MINIREVIEW

New Trends in Asymmetric Phase Transfer Catalysis

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Dedicated to Prof. Franco Cozzi on the occasion of his 70th birthday.

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Abstract: Phase Transfer Catalysis (PTC) is a powerful tool to perform reactions in a practical fashion, both in laboratory and industrial scale. Significant cost savings and major process improvements can be achieved in reactions performed under PTC conditions. In the last few years remarkable results in stereoselective reactions were achieved using chiral, non-racemic quaternary ammonium salts. Moreover, the use of bulky, chiral phosphate anions paired with achiral cations to generate lipophilic ion pairs allowed to design new avenues for the stereoselective construction of important building blocks. Hydrogen bond interactions were also shown to provide new pathways for asymmetric nucleophilic substitutions using insoluble reagents under PTC conditions. This review will focus on recent advances in developing practical synthetic routes to construct molecules in a stereoselective fashion under PTC conditions.

1. Introduction

Phase transfer catalysis (PTC) has been introduced more than 50 years ago as a tool to perform reactions involving anions in a practical fashion.[1] This methodology has flourished in the next decades after basic principles have been fully elucidated.[2] Important cost savings and process improvements are often achieved under PTC conditions. Indeed, PTC is nowadays widespread for academic as well as industrial applications[3] and the market of phase transfer catalysts has continuously grown in the past reaching 1,000 USD Million size.

One of the most striking advantages of PTC is the possibility to replace expensive solvents and dangerous bases such as sodium hydride,[4] requiring strictly anhydrous conditions, with cheap aqueous bases and apolar, environmentally friendly and easily recyclable solvents. Ammonium and phosphonium salts have been also used in the CO_2 fixation producing excellent yields of cyclic carbonates under mild conditions.[5]

PTC N-alkylations, cyclopropanation and oxidations have been carried out under flow conditions to overcome mass and heat transfer limitations.[6]

Although PTC plays a key role in several fields as shown by numerous examples continuously appearing in the literature,[7] this review will focus on recent asymmetric applications using chiral phase transfer catalysts.[8] On one hand excellent results, both as regards to chemical yield and stereoselectivity, have been obtained by using various classes of chiral onium salts in the traditional PTC field. On the other hand, during the last decade new synthetic pathways have been designed by using chiral,

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binaphthol derived phosphate anions and chiral bis-urea hydrogen bond donors.

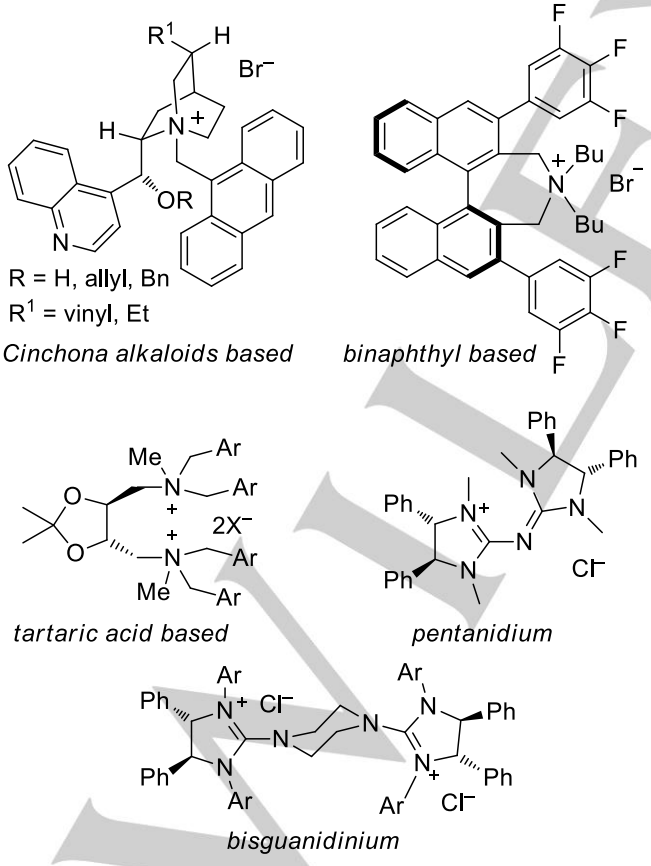
This minireview is not intended to be exhaustive due to the large number of applications of asymmetric PTC continuously appearing in the literature. Rather, significant current trends will be presented herein to highlight those new tools considered at the sole author discretion more useful to develop practical protocols capable to quickly generate molecular complexity.

2. Ammonium Phase Transfer Catalysts

Since the first pioneering work at Merck,[9] many other groups have contributed to the blossoming of asymmetric PTC through the development of new, efficient catalysts and their application to a variety of reactions. *Cinchona alkaloids* based catalysts first emerged as cheap and easily available compounds.[10] Soon, binaphthyl-based quaternary ammonium catalysts proved to be a new, versatile and efficient class capable to provide excellent stereoselectivity with lower catalyst loadings.[11]

Some physical evidences about the interaction of these catalysts with neutral molecules have recently been demonstrated,[12] thus providing an useful tool to design new catalysts and rationalize previously described enantioselective PTC reactions.

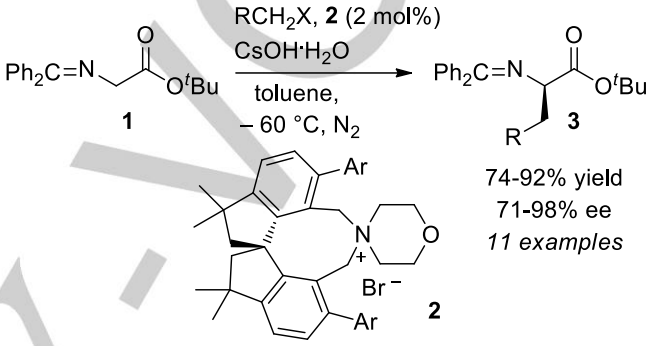
Tartaric acid based catalysts,[13] pentanidium[14] and (bis)guani dinium[15] as well as chiral phosphonium[16] and sulfonium salts[17] have also been developed, thus greatly enlarging the number of catalysts available to pursue asymmetric applications of PTC (Scheme 1).



Scheme 1. Some typical chiral ammoniums salts.

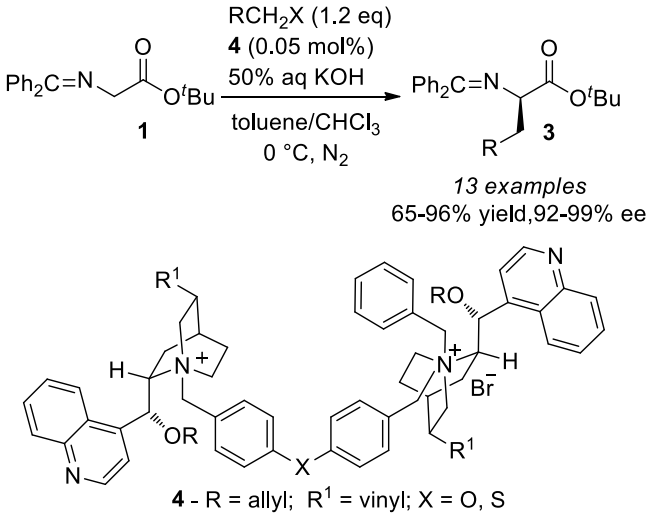
Consequently, asymmetric PTC is undoubtedly one of the most powerful catalytic tools to assemble scaffolds that often are not so easy to access through other protocols. Excellent reviews have described the field in the past.[18]

The benchmark alkylation of *tert*-butyl glycinate Schiff base **1** still remains the preferred test to investigate the activity of new asymmetric catalysts. For example, a new class of C_2-symmetric spirocyclic quaternary ammonium salts **2**, based on tetramethyl-1,1-spiro biindane, which possess more rigid and stable backbones and smaller dihedral angles, has been prepared from cheap bis-phenol A and was found to generate the C-alkylated compounds **3** in good to excellent yield and enantioselectivity (Scheme 2).[19]



Scheme 2. Imine alkylation with tetramethyl-1,1-spiro biindane based PT catalysts.

The highly accessible *Cinchona*-derived dimeric hydro cinchonidinium PTCs with aromatic linkers were previously shown to provide higher enantioselectivity than monomeric PTCs, under more practical conditions as regards to reaction times and temperature in the same alkylation of 1.[20] More recently, similar dimeric catalysts **4** with a diphenyl ether/thioether linker could provide excellent results with a significantly lower catalyst loading in the range of 0.01-0.05 mol% (Scheme 3).[21]

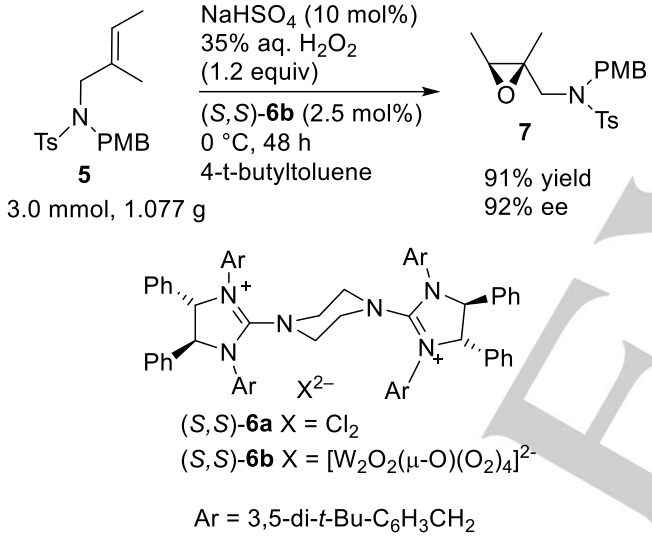


Scheme 3. Low loading dimeric *Cinchona* derived phase transfer catalysts.

Moreover, a slight excess only of the alkylation agent was used and the size of the ester did not influence the yield and the stereoselectivity.

In dimeric quinuclidinium species it is presumed that one quinuclidinium would interact with the enolate anion, whereas the second would facilitate the S_N2 alkylation through interaction with the leaving group. The DFT calculated transition state was in accordance with this hypothesis.

The challenging enantioselective oxidation of a variety of allylic and homoallylic amines such as **5** to a range of chiral aminoepoxides **7** was achieved under the catalysis of a chiral bisguanidinium tetraperoxyditungstate **6** in the presence of green hydrogen peroxide as the stoichiometric oxidant (Scheme 4).[22] The active catalyst **6b**, whose structure could be ascertained through X-ray crystallography, can be easily prepared by mixing the bisguanidinium chloride **6a** with $Na_2WO_4{\cdot}2H_2O$ and H_2O_2 or generated in situ in the presence of catalytic amount of Ag_2WO_4. In this case the authors proposed that the formation of AgCl drives to completion the generation of the ion pair catalyst thus improving the conversion and the stereoselectivity.



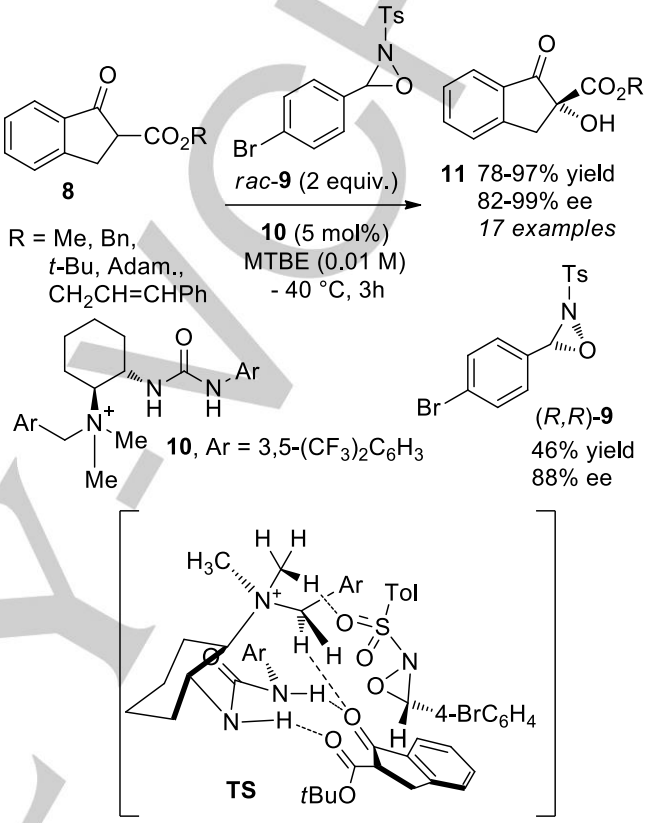
Scheme 4. Gram scale epoxidation of allylic amines.

The best results were obtained in 4-t-butyltoluene as solvent in the presence of $NaHSO_4$ as additive. The latter might have a role in the re-oxidation of the reduced catalyst in the aqueous phase after oxygen delivery in the organic phase.

2.1. Bifunctional Catalysts

Bifunctional quaternary ammonium catalysts have shown their great capability to promote highly stereoselective reactions. Bifunctional catalysts are not only provided with the onium moiety but also with a group capable to interact with the reagent preorganizing a highly ordered transition state. Thus, a higher reactivity and stereoselectivity can typically be achieved in the presence of hydroxy, amino or urea groups. [23] A few illustrative examples are reported in this section to underline the role of the additional functional group. Other examples will also be found in the next sections focused on reaction types.

The enantioselective α-hydroxylation of β-ketoesters **8** with oxaziridine **9** could be obtained with the *trans*-cyclohexane diamine derived bifunctional chiral ammonium salt **10**, under base-free conditions with the simultaneous kinetic resolution of the oxaziridine **9** (Scheme 5).[24]

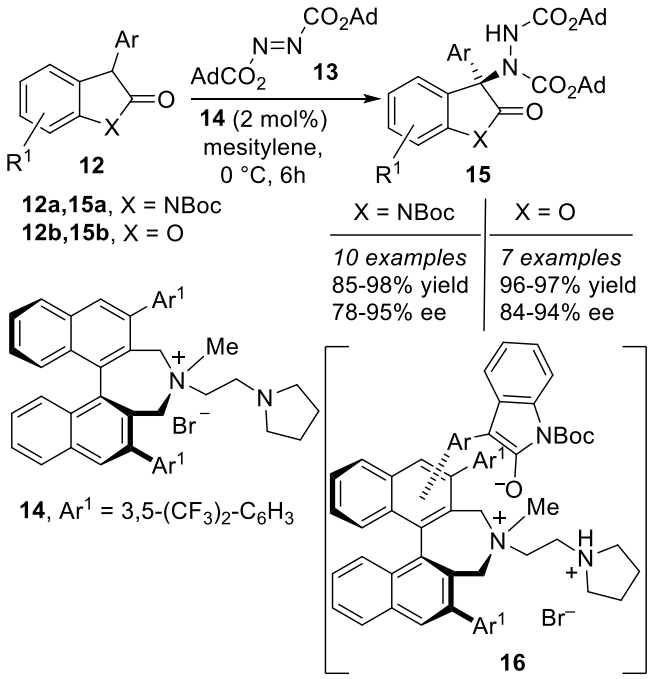


Scheme 5. Enantioselective α-hydroxylation of β-ketoesters.

It is worth noting that both the quaternary ammonium and the urea groups were needed to achieve high hydroxylation enantioselectivity. The lowest-energy transition state **TS** leading to the *R* enantiomer could be identified through DFT calculations. Strong H-bond interactions between urea NHs and the carbonyl oxygen atoms of **8** as well as interaction of one benzylic CH to the carbonyl oxygenatoms are the key features of the **TS**. Analogously, the enantioselective α-halogenation of β-ketoesters **8** was reported.[25]

A novel chiral binaphthyl ammonium salt **14** provided with an amino side arm has been designed for the highly enantioselective amination of 3-phenyloxindoles **12a** and 3-arylbenzofuran-2(3*H*)-ones **12b** with bis(adamantyl)azodicarboxylate (**13**) (Scheme 6). The presence of the amino group was crucial for the stereoselectivity. It is worth noting that the commercially available chiral binaphthyl ammonium salt shown in Scheme 1, not provided with the amino side arm, gave a racemic product, even though in excellent yield.[26]

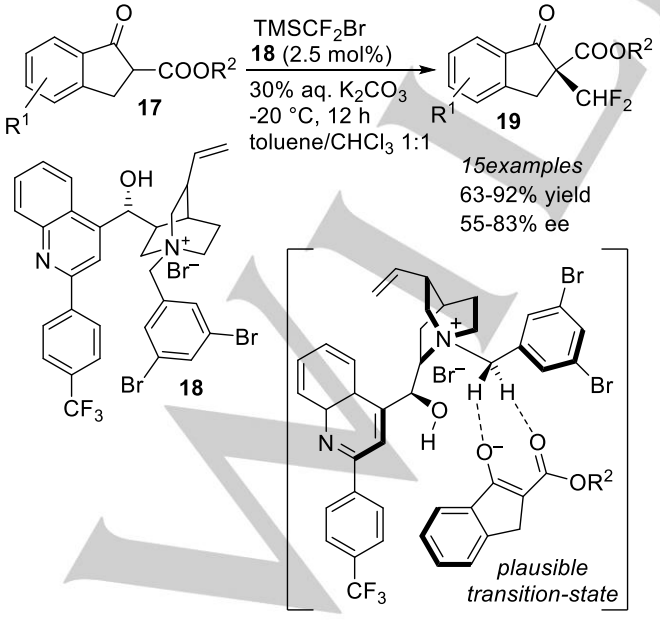
The reaction was proposed to proceed through preferential alkylation of the enolate *Re*-face in the ion pair **16** as a consequence of π-π interaction of Ar and binaphthyl groups. This



Scheme 6. Enantioselective amination of benzocondensated heterocycles.

mechanism is corroborated by DFT calculations as well as the absolute configuration elucidation of compounds **15** as determined through X-ray diffraction analysis.

A simple and new approach to the asymmetric difluoro methylation of β-ketoesters **17** has been achieved through a C-2' arylated Cinchona derived catalyst **18**.[27] A variety of indanone derived β-keto esters **19** have been prepared with good yields and excellent *C/O* selectivity with up to 83% ee by using commercially available (bromodifluoromethyl)trimethylsilane ($TMSCF_2Br$) (Scheme 7).



Scheme 7. Asymmetric difluoromethylation of β-ketoesters.

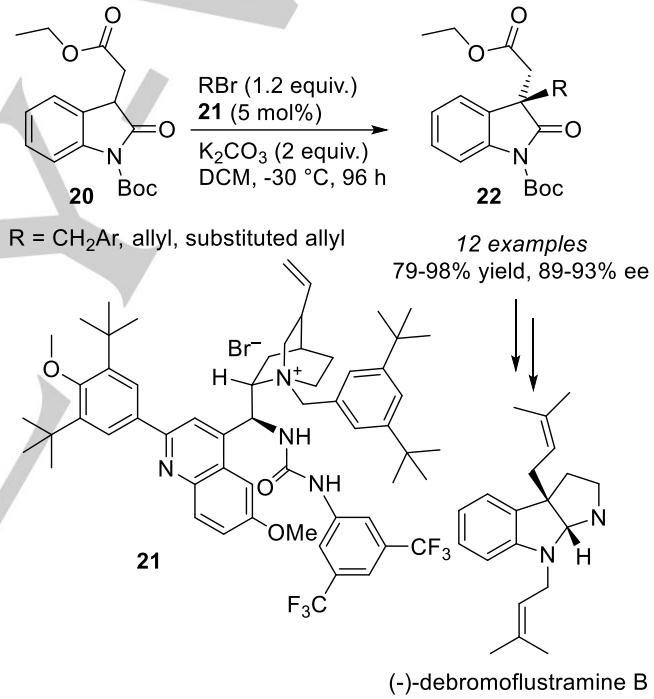
The reaction was proposed to proceed through electrophilic difluoromethylation of a chiral enolate-PTC complex by the difluorocarbene generated *in situ* under basic conditions.

The authors proposed a transition state involving hydrogen-bonding interactions in addition to the usual ion pair interaction.

The enantioselective alkylation of the 2-oxindole backbone **20** under the catalysis of a new bifunctional PTC catalyst **21** bearing a urea hydrogen bond donating group,[28] provided a variety of 3-alkylated compounds **22** in high yield and excellent enantioselectivity (Scheme 8).[29] The introduction of a bulky phenyl group at C-2 of the catalyst's quinoline moiety proved to be quite beneficial to increase the enantioselectivity.

Although previous calculations have demonstrated attractive O-C-H interactions of the *o*-hydrogen atom of a similar phenyl unit with a squaramide-bound enolate,[30] the crucial role of the C-2 aryl unit to ensure significantly higher enantioselectivity could not be elucidated.

This method has been applied to the concise enantioselective synthesis of pyrroloindoline alkaloids such as (–)-debromo flustramine B, exhibiting remarkable biological properties.

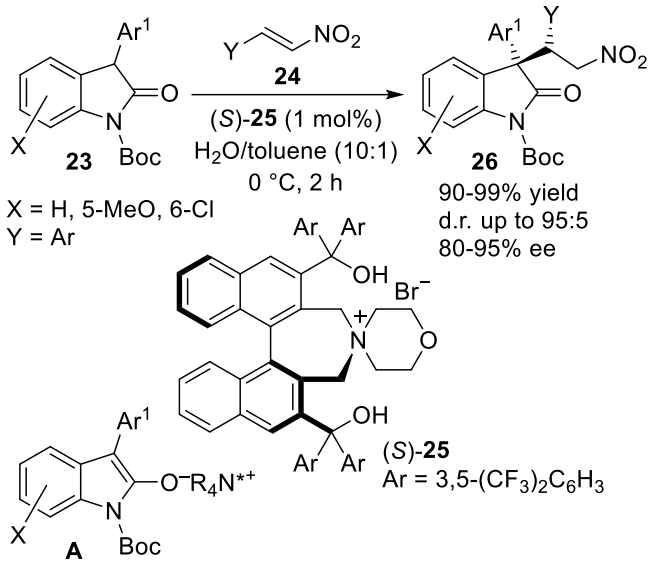


Scheme 8. Enantioselective alkylation of 2-oxindole derivatives.

2.2. Base free PTC

Some asymmetric PTC reactions were shown to proceed under base-free conditions, mainly with enolizable substrates under aqueous/organic biphasic conditions in the presence of binaphthyl bifunctional catalysts.

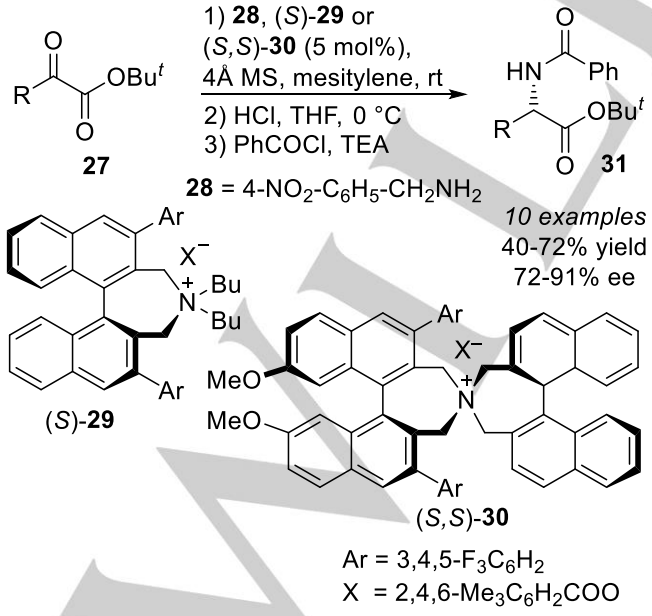
The first report describing the Michael addition of 3-aryloxindoles **23** to β-nitrostyrenes **24** in the presence of quaternary morpholinium catalyst **25** to give α-nitroethyl derivatives **26** (Scheme 9)[31] was later extended to other reactions.[32]



Scheme 9. Michael addition of 3-aryloxindoles to nitroolefines.

Under these water rich biphasic conditions (H_2O/toluene 10:1) the HBr generated by reaction of the substrate with the ammonium bromide catalyst moves to the aqueous phase thus enabling a smooth enantioselective conjugate addition of the chiral ammonium enolate **A** thus formed to nitrostyrenes **24** in the toluene phase without risk of enolate reprotonation. Indeed, the reaction does not proceed at all in toluene in the absence of water due to enolate protonation by in situ generated HBr.

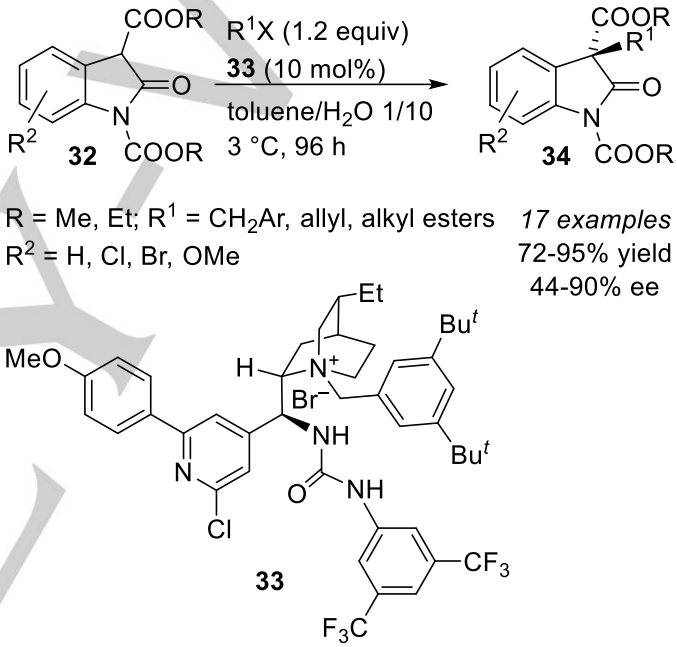
More recently the reaction yield and the stereoselectivity obtained in the base free biomimetic transamination of α-keto esters **27** with *p*-nitrobenzylamine (**28**) were found to greatly depend from the counteranion of catalyst (*S*)-**29** or (*S,S*)-**30** (Scheme 10).[33]



Scheme 10. Enantioselective amination of α-keto esters to α-amino esters.

Quaternary ammonium 2,3,4-trimethylbenzoates exhibited higher reactivity and enantioselectivity than bromides or acetates. A ion pair transition state involving the formation of a *E*-enolate anion paired with the ammonium cation has been proposed in accordance with the observed absolute configuration of the α-amino esters **31**.

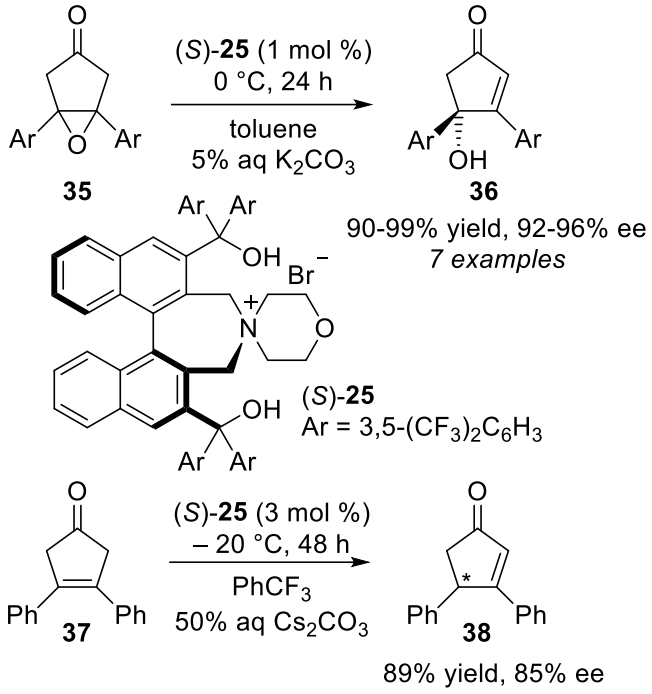
The water-rich base-free protocol has recently been used for the enantioselective alkylation of 2-oxindoles **32** bearing an additional ester moiety for further functionalization (Scheme 11). Excellent yields have been obtained in several cases in up to 90% ee. It is worth noting that the PTC alkylation under standard basic conditions afforded low enantioselectivity. This behaviour might be ascribed to the increased acidity of the α-hydrogen favouring the uncatalyzed background reaction in the presence of base.[34] Lower ees were obtained by using allyl iodide or α-iodoesters in order to include additional functionalities useful for product manipulation.



Scheme 11. Alkylation of *N*-carboxyalkyl oxindoles.

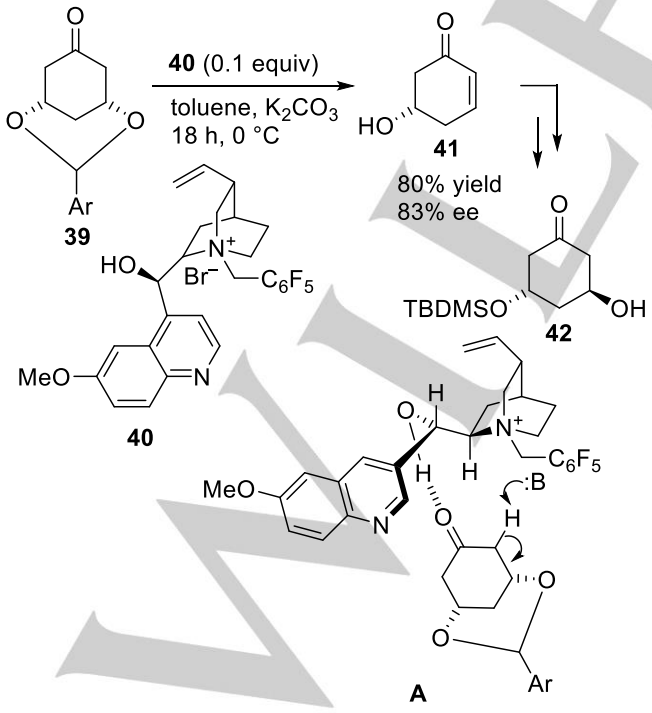
2.3. Desymmetrization

Although huge developments of PTC, the asymmetric desymmetrization of cyclic ketones under PTC conditions has remained elusive until recently. A highly enantioselective desymmetrization of *meso*-diarylepoxy ketones **35** to 3-hydroxy-cyclopentenones **36** has been achieved with the bifunctional catalyst (*S*)-**25** under mild conditions. Low ees were obtained with alkyl-substituted epoxy ketones. This simple protocol was adapted to the enantioselective isomerization of the cyclic β-enone **37** (Scheme 12).[35]



Scheme 12. Desymmetrization of *meso*-epoxy ketones **35** and isomerization of 3-unsaturated ketones **37**.

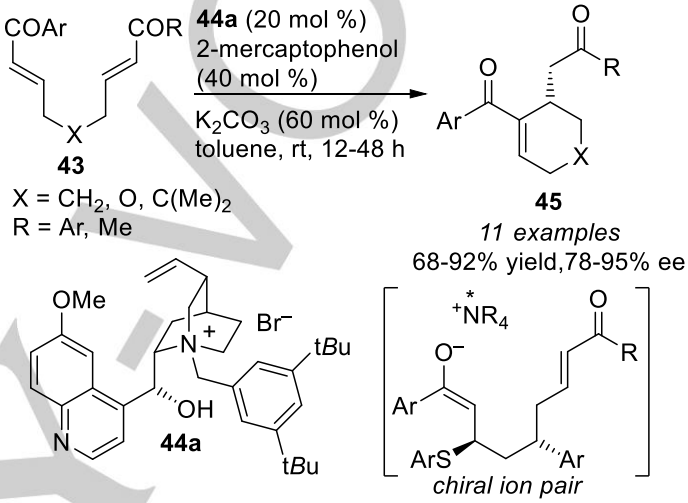
Under similar conditions the desymmetrization of 3,5-*O*-arylidene cyclohexanones **39** has been developed with the catalysis of readily available *Cinchona*-derived catalyst **40**. The (*S*)-5-hydroxycyclohex-2-enone (**41**) thus obtained in 80% yield and 83% ee has later been converted into paricalcitol key intermediate **42** (Scheme 13).[36]



Scheme 13. Synthesis of a paricalcitol intermediate **42** by desymmetrization of 3,5-*O*-arylidene cyclohexanones **39**.

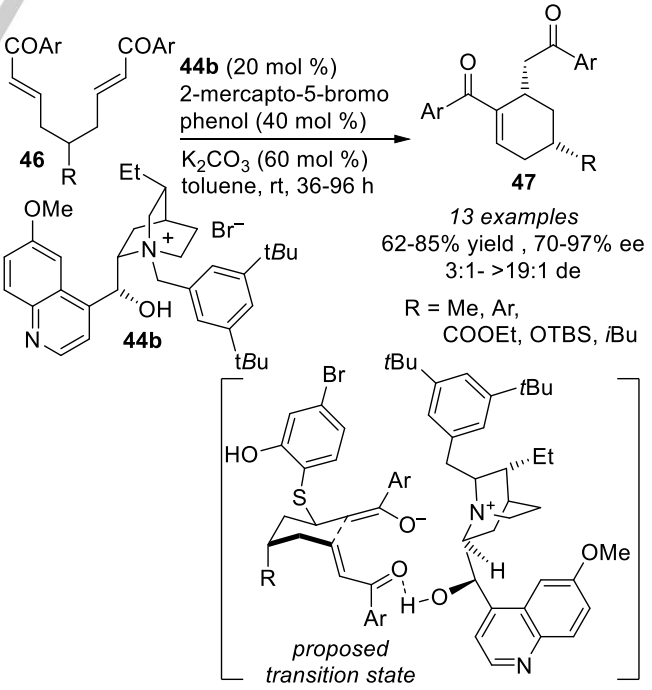
Authors believe the reaction proceeds through the selective deprotonation of the α-H of the methylene group, followed by elimination of the acetal moiety. The interaction of the C_9-OH of **40** with the carbonyl group of the substrate favor the transition state **A** leading to (*S*)-**41** due to the absence of steric hindrance between the quinoline fragment and the acetal moiety.

Various types of linear bis-enones **43,46** and **48** underwent the Rauhut-Currier asymmetric intramolecular reaction through double thiol/PTC activation.[37] The reversible sulfur addition of the thiol catalyst to the prochiral bis-enone **43** could form under chiral PTC catalysis a chiral ion pair capable to generate enantioenriched products **45** through cyclization (Scheme 14).



Scheme 14. PT catalyzed Rauhut-Currier asymmetric intramolecular reaction.

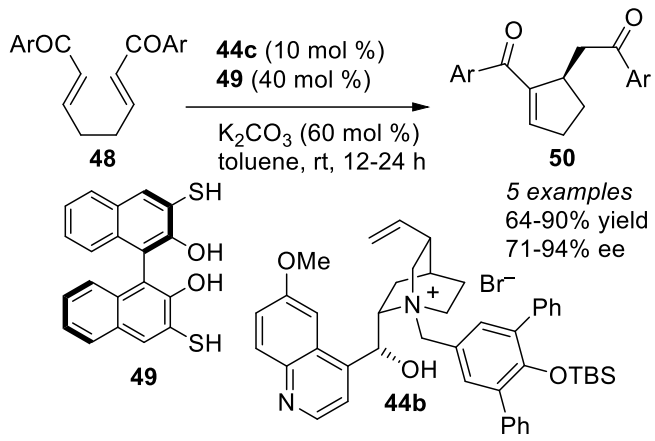
The method could be successfully adapted to δ-substituted bis-enones **46** providing the corresponding cyclic compounds **47** in good to excellent stereoselectivity (Scheme 15).



Scheme 15. Cyclization of δ-substituted bis-enones **46**.

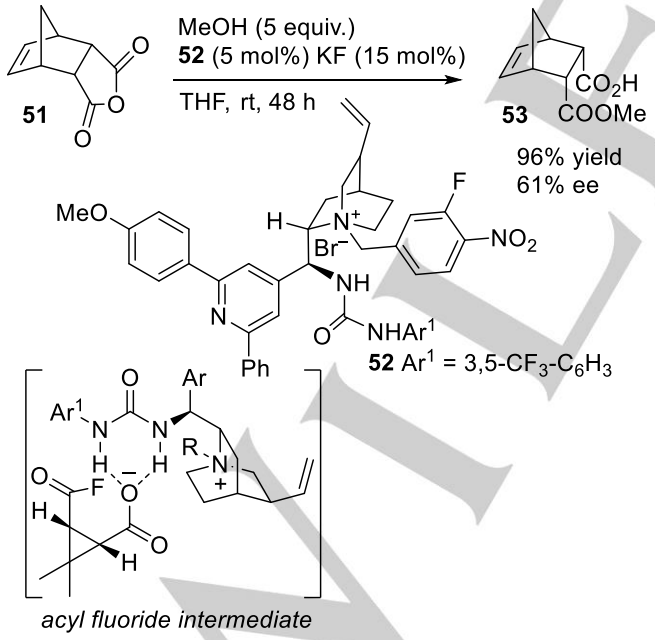
The authors proposed a transition state involving a thiol attack to the bis-enone from the opposite side of the aryl substituent in the δ-position, followed by the enolate to enone attack from the *Si*-face through a chair-like transition state stabilized via the H-bonding interaction of the C_9-OH of the catalyst.

A few five-membered diketones **50** could also be generated in the presence of an axially chiral thiol **49** and a more sterically hindered PTC catalyst **44b** (Scheme 16).



Scheme 16. Cyclization of unsaturated diketones in the presence of an axially chiral thiol.

Thus, the PTC method proved to be a versatile tool to provide a variety of six and five-membered motifs in moderate to high yields and good to excellent stereoselectivity.



Scheme 17. Fluoride-catalyzed methanolysis desymmetrization of *meso*-anhydrides.

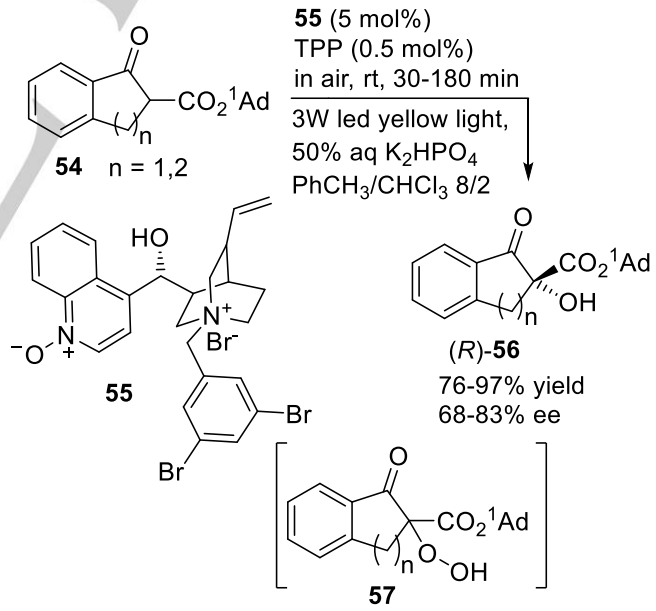
The desymmetrization of *meso*-anhydrides such as **51** was developed through fluoride-catalyzed methanolysis in the presence of the quinine-derived catalyst **52**, bearing a phenyl group on the C-2 of the quinoline fragment (Scheme 17).[38]

A range of *meso*-anhydrides could be converted to methyl hemiesters such as **53** in 84-98% yield in up to 61% ee in the case of *cis* norbornene-5,6-*endo*-dicarboxylic anhydride (**51**). Authors proposed a catalytic cycle initiated by the nucleophilic addition of the fluoride ion, solubilized through ion exchange with the chiral catalyst, on the electrophilic anhydride carbonyl moiety. The resulting acyl fluoride intermediate, stabilised through interaction with the urea group of **52**, is converted to the desired **53** through methanolysis. The acyl fluoride intermediate could be detected by ^{19}F NMR spectroscopy by using benzoic anhydride as starting material.

2.4. Photohydroxylation

Although molecular oxygen is the cheapest oxidant commonly used in most industrial oxidation processes, it is seldom employed in organocatalysis due to lack of reactivity of the nonexcited triplet state ($^1O_3$) of molecular oxygen under mild conditions.[39] On the other hand, photosensitization can generate the more reactive single state ($^1O_2$).

The enantioselective α-hydroxylation of β-ketoesters **54** has been developed under PTC conditions in the presence of light and tetraphenylporphine (TPP) as the photosensitizer.[40] Further work enabled to discover doubly quaternized *N*-oxide *Cinchona*-derived compounds **55** as more efficient catalysts (Scheme 18).[41]

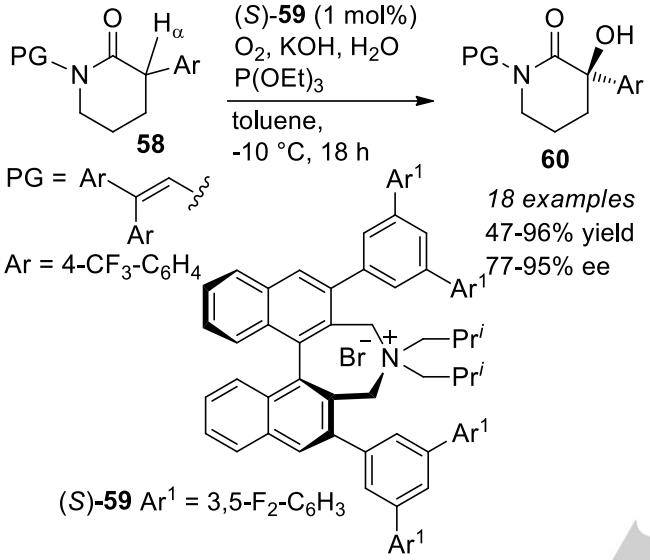


Scheme 18. Enantioselective α-hydroxylation of β-ketoesters.

Authors proved mass spectroscopic evidences in favor of the hydroperoxide **57** as a reaction intermediate. The catalyst could be easily recycled due to the very low solubility in both organic and aqueous phases and was reused for up to six runs with the same results as regards the yield and enantioselectivity.

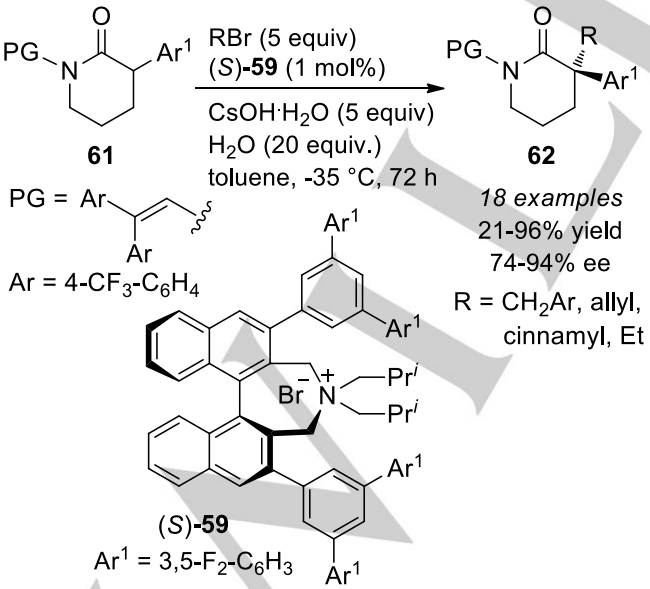
Good to excellent yields of **56** with ee up to 83% could be obtained with 1-adamantyl esters **54**, whereas lower ees were reached with

less hindered ester groups and β-ketoamides. The photosensitizer has later been grafted to the ammonium salt.[42]
More recently, the asymmetric synthesis of α-aryl-α-hydroxy-δ-lactams **60** has been achieved by hydroxylation of *N*-protected lactams **58** in the presence of the binaphthyl catalyst (*S*)-**59**.
The best results both in terms of reactivity and stereoselectivity could only be obtained with a electronwithdrawing *N*-protecting group such as 2,2-(4-trifluoromethyl)diphenylvinyl, capable to increase the acidity of the α-hydrogen (Scheme 19).[43]



Scheme 19. Asymmetric synthesis of α-aryl-α-hydroxy-δ-lactams.

The same achiral auxiliary was found to be crucial also in the asymmetric alkylation of 3-arylpiperidin-2-ones **61** under PTC conditions (Scheme 20).[44]

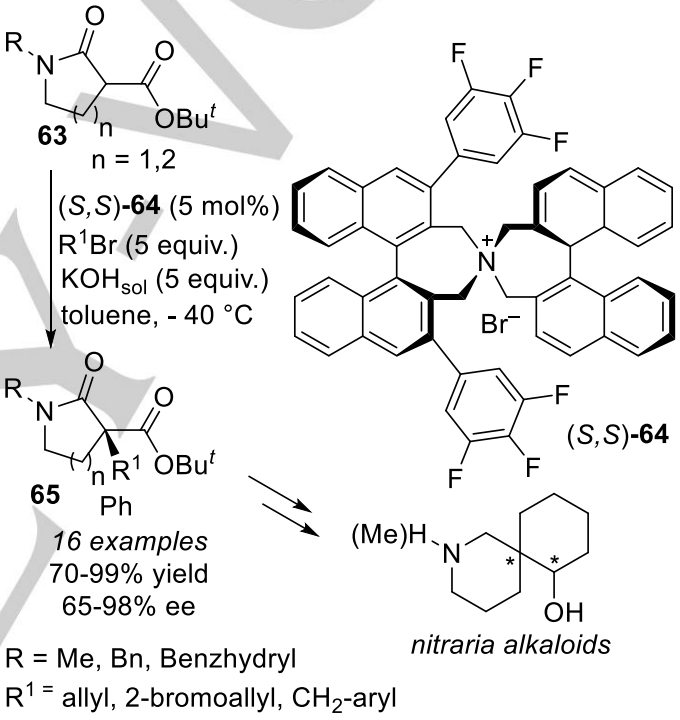


Scheme 20. Asymmetric alkylation of 3-arylpiperidin-2-ones.

Further synthetic elaboration allowed to remove the nitrogen protecting group under acidic conditions to generate δ-lactams. On the other hand, piperidines resulting from N-deprotection and carbonyl reduction could be directly obtained by treatment with BH_3·THF at room temperature. In both derivatizations no erosion of enantiopurity was observed.

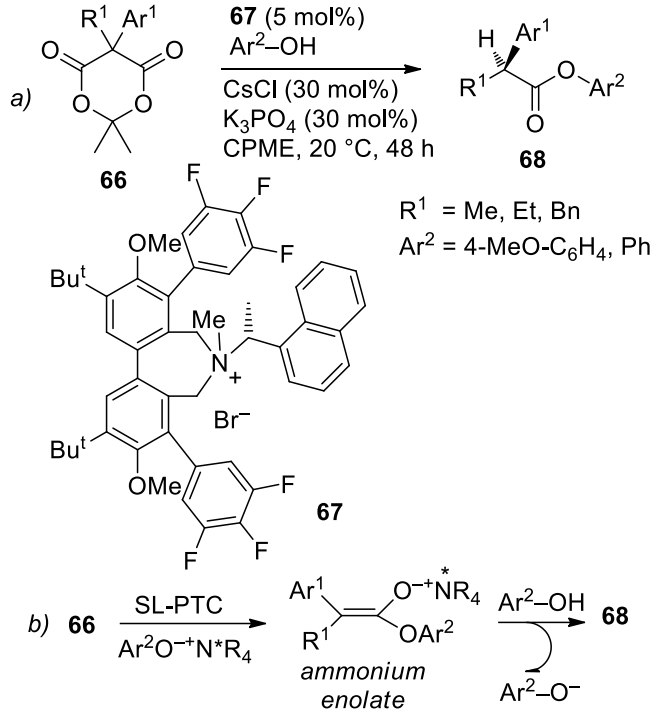
2.5. C-ALKYLATIONS

The enantioselective α-alkylation of γ-butyrolactams (**63**, n = 1) and δ-valerolactams (**63**, n = 2) with various activated electrophiles under SL-PTC conditions in the presence of catalyst (*S,S*)-**64** afforded the corresponding C-alkylated compounds **65** in excellent yields and enantioselectivities (Scheme 21).[45]



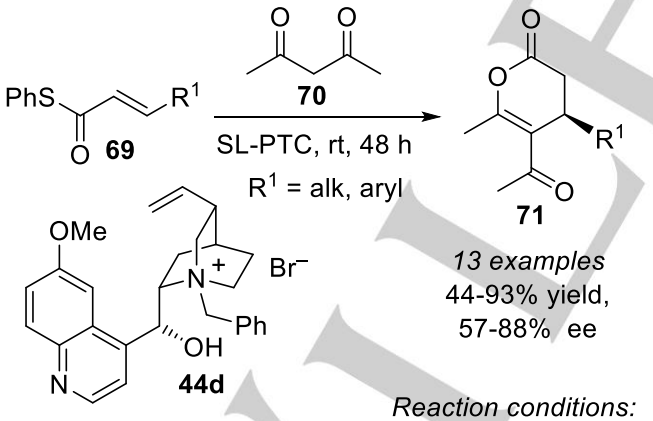
Scheme 21. Enantioselective α-alkylation of γ-butyrolactams and δ-valerolactams.

These lactams, bearing a quaternary stereocenter, have been successfully converted into some *Nitraria* alkaloids exhibiting promising pharmacological effects.
The decarboxylative protonation of Meldrum's acid derivatives **66** under PTC conditions allowed to generate 2-aryl propionic derivatives **68** in good yields with up to 70% ee. (Scheme 22, a).[46] The reaction proceeds through the formation in situ of a chiral ammonium phenoxide ion pair ($Ar_2O^{-+}N^*R_4$) capable to start a reaction cascade leading to a chiral ammonium enolate through subsequent elimination of acetone and CO_2 (Scheme 22, b). The ammonium enolate undergoes enantioselective protonation with *p*-methoxyphenol at the same time regenerating the chiral ammonium phenoxide catalyst.



Scheme 22. a) Enantioselective protonation of acyclic enolates under PTC; b) proposed reaction mechanism.

A similar, in situ generated *Cinchona*-derived quaternary ammonium enolate was proposed to be involved in the stereoselective domino Michael-cyclization reaction of cinnamic thioesters **69** with acetylacetone (**70**) in the presence of catalyst **44d** (Scheme 23).[47]



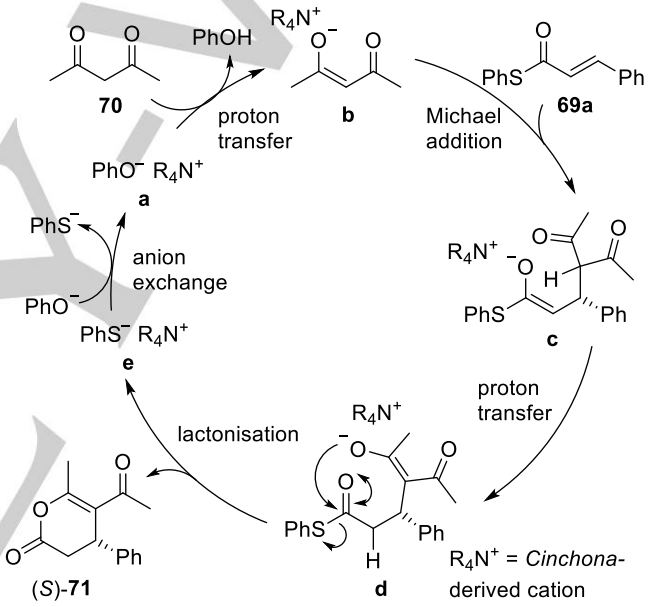
Scheme 23. Enantioselective synthesis of 3,4-dihydropyran-2-ones.

The addition of phenol as cocatalyst to generate a chiral quaternary ammonium phenoxide salt allowed to significantly increase the ee by suppressing the undesired uncatalyzed background reaction.[48]

A variety of 3,4-dihydropyran-2-ones **71**, useful building blocks for the synthesis of valuable organic compounds such as 2-pyrones and γ-lactones, was prepared in up to 93% yields and up to 88% ees.

The reaction was proposed to begin with deprotonation of acetylacetone (**70**) by a basic phenoxide anion of chiral quaternary ammonium phenoxide salt **a**. The chiral ammonium−enolate complex **b** thus formed performs a stereoselective Michael addition to the electrophilic olefin moiety of the cinnamic thioester **69**, where the enantiofacial selectivity is directed by the interaction of the enolate with the chiral *Cinchona*-derived cation.

The resulting intermediate **c** proceeds via an intramolecular proton transfer to form intermediate **d**, which finally undergoes the enantioselective lactonisation to give 3,4-dihydropyran-2-one (*S*)-**71**. The resulting chiral ammonium thiophenolate **e** may then undergo an ion exchange to regenerate **a**, thus closing the catalytic cycle (Scheme 24).



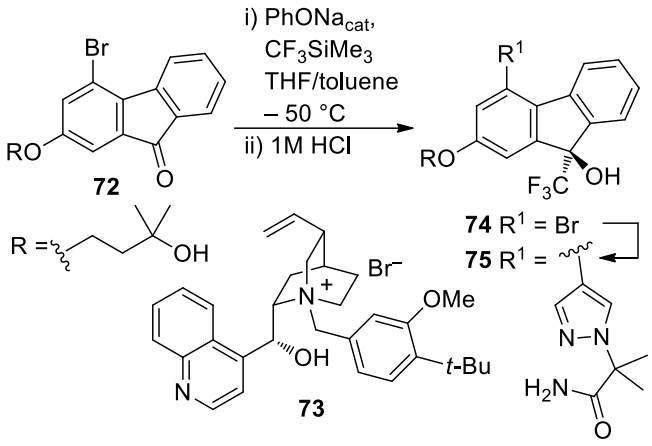
Scheme 24. Proposed pathway for the addition-cyclisation route to 3,4-dihydropyran-2-ones.

2.6 Trifluoromethylation

The nucleophilic trifluoromethylation of carbonyl derivatives under asymmetric PTC conditions proved to be a powerful tool to access a variety of fluorinated building blocks useful to generate pharmaceuticals and agrochemicals. Indeed, it is very well known that the steric and electronic effects induced by the incorporation of fluorine atoms can significantly modify the chemical and physical properties of organic molecules.[49]

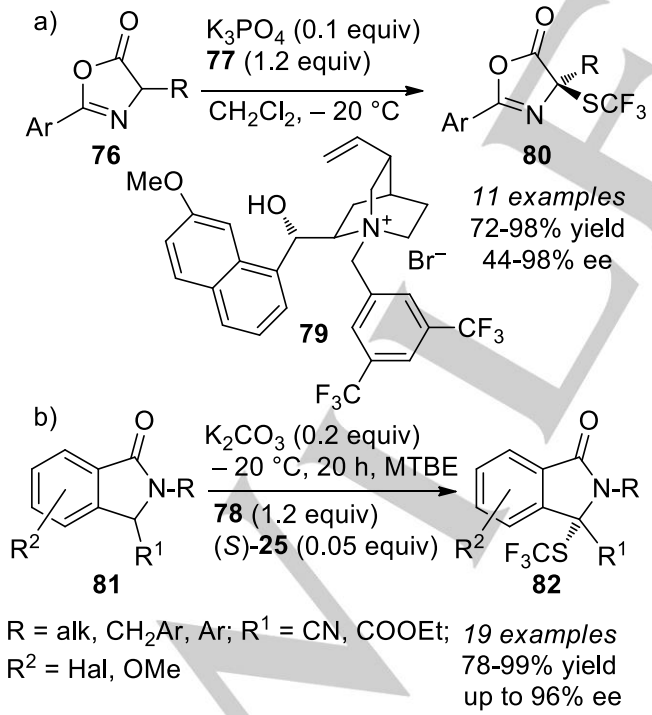
Both aldehydes and ketones were subjected to trifluoro methylation under PTC conditions using CF_3SiMe_3 in the presence of *Cinchona*-derived catalysts. After the first report appeared in 1994,[50] the optimization of the substituent on the quaternary nitrogen[51] as well as the use of additives[52] were crucial to provide good to excellent yield and enantioselectivity. Somewhat lower ees were usually obtained with aldehydes with respect to ketones.[53]

The PTC procedure is practical and well established and has been recently adopted for the synthesis of a pyruvate dehydrogenase kinase inhibitor **75** (Scheme 25).[54]



Scheme 25. Asymmetric trifluoromethylation under PTC conditions.

The crucial asymmetric trifluoromethylation of fluorenone **72** has been carried out with the ammonium catalyst **73** (0.05 equiv) at – 50 °C in the presence of catalytic sodium phenoxide to generate the trifluoromethyl anion. After acidic hydrolysis of the silylated alcohol the product **74** was isolated with a 70.5% ee which could be enhanced to 98.9% (overall yield 66%) by crystallization.



Scheme 26. Asymmetric trifluoromethylthiolation of azlactones **76** and isoindolinones **81**.

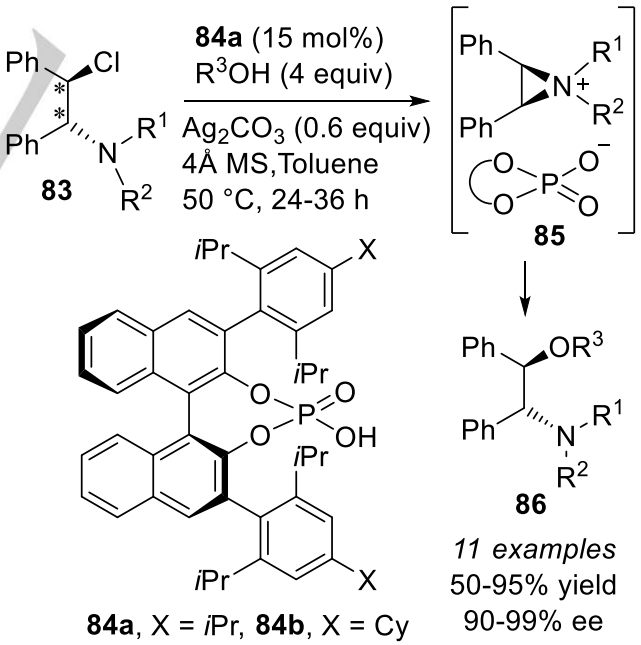
The trifluoromethylthio- and trifluoromethoxy groups have also emerged as useful tool to investigate the influence of both fluorine and heteroatoms on the physicochemical and biological properties of organic molecules.[55] For example, azlactones **76**[56] and isoindolinones **81**[57] have recently been subjected to a trifluoromethylthiolation protocol under PTC conditions using *N*-(trifluoromethylthio)phthalimide (**77**) and *N*-(trifluoromethylthio)-succinimide (**78**) under PTC conditions (Scheme 26). A catalytic amount of base was enough to ensure complete substrate conversion since the succinimide/phthalimide species, formed in situ after delivering their SCF_3 group, work themselves as bases.

3. Chiral Anion Phase-Transfer Catalysis (APTC)

Although a great variety of stereoselective reactions could be carried out with excellent results by using PTC catalysts bearing a chiral cation, this field of application remained necessarily confined to reactions involving anions as reagents. The border has been crossed with the use of PTC catalysts bearing a chiral anion paired with an achiral cation, thus providing a new platform to greatly expand the field of application of PTC to asymmetric synthesis.

Indeed, in the last decade chiral phosphate anions derived from binaphthol, such as **84a** (TRIP), provided a powerful tool to easily construct several scaffolds with high enantioselectivities.

The first successful application of the concept, developed by Toste to generate β-amino ethers **86** that would be otherwise difficult to be accessed by Williamson ether synthesis due to elimination and low reactivity of the required electrophiles, is illustrative (Scheme 27).



Scheme 27. Synthesis of β-amino ethers through anionic PTC.

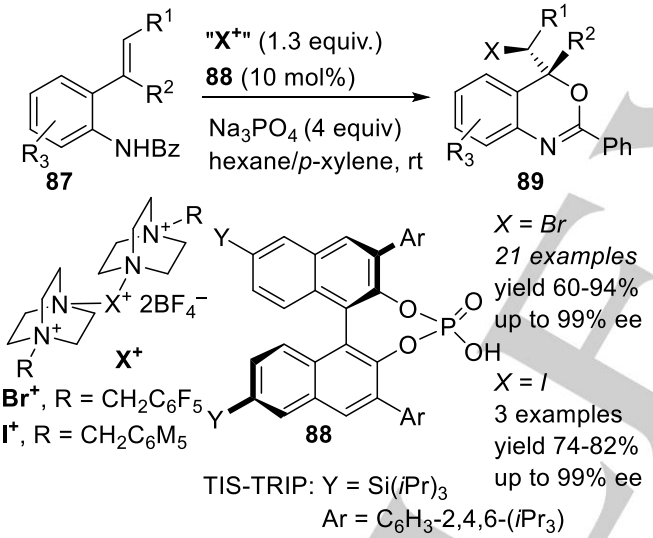
The ring opening of the meso-aziridinium intermediates **85**, generated *in situ* from racemic β-chloroamines **83**, with a variety of secondary, tertiary, and relatively hindered primary alcohols provided β-amino ethers **86** in high yield and enantioselectivity.[58]

The asymmetric PTC process is greatly facilitated by the high solubility of the chiral ion pair **85** in the low polarity toluene solvent. The choice to use Ag_2CO_3 as an insoluble silver salt to generate the soluble ion pair **85** enables to suppress the background reaction leading to the racemic product, as it would be possible in the presence of other soluble silver salts. Moreover, when the same reaction was carried out under homogeneous conditions, a complex mixture of compounds was obtained.

The same concept has been applied to a variety of enantioselective fluorinations using Selectfluor as a insoluble electrophilic fluorinating agent which could be transformed into a highly reactive, soluble fluorinating agent after pairing with the chiral phosphate anion.[59]

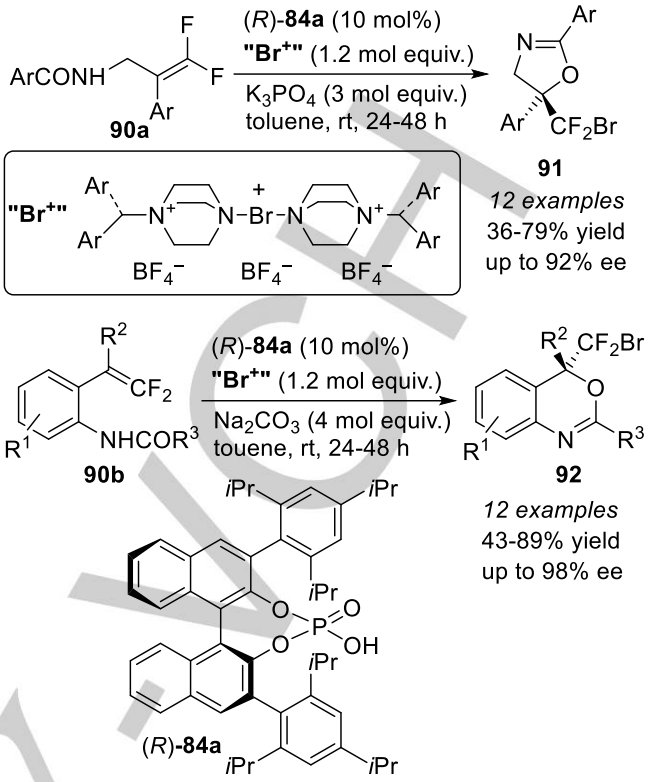
3.1. Halocyclization

Chiral anion PTC proved useful to develop a number of halocyclization reactions leading to synthetically useful compounds. Some work was needed to generate a reactive, insoluble, halogenating agent $\mathbf{X^+}$ ($\mathbf{Br^+}$, $\mathbf{I^+}$). The optimization of the electrophilic halogenonium/phosphate anion pair enabled to generate halogenated 4*H*-3,1-benzoxazines **89** from o-anilidostyrenes **87**, with excellent yield and enantioselectivity (Scheme 28).[60]



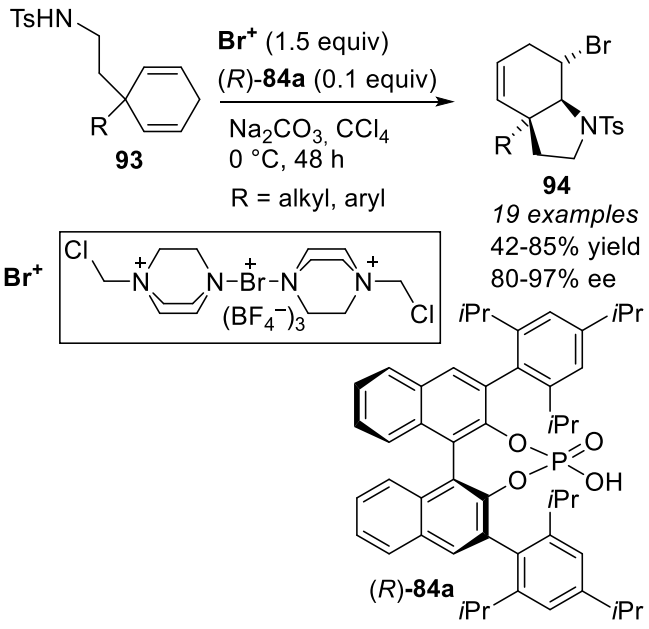
Scheme 28. Enantioselective halocyclization of α-anilidostyrenes.

The same protocol was later adapted to the bromocyclization of difluoroalkenes **90a,b** to generate bromodifluoromethyl-containing oxazolines **91** and oxazines **92** in a regio- and enantioselective fashion (Scheme 29).[61] The reaction outcome was found to be strongly influenced by the achiral DABCOonium based brominating agent "Br^+".



Scheme 29. Enantioselective bromocyclization of *gem*-difluoroalkenes.

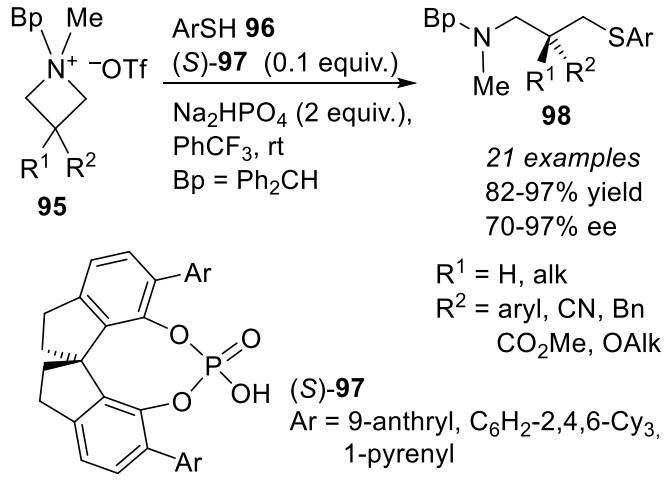
Moderate conversion as well as significantly lower enantio selectivity was observed in the absence of base, thus confirming the crucial role of the chiral phosphate anion in rate acceleration. The same approach has been applied to the desymmetrization of cyclohexa-1,4-dienes **93** to generate *cis*-aryloctahydroindoles **94** with one all carbon quaternary stereocenter in good yields and excellent enantioselectivities (Scheme 30).[62]



Scheme 30. Desymmetrization of cyclohexa-1,4-dienes.

3.2. Azetidinium ring opening

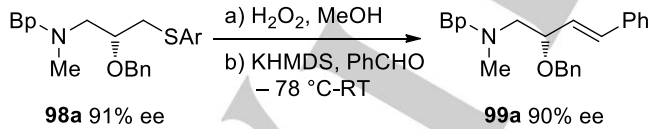
The first stereoselective intermolecular ring opening of a variety of *N,N*-alkylazetidiniums triflates **95** with arylthiols **96** has been achieved through chiral anion PTC with a SPINOL-derived chiral phosphoric acid (*S*)-**97** (Scheme 31).[63] A variety of thiols such 2-mercaptobenzothiazoles, benzoxazole-2-thiol,1,3,4-thiadiazole-2-thiol, and quinolone-2-thiol were all shown to be useful nucleophiles to provide the corresponding amines **98** bearing a stereocenter in the β-position in high yield and enantioselectivity.



Scheme 31. Azetidinium ring opening with thiols.

High stereocontrol could be obtained when diastereoisomeric mixtures of azetidinium triflates **95** were used as substrates. Stereoconvergence leading to the same (*R*)-isomer was found when *cis*-**95** and *trans*-**95** isomers were separately reacted under optimized conditions. However, the *cis* isomer reacted faster and in higher enantioselectivity. A transition state model was proposed by authors to explain this behavior.

A concise, metal-free synthesis of a variety of amines **98** bearing a stereocenter in the β-position was thus designed. These compounds can be readily derivatized as shown by the two steps conversion of **98a** to the alkene **99** through sulfur oxidation followed by olefination with benzaldehyde (Scheme 32).



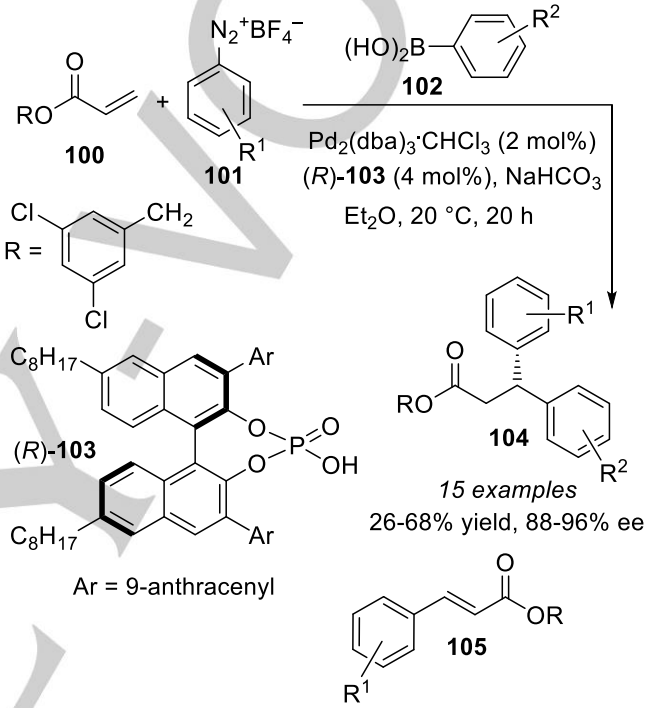
Scheme 32. Derivatization of β-chiral amines.

The benzydryl group (Ph_2CH) can be removed easily by using the Et_3SiH/CF_3COOH protocol. Both transformations proceed without erosion of ee.

3.3. Palladium driven APTC

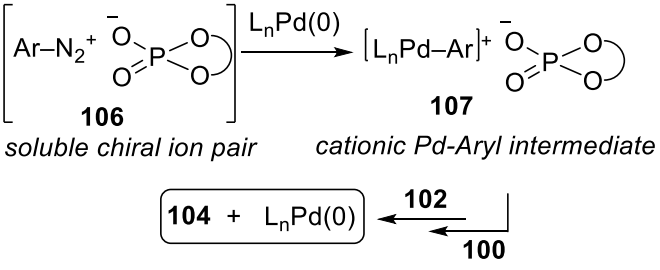
The anionic PTC approach could be combined with Palladium catalysis in order to develop the previously elusive enantio selective three-component reaction to generate the 1,1-diarylalkane motif (Scheme 33).[64]

Indeed, substituted benzyl acrylates **100** were reacted with aryldiazonium salts **101** and arylboronic acids **102** in the presence of base and catalyst (*R*)-**103**. The corresponding 3,3-diaryl propanoates **104** have been generated in high ee with moderate to good yields due to the competitive formation of the Heck product **105**.



Scheme 33. Palladium catalysed enantioselective synthesis of 3,3-diarylpropanoates.

The soluble ion pair **106** generated from the phosphate anion and the aryl diazonium cation is subjected to oxidative addition by Pd(0) in the key step of the process (Scheme 34). The cationic Pd-aryl intermediate **107** thus formed[65] undergoes an enantio selective migratory insertion of the acrylate **100** thus initiating the reaction cascade leading to the product **104** and regeneration of the Pd(0) species.

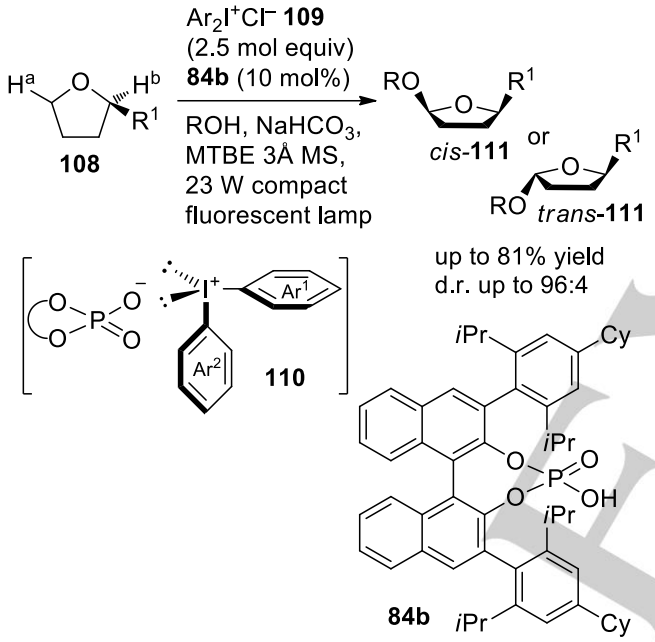


Scheme 34. Simplified mechanism for 1,2-diarylation of acrylates **100**.

The stereocontrol was found to be strictly related to the catalyst as well as the substitution pattern of the benzyl acrylate.
Extensive mechanistic investigations allowed to collect evidences in favor of noncovalent interactions between the benzyl group and the catalyst due to π-stacking interactions between the phosphoric acid 9-anthracenyl substituent and the substrate. The electronic and steric nature along with the position of benzyl acrylate substituents were shown to dramatically influence the stereoselectivity.[66]

3.4. Radical driven APTC

Radical mediated asymmetric reactions could also be carried out under anionic PTC conditions. The stereoselective acetalization of cyclic ethers **108** could be achieved in the presence of photochemically active diaryliodonium species **109** (Scheme 35).[67]

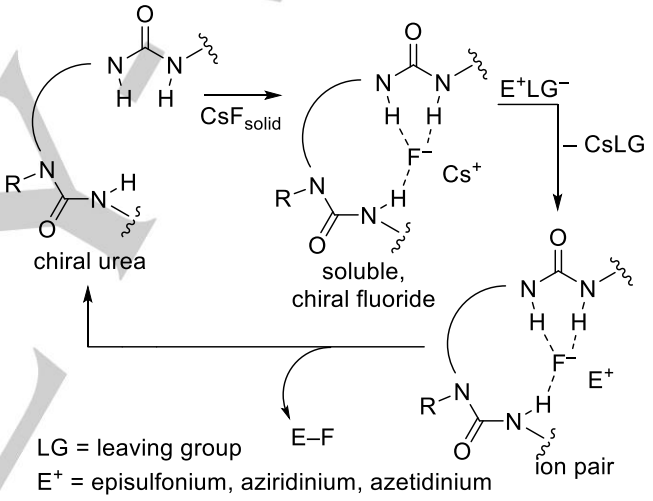


Scheme 35. Stereoselective α-C(sp^3)-H acetalization of cyclic ethers.

The reaction was proposed to proceed through hydroalkoxylation of an enol ether catalyzed by the chiral phosphate-paired Lewis-acidic diaryliodonium species **110**. Thus, a simple route to chiral disubstituted furan (e.g. *cis*-**111** with (*R*)-**84b** and *trans*-**111** with (*S*)-**84b**) and pyran acetals, useful intermediates for drug discovery and DNA sequencing, was developed.
A large excess (25:1) of the substrate was needed in order to limit the formation of aldehydes and aryl ethers through alcohol oxidation and arylation. However, the unreacted starting material **108** could be recovered by distillation since a stoichiometric amount only was consumed.

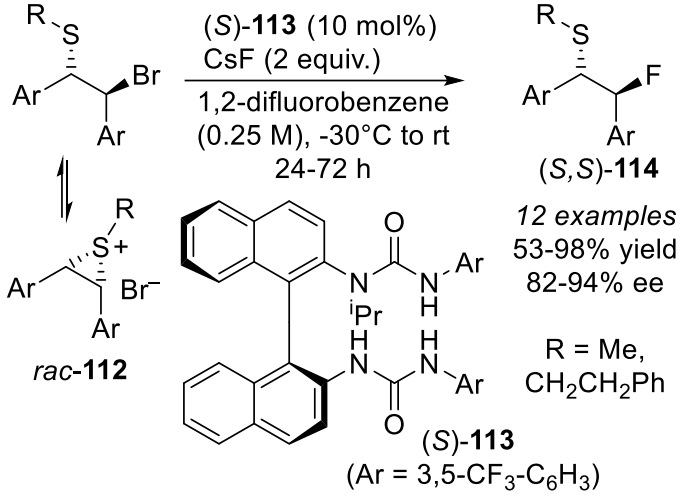
4. Hydrogen Bonding Phase Transfer Catalysis

The nucleophilic displacement of leaving groups is one of the main methods commonly used to generate a variety of fluorinated agrochemical and pharmaceutical compounds bearing unique physicochemical and biological features. Quaternary ammonium fluorides have often been used as organic soluble sources of nucleophilic naked fluorides.
Many research efforts have been directed to remove the hydration sphere stabilizing the fluoride anion in order to increase its reactivity. However, at the same time the formation of an increased amount of olefin byproducts through elimination driven by the high basicity of the "anhydrous" fluoride was observed.
The influence of ionic interactions of the fluoride ion with additional water (TBAF · 5 H_2O),[68] or alcohol molecules[69] on the S_N2/E2 ratio was investigated.
Further studies on urea-fluoride complexes[70] laid the founda tions for the new catalytic asymmetric fluorination protocol using a chiral H-bond donor as a phase-transfer catalyst capable to bring a solid, otherwise unsoluble reagent such as CsF in solution as a chiral hydrogen-bonded fluoride complex.[71]
The ion pairing of the latter with a cationic electrophile E^+, followed by stereoselective fluoride delivery, provides the chiral fluorinated molecule E–F along with the regenerated urea catalyst (Scheme 36).[72]



Scheme 36. General mechanism for hydrogen bonding PTC with chiral bis-urea catalyst.

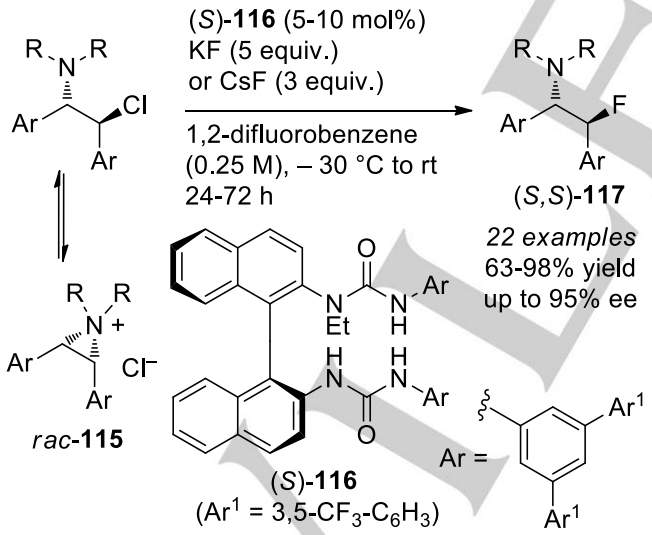
Thus, enantioselective fluorinations using cheap and easily available alkali-metal fluorides under practical conditions became available through this new hydrogen bonding phase transfer catalysis (HB-PTC) pathway.
The concept was first demonstrated through the enantioselective fluorination of racemic β-bromosulfides *rac*-**112** to enantio enriched β-fluorosulfides (*S,S*)-**114** in good yield and ees in the presence of chiral bis-urea catalyst (*S*)-**113** (Scheme 37).[73] The reaction proceeds through the fluoride attack on the in situ formed episulfonium ion with retention of configuration.



Scheme 37. Enantioselective synthesis of β-fluorosulfides.

The stronger H-bonding of fluoride ion with respect to bromide ion, generated from the ring opening of the sulfonium species, is essential to ensure complete conversion.[74]

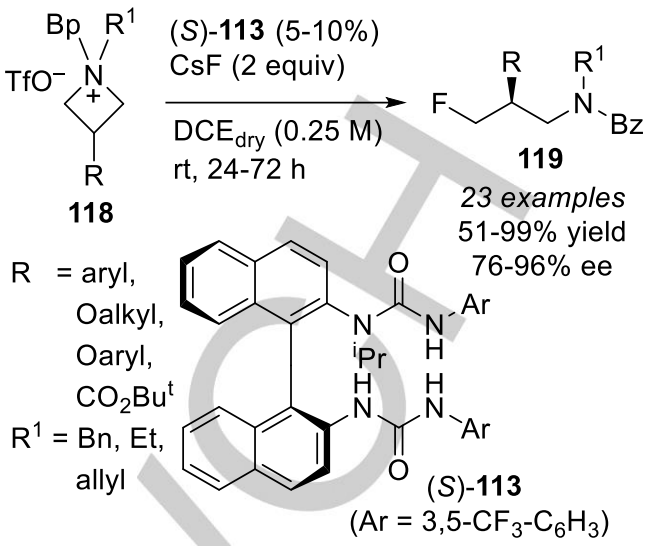
Racemic β-haloamines **115** could also be subjected to a similar approach to generate β-fluoroamines **117**, a well known class of remarkable compounds in medicinal chemistry (Scheme 38). *N,N* diallyl derivatives, enabling a simple conversion to primary amines after deallylation, along with a variety of *N,N*-disubstituted tertiary amines were successfully used as substrates. It is also worth noting that cheaper potassium fluoride could be used as fluorinating agent.[75]



Scheme 38. Enantioselective fluorination of aziridiniums.

The terphenyl substituted bis-urea (*S*)-**116** was required to provide high enantioselectivity.

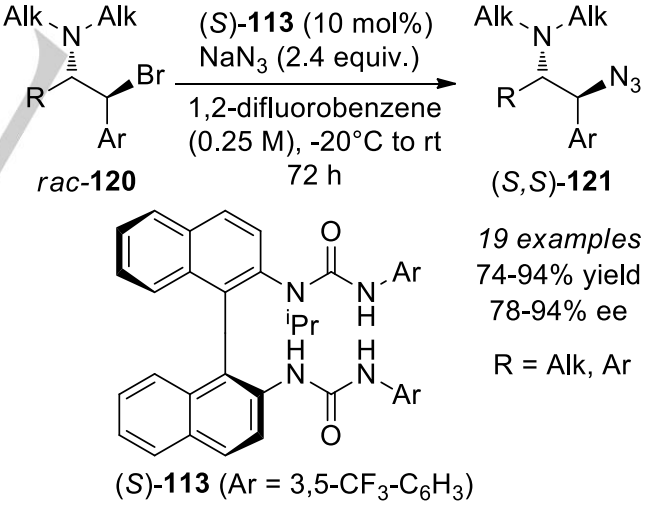
A variety of γ-fluoroamines **119** could be prepared through the enantioselective ring opening of azetidinium triflates **118** with cesium fluoride under the catalysis of bis-urea (*S*)-**113** (Scheme 39).[76]



Scheme 39. Enantioselective fluorination under HB-PTC conditions.

It is notable that no reaction was observed by using CsF or TBAF under chiral anion PTC conditions previously described to open the azetidinium ring with thiols.[63]

It is worth noting that the HB-PTC protocol could be extended to non–fluorinated alkali metal salts such as NaN_3. It was therefore possible to generate a variety of β-azido amines **121** in high yields and ees through desymmetrization of aziridinium ions generated in situ from β-bromoamines **120** (Scheme 40).[77]



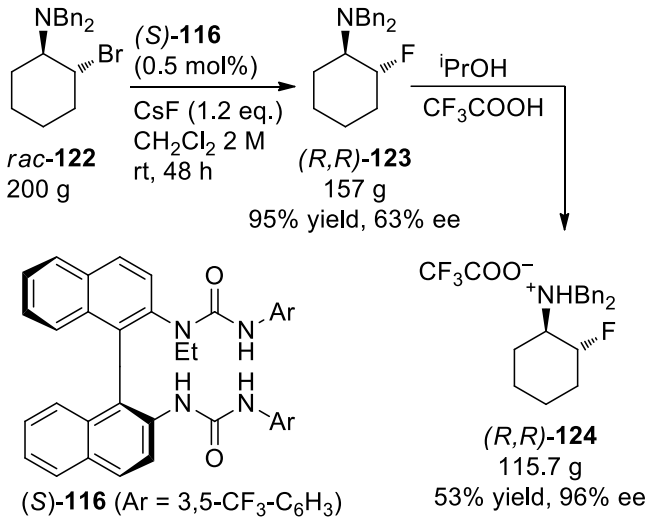
Scheme 40. Enantioselective azidation under HB-PTC conditions.

It was shown that reactions could not proceed significantly without the bis-urea catalyst. On the other hand, when the reaction was carried out in the presence of both bis-urea catalyst and soluble sources of nucleophiles such as $Bu_4N^+F^-$ or $Bu_4N^+N_3^-$ high yields of racemic products were obtained.

The typical operational simplicity of PTC was confirmed since it was not necessary to avoid moisture or use inert atmosphere under HB-PTC.

Indeed, the hectogram scale enantioselective fluorination of *trans-N,N*-dibenzyl-2-bromocyclohexan-1-amine *rac*-**122** could generate the corresponding β-fluoroamine (*R,R*)-**123** in 95% yield with the same enantioselectivity obtained in the small scale experiment (Scheme 41).[78]

The catalyst loading could be significantly decreased to 0.5 mol%. The catalyst could be recovered by crystallization (heptane-EtOH, 52% yield) and furnished the same results in terms of yield and enantioselectivity in another batch.



Scheme 41. Scale-up of the enantioselective fluorination.

The enantiomeric ratio could be significantly increased by a single crystallization of the trifluoroacetate salt (R,R)-**124**.

The CsF particle size and water content were found to be important for reproducibility as well as an optimal suspension of CsF.

5. Conclusions

This mini-review reports some recent achievements in stereoselective reactions carried out under PTC conditions. The results clearly show that PTC is nowadays not only very useful to develop sustainable processes but also a powerful tool to construct a variety of chiral motifs under mild and practical conditions.

Indeed, in the last few years several new pathways for stereoselective PTC reactions could be designed by the use of chiral phosphate anions paired with achiral cations, thus reversing the classical use of chiral onium cations paired with achiral anions.

It is worth noting that the combination of anionic PTC with palladium or radical chemistry greatly expands the scope of asymmetric PTC.

Moreover, the recent use of chiral bis-urea hydrogen bond donors made possible the use of ionic compounds as reagents in enantioselective PTC protocols.

Thus, new effective catalysts could be added to the older, well established and continuously optimized chiral onium salts.

An increased use of asymmetric PTC in the pharmaceutical industry could be seen in the last few years and can be expected to even increase in the future. Indeed, drugs are often complex, multifunctional compounds and their synthesis can take full advantage of several enantioselective reactions exploiting the various classes of catalysts described in this mini-review.

At the same time a competitive advantage can be gained due to the lower amount of waste produced and the lower amount of energy consumed with respect to traditional non-PTC methods.

Acknowledgements ((optional))

Acknowledgements Text.

Keywords: Phase Transfer Catalysis • organocatalysis • asymmetric catalysis • chiral ammonium salts • chiral phosphoric acids • bis-urea hydrogen bond donor

Entry for the Table of Contents

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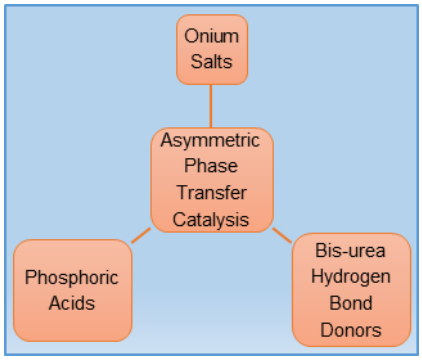

Asymmetric phase transfer catalysis constitutes an ever increasingly useful tool to construct chiral skeletons under mild and practical conditions. This mini-review describes new concise pathways for the synthesis of chiral motifs made possible by the design of new chiral PTC catalysts such as chiral onium salts, chiral phosphate anions and chiral bis-urea hydrogen bond donors.

Institute and/or researcher Twitter usernames: @angmer97

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