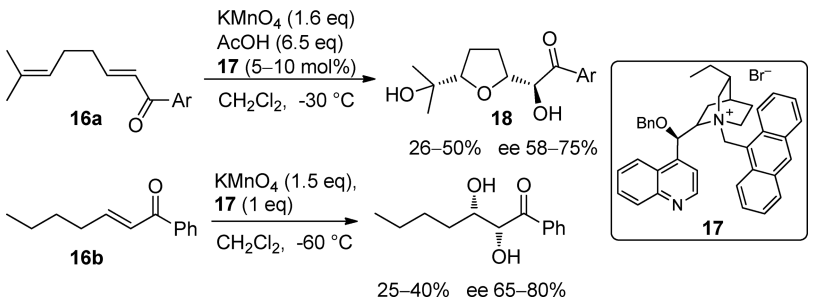


2.5. Potassium Peroxomonosulfate. Potassium peroxomonosulfate $KHSO_5$[30] is an inorganic, stable, water-soluble, and environmentally safe oxidant. It is also commercially available and inexpensive; therefore, it has been used under PTC biphasic conditions for various oxidations such as the alkene epoxidation through in situ dimethyl dioxirane generation.[31]

More recently various phenols **25** have been converted regioselectively to *o*-quinones **26** under solid–liquid (SL) PTC conditions in the presence of catalytic amount of 2-iodobenzenesulfonic acid (proIBS) and oxone as co-oxidant (Scheme 10).[32]

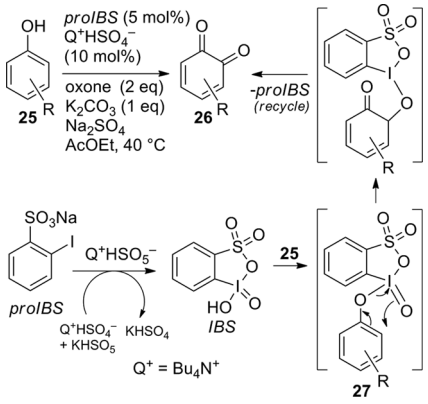
Although several examples of phenol to quinones oxidation have been previously reported, they all used stoichiometric

Scheme 7. Permanganate Promoted Asymmetric Dihydroxylation



DOI: 10.1021/acs.oprd.5b00385
Org. Process Res. Dev. XXXX, XXX, XXX–XXX

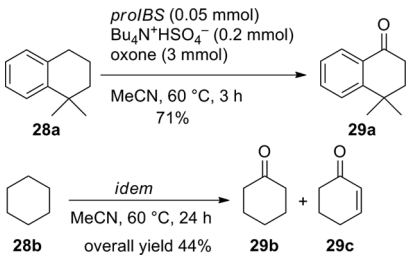
Scheme 10. Regioselective Oxidation of Phenols to 1,2-Quinones



amounts of hypervalent iodine(V) compounds and dipolar aprotic solvents such as DMF. Therefore, this PTC procedure represents a more practical and efficient method to generate these useful intermediates for the synthesis of biologically important compounds. The regioselectivity observed has been tentatively ascribed (Scheme 10) to the formation of a iodine(V)−phenol complex **27** from 2-iodoxy benzenesulfonic acid (IBS), formed in situ by oxidation of proIBS with $Bu_4N^+HSO_5^-$. After oxygen transfer and *o*-quinone **26** formation, the catalytic cycle can proceed by successive oxidations by $Bu_4N^+HSO_5^-$. It is worth noting that the same reaction afforded mainly *p*-quinones when carried out in aqueous acetonitrile.

The oxidation of benzylic methylene compounds **28** to ketones **29** was realized with good-to-excellent yields through a similar approach (Scheme 11).[33] Various alkanes were also found to be reactive, although lower yields of oxygenated products could be obtained.

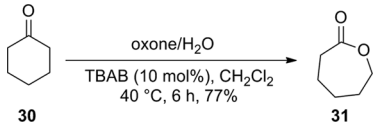
Scheme 11. IBS Catalyzed Oxidation of Benzylic Methylenes and Alkanes



One of the most remarkable features of PTC is the possibility to perform reactions in an aqueous/organic biphasic mixture without hydrolysis of sensitive organic reagents or products. In fact, water phase serves as reservoir of inorganic reagents to be extracted in the organic phase by the PT catalyst. However, the interphase protects the hydrolysis-sensitive organic compounds from hydrolysis. For example *ε*-caprolactone **31** has been prepared by oxidation of cyclohexanone **30** with oxone under LL-PTC (Scheme 12).[34]

The reaction has been performed by heating at 40 °C a heterogeneous mixture consisting of a aqueous solution of oxone with a dichloromethane solution of cyclohexanone and TBAB. It is worth noting that the conversion of **30** was higher (98%) in the absence of TBAB; however, 6-hydroxyhexanoic

Scheme 12. Bayer-Villiger Oxidation under LL-PTC Conditions

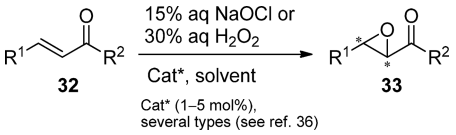


acid deriving from *ε*-caprolactone **31** hydrolysis was formed as a single product.

2.6. Epoxidation. A chiral secondary amine catalyst has been used in the epoxidation of simple olefins by using oxone as the stoichiometric oxidant under PTC conditions.[35]

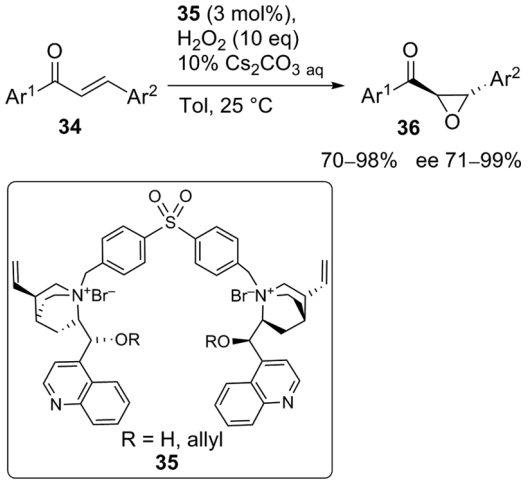
Enantiomerically enriched *α,β*-epoxyketones **33** are versatile building blocks that have been obtained previously from enones **32** with a variety of efficient strategies under PTC conditions using practical oxygen sources such as NaClO or H_2O_2 (Scheme 13).[36]

Scheme 13. Enones Epoxidation under PTC Conditions



A new type of bis-quaternary cinchonidine based ammonium bromides **35** has been used for the oxidation of a variety of chalcones **34** to the corresponding epoxides **36** with excellent yield and enantioselectivity (Scheme 14).[37]

Scheme 14. Asymmetric Synthesis of Chalcones

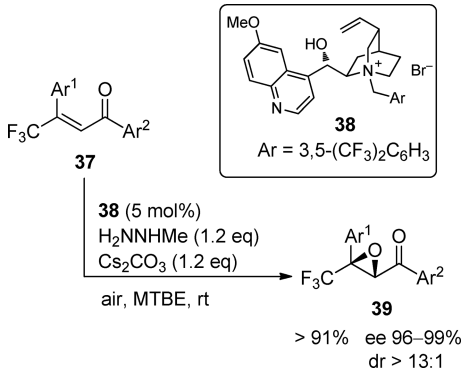


β,β-Disubstituted enones proved to be quite recalcitrant substrates toward epoxidation. In particular, *β,β*-disubstituted enones **37** bearing a trifluoromethyl group could not be converted to the corresponding epoxides **39** until the asymmetric aerobic oxidation, induced by H_2N-NHMe and catalyzed by the cinchonidinium salt **38**, was recently discovered (Scheme 15).[38] The authors proposed that this epoxidation proceeds through the in situ generation of highly reactive and pure H_2O_2. In fact, when 50% H_2O_2 was used instead of the air/base/methylhydrazine system, the same stereoselectivity was observed, although in a lower 66% yield.

A more practical approach has been developed by using 30% H_2O_2 as oxidant in the presence of a pentafluorobenzyl

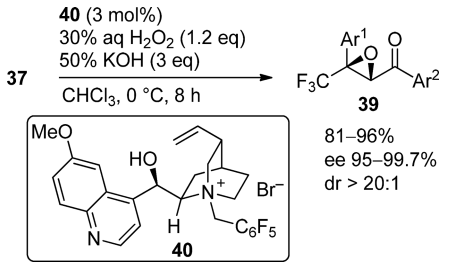
DOI: 10.1021/acs.oprd.5b00385
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

Scheme 15. Aerobic Epoxidation of β-Trifluoromethyl-β,β-disubstituted Enones



s16 quinidine-derived ammonium salt **40** (Scheme 16).[39] Also this simplified protocol, that does not use an hazardous compound

Scheme 16. Asymmetric Enone Epoxidation



such as methylhydrazine, afforded β-trifluoromethyl-α,β-epoxy ketones **39** with high yield and enantioselectivity.

Chiral octahedral complexes of Co(III) have also recently been used as catalysts for the asymmetric epoxidation of chalcones under PTC conditions, although with moderate ee's.[40]

3. HALOGENATION

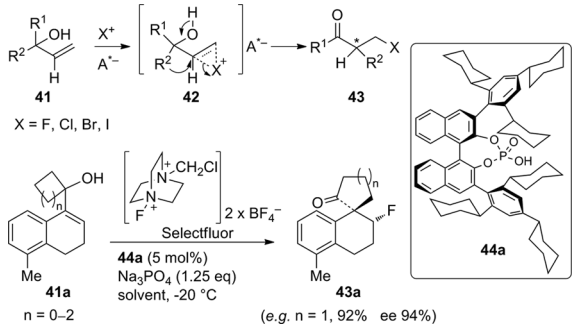
The importance of halogenated organic molecules both as intermediates for further transformations and biologically active compounds stimulated the study for alternative new syntheses of these compounds. PTC oxidative introduction of halogens is carried out by addition to an olefinic bond of a halogen cation or by methylene functionalization of activated compounds by this species and by halogen radical H substitution on a unactivated sp^3 carbon atom.

A recent paper reports the application of the asymmetric counteranion-directed catalysis[41] (ACDC) to the enantioselective synthesis of β-halogenated by semipinacol rearrange- s17 ment of α,α-disubstituted allylic alcohols **41** (Scheme 17).[42]

The intermediate haliranium cation **42** (X = F, Cl, Br, I) rearranges through a Wagner–Meerwein alkyl migration to the haloketones **43**. The haliranium formation is promoted by a chiral PT catalyst formed in situ from the anion of liposoluble enantiopure sterically crowded BINOL-phosphoric acid, with an achiral cationic insoluble halogenating agent, e.g., Selectfluor, in the fluorination reactions. This strategy allows to inhibit the undesired background reaction leading to racemic products due to poor contact between the reactant and the halogenating agent located in different phases.

For example, the strained allylic alcohol **41a** reacts with the sodium salt of nonracemic phosphoric acid **44a** and Selectfluor

Scheme 17. Synthesis of β-Halogenated Ketones



to give the spiroketone **43a** (Scheme 17). The authors propose a mechanism hypothesis based on the investigation on substituent effect and kinetic isotopic effect of the fluorination/semipinacol reaction.

ACDC promoted by TRIP and its derivatives **44** was applied to several transformations mediated by oxidative halogenation, such as the fluorination/cyclization of *N*-allyl amides to oxazolines,[43] fluorination of enamides[44] and, more recently, to the halocyclization of benzanilides such as **45a**,[45] fluorocyclization of homologue benzamides **45b** with Selectfluor and Cy-TRIP (**44a**),[46] and to the α-fluorination of cyclohexanones,[47] e.g., **46** (Scheme 18). s18

An analogous strategy was applied to the conversion of allylic alcohols **47** into the corresponding α-fluoro homoallylic alcohols **49**.[48] The fluorination–elimination process is promoted by the in situ transformation of the alcohol into an arylboronic ester **48**. This function, in conjunction with a TRIP-derived PT anionic agent, operates as temporary enantiodirecting group.

This anionic PTC concept has been also exploited for the asymmetric fluorolactonization of vinylbenzoic acids **50** to give fluorinated isobenzofuranones **52** in high ee's (Scheme 19) in s19 the presence of a new chiral binaphthyl catalyst **51**.[49]

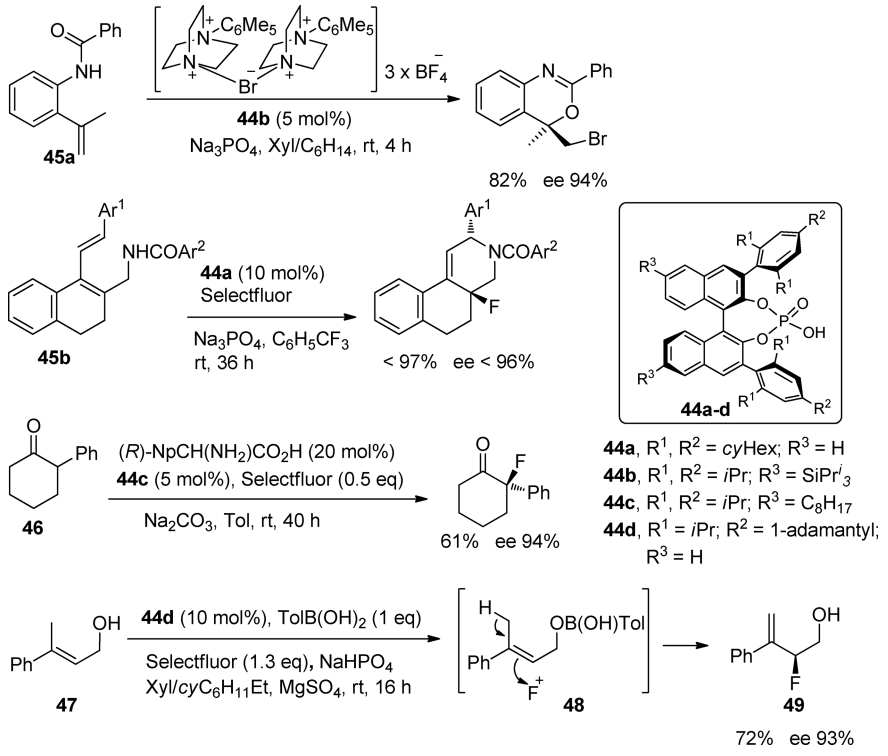
Classical cationic PTC conditions have been applied to the electrophilic α-chlorination of activated methylene compounds **53** (Scheme 20),[50] such as 1,3-diketones (X = Ar), β-keto s20 esters or amides (X = OR or NHPh), and nitriles **54**. This metal-free protocol employs NaCl as chloride source and the hypervalent iodine compound IBX-SO_3K as mild oxidant for the umpolung of halide reactivity. A lipophilic quaternary ammonium chloride as PT catalyst is necessary for good conversion of the starting material.

The asymmetric chlorination of β-keto ester **55a** has been carried out by using *N*-chloro succinimide (NCS) as chlorinating agent in the presence of a binaphthyl derived chiral phosphonium salt **56** (Scheme 20).[51] A similar activated ester **55b** was α-fluorinated with high ee's by using *N*-fluorobenzenesulfonimide (NFSI) in the presence of a PT catalyst **57** containing a urea or thiourea unit.[52] This family of asymmetric catalysts were also found to be effective in the Michael addition of glycine Schiff bases to various Michael acceptors and in the aldol-initiated cascade reaction.[53]

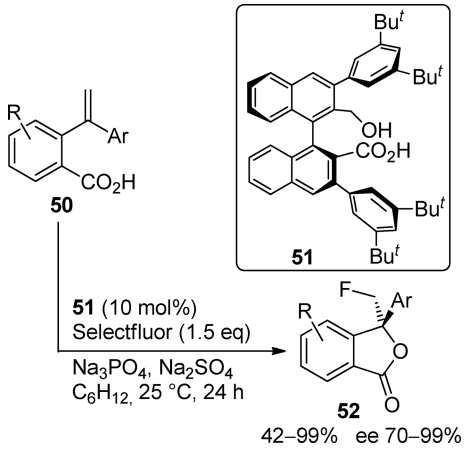
Finally, manganese tetraphenyl- and tetramesityl porphyrin promote the NaOCl chlorination of unactivated aliphatic hydrocarbons in the presence of TBAB under LL-PTC conditions.[54]

DOI: 10.1021/acs.oprd.5b00385
Org. Process Res. Dev. XXXX, XXX, XXX–XXX

Scheme 18. Asymmetric Halocyclization



Scheme 19. PTC Route to Isobenzofuranones



4. C–H ALKYLATION

In the last 25 years asymmetric PTC has become a reliable methodology to generate a variety of compounds under mild conditions. The first successful alkylation of *N*-(diphenylmethylene) glycine *tert*-butyl ester has become a standard benchmark reaction to test the new PT catalysts that have been introduced during these years. Many excellent reviews have appeared on the topic covering the literature until the middle of 2012;[55] therefore, only the latest applications are reported herein.

The alkylation of α-acetamidomalonates **58** under PTC conditions with the chiral binaphthyl catalyst **59** afforded the α-acetamido-α-alkylmalonates **60** in high yields and ee's (Scheme 21).[56] The two different ester groups, responsible for the stereoselectivity observed in the enolate alkylation, can be selectively hydrolyzed under acidic or catalytic hydrogenation and alkali basic conditions, thus facilitating further transformations toward the synthesis of various chiral compounds bearing a quaternary carbon center. More versatile α,α-dialkylmalonates **63** have been obtained through double PTC alkylation of 4-bromo benzylideneamino *tert*-butyl α-methylmalonate (**61**) since the intermediate 4-bromobenzyloxime ester **62** could be selectively hydrolyzed by 1N NaOH (Scheme 21).[57]

A new class of easily accessible positively charged Co(III) chiral complexes **65** have been used in the benchmark alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester with ee's up to 94% (Scheme 22).[58]

The nucleophilic opening of racemic 2,2-disubstituted aziridines **66** by 3-alkyl oxindoles **67**, under SL-PTC conditions, afforded the 3-alkylated compounds **68** bearing two contiguous all carbon quaternary stereocenters with excellent yields and ee's (Scheme 23).[59] This ring opening, which is catalyzed by the chiral 1,2,3-triazolium salt **69**, represents an unusual case of completely regioselective attack at the more substituted carbon of the aziridine ring.

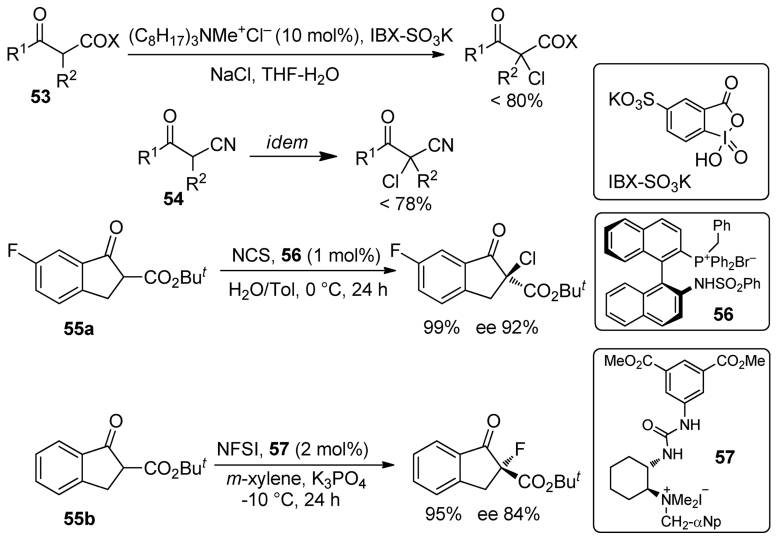
The ring opening of aziridines have also been exploited to generate quaternary carbon stereogenic atoms bearing ethylene-amino and propylene-amino moieties in a highly enantioselective and diastereoselective fashion by using a cinchona alkaloid-derived PT catalyst bearing the bulky adamantoyl ester group.[60]

A variety of indolenines **72** have been generated in good to excellent ee's from 2-(2-isocyanoaryl)-2-arylacetonitriles **70** by an intramolecular 5-*endo-dig* cyclization of the benzylic carbanion onto the *o*-isonitrile group carried out in the presence of the cinchona catalyst **71** (Scheme 24).[61]

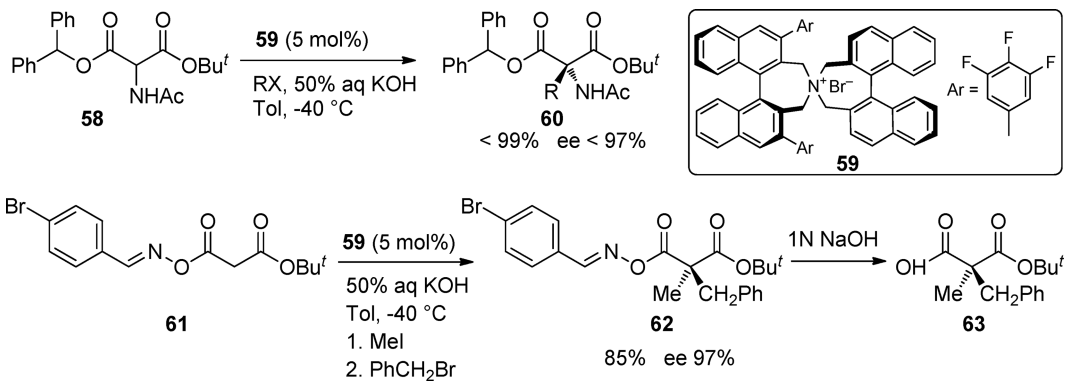
Indolenines has been reduced in situ to stable indolines **73** or reacted under acidic conditions with electron rich aromatics such as 3-(dimethylamino)phenol to give 2-substituted indolines **74** without erosion of ee. The stereoselectivity observed was strongly influenced by the PT catalyst used. The best

DOI: 10.1021/acs.oprd.5b00385
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

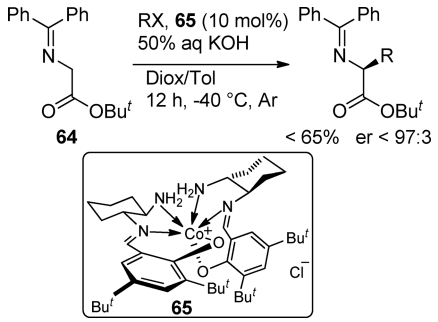
Scheme 20. Electrophilic α-Halogenation



Scheme 21. Synthesis of Enantiopure Malonates



Scheme 22. Use of Co(III) Complexes as PT Catalysts



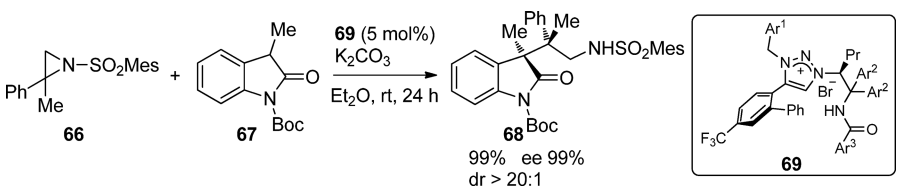
results have been obtained with a tailored bifunctional catalyst bearing a Brønsted acid site capable to activate the isonitrile, thus favoring a preorganized transition state along with the chiral cation.[62]

The enantioselective nucleophilic aromatic arylation (S_NAr) of β-keto ester **55c** with activated aromatic fluorides has been realized under PTC conditions with the benzoylated cinchonidinium salt **75** (Scheme 25).[63]

Moreover, the S_NAr of 3-aryloxindoles **76** on aryl fluorides with the binaphthyl bifunctional quaternary phosphonium bromide **77** (Scheme 26) as PT catalyst, afforded triarylmethanes **78** with good to high enantioselectivities.[64]

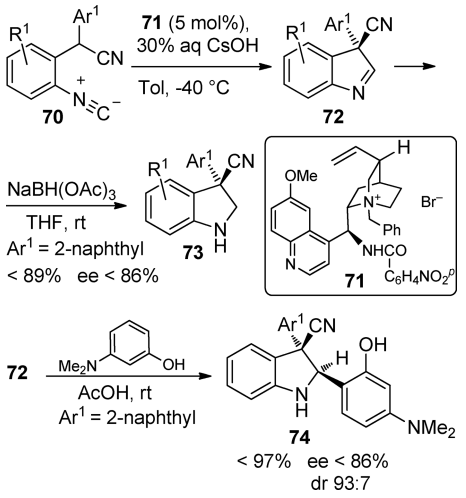
However, both methods suffer from limited scope, since only electron-deficient fluoroarenes could be employed. On the contrary, less reactive fluoroarenes could be activated by forming the corresponding arene-chromium complexes. The α-arylation of various α-amino acid derivatives **79** with chromium complexes **80** derived from electron donating fluoroarenes under LL−PTC conditions with binaphthyl modified chiral PT catalyst **81** afforded α,α-disubstituted α-amino esters **82** with good yield and high ee's after treatment with aqueous HCl for

Scheme 23. Ring Opening of Aziridines

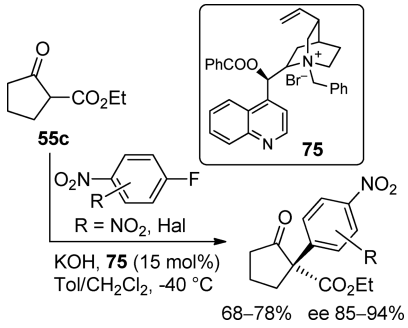


DOI: 10.1021/acs.oprd.5b00385
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

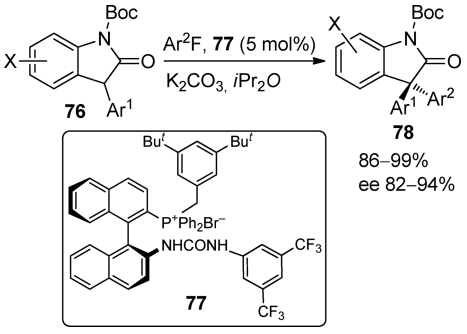
Scheme 24. Enantioselective Synthesis of Indolines



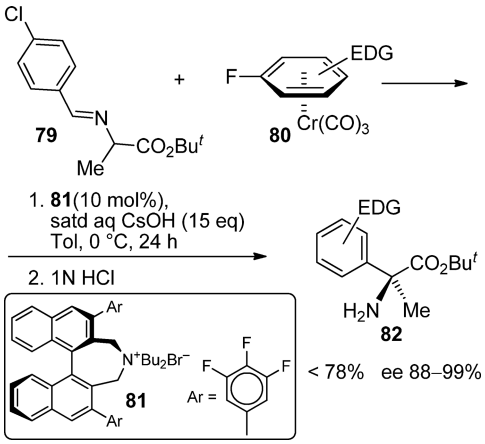
Scheme 25. S_NAr Arylation of β-Keto Esters



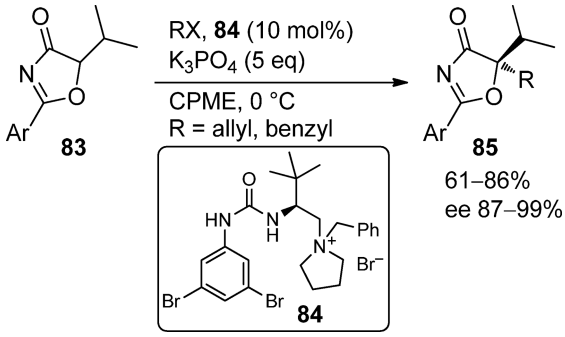
Scheme 26. S_NAr Arylation of 3-Aryloxindoles



Scheme 27. Asymmetric Arylation of α-Amino Acid Derivatives



Scheme 28. Alkylation of 5*H*-Oxazol-4-ones



hydrolysis of the imine moiety and removal of chromium (Scheme 27).[65]

A highly enantioselective alkylation of 5*H*-oxazol-4-ones **83** with benzyl and allyl bromides has been carried out under SL-PTC conditions, by using a L-*tert*-leucine derived urea-ammonium salt **84** (Scheme 28).[66] Although a huge excess of alkylating agents was required, a variety of dialkylated compounds **85** could be generated with good yields and high ee's, thus giving access to useful chiral α-hydroxy carboxylic acids or amides by simple functional group manipulations.

5. BASE-FREE PTC

Some quite reactive substrates have been recently subjected to asymmetric PT reactions in the absence of base.[67] Lipophilic bifunctional ammonium or phosphonium salts have shown to be essential for the outcome of the reactions. It is also worth noting that the aqueous−organic system is crucial to obtain high conversion. Indeed, the base-free reaction was sluggish when carried out in a homogeneous system by using various organic solvents under otherwise identical conditions. Amination of nitroolefins **86**, conjugate additions of α-substituted nitroacetates **88** to maleimide, and 3-substituted oxindoles **89** to acrolein, direct aldol reaction of α-substituted nitroacetates **88** with aqueous formaldehyde, have all been performed without base and in the presence of a binaphthyl-bifunctional PT catalyst **87** or **90**, affording the corresponding products in good to high yields and ee's (Scheme 29).

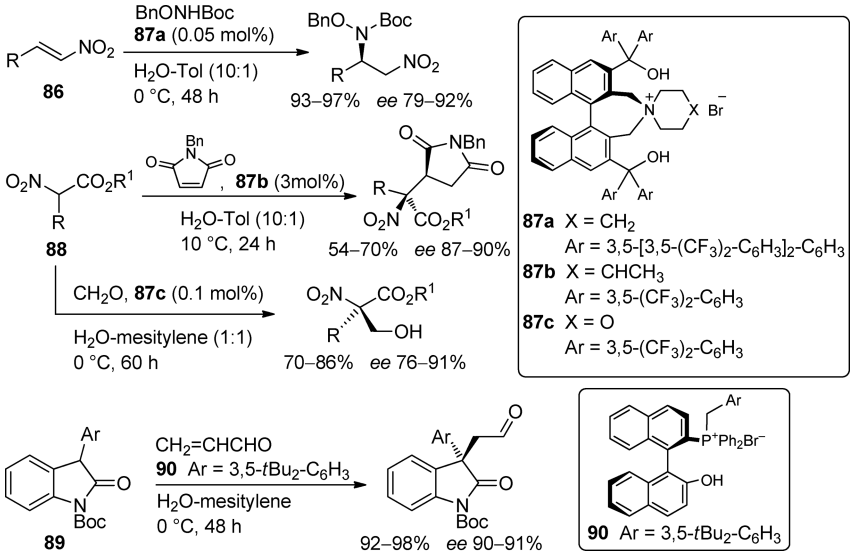
6. DEPOLLUTION

The PTC capability to extract anions from the aqueous to the organic phase has been used to destroy harmful nucleophiles (for example phenoxide and cyanide anions) present in low concentrations in aqueous waste streams.[68] The treatment of the aqueous stream with a PT catalyst and an electrophilic reagent (for example an alkyl halide) entails the 2-fold advantage of purifying the waste stream generating at the same time a saleable product, therefore increasing the profitability of the whole process (Scheme 30). The concentration of these anions in water decreased from 10 000 ppm to less than 1 ppm in 2−3 h at less than 70 °C.

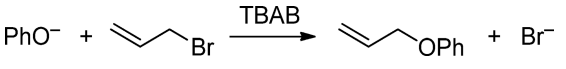
A novel technology for depollution from toxic polyhalogenated compounds has been developed by using a mixture of H_2O_2, NaOH in the presence of Aliquat 336 as PT catalyst (Scheme 31).[69] The reaction has been carried out at 298 K in an adiabatic reactor in order to take advantage of the heat released by the exothermic reaction to reach completion after

DOI: 10.1021/acs.oprd.5b00385
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

Scheme 29. Stereoselective Base-Free PTC Reactions



Scheme 30. PTC Reaction under Dilute Aqueous Conditions



Scheme 31. Haloalkane Mineralization

$$CCl_4 + 4NaOH + 6H_2O_2 \xrightarrow{\text{Aliquat 336}} Na_2CO_3 + 2NaCl + Cl_2 + 2.5O_2 + 8H_2O$$

5−10 min only (T_{max} of 343 K was reached after 1 min). Total destruction of various harmful polyhalomethanes and polyhaloethylenes has been obtained in 10 min affording solid Na_2CO_3 and NaCl.[70] Formation of chlorine has also been proved by detection of (1,2-dichloroethyl)benzene by passing the effluent gas through a styrene trap.

The results led the authors to propose a reaction mechanism involving extraction of the nucleophilic superoxide anion by the PT catalyst into the organic phase (CCl_4 or other halogenated compound) where it rapidly converts CCl_4 to Na_2CO_3 and NaCl. The technology seems to be promising for treating nonaqueous phase liquids (NAPLs) that are byproducts of many industrial processes and actually require extraction from water bulk.

7. SUMMARY AND OUTLOOK

This mini-review aims to illustrate the benefits of PTC in oxidation reactions through the most recent synthetic applications. The use of cheap and harmless oxidants such as NaClO and H_2O_2 under PTC conditions allows to develop practical procedures. Moreover, toxic heavy metal species and dipolar aprotic solvents can be avoided thus cooperating to the sustainability of the PTC method.

Many industrial manufacturing processes take advantage of this methodology in order to develop more profitable alternatives to existing procedures by reducing the amount of waste and using milder reaction conditions. Continuous processes under PTC conditions has recently been investigated through microreactors or traditional equipment.[19,71]

Chiral anionic PTC has greatly expanded the scope of asymmetric halogenation whereas it has also been discovered that some reactive substrates may react under aqueous−organic biphasic systems without the need of any added base.

Bifunctional chiral ammonium salts have emerged as powerful catalysts to promote reactions in a highly stereoselective fashion.

New concept catalysts such as cyclopropenium,[72] pentanidium,[73] and 2-oxopyrimidinium[74] PT catalysts have also been recently developed and found to be effective even in enantioselective reactions.

In summary, the results presented here witness that after decades from its blossom PTC still arouses and promises a great deal of interest both in academia and industry due to its special features facilitating the development of new reaction paths and sustainable procedures.

AUTHOR INFORMATION

Corresponding Author

*E-mail: Domenico.albanese@unimi.it.

Notes

The authors declare no competing financial interest.

REFERENCES

(1) (a) Dehmlow, E. V.; Dehmlow, S. S. *Phase Transfer Catalysis*, 3rd ed.; Wiley-VCH: Weinheim, 1993. (b) Starks, C. M.; Liotta, C. L.; Halpern, M. *Phase-Transfer Catalysis*; Chapman & Hall: New York, 1994. (c) *Handbook of Phase-Transfer Catalysis*; Sasson, Y., Neumann, R., Eds.; Blackie Academic & Professional: London, 1997. (d) *Phase-Transfer Catalysis*; ACS Symposium Series 659; Halpern, M. E., Ed.; American Chemical Society: Washington, DC, 1997. (e) Albanese, D. *Phase-Transfer Catalysis*; Kirk-Othmer Encyclopedia of Chemical Technology; 10.1002/0471238961.0301200104050813.a01.pub2.

(2) (a) Tan, J.; Yasuda, N. *Org. Process Res. Dev.* **2015**, 10.1021/acs.oprd.5b00304. (b) Bulger, P. G. In *Comprehensive Chirality*, Vol. 9; Carreira, E. M., Yamamoto, H., Eds.; Elsevier: Amsterdam, 2012.

(3) Bogdal, D.; Galica, M.; Bartus, G.; Wolinski, J.; Wronski, S. *Org. Process Res. Dev.* **2010**, *14*, 669−683.

(4) Starks, C. M. *J. Am. Chem. Soc.* **1971**, *93*, 195−199.

(5) Sheldon, R. A.; Dakka, J. *Catal. Today* **1994**, *19*, 215−245.

(6) Russo, V.; Tesser, R.; Santacesaria, E.; Di Serio, M. *Ind. Eng. Chem. Res.* **2013**, *52*, 1168−1178.

(7) Campos-Martin, M.; Blanco-Brieva, G.; Fierro, J. L. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 6962−6984.

DOI: 10.1021/acs.oprd.5b00385
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

(8) For a previous review on oxidation under PTC conditions, see: Schrader, S.; Dehmlow, E. V. *Org. Prep. Proced. Int.* **2000**, *32*, 123−152.
(9) Sato, K.; Aoki, M.; Takagi, J.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 12386−12387.
(10) (a) Sato, K.; Aoki, M.; Noyori, R. *Science* **1998**, *281*, 1646−1647. (b) Antonelli, E.; D'Aloisio, R.; Gambaro, M.; Fiorani, T.; Venturello, C. *J. Org. Chem.* **1998**, *63*, 7190−7206.
(11) The global warming potential of N_2O is around 300 times higher than that of CO_2.
(12) Noyori, R.; Aoki, M.; Sato, K. *Chem. Commun.* **2003**, 1977−1986.
(13) € 1650/t, January 2013. ICIS Pricing and ICIS News; http://www.icispricing.com/il_shared/Samples/Subpage121.asp; http://www.icispricing.com/il_home.asp.
(14) (a) Wen, Y.; Wang, X.; Wei, H.; Li, B.; Jin, P.; Li, L. *Green Chem.* **2012**, *14*, 2868−2875. and references therein. (b) Shang, M.; Noël, T.; Wang, Q.; Hessel, V. *Chem. Eng. Technol.* **2013**, *36*, 1001−1009.
(15) (a) Kadyrov, R.; Hackenberger, D. *Top. Catal.* **2014**, *57*, 1366−1371. (b) Godard, A.; Thiebaud Roux, S.; De Caro, P.; Vedrenne, E.; Moulongui, Z. Oxidative cleavage of fatty compounds. US Patent 9,090,552, Jul 28, 2015.
(16) Zaldman, B.; Kisilev, A.; Sasson, Y.; Garti, N. *J. Am. Oil Chem. Soc.* **1988**, *65*, 611−615.
(17) Wang, H.; Hu, R.; Yang, Y.; Gao, M.; Wang, Y. *Catal. Commun.* **2015**, *70*, 6−11.
(18) Izumi, Y.; Ichihashi, H.; Shimazu, Y.; Kitamura, M.; Sato, H. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 1280−1287.
(19) (a) Lee, G. A.; Freedman, H. H. *Tetrahedron Lett.* **1976**, *17*, 1641−1644. (b) Abramovici, S.; Neumann, R.; Sasson, Y. *J. Mol. Catal.* **1985**, *29*, 299−303. (c) Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559−2562.
(20) Leduc, A. B.; Jamison, T. F. *Org. Process Res. Dev.* **2012**, *16*, 1082−1089.
(21) Zhang, Y.; Born, S. C.; Jensen, K. F. *Org. Process Res. Dev.* **2014**, *18*, 1476−1481.
(22) Taha, N.; Sasson, Y. *Org. Process Res. Dev.* **2010**, *14*, 701−704.
(23) Recupero, F.; Punta, C. *Chem. Rev.* **2007**, *107*, 3800−3842.
(24) Lian, M.; Li, Z.; Cai, Y.; Meng, Q.; Gao, Z. *Chem. - Asian J.* **2012**, *7*, 2019−2023.
(25) Lian, M.; Li, Z.; Du, Y.; Meng, Q.; Gao, Z. *Eur. J. Org. Chem.* **2010**, *2010*, 6525−6530.
(26) Ogoshi, T.; Ueshima, N.; Yamagishi, T.-a. *Org. Lett.* **2013**, *15*, 3742−3745.
(27) Brown, R. C. D.; Keily, J. F. *Angew. Chem., Int. Ed.* **2001**, *40*, 4496−4498.
(28) Bhunnoo, R. A.; Hu, Y.; Lainé, D. I.; Brown, R. C. D. *Angew. Chem., Int. Ed.* **2002**, *41*, 3479−3480.
(29) Wang, C.; Zong, L.; Tan, C.-H. *J. Am. Chem. Soc.* **2015**, *137*, 10677−10682.
(30) Peroxomonosulfate is known as Caro's salt (caroate) or oxone and is best represented by the formula $2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$.
(31) (a) Curci, R.; Fiorentino, M.; Troisi, L. *J. Org. Chem.* **1980**, *45*, 4758−4760. (b) Dehmlow, E. V.; Vehre, B.; Makrandi, J. K. *Z. Naturforsch., B: J. Chem. Sci.* **1985**, *40*, 1583−1585. (c) Denmark, S. E.; Forbes, D. C.; Hays, D. S.; DePue, J. S.; Wilde, R. G. *J. Org. Chem.* **1995**, *60*, 1391−1407. (d) Aggarwal, V. K.; Lopin, C.; Sandrinelli, F. *J. Am. Chem. Soc.* **2003**, *125*, 7596−7601.
(32) Uyanik, M.; Mutsuga, T.; Ishihara, K. *Molecules* **2012**, *17*, 8604−8616.
(33) Cui, L.-Q.; Liu, K.; Zhang, C. *Org. Biomol. Chem.* **2011**, *9*, 2258−2265.
(34) Baj, S.; Chrobok, A.; Siewniak, A. *Appl. Catal., A* **2011**, *395*, 49−52.
(35) Aggarwal, V. K.; Lopin, C.; Sandrinelli, F. *J. Am. Chem. Soc.* **2003**, *125*, 7596−7601.
(36) For previous results on asymmetric epoxidation of electron-deficient olefins under PTC conditions, see: Herchl, R.; Waser, M. *Tetrahedron* **2014**, *70*, 1935−1960.
(37) Ashokkumar, V.; Balasaravanan, R.; Sadhasivam, V.; Jenofar, S. M.; Siva, A. *J. Mol. Catal. A: Chem.* **2015**, *409*, 127−136.
(38) Kawai, H.; Okusu, S.; Yuan, Z.; Tokunaga, E.; Yamano, A.; Shiro, M.; Shibata, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 2221−2225.
(39) Wu, S.; Pan, D.; Cao, C.; Wang, Q.; Chen, F.-X. *Adv. Synth. Catal.* **2013**, *355*, 1917−1923.
(40) Larionov, V. A.; Markelova, E. P.; Smol'yakov, A. F.; Savel'yeva, T. A.; Maleev, V. I.; Belokon, Y. N. *RSC Adv.* **2015**, *5*, 72764−72771 For the structure of the catalyst, see Scheme 22.
(41) (a) Mahlau, M.; List, B. *Angew. Chem., Int. Ed.* **2013**, *52*, 518−533. (b) Brak, K.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2013**, *52*, 534−561.
(42) Romanov-Michailidis, F.; Romanova-Michaelides, M.; Pupier, M.; Alexakis, A. *Chem. - Eur. J.* **2015**, *21*, 5561−5583.
(43) Rauniyar, V.; Lackner, A. D.; Hamilton, G. L.; Toste, F. D. *Science* **2011**, *334*, 1681−1684.
(44) Phipps, R. J.; Hiramatsu, K.; Toste, F. D. *J. Am. Chem. Soc.* **2012**, *134*, 8376−8379.
(45) Wang, Y.-M.; Wu, J.; Hoong, C.; Rauniyar, V.; Toste, F. D. *J. Am. Chem. Soc.* **2012**, *134*, 12928−12931.
(46) Shunatona, H. P.; Früh, N.; Wang, Y.-M.; Rauniyar, V.; Toste, F. D. *Angew. Chem., Int. Ed.* **2013**, *52*, 7724−7727.
(47) Yang, X.; Phipps, R. J.; Toste, F. D. *J. Am. Chem. Soc.* **2014**, *136*, 5225−5228.
(48) Zi, W.; Wang, Y.-M.; Toste, F. D. *J. Am. Chem. Soc.* **2014**, *136*, 12864−12867.
(49) (a) Egami, H.; Asada, J.; Sato, K.; Hashizume, D.; Kawato, Y.; Hamashima, Y. *J. Am. Chem. Soc.* **2015**, *137*, 10132−10135. (b) For the first fluorolactonization to isobenzofurans see: Parmar, D.; Maji, M. S.; Rueping, M. *Chem. - Eur. J.* **2014**, *20*, 83−86.
(50) Umland, K.-D.; Mayer, C.; Kirsch, S. F. *Synlett* **2014**, *25*, 813−816.
(51) Shirakawa, S.; Maruoka, K. *Tetrahedron Lett.* **2014**, *55*, 3833−3839.
(52) Novacek, J.; Waser, M. *Eur. J. Org. Chem.* **2014**, *2014*, 802−809.
(53) Tiffner, M.; Novacek, J.; Busillo, A.; Gratzer, K.; Massa, A.; Waser, M. *RSC Adv.* **2015**, *5*, 78941−78949.
(54) Liu, W.; Groves, J. T. *J. Am. Chem. Soc.* **2010**, *132*, 12847−12849.
(55) (a) O'Donnell, M. J. *Acc. Chem. Res.* **2004**, *37*, 506−517. (b) Lygo, B.; Andrews, B. I. *Acc. Chem. Res.* **2004**, *37*, 518−525. (c) Maruoka, K. *Org. Process Res. Dev.* **2008**, *12*, 679−697. (d) Shirakawa, S.; Maruoka, K. *Angew. Chem., Int. Ed.* **2013**, *52*, 4312−4348.
(56) Ha, M. W.; Lee, M.; Choi, S.; Kim, S.; Hong, S.; Park, Y.; Kim, M.-h.; Kim, T.-S.; Lee, J.; Lee, J. K.; Park, H.-g. *J. Org. Chem.* **2015**, *80*, 3270−3279.
(57) Park, C.; Ha, M. W.; Kim, B.; Hong, S.; Kim, D.; Park, Y.; Kim, M.-h.; Lee, J. K.; Lee, J.; Park, H.-g. *Adv. Synth. Catal.* **2015**, *357*, 2841−2848.
(58) Belokon, Y. N.; Maleev, V. I.; North, M.; Larionov, V. A.; Savel'yeva, T. F.; Nijland, A.; Nelyubina, Y. V. *ACS Catal.* **2013**, *3*, 1951−1955.
(59) Ohmatsu, K.; Ando, Y.; Ooi, T. *J. Am. Chem. Soc.* **2013**, *135*, 18706−18709.
(60) Moss, T.; Barber, D. M.; Kyle, A. F.; Dixon, D. J. *Chem. - Eur. J.* **2013**, *19*, 3071−3081.
(61) Li, M.; Woods, P. A.; Smith, M. D. *Chem. Sci.* **2013**, *4*, 2907−2911.
(62) For a review about bifunctional chiral quaternary ammonium salts see: Novacek, J.; Waser, M. *Eur. J. Org. Chem.* **2013**, *2013*, 637−648.
(63) Bella, M.; Kobbelgaard, S.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 3670−3671. Kobbelgaard, S.; Bella, M.; Jørgensen, K. A. *J. Org. Chem.* **2006**, *71*, 4980−4987.
(64) Shirakawa, S.; Koga, K.; Tokuda, T.; Yamamoto, K.; Maruoka, K. *Angew. Chem., Int. Ed.* **2014**, *53*, 6220−6223.
(65) Shirakawa, S.; Yamamoto, K.; Maruoka, K. *Angew. Chem., Int. Ed.* **2015**, *54*, 838−840.

DOI: 10.1021/acs.oprd.5b00385
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

669 (66) Duan, S.; Li, S.; Ye, X.; Du, N.-N.; Tan, C.-H.; Jiang, Z. *J. Org.*
670 *Chem.* **2015**, *80*, 7770−7778.
671 (67) Shirakawa, S.; Maruoka, K. *Tetrahedron Lett.* **2014**, *55*, 3833−
672 3839.
673 (68) (a) Bielski, R.; Joyce, P. J. *Org. Process Res. Dev.* **2003**, *7*, 551−
674 552. (b) Bielski, R.; Joyce, P. J. *Catal. Commun.* **2003**, *4*, 401−404.
675 (69) Stoin, U.; Shames, A. L.; Sasson, Y. *RSC Adv.* **2013**, *3*, 24440−
676 24446.
677 (70) A less general protocol has been previously described: Snir, E.;
678 Sasson, Y. *Org. Process Res. Dev.* **2008**, *12*, 765−770.
679 (71) Teoh, S. K.; Sa-ei, K.; Noorulameen, M. S.; Toh, Q. Y.; Ng, Y.
680 L.; Sharratt, P. N. *Chem. Eng. Res. Des.* **2015**, *100*, 467−480.
681 (72) (a) Bandar, J. S.; Lambert, T. H. *J. Am. Chem. Soc.* **2012**, *134*,
682 5552−5555. (b) Mirabdolbaghi, R.; Dudding, T.; Stamatatos, T. *Org.*
683 *Lett.* **2014**, *16*, 2790−2793. (c) *Chem. - Eur. J.* **2015**, *21*, 7365−7368.
684 (73) Ma, T.; Fu, X.; Kee, C. W.; Zong, L.; Pan, Y.; Huang, K.-W.;
685 Tan, C.-H. *J. Am. Chem. Soc.* **2011**, *133*, 2828−2831. (b) Zong, L.;
686 Ban, X.; Kee, C. W.; Tan, C.-H. *Angew. Chem., Int. Ed.* **2014**, *53*,
687 11849−11853.
688 (74) Sheshenev, A. E.; Boltukhina, E. V.; White, A. J. P.; Hii, K. K.
689 (Mimi) *Angew. Chem., Int. Ed.* **2013**, *52*, 6988−6991.10.1002/
690 anie.201300614

DOI: 10.1021/acs.oprd.5b00385
Org. Process Res. Dev. XXXX, XXX, XXX−XXX