New Applications of Phase Transfer Catalysis in Organic Synthesis

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Abstract: The review will focus on recent applications of phase transfer catalysis (PTC) in organic synthesis. New developments in the synthesis of chiral phase transfer catalysts and their application in a variety of asymmetric transformations will be covered. In addition, new applications of achiral catalysts will be presented.

Keywords: Phase transfer catalysis, asymmetric catalysis, organocatalysis, alkylation, epoxidation, synthetic methods.

1. INTRODUCTION

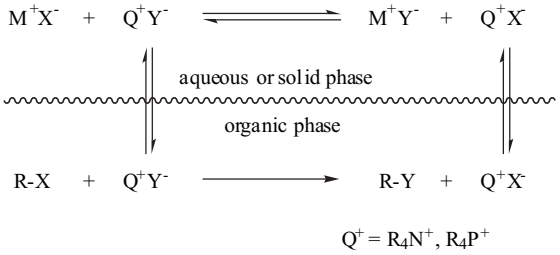
Phase transfer catalysis (PTC) is a powerful tool to carry out reactions with environmentally benign reagents and solvents. Mild reaction conditions, safety, operational simplicity and selectivity, and easy scale-up, are widely accepted typical features of PTC processes. Moreover, the great development in asymmetric PTC reactions in the last decade has enormously increased the synthetic potential of this methodology [1].

Unlike commonly used methodologies in organic synthesis, 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 organic reactants and the PTC catalyst. Ionic reagents may be dissolved in the aqueous phase (liquid-liquid, LL-PTC) or used in the form of powdered solids (solid-liquid, SL-PTC) suspended in the organic medium. Under PTC conditions, the reacting anions are continuously brought into the organic phase, where the reaction occurs by catalytic amounts of lipophilic transport agents, usually a quaternary ammonium or phosphonium salt. In the absence of the latter, the reaction proceeds at a very low rate, if any.

In the simple case of the aliphatic nucleophilic substitution of alkyl halides R-X in an aqueous-organic or solid-organic two-phase system, in the presence of catalytic amounts of a quaternary onium salt Q^+X^- and an excess of a metal salt M^+Y^-, the catalyst transfers the reacting anion Y^- into the organic phase as lipophilic, unsolvated and therefore very reactive ion pair Q^+Y^- (Scheme **1**).

Reactions that can take full advantage of PTC methodology are divided into two groups:

- reacting anions in the form of sodium or potassium salt (e.g. NaN_3, $KMnO_4$) are simply transferred by lipophilic cations into the organic phase in the form of lipophilic ion pairs, generated through continuous ion exchange.
- reacting anions are generated *in situ* through deprotonation of the C-H, O-H, N-H or S-H precursors by the action of an inorganic base. The catalyst participates in the formation and transport of the reacting anions into the organic phase.



Scheme 1.

Detailed description of basic principles, mechanism and field of application of PTC can be found in various excellent books and reviews [2].

This review will focus on recent application of chiral and achiral phase transfer catalyst to organic synthesis.

2. ASYMMETRIC PHASE TRANSFER CATALYSIS

2.1. Alkylation

The PTC alkylation of protected glycine derivatives, such as *N*-(diphenylmethylene)glycine *tert*-butyl ester (**1**) has been widely exploited for the asymmetric synthesis of a wide variety of α-amino acids **3**. This approach was introduced by O'Donnell using the pseudoenantiomeric catalysts derived from cinchonine or cinchonidine (for example **4**) to give the monoalkylated products **2**, that can be efficiently converted into α-amino acids **3** (Scheme **2**) [3]. The efficiency of the process was later improved by using the so-called third generation catalysts **5**, bearing the 9-anthracenylmethyl substituent on the quaternary nitrogen atom, developed independently by Corey [4] and Lygo [5]. More recently, the high efficiency of dimeric and trimeric *Cinchona* alkaloid catalysts **6,7** has been demonstrated by Park and Jew [6].

C_2-symmetric *N*-spiro chiral quaternary ammonium bromides **8**, bearing a chiral binaphthyl structure, were introduced by Maruoka [7]. With these latter quaternary ammonium compounds, a high enantiomeric excess of alkylated compounds **2** could be obtained under mild conditions in short reaction times.

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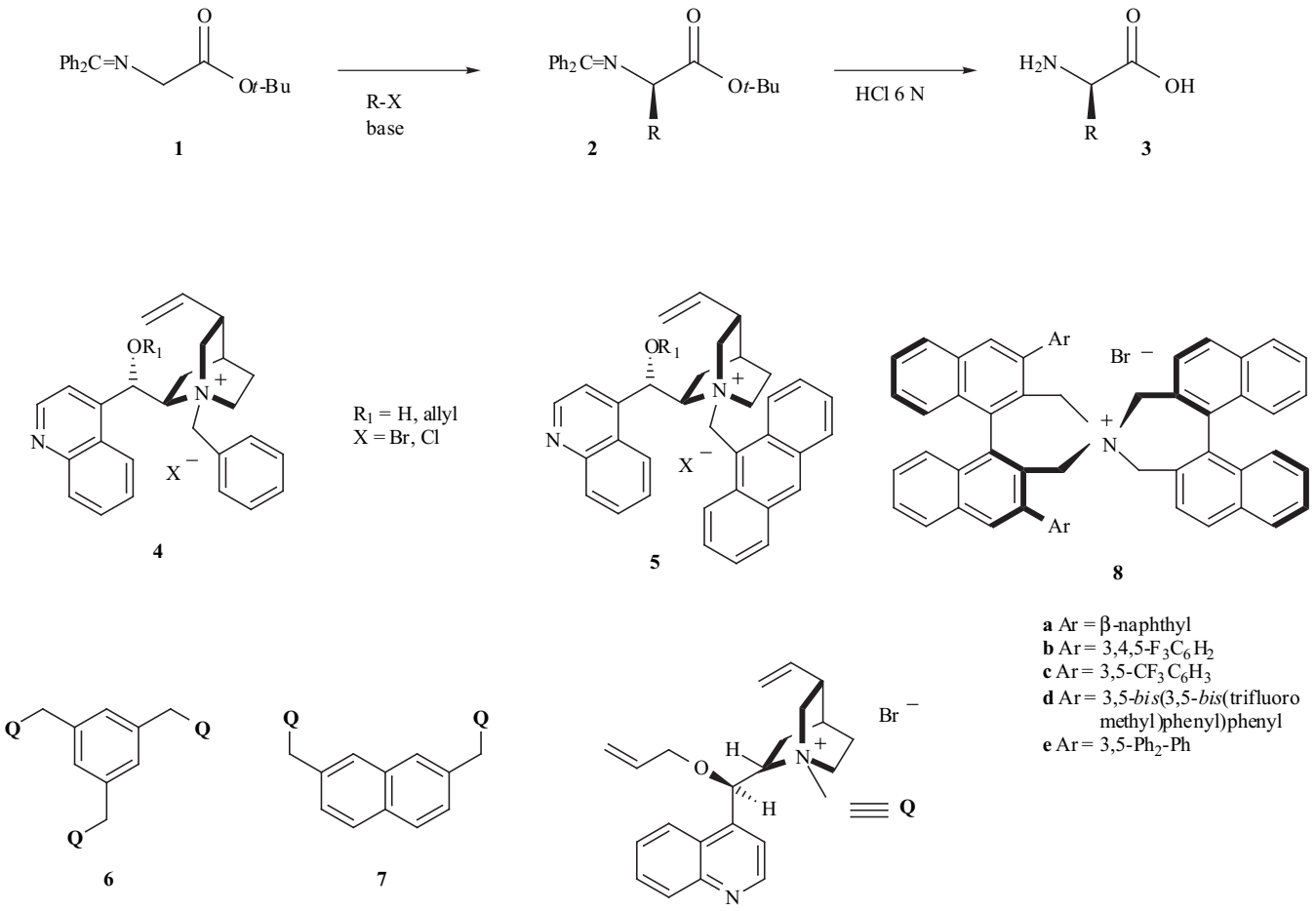
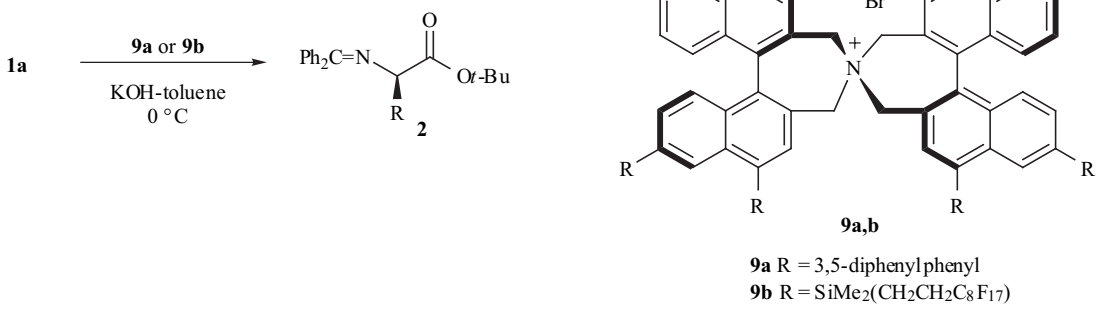


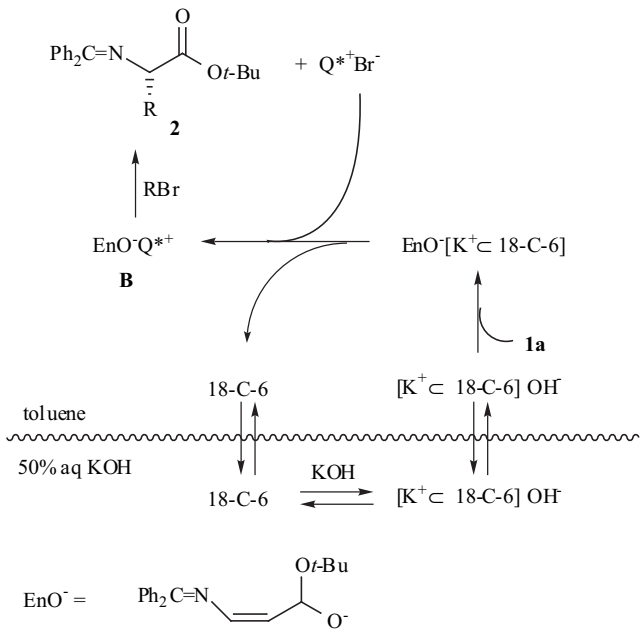
Scheme 2.

The enantioselective synthesis of amino acids through alkylation of glycine imines has been recently reviewed by Maruoka, Lygo and O'Donnell [8]. Later on, Maruoka reported a new symmetrically substituted spiro-type chiral ammonium salt that allowed a simplified synthesis [9]. Excellent results were obtained in the usual alkylation of *tert*-butyl ester **1a** with 4,4',6,6'-tetrakis(3,5-diphenyl-phenyl)binaphthyl ammonium salt **9a**. A similar fluorous catalyst **9b** was prepared introducing fluoroalkyl chains on the 4,4',6,6' positions. Good to high ee were found in the alkylation of **1a** with benzyl and propargyl halides [10] (Scheme **3**).

A dramatic rate enhancement has been achieved by using achiral PT agents as co-catalysts in the presence of the chiral 3,5-diphenyl-phenyl catalyst **8e** [11]. On one hand, the achiral catalyst aids the extraction of base into the organic phase. On the other hand, the subsequent, extremely fast, enolate exchange with the chiral catalyst ($Q^{*+}Br^-$) could generate the quaternary ammonium enolate **B**, which generates the alkylated product **2** with high enantio-selectivity. Under optimized conditions, 18-crown-6 and **8e** have both been used in 0.05 mol %, affording the benzylated compound in a 90% yield and 98% ee after 3h (Scheme **4**).



Scheme 3.

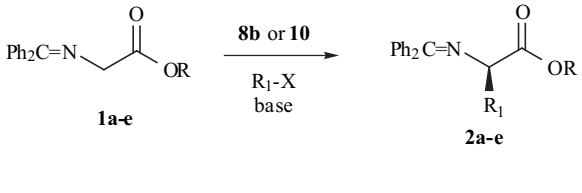


Scheme 4.

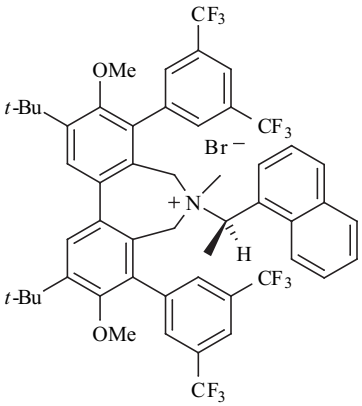
Although many efforts have been directed towards optimization of reaction conditions and design of new highly effective catalysts, only *tert*-butyl ester **1a** has routinely been used in order to avoid hydrolysis under basic conditions and attain higher enantioselectivity. This can cause difficulties in further functionalization of alkylated products. This issue has recently been addressed by using **8b** and **10** as chiral phase transfer catalysts in a 50% aq KOH-toluene biphasic system at 0 °C (Scheme **5**). Lygo employed a new catalyst **10** [12] in the alkylation of various glycine imine esters **1a-d** showing that excellent results could be obtained with benzhydryl ester **1b**, thus representing an excellent alternative to *tert*-butyl ester **1a** [13].

On the other hand, Maruoka successfully employed ethyl and methyl esters **1d,e** by using catalyst (*S,S*)-**8b** (Ar = 3,4,5-F_3-C_6H_2). The same catalyst allowed the asymmetric quaternarization of aldimine Schiff bases [14]. The alkylation products thus obtained can be subjected to further derivatization to synthetically useful chiral building blocks.

The asymmetric alkylation of *N*-(diphenylmethylene) glycine *tert*-butyl ester (**1a**) has been shown to proceed smoothly on clays and alumina loaded with KOH at room



1,2: **a** R = *t*-Bu
b R = Ph_2CH
c R = $PhCH_2$
d R = Et
e R = Me



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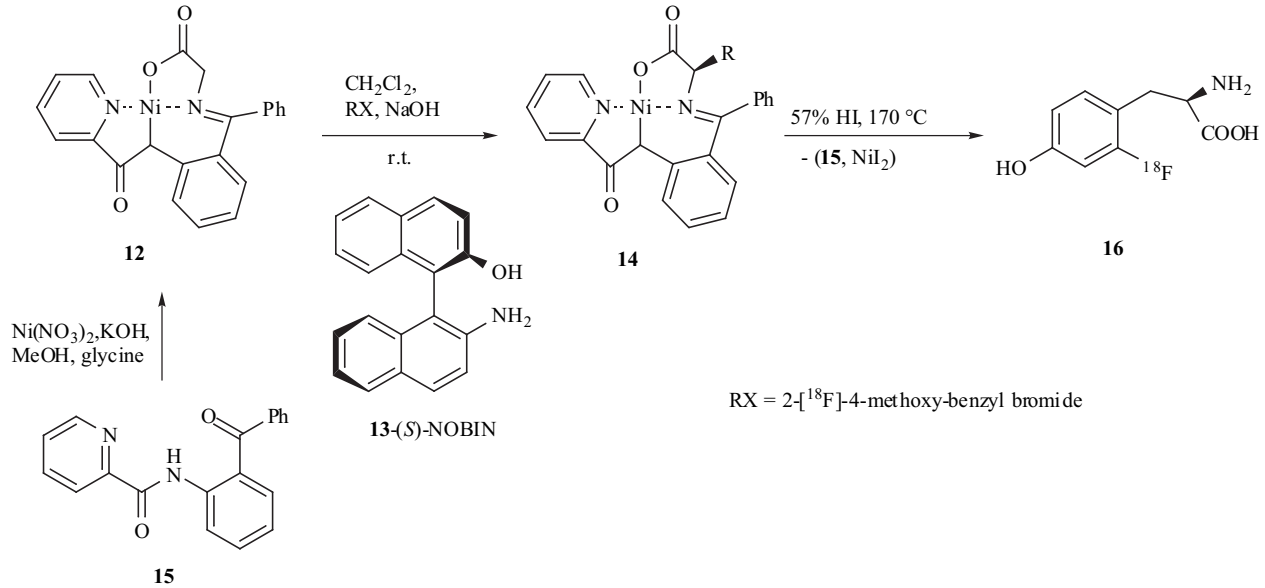
Scheme 5.



RX = 2-[^{18}F]-4-methoxy-benzyl bromide

Scheme 6.

temperature, in the presence of commercially available *N*-anthracenylmethylcinchonidinium chloride (**11**), affording alkylated products in high yields and good enantioselectivities [15].

The synthetic approach to α-amino acids through enantioselective alkylation under PTC conditions has been exploited in the synthesis of radiopharmaceuticals widely used in positron emission tomography (PET). Thus, 6-[^{18}F]fluoro-*L*-dopa and 2-[^{18}F]-*L*-tyrosine have been obtained through alkylation of glycine imine *tert*-butyl ester (**1a**) with the *O*-allyl-*N*-(9-anthracenylmethyl) cinchonidinium catalyst **5** [16] or through alkylation of ketimine nickel complex **12**, in the presence of 2-amino-2'-hydroxy-1,1'-binaphthyl [(*R*) or (*S*)-NOBIN] **13** as catalyst (Scheme **6**) [17].

The Ni(II) complex of glycine Schiff base (*S*)-**17** has been used in an efficient synthesis of (*2S,4S*)-4-aminoglutamic acid (**19**) [18]. When a dichloromethane solution of (*S*)-**17** was stirred at room temperature in the presence of 30% aqueous NaOH and $Bu_4N^+Br^-$ (TBAB) as PT catalyst, diastereo- and enantiomerically pure Ni(II) complex **18** was isolated. The latter generates (*2S,4S*)-4-aminoglutamic acid (**19**) and ligand (*S*)-**20**, that can be recycled for the synthesis of **17** (Scheme **7**).

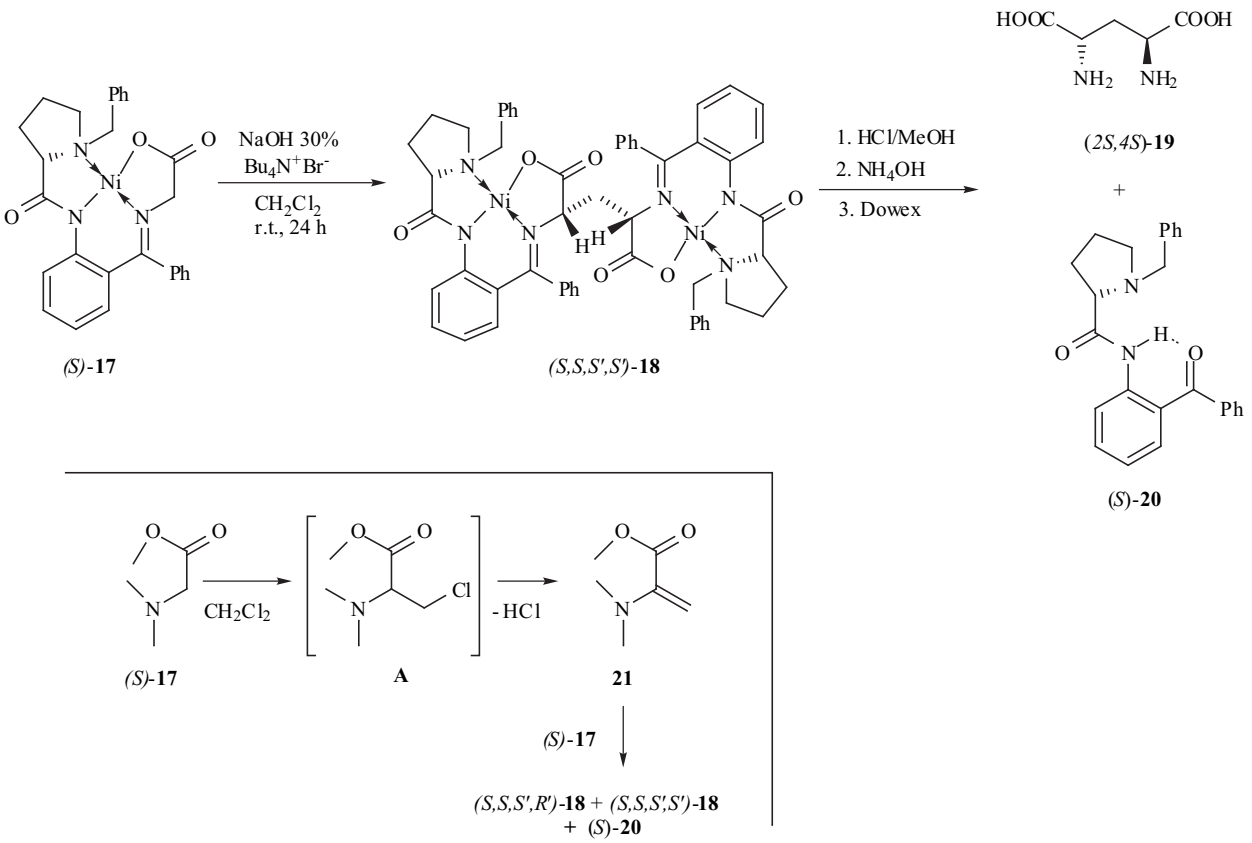
The reaction proceeds through initial formation of a diastereoisomeric 1:1 ratio of complexes **18**, most likely through *mono*-alkylation leading to intermediate **A**, followed by dehydrochlorination and Michael addition between **21** and (*S*)-**17** (Scheme **7**). One of the diastereoisomers was found to be unstable under reaction conditions, epimerizing to the more stable (*S,S,S',S'*)-**18** stereoisomer, along with partial decomposition to (*S*)-**20**.

Counter Ion Effect

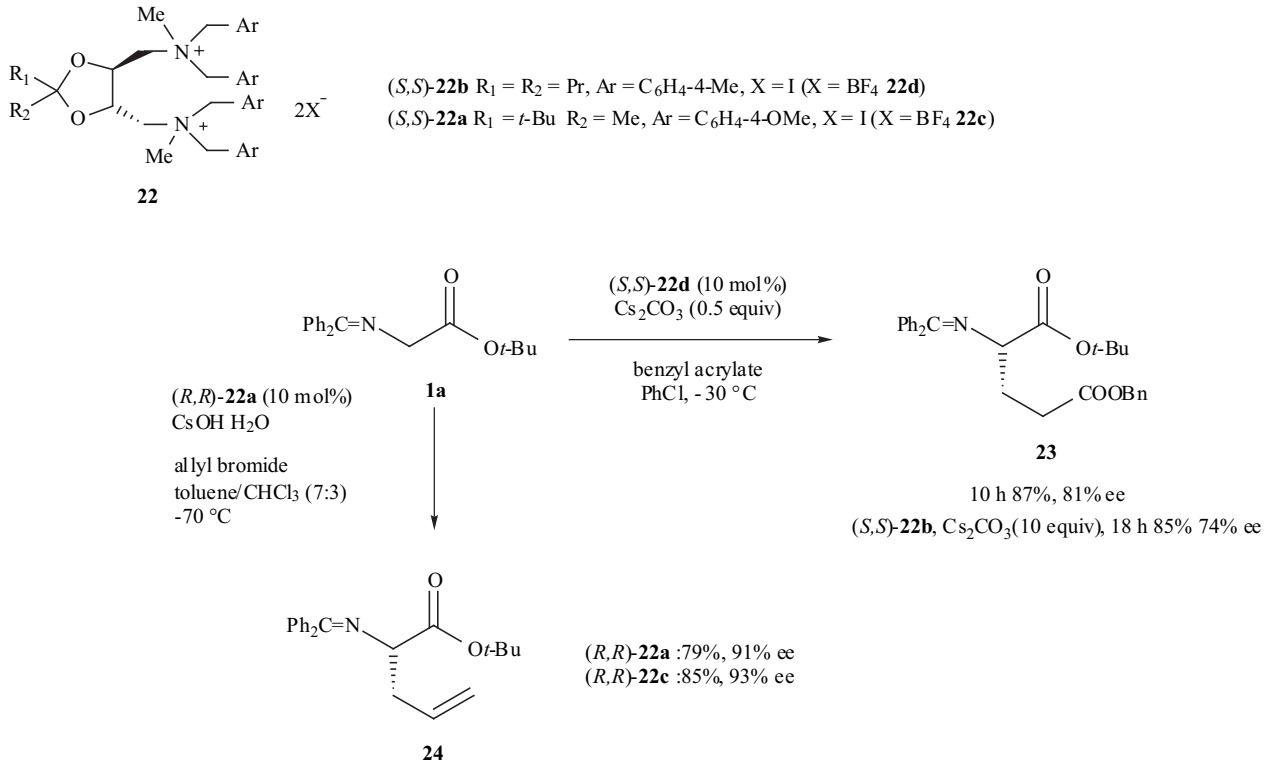
Novel two-centre PT catalysts **22** have been readily prepared from *L*- or *D*- tartrate in five steps using inexpensive reagents [19]. The fine-tuning of the catalyst through variation of the ketal and aromatic moieties (R_1, R_2 and Ar), allows optimization of the enantiomeric excess in alkylation and Michael reactions. For example, **22a** proved to be the best catalyst for alkylations, whereas **22b** afforded the best results in Michael additions (Scheme **8**).

Drastic counter anion effects were observed in the Michael addition of **1a** to benzyl acrylate towards the synthesis of aeruginosin 298-A and its analog [20]. In fact, the use of tetrafluoroborate catalyst **22d** instead of the iodide **22b** afforded higher ee in a short reaction time and with only 0.5 equiv of Cs_2CO_3, instead of a large excess of the latter. In contrast to commonly used *Cinchona* alkaloid derived catalysts, compounds of type **22** are extremely stable under basic conditions and can be easily recovered (80-90% yield) and reused.

A significant counter ion effect has also been observed in the asymmetric alkylation of **1a** employing catalyst **22** [21] or in the presence of dimeric anthryl-derived *Cinchona* ammonium salts **25** (Fig. **1**) [22]. Remarkable increments of ees have generally been achieved with *O*-allylated dimeric catalysts carrying a hexafluorophosphate counter ion.



Scheme 7.



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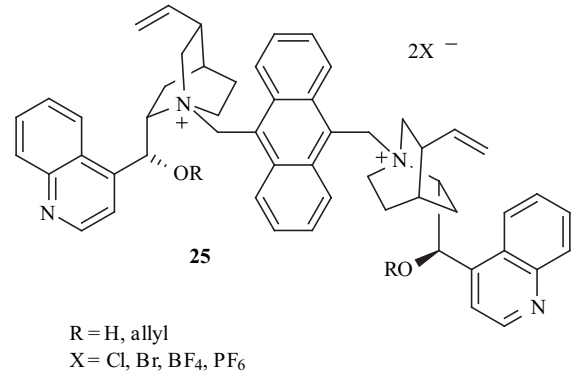
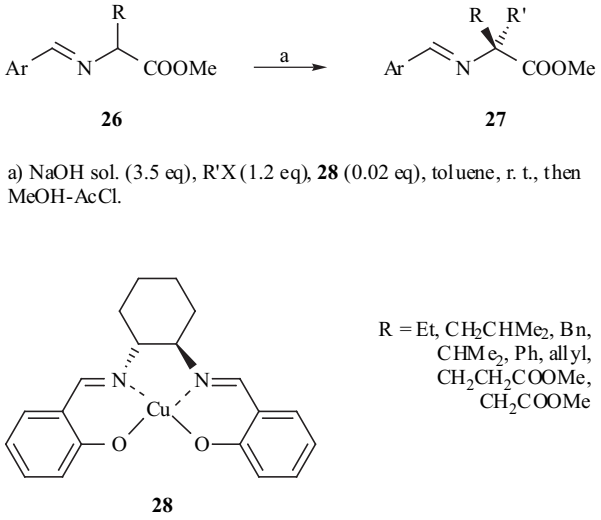


Fig. (1).

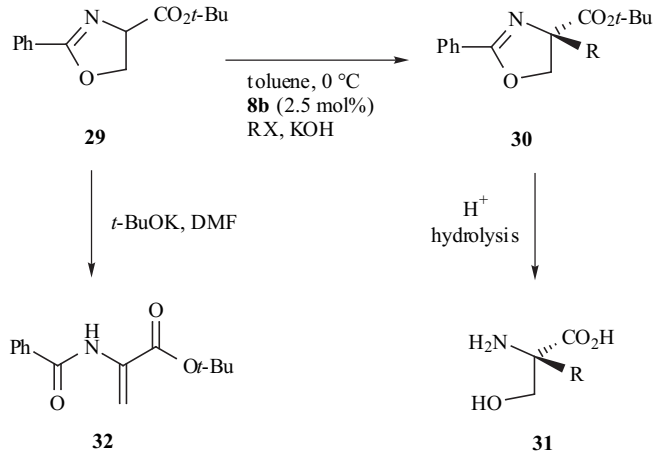


Scheme 9.

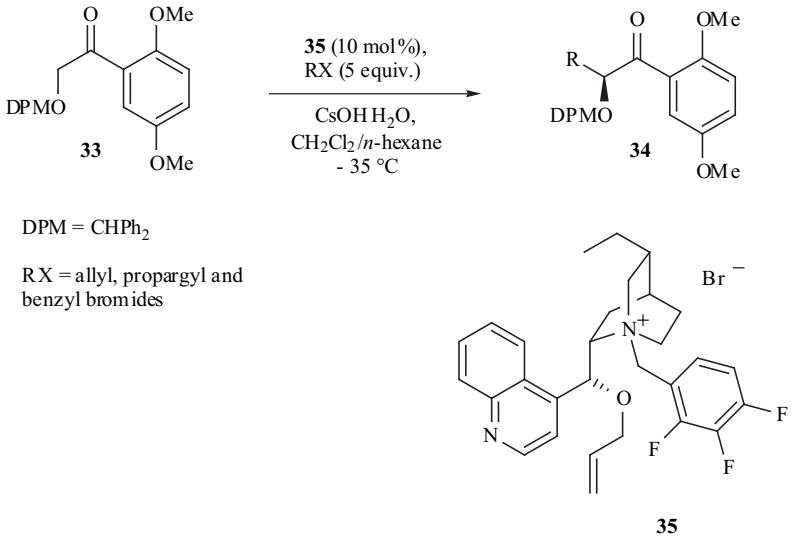
The asymmetric alkylation of a range of enolates derived from α-amino esters **26** have also been carried out in the presence of Cu(salen) complex **28** under SL-PTC conditions (Scheme **9**). The enantioselectivity decreases as the side chain R increases in size, and particularly as it becomes branched to the α-position of the amino acid [23]. Methyl esters can be used as substrates.

Phenyl Oxazolines Alkylation

Chiral α-alkyl serines **31** have been easily prepared through asymmetric phase transfer alkylation of phenyl oxazoline **29**, followed by acidic hydrolysis (Scheme 10) [24]. The oxazoline moiety enhances the acidity of the α proton and enables the simultaneous protection of both the amino and hydroxy group in the serine ester. High ees and chemical yields were obtained with 2.5 mol% of catalyst **8b**,



Scheme 10.



Scheme 11.

whereas no β-elimination or substitution was observed. The acidic hydrolysis of **30** (HCl 6 N), followed by purification through an ion-exchange resin generated optically pure α-alkylserines **31** in excellent yields and 93-97% *ee*.

On the other hand, benzamidoacrylate **32** was isolated in 98% yield when **29** was treated with *tert*-BuOK under homogeneous conditions in DMF as solvent [25].

Glycolate Alkylation

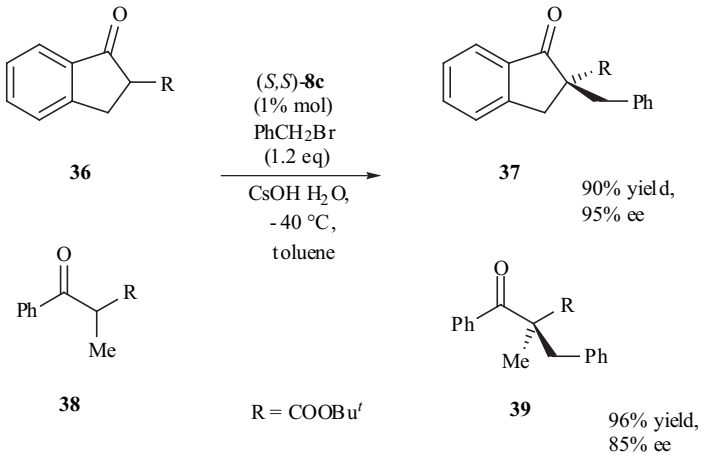
The asymmetric glycolate alkylation has been carried out previously by the aid of chiral auxiliaries [26], since the use of PTC procedure was hampered by the low acidity of alkoxyesters substrates ($pK_a \sim 28$). However, more acidic diphenylmethyloxy-2,5-dimethoxyacetophenones **33** ($pK_a \sim 22$) have recently been successfully used as surrogates, affording alkylated compounds **34** in high yields and enantioselectivities (Scheme **11**) [27].

The best results have been obtained with *N*-(trifluorobenzyl)- catalyst **35** and caesium hydroxide as base at – 35 °C in a dichloromethane/*n*-hexane solvent mixture. Various allyl, propargyl and benzyl halides afforded the corresponding aryl ketones **34** in a 78-99% yield and 80-90% *ee*. The latter have been converted into α-hydroxy esters by selective transesterification or *bis*-TMS peroxide Baeyer-Villiger oxidation.

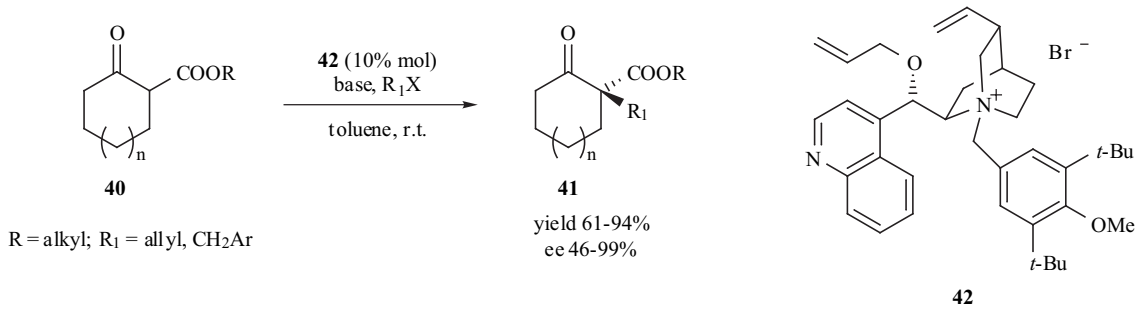
β-Keto Esters Alkylation

The catalytic asymmetric alkylation of β-keto esters provides a useful tool for the construction of organic molecules containing stereogenic quaternary carbon atoms. A few examples of the palladium-catalyzed asymmetric allylation of β-keto esters have been reported [28]. The same reaction has been carried out under PTC conditions using a phosphonium salt catalyst with low efficiency [29], and more recently with excellent results by using chiral ammonium salts. The enantioselective alkylation of cyclic compound **36** and acyclic β-keto ester **38** has been accomplished by using *N*-spiro C_2-symmetric ammonium salt **8c** [30]. Excellent yields were obtained in short reaction times with 85-97% *ees* under SL-PTC conditions using $CsOH \cdot H_2O$ as base at – 40 °C in toluene (Scheme **12**).

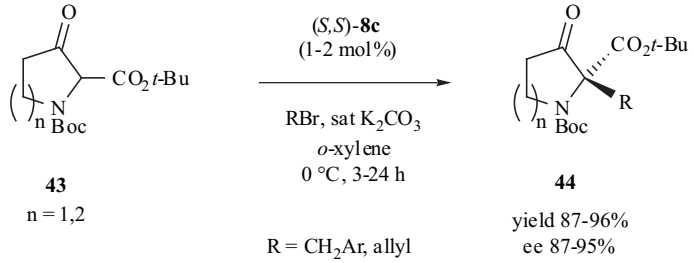
The enantioselective alkylation of various cyclic β-keto esters has also been achieved by using KOH or K_2CO_3 as base and cinchonine-derived ammonium salt **42** (Scheme **13**) [31].



Scheme 12.



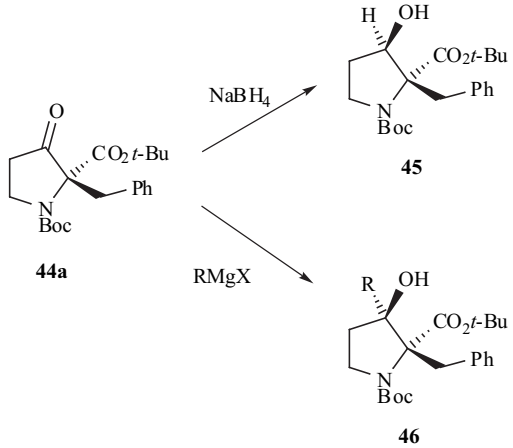
Scheme 13.



Scheme 14.

The asymmetric synthesis of aza-cyclic α-amino acid derivatives **44**, bearing quaternary stereocenters, has been achieved by the PTC alkylation of 3-oxoprolines **43** using (*S,S*)-**8c** as catalyst (Scheme **14**) [32].

The best results have been obtained under LL-PTC conditions using a saturated aqueous K_2CO_3 solution as base in *o*-xylene at 0 °C due to the instability of the compound **43** under strongly basic conditions. A series of alkylated 3-oxo-proline and 3-oxopipecolic acid derivatives has been isolated in high yields and enantioselectivities. Subsequent reduction and alkylation of the 3-keto carbonyl moiety occurred in a diastereoselective fashion, most likely through the formation of a chelate involving the ester and ketone groups (Scheme **15**).

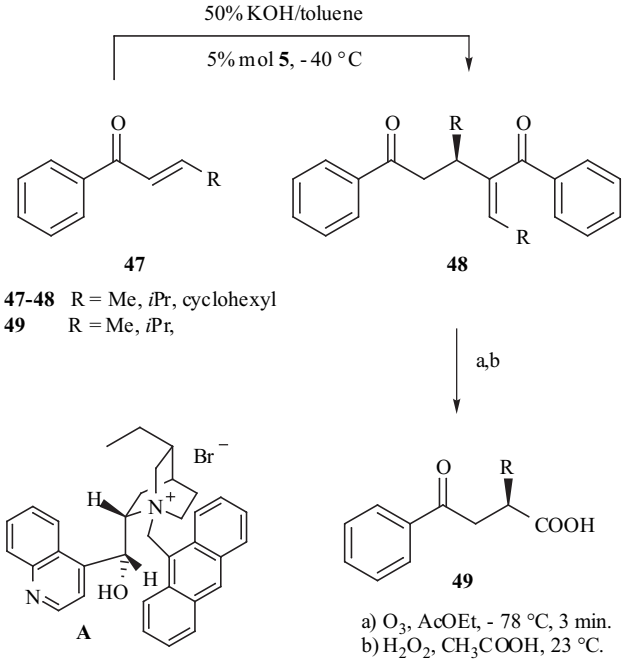


Scheme 15.

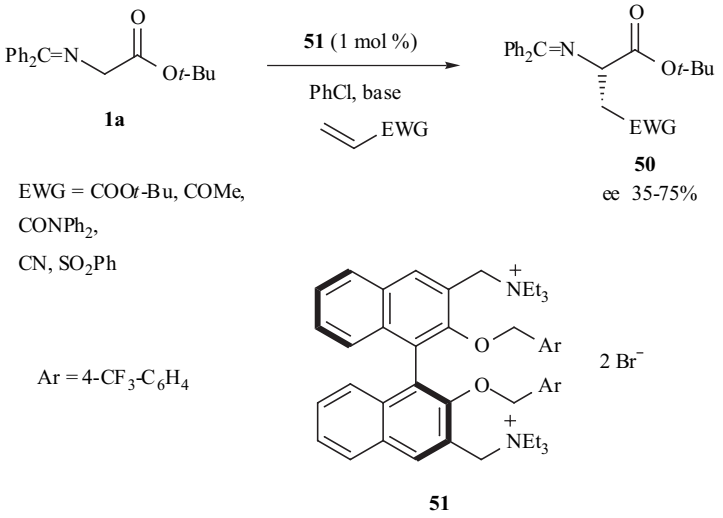
2.2. Michael Addition

Chiral PT catalysts of the *N*-(9-anthracenylmethyl) series **5** have been successfully used in Michael reactions to synthesize various functionalized α-alkylamino acids [8b,d].

More recently, the dimerization of α,β-enones **47** bearing a γ-proton has been reported to proceed in a highly enantioselective fashion under LL-PTC conditions [33], in the presence of 50% KOH and 2.5 mol% of catalyst **A** (Scheme **16**). The dimerization occurs through enantioselective Michael reaction, followed by base catalyzed double bond transposition. Products **48** thus obtained are useful intermediates for the synthesis of chiral γ-ketoacids **49**, important backbones for the preparation of peptide isosteres in drug discovery. Chiral γ-ketoacids **49**, whose preparation was troublesome, have been easily isolated by ozonolysis of **48**, followed by oxidation with hydrogen peroxide.



Scheme 16.



Scheme 17.

New chiral quaternary *bis* ammonium salt **51** has been synthesized from (*S*)-BINOL and reported to promote the Michael addition of glycine Schiff base **1a** to various Michael acceptors in generally good chemical yields and moderate ees (Scheme **17**) [34]. The stereoselectivity was found to be strongly affected by substituents on the aromatic ring and the ammonium moiety.

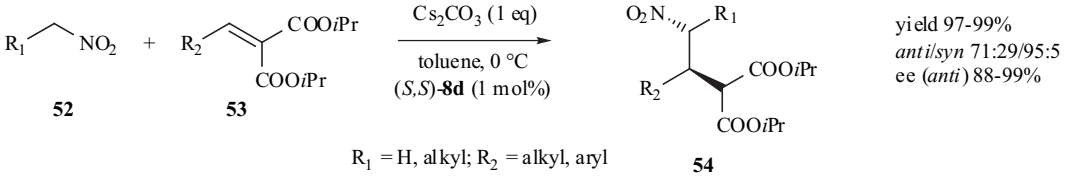
Conjugate Addition

The nucleophilic addition of nitroalkanes to α,β-unsaturated carbonyl compounds is a powerful tool for the synthesis of various building blocks bearing the nitro group, useful for further functional group modification [35]. The enantioselective Michael addition of nitromethane to enones catalyzed by chiral quaternary ammonium salts has been reported [36]. The first example of the conjugate addition of a nitroalkane **52** to an ester acceptor has recently been disclosed (Scheme **18**) [37]. The reaction has been carried out by mixing reactants in the presence of a stoichiometric base and a chiral quaternary ammonium bromide in toluene at 0°C. The optimization of the reaction conditions indicated that the best result could be obtained by using diisopropyl esters **53**, caesium carbonate as base and the radially extended binaphthyl chiral catalyst (*S,S*)-**8d**. Lower stereoselectivities have been obtained by using ethyl- and *tert*-butyl benzylidenemalonates as acceptors and different *N*-spiro ammonium bromides (for example **8c**).

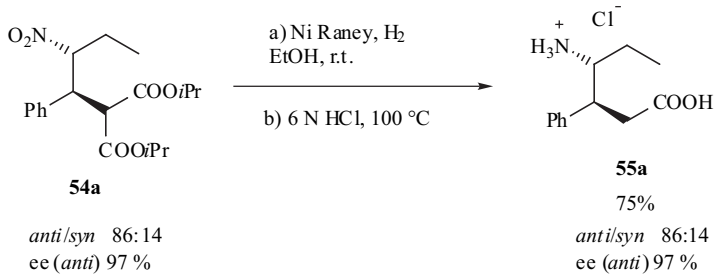
Various nitroalkanes **52** have been employed as substrates affording the corresponding conjugate addition products **54** in quantitative yield and excellent stereoselectivities. Similar results, both as regards to chemical yield and stereoselectivity, can be obtained in longer reaction time with only 0.1% mol of catalyst. γ-Nitro malonates **54** thus obtained can be easily transformed into γ-amino acids **55** without loss of diastereo- and enantiomeric excess, as demonstrated in the case of diisopropyl 2-(2-nitro-1-phenylbutyl)malonate (**54a**) (Scheme **19**).

2.3. Mannich Reaction

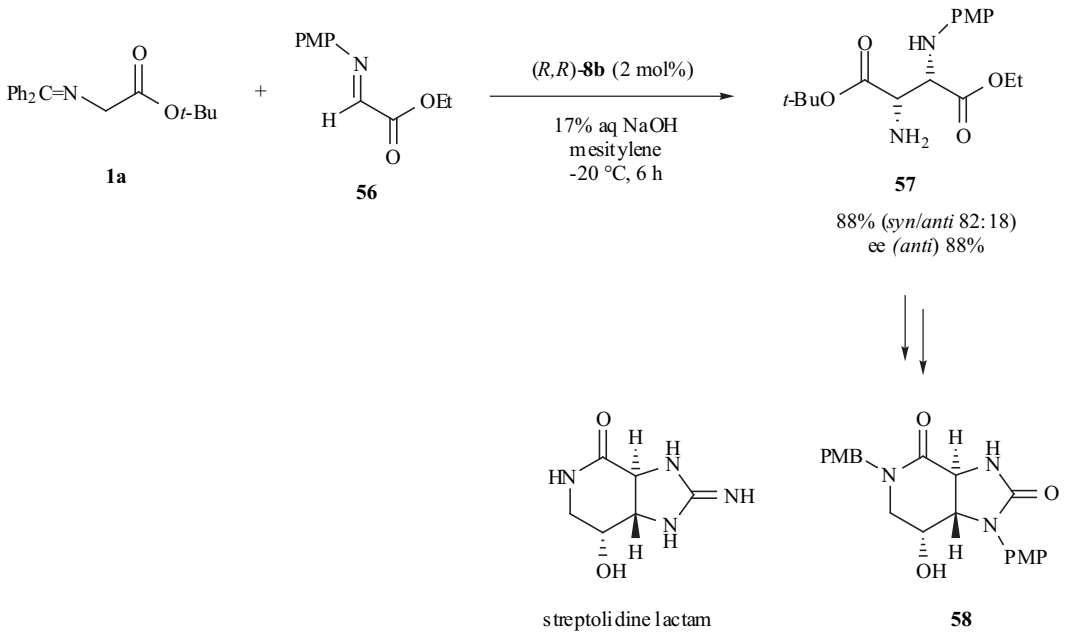
The Mannich reaction of the benzophenone Schiff base of *tert*-butyl glycinate **1a** with α-imino ester **56** has been accomplished in a highly enantioselective fashion by using a C_2-symmetric *N*-spiro quaternary ammonium bromide **8b** as



Scheme 18.



Scheme 19.



Scheme 20.

catalyst [38]. The reaction has been performed at – 20 °C in the presence of 17% aq NaOH as base affording 3-amino aspartate derivative **57** in 88% yield (Scheme **20**). The latter tartaric acid nitrogen analog, bearing differentiated ester groups has been exploited in the synthesis of **58**, a precursor of streptolidine lactam, the core structure of a family of potent antibiotics isolated from microbial sources.

2.4. Aldol Reaction

The catalytic asymmetric aldol reaction of glycine equivalents and aldehydes is one of the most powerful strategies to construct β-hydroxy-α-amino acids, whose utility as structural components of many biologically active molecules, and as chiral building blocks in organic synthesis has found numerous applications.

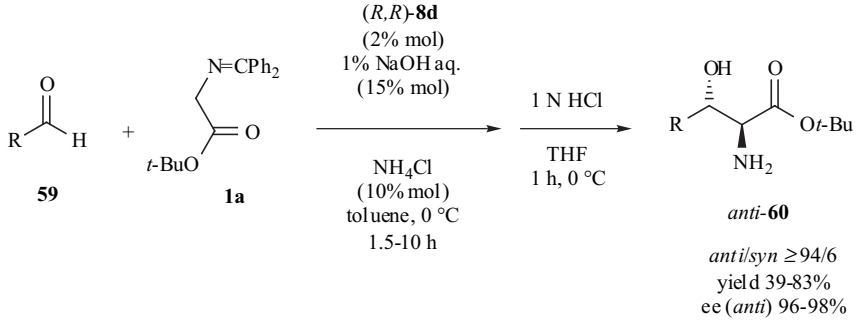
The aldol coupling of aldehydes with silyl ketene acetal derived from glycinate-benzophenone Schiff base, catalyzed by a cinchonidine-derived ammonium bifluoride, afforded *syn*-β-hydroxy-α-amino esters with good to excellent ees [39].

A new highly efficient asymmetric aldol reaction of a glycinate Schiff base with aldehydes has been carried out under liquid-liquid PTC conditions [40]. The optimized conditions were reaction of **1a** and aldehydes **59** (2 eq) in toluene at 0 °C in the presence of catalytic amounts of 1% NaOH, ammonium chloride and (*R,R*)-**8d** as a chiral PT catalyst. A wide range of aldehydes afforded almost exclusively *anti*-β-hydroxy-α-amino ester **60** (*anti*/*syn* ≥ 94/6) with good yields and excellent ees (Scheme **21**).

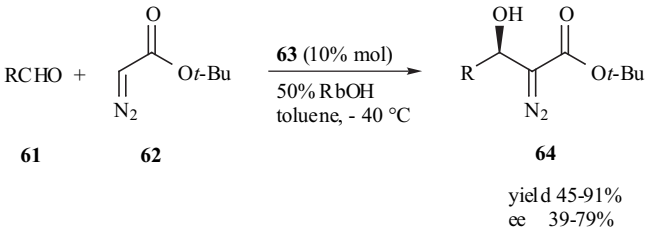
When the reaction was carried out under similar conditions, but using 2 equiv of 1% aq. NaOH in the absence of NH_4Cl, the stereoselectivity was found to depend strongly on the aldehyde employed. A mechanistic investigation revealed that this behavior was due to a retro aldol reaction that had been suppressed by reducing the amount of aqueous base and adding NH_4Cl to control the pH of the mixture [40b].

The catalytic asymmetric aldol reaction between a α-diazoester and various aldehydes has also been investigated under LL-PTC conditions using *N*-(9-anthracenylmethyl)-cinchoninium chloride (**63**) as catalyst (Scheme **22**) [41].

Under optimized conditions, various aromatic and aliphatic aldehydes **61** were reacted with *tert*-butyl diazoacetate (**62**) in the presence of 50% RbOH in toluene at – 40 °C, affording α-diazo-β-hydroxy esters **64** in good yields and moderate to good enantioselectivity.



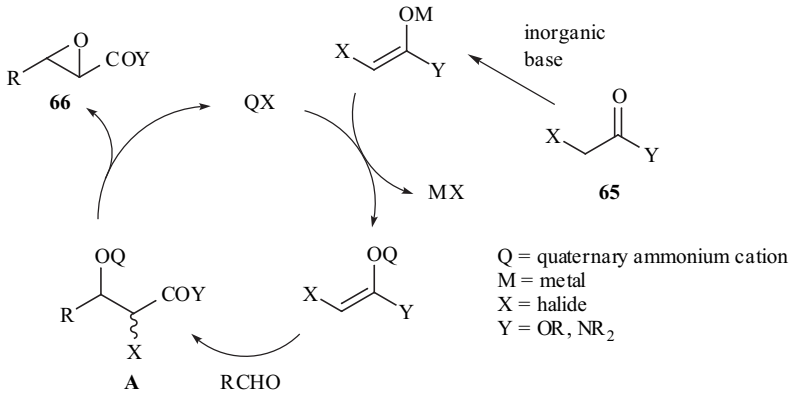
Scheme 21.



Scheme 22.

2.5. Darzens Reaction

The Darzens reaction has been widely exploited for the synthesis of epoxides [42]; however, there have been few reports on its successful application to asymmetric synthesis, only in the presence of chiral auxiliaries or external ligands [43]. A catalytic asymmetric protocol has been developed by using chiral ammonium salts [44] or crown ethers as catalysts [45], since they are regenerated after intramolecular cyclization of the intermediate aldol **A** (Scheme **23**). Epoxides **66** are generally obtained in moderate ees.



Scheme 23.

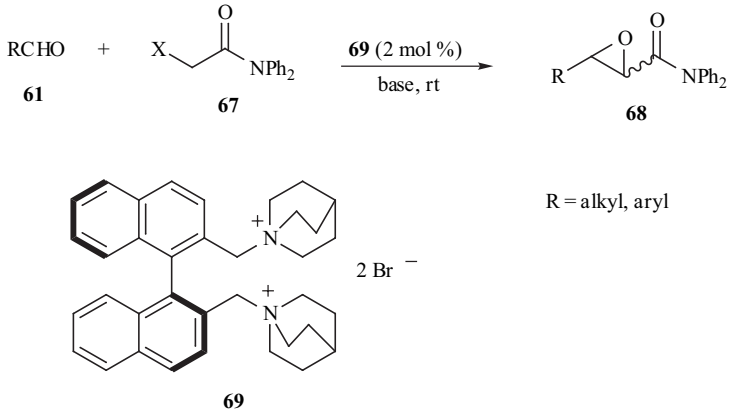
A new chiral catalyst **69** was synthesized by bromination of (*R*)-2,2'-dimethyl-1,1'-binaphthyl, followed by quaternarization with quinuclidine. Good to excellent chemical yields of epoxides **68** have been obtained through the Darzens reaction of α-haloamides **67** with aldehydes in the presence of **69** and $RbOH{\cdot}H_2O$ or Cs_2CO_3 as base, although with low to moderate diastereo- and enantioselectivities (Scheme **24**) [46].

The synthesis of α,β-epoxy carbonyl compounds through the Darzens condensation of aromatic aldehydes with ethyl chloroacetate has also been carried out in the presence of a polystyrene-supported quaternary ammonium salt [47].

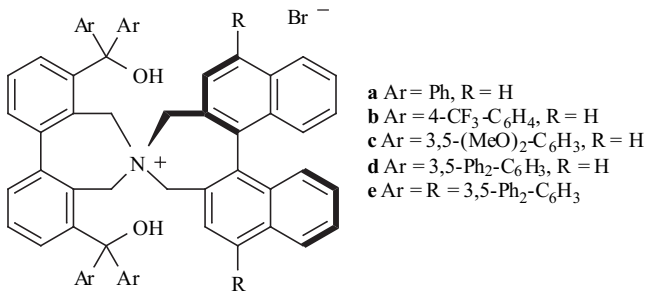
2.6. Epoxidation

The catalytic asymmetric epoxidation of electron-deficient olefins has been accomplished through different catalysts [48]. In particular, the phase transfer catalyzed epoxidation of α,β-unsaturated ketones is particularly attractive due to its operational simplicity, non-metal containing catalyst, and environmentally friendly conditions. After the pioneering work of Wynberg [49], the epoxidation of chalcones has been efficiently carried out in the presence of the *N*-(9-anthracenylmethyl) catalyst **5** by using commercially available sodium hypochlorite [50] or 65% potassium hypochlorite [51]. The latter allowed higher enantioselectivity to be attained; however, the reagent has the drawback of being unstable and must be freshly prepared.

A new chiral quaternary ammonium bromide **70**, bearing a diphenylhydroxymethyl substituent at the 3,3'-position of a biphenyl subunit, afforded excellent results with commercially available 13% NaOCl in toluene at 0 °C (Scheme **25**) [52]. On the basis of single-crystal X-ray diffraction analysis of **70e**-PF_6, the authors suggest that the



Scheme 24.



Scheme 25.

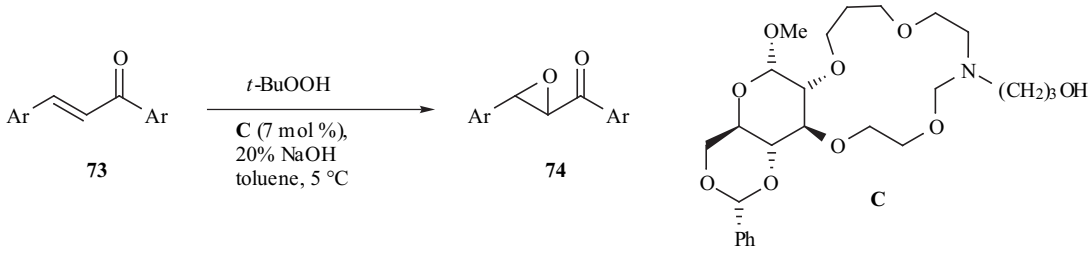
diphenylhydroxymethyl moiety brings enones inside a cavity through hydrogen-bonding interactions, thus providing an ideal proximity to hypochlorite ion for the conjugate addition process, resulting in bond formation with enantiofacial differentiation.

Moreover, the catalyst having the same structure but lacking of hydroxy group almost lost catalytic activity and diminished stereoselectivity (3% yield, 46% ee) under otherwise identical reaction conditions. A series of representative chalcone derivatives **71** have been epoxidized with excellent yields and enantioselectivities.

The epoxidation of chalcones has also been investigated in the presence of glucose- and mannose-based lariat ether catalysts (Scheme **26**) [53]. The reaction was carried out in a liquid-liquid two-phase system in toluene at 5 °C by using 20% aq NaOH as base and *tert*-butyl hydroperoxide as oxidant.

Since the pioneering report by Juliá [54], the procedure has later been improved by several groups [55]. It has recently been disclosed that the addition of a typical PT catalyst, for example $Bu_4N^+Br^-$ (TBAB) dramatically increases the rate of reaction, allowing a sharp reduction of oxidant and base employed (Scheme **27**).

Under the new reaction conditions, good results have been obtained by using aqueous NaOCl as the oxidizing agent. Moreover, the higher temperature polymerization of poly-*L*-leucine afforded a more active catalyst that does not need a long pre-activation period as the standard material [56]. Although the active catalytic species is not well recognized, the PT catalyst should aid the hydroperoxide anion transport through phase boundary. The same procedure has been employed for the asymmetric epoxidation of arylalkenyl sulfones [57].

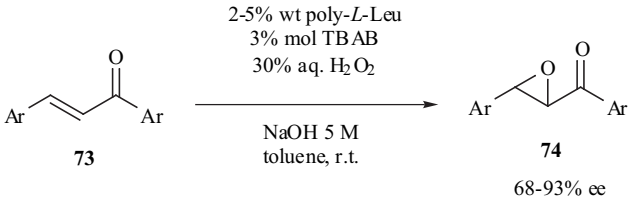


Scheme 26.

It was found that *N*-substituents greatly affected the yields and enantioselectivities. The γ-hydroxypropyl glucose-based lariat ether catalyst **C** afforded the best results in the epoxidation of α-benzylideneacetophenone (**73a**) at 5 °C, generating the epoxyketone **74a** (Ar = Ph) in 82% yield and 92% ee. The epoxidation of a series of substituted chalcones with **C** at room temperature afforded the corresponding *trans*-epoxy-ketones in a 73-82% ee. The reaction proceeds through the nucleophilic attack of the chiral crown complexed *t*-$BuOO^-$ anion. The effect of the nitrogen substituent can likely be ascribed to its possible cooperation in the cation complexation. The catalysts derived from mannose afforded enantiomeric epoxyketones with similar stereoselectivities.

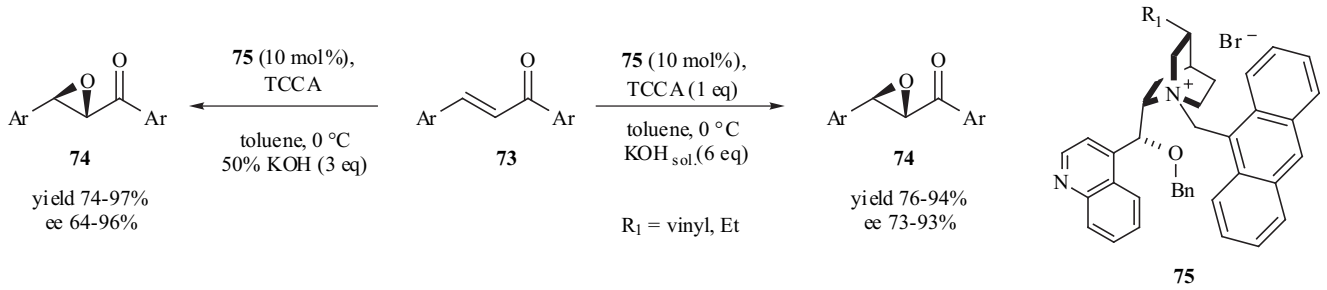
Juliá-Colonna Epoxidation

Chiral polyamino acids have also been used as catalysts in the epoxidation of chalcone with good enantioselectivity.



Scheme 27.

Trichloroisocyanuric acid (TCCA) has been used as a cheap and readily available oxidant in the enone epoxidation under asymmetric PTC conditions using the catalyst **75** (Scheme **28**) [58]. Good results have been obtained under liquid-liquid conditions, using 50% aq KOH as base, and under solid-liquid conditions, using solid KOH. The latter non-aqueous procedure allows an easier product recovery, excluding formation of wet viscid isocyanuric acid.



Scheme 28.

Oxidative Cyclization

The oxidative cyclization of 1,5-dienes has been used to access tetrahydrofurans diols, an important unit found in many natural and synthetic biologically active molecules [59]. This approach leads to the stereospecific formation of up to four new stereocenters and has previously been achieved with chiral auxiliaries [60].

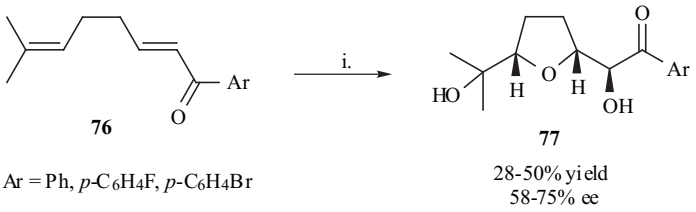
The oxidative cyclization of enones **76** has recently been carried out under PTC conditions, affording enantiomerically enriched tetrahydrofuran diols **77** (Scheme **29**). The best results have been obtained in CH_2Cl_2 at – 30 °C, by using solid $KMnO_4$ and quaternary ammonium bromide **75** [61]. Although tetrahydrofuran diols **77** are isolated in moderate yields, promising enantioselectivities, comparable with the diastereoselectivity obtained in the oxidative cyclization of dienes bearing Oppolzer sultam chiral auxiliary [60a], have been obtained in the construction of three stereocenters in a single step from an achiral substrate.

The yield increased by using more polar solvent, however, lower ees were obtained due to a background oxidation, as confirmed by reactions carried out without PT catalyst.

Oxone Epoxidation

Amines have been shown to promote the epoxidation of alkenes by using oxone buffered with $NaHCO_3$/pyridine as oxidant [62]. Significant enantioselectivities have been obtained in the presence of chiral amines. More recently, better results have been achieved by using the hydrochloride amine salts as catalyst [63]. Several pieces of evidence suggest that the epoxidation occurs through an electrophilic oxidation where the active oxidant is peroxymonosulfate ammonium salt of type **A**, generated *in situ* (Scheme **30**).

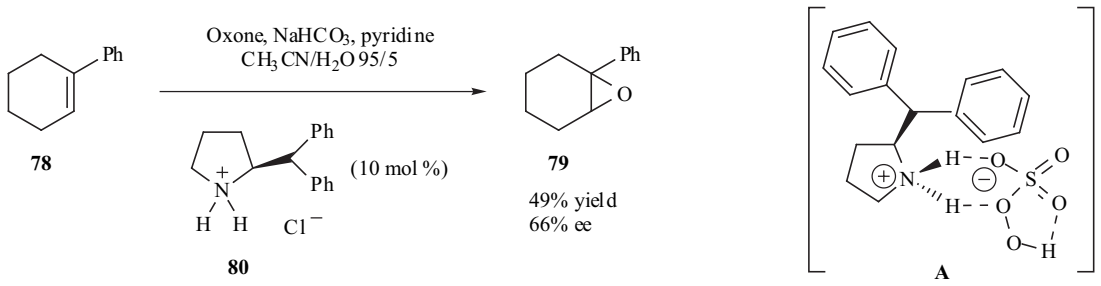
In particular, a series of pyrrolidine ammonium salts with different levels of alkylation has been prepared and tested as catalysts showing that conversion and enantioselectivity increases with the number of N-H's available. It is believed therefore that the protonated ammonium salt behaves as the PT catalyst (dissolving the oxidant) and activates the peroxymonosulfate as well, through hydrogen bonding, thus generating a more electrophilic species.



Scheme 29.

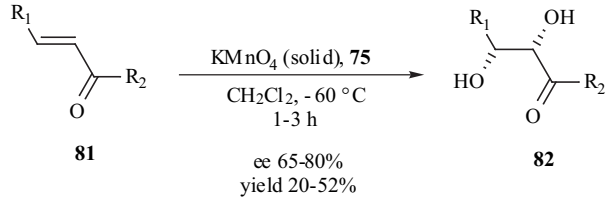
2.7. Dihydroxylation

The asymmetric, osmium tetraoxide catalyzed, dihydroxylation of olefins has found widespread applications



Scheme 30.

in organic synthesis [64]. A new approach to asymmetric dihydroxylation of enones **81** has been investigated under SL-PTC conditions by using $KMnO_4$ as the oxidant in the presence of the chiral ammonium salt **75** (Scheme **31**) [65]. A relatively fast and clean reaction occurred, however, prolonged reaction times led to lower yields. Moreover, the PT agent was destroyed under the oxidation conditions, therefore an equimolar amount of **75** was required.



81 **82**

Scheme 31.

2.8. Nucleophilic Additions

The enantioselective nucleophilic addition of a trifluoromethyl anion to the carbonyl group of methyl ketones **83** has been accomplished using a new easily prepared cinchonine-derived catalyst **85** (Scheme **32**) [66]. The careful optimization of reaction conditions, namely the choice of protecting group of the primary alcohol, solvent, temperature, nature and amount of catalyst, allowed generating the desired trifluoromethylated compound **84** in 92% ee. However, the catalyst **85** did not prove to be generally applicable to a variety of ketones.

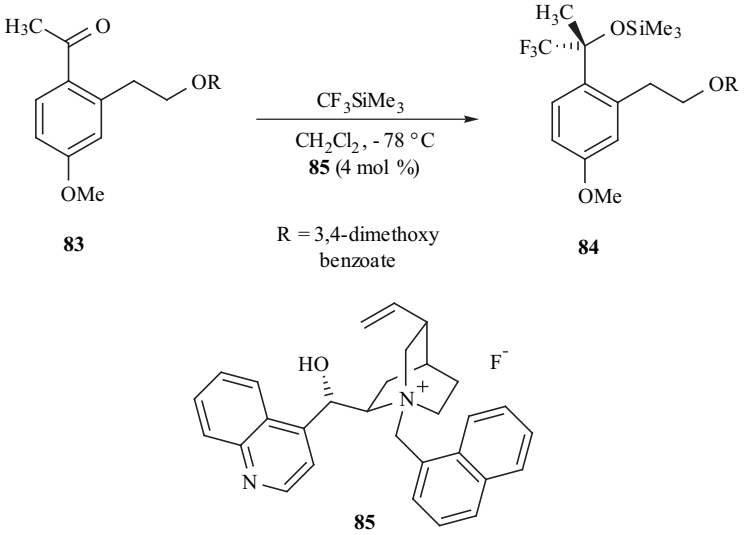
2.9. Halolactonization

The stereoselective iodolactonization of *trans*-5-aryl-4-pentenoic acids **86** have been carried out under LL-PTC conditions in the presence of cinchonidine-derived quaternary ammonium salts **89** generating a mixture of two iodolactonized regioisomers with fair to excellent yield (37-98%) and moderate ees (*exo* = 42%, *endo* = 31%) (Scheme **33**) [67].

An aromatic substituent at the 5-position of acids **86** was found to be necessary for stereoselectivity and strongly influenced the regioselectivity. Electron-donating aryl groups favored *endo* products **88**, whereas electron-withdrawing substituents on the aromatic moiety favored *exo* products **87**. Although the stereoselectivity observed is only moderate, the new procedure represents the first catalytic asymmetric iodolactonization reported to date.

2.10. Supported Catalysts

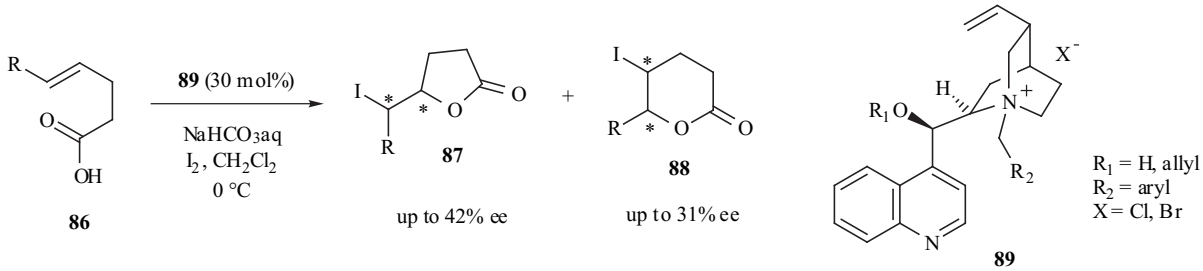
Soluble polymer-supported chiral ammonium salts have been prepared by anchoring various *Cinchona*-derived alkaloids to modified poly(ethylene glycol)s [68]. Insoluble PTC catalysts have also been prepared by anchoring *Cinchona*-derived alkaloids to various commercially available polystyrene-related supports, such as the Merrifield resin and polystyrene-grafted polypropylene [69]. Moderate enantioselectivity has generally been obtained in the asymmetric alkylation of *N*-(diphenylmethylene)glycine esters with these ammonium salts. The insoluble catalysts



83 R = 3,4-dimethoxy benzoate **84**

85

Scheme 32.



86 **87** up to 42% ee **88** up to 31% ee **89**

Scheme 33.

could be easily separated and reused [69], whereas modified poly(ethylene glycol)s were found to be less stable under reaction conditions [68].

2.11. Chiral Anions

Asymmetric PTC provides a powerful tool for carrying out a wide range of reactions involving prochiral anions in a stereoselective fashion.

On the other hand, the ability of chiral anions to induce asymmetry in the reactions of prochiral cations has been investigated by using various D_2-symmetric *bis*[1,1'-bis-naphtolato] borates **95a-e** derived from (*R*)- or (*S*)-binaphtols and tributylammonium TRISPHAT salt **96** [70] (Scheme **34**). The addition of *N*-methyl indole (**91**) to benzylidenedimethylammonium ion (**90**), and the ring opening of 1,2-diphenyl-3-azonia-spiro[2,4]heptane (**93**) with an amine nucleophile, were chosen as model reactions.

The addition of **91** to the iminium salt **90** proceeded with ees (3-11%) not significantly higher than estimated experimental error, whereas the ring opening of the aziridinium ion **93** with benzylamine afforded in all cases low, but significant ees (≤ 15%). Moreover, similar levels of opposite senses of inductions were observed for enantiomeric catalysts.

The selective stabilization of one of the enantiomeric transition states by ion-pairing with the chiral anion would account for the enantiomerically enriched products.

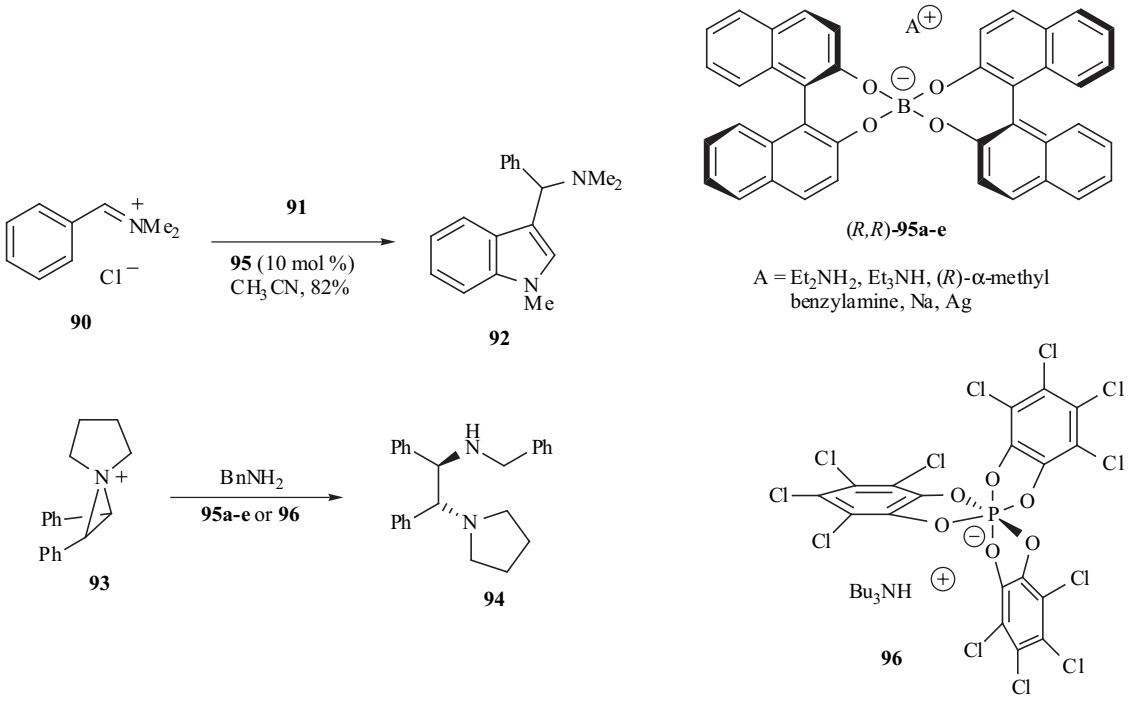
3. ACHIRAL PHASE TRANSFER CATALYSIS

3.1. Michael Addition

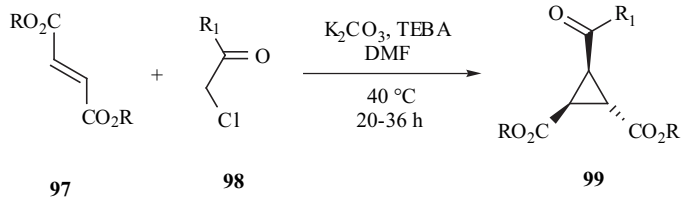
Michael initiated ring-closure reactions are a powerful tool for the preparation of cyclopropanes bearing electron deficient substituents [71]. A practical synthetic procedure for the synthesis of 1,2,3-*tris*-substituted cyclopropanes **99** has been developed using K_2CO_3 as base in the presence of a PT catalyst (Scheme **35**) [72]. The slow rate of addition of fumarates **97** and ethyl chloroacetate or chloroacetone **98** to the heterogeneous mixture of K_2CO_3 in DMF is of paramount importance for the outcome of the reaction. Under these conditions, cyclopropanes **99** are isolated in reasonably good yields using inexpensive starting materials with an easily scalable procedure.

3.2. Benzoin Condensation

The utility of the benzoin condensation for the concise synthesis of α-hydroxy ketones is well documented. However, mixtures of the four possible products are obtained

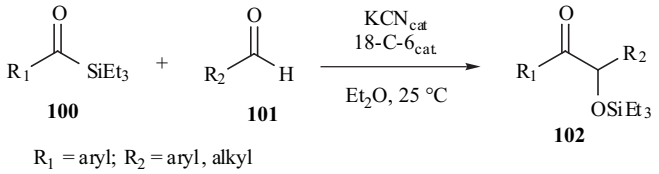


Scheme 34.



Scheme 35.

in the coupling of two different aldehydes, the product distribution being generally determined by their relative thermodinamically stability. A new regiospecific cross silyl benzoin reaction between acylsilanes **100** and aldehydes has been carried out under SL-PTC conditions by using KCN in the presence of 18-Crown-6 (18-C-6) as catalyst (Scheme **36**) [73].



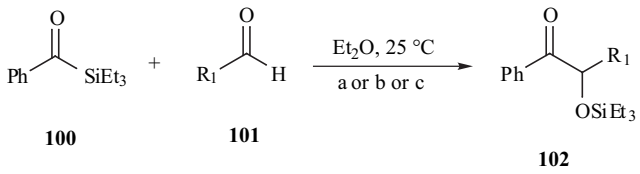
100 **101** **102**

R_1 = aryl; R_2 = aryl, alkyl

Scheme 36.

In the original procedure, 30 mol % of solid KCN and 10 mol % of 18-Crown-6 were used under anhydrous conditions and inert atmosphere. However, it was later discovered that slightly higher yields in a drastically reduced reaction time could be obtained by addition of small amounts of water [74]. It is well-known that the addition of small amounts of water to a solid-liquid PTC reaction mixture can produce large effects on reaction rates. This is due to the formation of a third phase that has been given the name "omega phase", containing various species during the course of the reaction and providing an alternative lower energy pathway for transfer of species across phases [75].

As a consequence of the beneficial effect of trace amounts of water, the benzoin condensation has efficiently been performed with 10 mol % catalyst loading when unpurified, undried Et_2O was used. Even faster reactions have been obtained by using $Bu_4N^+CN^-$ (10 mol %) as catalyst or acetone cyanohydrin as a source of cyanide anion (Scheme **37**).



100 **101** **102**

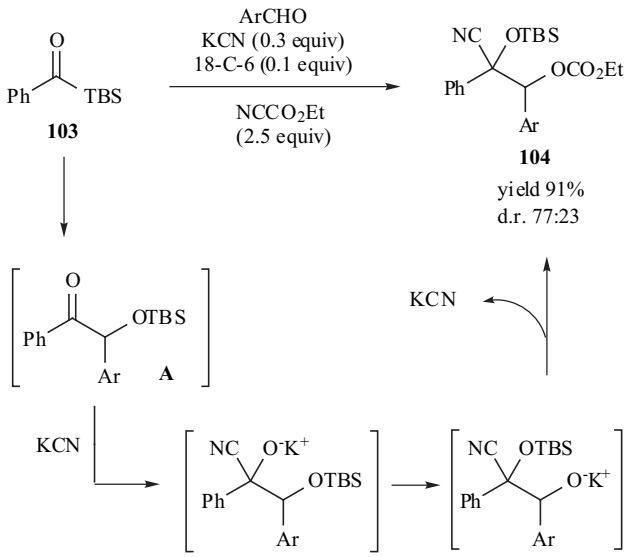
R_1 = 4-OMe-C_6H_4-

a) KCN (0.1 eq), 18-C-6 (0.1 eq), 6 h, 88%. b) $Bu_4N^+CN^-$ (0.1 eq), 30 min, 88%. c) acetone cyanohydrin (0.1 eq), KOH_{sol} (0.1 eq), Bu_4NBr (0.1 eq), 5 min, 77%.

Scheme 37.

The homobenzoin adducts are not formed. Either regioisomeric benzoin adducts **102** may be prepared through opportune selection of the acylsilane and aldehyde due to the kinetic control inherent in the acylsilane reaction.

When ethyl cyanoformate was added to the reaction mixture after complete conversion of the acylsilane **103**, the silyloxy ketone intermediate **A** undergoes a sequential cyanation, 1,4-silyl migration and *O*-acylation with ethyl cyanoformate generating silyl cyanohydrin carbonate **104** as a single regioisomer, at the same time releasing the cyanide catalyst (Scheme **38**). Thus, the sequential silyl benzoin addition/cyanation-*O*-acylation allows the formation of two new C-C bonds in excellent yield.



Scheme 38.

The mechanism of the cross silyl benzoin addition has been proposed on the basis of crossover studies and a number of unambiguous experiments designed to ascertain the reversibility of key steps [74].

3.3. Epoxide Ring Opening

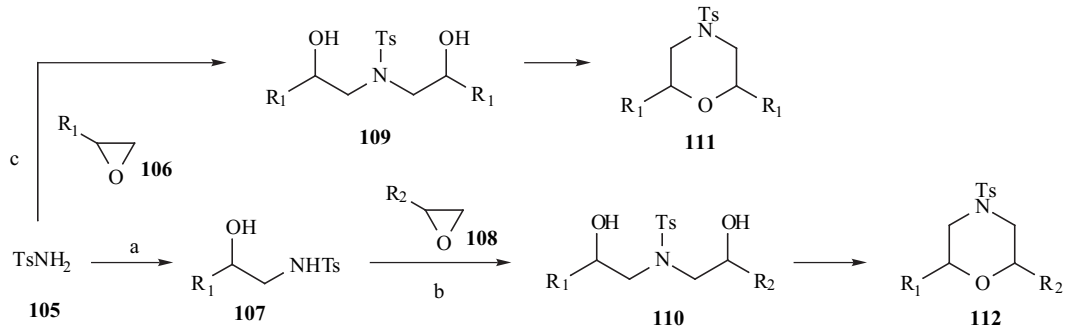
Various 2,6-disubstituted morpholines have been prepared through the regioselective ring opening of oxiranes with *p*-toluenesulfonamide under SL-PTC conditions, using a catalytic amount of alkaline metal carbonates and TEBA (Scheme **39**) [76].

Symmetric hydroxysulfonamides **109** have been isolated in excellent yields through the direct dialkylation of *p*-toluenesulfonamide (**105**) with excess oxirane. On the other hand, non-symmetric hydroxysulfonamides **110** have been prepared by a two-step alkylation protocol using two different epoxides. Hydroxysulfonamides **109,110** have been cyclized to morpholines **111,112**, useful building blocks in the synthesis of pharmaceuticals and agrochemicals.

3.4. Fluorination

The selective fluorination of organic molecules through nucleophilic substitution of halogens or sulfonates is of great practical interest [77]. This reaction has been carried out under SL-PTC conditions, however, the high basicity of fluoride anions causes decomposition of tetraalkyl ammonium cations and β-elimination as side by-products. Hypervalent pentacoordinated silicon [78] and tin [79] reagents have also been used as a source of nucleophilic fluoride, however, their high price and molecular weight limited the use of these compounds in practical synthesis.

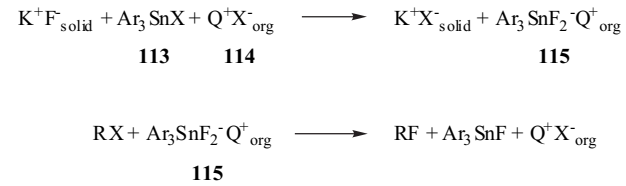
A new SL-PTC procedure has recently been developed employing triorganotin halides **113** as co-catalysts in the presence of $Bu_4N^+HSO_4^-$ **114** and solid KF [80]. The fluorination occurs *via* continuous formation of lipophilic hypervalent triorganodifluorostannate anions **115** acting as fluorinating agent in the organic phase. Triphenyltin fluoride or the less expensive chloride can be used as co-catalysts, since the latter is converted *in situ* into fluoride, which is



a) **106** (50 mol %), K_2CO_3 (5 mol %), TEBA (5 mol %), dioxane 90 °C. b) **108** (110 mol %), M_2CO_3 (10 mol %) TEBA (10 mol %), dioxane 90 °C. c) **106** (300 mol %), M_2CO_3 (10 mol %), TEBA (10 mol %), dioxane 90 °C

Scheme 39.

regenerated in the fluorination step and reacts again with KF (Scheme **40**).

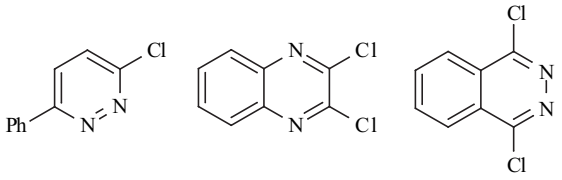


Scheme 40.

Although this procedure is of general application, it is particularly well suited for fluorinations of substrates prone to β-elimination. In fact, the basic character of fluoride anion in strongly diminished and this typical side reaction is drastically reduced, if not suppressed.

When the reaction is carried out in sulfolane, the fluorination occurs, although in longer reaction times, even in the absence of the quaternary ammonium salt, due to the solubility of $Ph_3SnF_2^-K^+$ in this solvent [81].

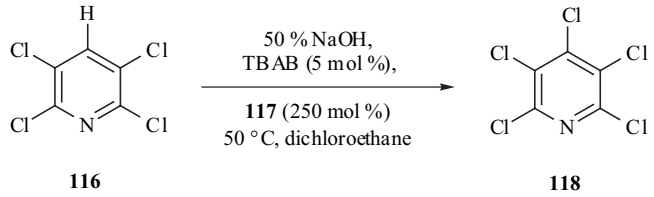
Some chlorodiazines have been reacted with KF under solvent-free conditions in the presence of a phase transfer agent, with or without microwave activation (Scheme **41**) [82]. Selective and efficient mono and difluorinations have been obtained, with higher yields and selectivities over published methods.



Scheme 41.

3.5. Chlorination

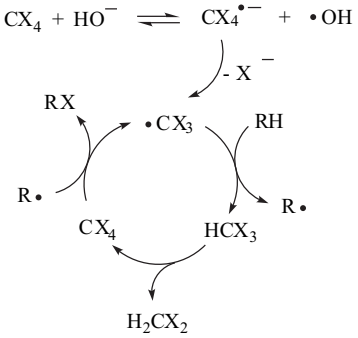
The chlorination of 2,3,5,6-tetrachloropyridine (**116**) has been efficiently carried out in mild conditions in the presence of TBAB and 50% aq. NaOH. Carbon tetrachloride or hexachloroethane (**117**) have been used as chlorinating agents [83]. The latter afforded higher selectivity (96% vs 80%) and provided the additional advantage that co-produced tetrachloroethylene can be recycled to **117** (Scheme **42**). The reaction is likely to proceed through the formation of a carbanionic intermediate as indicated by H/D exchange experiments. In fact, when **116** was treated with either D_2O or $CDCl_3$ in the presence of NaOH, 90% deuterium exchange was observed after 3 h at room temperature, generating the expected 4-deuterated pyridine. Solid K_3PO_4, a base weaker than NaOH, was also found to promote H/D exchange and chlorination, although in a lower 70% selectivity.



Scheme 42.

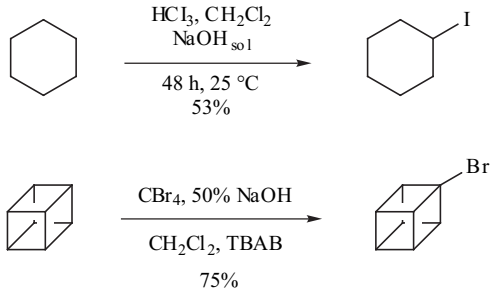
3.6. Radical Reactions

Radical reactions in biphasic media are well-known [84]. For example, the controlled substitution of an aliphatic C-H bond can be achieved through the alkane halogenations under PTC conditions [85]. A typical halogenation protocol involves stirring the alkane (eventually in the presence of an inert organic solvent) with concentrated aqueous or solid base such as NaOH, in the presence of the halogenating reagent (CX_4 or CHX_3, X = halogen) and a quaternary ammonium salt. The SET oxidation of poorly solvated OH^- with CX_4 produces a radical anion that dissociates into a halide anion and a CX_3 radical, responsible for the C-H activation (Scheme **43**) [86].



Scheme 43.

The overall reaction provides a haloalkane and dihalomethane through C-H abstraction, base catalyzed disproportionation and X-abstraction. The low concentration of products in the reactive region give rise to the highest selectivities reported for alkane radical halogenations. The preparative advantages of the PTC approach include the halogenation of unactivated hydrocarbons and use of inexpensive iodination reagents (CHI_3). The halogenation of highly strained hydrocarbons occurs without concomitant fragmentation or rearrangements, and mixed halogenations proceeds without halogen exchange, as shown in the synthesis of 1-bromo-3-chloro-5-fluoroadamantane (Scheme **44**) [87].



Scheme 44.

A range of radical reactions, initiated by photolysis of decacarbonyldimanganese $Mn_2(CO)_{10}$ have recently been performed in an aqueous-organic two-phase system in the presence of 5M NaOH and triethylbenzylammonium chloride (TEBA) (Scheme **45**).

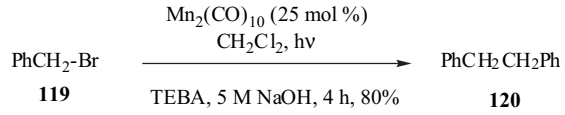
For example, the dimerization of benzyl bromide (**119**) and the halogen-atom transfer cyclization of 1,6-dienes **121a-c** afforded bibenzyl **120** and pyrrolidines **122 a-c** in good yields and short reaction times.

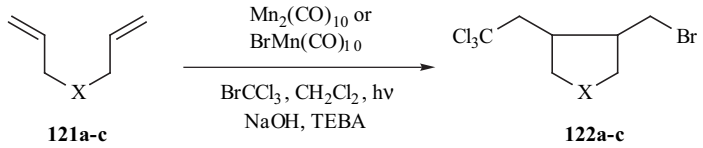
Under these reaction conditions, the efficient removal of manganese halide by-products, produced from radical reactions of alkyl halides, and regeneration of decacarbonyldimanganese was also achieved [88].

3.7. Phase Transfer Catalysis without Organic Solvent

PTC has typically been employed for replacement of strong bases such as BuLi, LDA and NaH that should be used under strictly anhydrous conditions. Additional advantages derive when alkaline metal hydroxides are used in the absence of organic solvent. A recent example is the practical synthesis of venlafaxine, a new generation antidepression drug, through condensation of *p*-methoxyphenylacetonitrile (**123**) with cyclohexanone (**124**). The reaction has been carried out without organic solvent, using 10% aqueous NaOH or KOH in the presence of tetrabutylammonium hydrogen sulfate ($Bu_4N^+HSO_4^-$) as PT catalyst (Scheme **46**) [89]. Quantitative yields of **125** are obtained in 1 h, during which the product precipitated from the aqueous medium and was recovered by filtration.

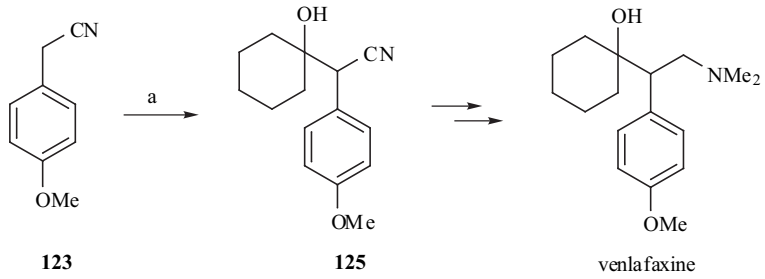
Another practical and economical procedure has been employed in the entirely organic solvent free synthesis of 2-substituted 3,4-dihydro-*2H*-1,4-benzoxazines **129**, investigated as potential intracellular calcium antagonists, serotonin





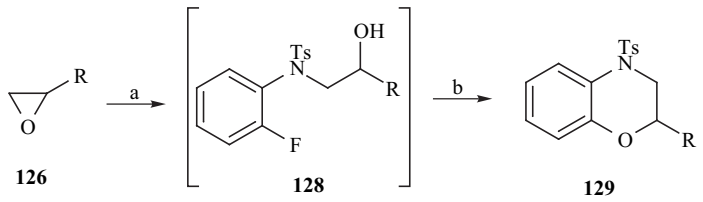
a, X = C(COOEt)$_2$; **b**, X = O; **c**, X = NCOCCl$_3$

Scheme 45.



a) **124**, 10% aq. NaOH, TBAHSO$_4$ (0.02 eq), 0-15 °C, 2 h

Scheme 46.



126 **128** **129**

a) **127**, TEBA (2 mol %), KF (4 mol%), 4 h, 90 °C. b) 50% NaOH, 90 °C, *n*-$C_{14}H_{29}N^{+}Me_3Cl^{-}$ (20 mol %), 1 h, 90 °C.

Scheme 47.

receptor antagonists and antibacterial agents (Scheme **47**) [90]. The ring opening of epoxides **126** with 2-fluoroaryl-sulfonamides **127** in the presence of a quaternary ammonium fluoride generated the hydroxysulfonamides **128** in excellent yields. The latter are then rapidly ring closed to benzoxazines upon addition of 50% aq NaOH and *n*-$C_{14}H_{29}N^{+}Me_3Cl^{-}$ to the reaction mixture. Pure benzoxazines **129** were isolated after filtration of the water diluted reaction mixture. The quaternary onium fluoride behaves as a base as well as PT catalyst and can be generated *in situ* from a cheap onium salt (for example TEBA) and an excess of potassium fluoride.

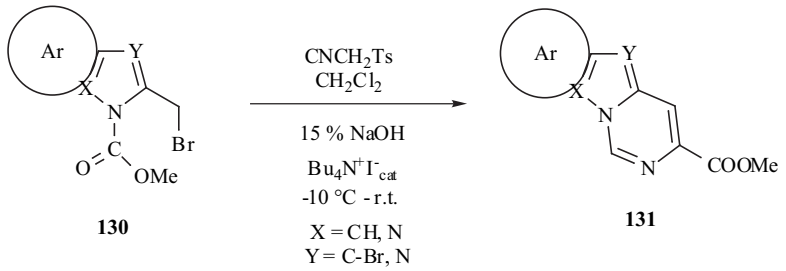
3.8. Heterocyclization

The heterocyclic core of variolines, a family of marine alkaloids with antitumor and antiviral activity, has been efficiently assembled through the *C*-alkylation of tosylmethyl isocyanide with bromomethyl azoles **130** under LL-PTC conditions using 15% aq NaOH as base [91]. The initially formed *mono*-alkylated intermediates generated tricyclic products **131** in moderate to good yields through intramolecular transfer of methoxycarbonyl group, followed by cyclization and 1,2-elimination of *p*-toluenesulfinic acid. Under the mild reaction conditions employed, the carbamate protecting group is stable and the reaction cascade producing the tricyclic compounds can smoothly take place (Scheme **48**).

3.9. Synthesis of Monodispersed Oligo(Ethylene Glycols)

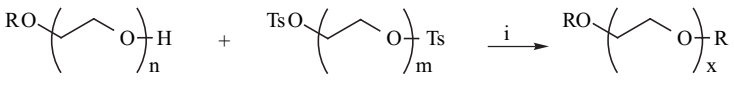
Monodispersed oligo(ethylene glycols) **135** have found widespread utility in the synthesis of crown ethers and podands, as well as biocompatible polymers. Bidirectional chain elongation of oligo(ethylene glycols) has been achieved by reacting *mono*-protected ethylene glycol derivatives **132** with *bis*-(tosylate)- or *bis*-(mesylate)-glycol derivatives **133** in the presence of NaH as base and THF or DMF as solvents. However, slow conversions have generally been observed along with elimination side-products.

A novel procedure has been reported employing powdered KOH in the presence of TBAB, without any organic solvent (Scheme **49**) [92]. Excellent yields of the *bis*-protected elongated ethylene glycol oligomers **134** were obtained in short reaction times with a simple work-up. The cleavage of allyl protecting group has been achieved in the presence of 10% Pd/C and APTS generating monodispersed oligo(ethylene glycols) **135** in good overall yields.



130 **131**

Scheme 48.



132 **133** **134** ii **135**

132,134 R = allyl
135 R = H

m, n = 1-4
x = 3,4,7-12

overall yields
65-84%

i) KOH_{sol}, TBAB (20 mol %), toluene 110 °C, 2h. ii) 10% Pd/C, APTS (5 mol%), MeOH-H_2O (24-1), 2-24 h, reflux.

Scheme 49.

4. INVERSE PHASE TRANSFER CATALYSIS

Although LL-PTC is classically performed extracting an anionic reagent from the aqueous to the organic phase, where the reaction occurs, examples are known where the opposite is true, namely a lipophilic reagent is transferred into the aqueous phase, where it reacts with a hydrophilic reactant. The latter procedure has been given the name of inverse phase transfer catalysis (IPTC) [93] and remained quite an unexplored field until recently when it received an increasing interest in order to use water as a cheap and environmentally friendly solvent. Cyclodextrins [94], pyridine derivatives [95] and calixarenes [96] have been used as catalysts.

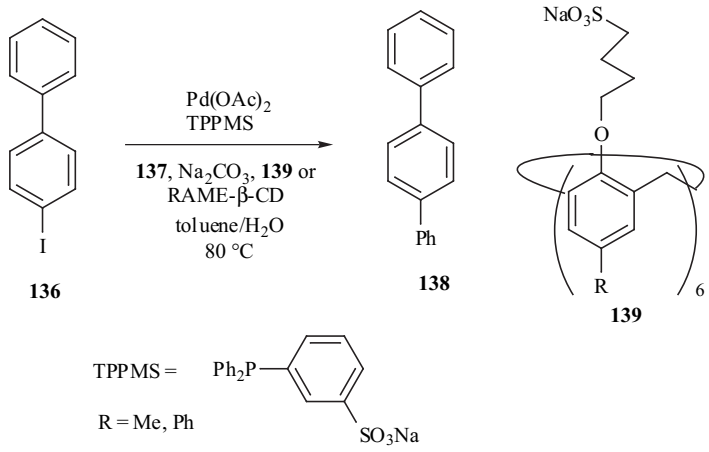
4.1. Suzuki Coupling

The palladium-catalyzed cross-coupling of aryl halides with organoboron compounds, known as the Suzuki-Miyaura reaction, is widely employed for the formation of carbon-carbon bonds. The reaction has been carried out in aqueous-organic two-phase systems with the catalyst immobilized in the aqueous phase by a water soluble phosphane [97]. However, in the case of water insoluble substrates, very low reaction rates have been observed due to low phase-transfer exchange.

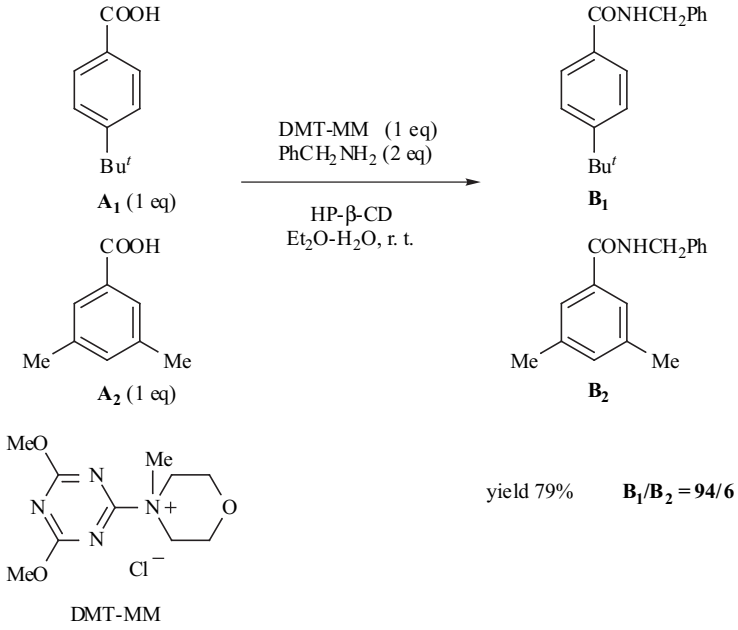
Randomly methylated β-cyclodextrins (RAME-β-CD) or calixarenes with extended hydrophobic host cavities and surface-active properties were shown to behave as efficient inverse phase transfer catalysts (IPTC) [98]. The cross-coupling reaction of 1-iodo-4-phenylbenzene (**136**) with phenylboronic acid (**137**) in aqueous medium was up to 92 times faster in the presence of these catalysts (Scheme **50**). Calixarenes **139** are more effective that cyclodextrins, nevertheless, the latter are of more practical use since they are cheap and commercially available.

4.2. Amidation

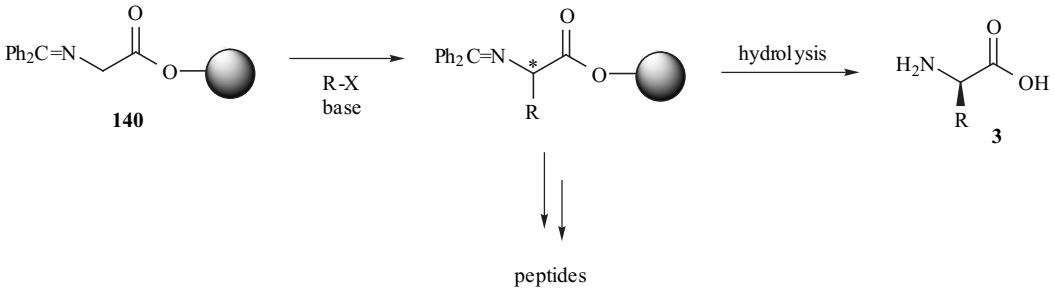
The substrate-selective amidation of carboxylic acid has also been carried out in a liquid-liquid two-phase system in the presence of commercially available (hydroxypropyl) cyclodextrin (HP-β-CD) as inverse PT catalyst [99]. A lipophilic carboxylic acid with a strong affinity for CD



Scheme 50.



Scheme 51.



Scheme 52.

cavity can be selectively transferred to the aqueous phase, where it reacts with water-soluble dehydrocondensing agent, 4-(4,5-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMT-MM). The acyloxytriazine thus obtained generates a hydrophobic amide, which transfers to the organic phase. A competitive experiment, employing equimolar amounts of 4-*tert*-butylbenzoic acid (**A_1**) and 3,5-dimethylbenzoic acid (**A_2**), showed that under optimized conditions, *N*-benzyl-4-*tert*-butylbenzamide (**B_1**) was obtained almost exclusively (Scheme **51**).

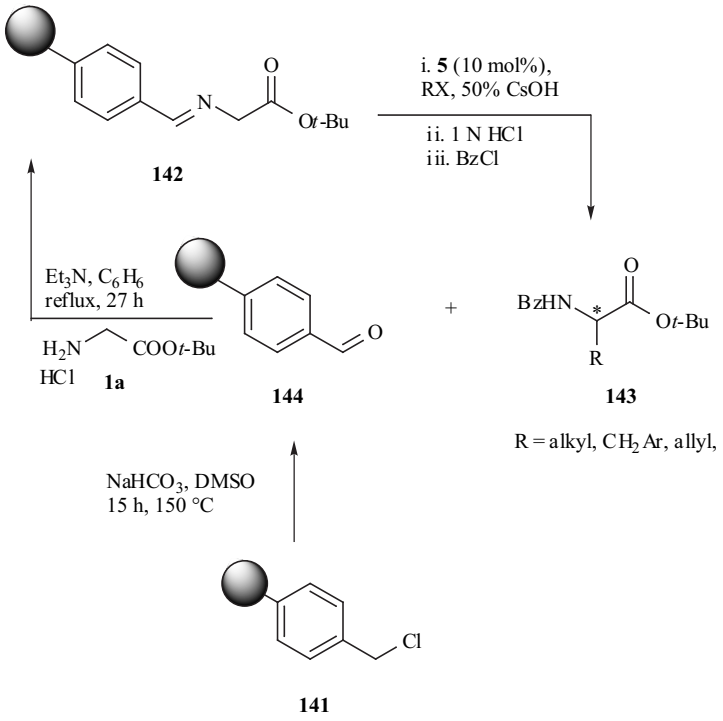
5. SOLID-PHASE REACTIONS

The solid-phase synthesis of unnatural amino acids and peptides has already been accomplished by alkylation or Michael addition of the benzophenone imine of glycine-Wang-resin **140** [100]. The enantioselectivities observed in asymmetric PTC alkylations were somewhat lower than those obtained from the solution-phase synthesis [101, 8d] (Scheme **52**).

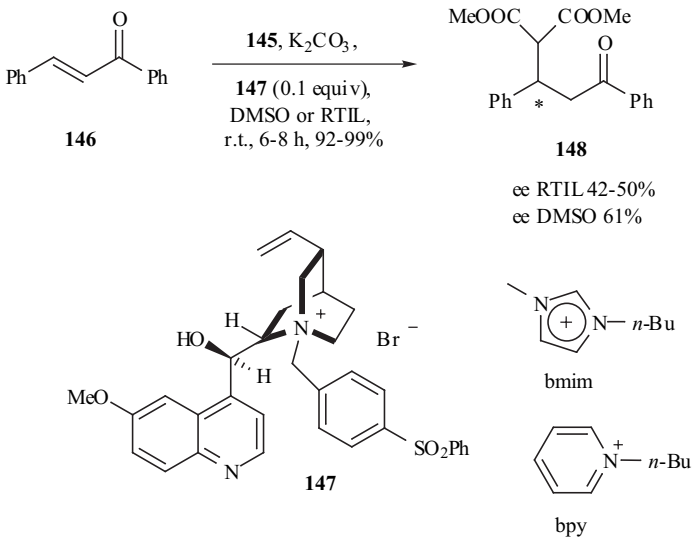
A new efficient procedure for the solid phase synthesis of α-amino acids through the PTC alkylation of resin bound *t*-butyl glycine-imine ester has recently been reported [102]. The resin bound aromatic imine **142** was prepared from Merrifield resin **141** through oxidation, followed by condensation with glycine *t*-butyl ester **1a**. When the alkylation step was carried out by using 50% aq CsOH as base and *O*-allyl-*N*-(9-anthracenylmethyl) cinchonidinium bromide catalyst **5**, high enantioselectivities were obtained. The acidic hydrolysis, followed by benzoylation, generated the *mono*-alkylated products **143** in 50-82% yields, along with **144** that could be recovered and directly recycled (Scheme **53**).

6. IONIC LIQUIDS

Room temperature ionic liquids (RTILs) have been recognized as a possible environmentally benign alternative to volatile solvents. Ionic liquids are comprised of bulky organic cations, therefore they are well suited for types of reactions for which PTC is effective. When nucleophilic displacements are carried out in ionic liquids as solvent, the latter can act as catalyst. The ionic liquids might not be as effective as catalysts as most PT agents, however, their high concentration ensures a high reaction rate. Several



Scheme 53.



Scheme 54.

nucleophilic displacements under aqueous-RTIL phase transfer conditions have been reported [103].

The use of RTILs as solvents in asymmetric alkylation of benzophenone imines in the presence of various catalysts produced very low ees due to competition with the catalysis of the achiral solvent.

The asymmetric Michael addition of dimethyl malonate (**145**) to 1,3-diphenylprop-2-en-1-one (**146**) in the presence of potassium carbonate as base and the quinine derived chiral quaternary ammonium salt **147** as PT catalyst has also been investigated (Scheme **54**) [104]. Moderate *ees*, although in excellent yields, were obtained both in organic solvents and various ionic liquids. The enantioselectivity was reversed in reactions carried out in [bmim]PF_6 and [bmim]BF_4 with respect to reactions carried out in organic solvents and [bpy]BF_4.

7. CONCLUSION

Established PTC technology is expected to keep on greatly improving non-PTC synthetic transformations. The typical features of PTC methodology are related with removal of organic solvents and dangerous or expensive bases along with simplicity of the procedure and high yields and purity of the products. This is particularly attractive from an industrial point of view, due to the increasing number of environmental laws, as PTC processes always produce much less industrial wastes and consume less energy when compared with the traditional ones.

In addition to the developing and implementing of PTC processes, future advances of PTC in organic synthesis are expected in the field of supercritical fluid PTC and from the incorporation of modern computational chemistry in the design of new inexpensive chiral phase transfer catalysts.

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