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EMERGING AREA

Chiral quaternary phosphonium salts: a new class of organocatalysts

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Phase-transfer catalysis has widely been used as a prime synthetic tool for both laboratory and industrial processes. During the last twenty years, asymmetric phase-transfer catalysis using chiral organocatalysts has attracted widespread interest. However, the scope of chiral phase-transfer catalysis has been limited mostly to the quaternary ammonium salts. As an emerging area, the recent developments in the application of quaternary phosphonium salts as chiral phase-transfer catalysts are discussed in this article.

1. Introduction

The most important application for onium salts such as quaternary ammonium and phosphonium salts in organic chemistry is as phase-transfer catalysts.[1] A phase transfer catalyst (PTC), in general, is an organocatalyst that facilitates the migration of a reactant from one phase into another phase where the reaction occurs.[2] Phase-transfer catalysis (PTC) has widely been used as a versatile tool for synthesis in various fields of organic chemistry, as it involves mild reaction conditions, simple experimental procedures and the use of environmentally benign, air/moisture-tolerant organocatalysts.[3] Phase transfer catalysts are especially useful in green chemistry – allowing water to be used and thus, reducing the need for organic solvents. These advantages make PTC an attractive option and a prime synthetic tool for both laboratory and industrial processes.

In general, phase-transfer catalysts for organic reactions are often onium salts such as quaternary ammonium and phosphonium salts, most of which are readily available. During the last twenty years, asymmetric phase-transfer catalysis using chiral catalysts has attracted widespread interest among synthetic chemists.[3] However, the scope of asymmetric PTC was limited mostly to the quaternary ammonium salts, despite the fact that

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Dieter Enders was born in 1946 in Butzbach (Germany). He received his Dr rer. nat. under the supervision of Professor D. Seebach in 1974. After postdoctoral studies at Harvard University with Professor E. J. Corey, he returned to Giessen, obtaining his habilitation in 1979. In 1980 he moved to the University of Bonn as an associate professor and in 1985 to his present position as Professor of Organic Chemistry at the RWTH Aachen University. His current research interests are asymmetric synthesis, new synthetic methods using organometallics, the stereoselective synthesis of biologically active compounds, and organocatalysis. He has been the recipient of many prizes, among them the Leibniz Prize, the Yamada Prize, the Max Planck Research Award, the Emil Fischer Medal, the Arthur C. Cope Scholar Award and the Robert Robinson Award.

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Thanh Vinh Nguyen was born in 1982 in Vietnam. After high school, he went to Sydney, Australia to study chemistry at University of New South Wales. He then moved to undertake his PhD in Organic Chemistry with Professor M. Sherburn at the Australian National University. He had worked to develop new synthetic methodologies for application in natural product synthesis and to work on the design and synthesis of large host molecules for drug-delivery. After graduating in 2010, he took up a position to work in Professor Dieter Enders group at the Institute of Organic Chemistry, RWTH Aachen, Germany under the auspices of an Alexander von Humboldt Postdoctoral Fellowship. His current research interests are synthesis of naturally occurring and bioactive compounds, asymmetric synthesis and medicinal chemistry.

the first example of an asymmetric chemical transformation catalyzed by a chiral quaternary phosphonium salt was introduced nearly fifteen years ago.[4] Considering the abundant structural and stereochemical diversity of phosphorus compounds currently available, it is of great importance to create a new domain in phase-transfer catalysis by exploiting the quaternary phosphonium salts. In light of that, the recent developments of phosphonium salts as a new class of chiral phase-transfer catalysts will be discussed.[5]

Ammonium salts as chiral phase-transfer catalysts

Apart from a few miscellaneous examples, the recently developed chiral ammonium salts for asymmetric synthesis can be classified into three categories:[3b] phase-transfer catalysts derived by the modification of cinchona alkaloids **1** (Fig. 1a), Maruoka's spiro quaternary ammonium salts **2**,**3** (Fig. 1b) and tartrate-derived quaternary ammonium salts **4**–**6** (Fig. 1c). Over the last two decades, these catalysts have been reported to facilitate a wide range of asymmetric organic reactions, including alkylation, aldol, Michael addition, Mannich, Darzens and Strecker reactions as well as the Neber rearrangement, epoxidation, fluorination, aziridination and dihydroxylation.[3] In rational designing and fine-tuning catalytic activity, PTCs obtained from cinchona alkaloids and tartrate-derived ammonium salts normally have to cope with more difficulties in comparison to Maruoka's catalysts.[3,4] Furthermore, the structural concept of Maruoka's catalyst could also be applied for phosphonium salts, as it generally involves simple alkylation reactions, for which nitrogen and phosphorus have similar reactivity, to construct the catalysts.

2. Preliminary studies in designing and using quaternary phosphonium salts as chiral phase-transfer catalysts

In the earliest example in this field, Manabe used chiral phosphonium salts **7** with multiple hydrogen-bonding sites to catalyze benzylation reactions of β-keto esters with moderate yield and enantioselectivity (Scheme 1).[4] Although providing a new concept for the design of phase-transfer catalysts, it was somehow ignored by the catalysis community for ten years[6] until recent studies by Maruoka and Ooi,[7,8] which have resolved the deadlock situation for the development of quaternary phosphonium salts as phase-transfer catalysts. This gap was probably due to the common belief that quaternary tetraalkylphosphonium salts are not reliable phase-transfer catalysts as they can form the corresponding ylides under basic conditions, which are normally required for phase-transfer reactions.[7] Therefore, the phosphonium salts for PTC have to be designed in such a way that there is no labile α-hydrogen for deprotonation. Another approach could be the employment of reaction conditions disfavoring the ylide formation. Fortunately, Maruoka and co-workers have recently reported several base-free phase-transfer asymmetric reactions catalyzed by bifunctional ammonium salt **3** (Fig. 1) under water-rich conditions.[9] Hence, it confirms the proof-of-principle that the quaternary phosphonium salts could serve as PTCs in base-free neutral reactions. Indeed, recent studies where phosphonium salts catalyzed several types of asymmetric reactions have demonstrated the feasibility of this research direction.

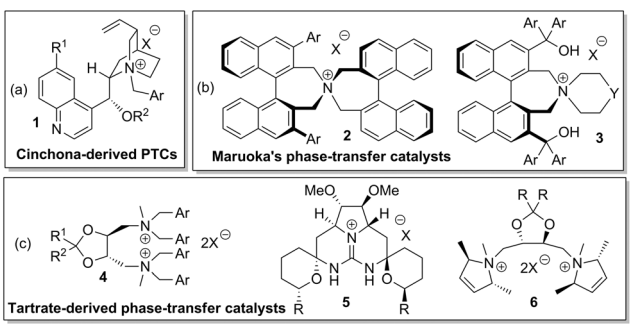
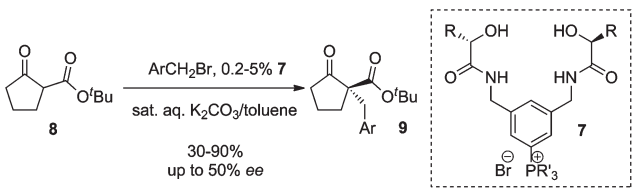


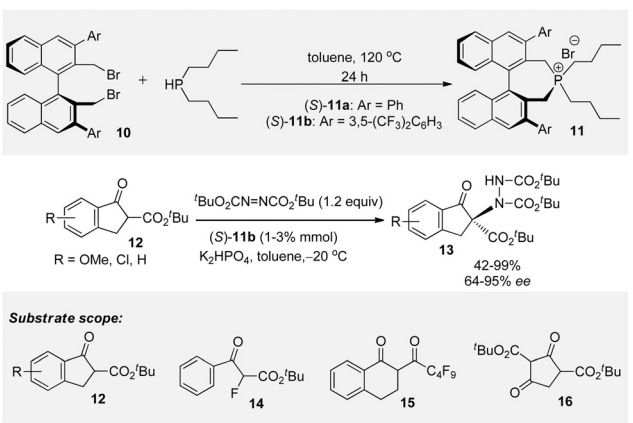
Fig. 1 Ammonium salts as chiral phase-transfer catalysts.

2.1. Maruoka's chiral phosphonium salts as PTCs

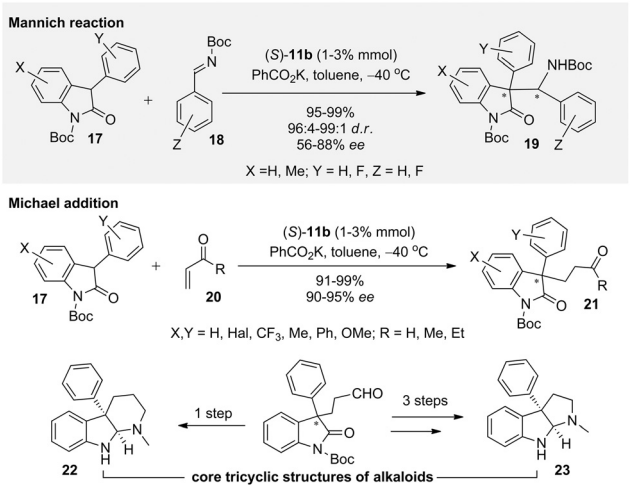
Based on their landmark contributions to ammonium PTC,[3] Maruoka's group was one of the first to make progress in phosphonium phase-transfer catalysis. In 2008 they reported the design and synthetic application of chiral binaphthyl-modified quaternary phosphonium salts, which conceptually resemble the structures of their ammonium "Maruoka catalysts®" **2** (Fig. 1).[3,7] In this elegant study, they employed the axially chiral dibromides **10** as basic chiral units to prepare C_2-symmetric chiral quaternary tetraalkylphosphonium bromides **11** (Scheme 2). Although (*S*)-**11a** induced poor to moderate enantioselectivity, (*S*)-**11b** showed excellent catalytic activity in the asymmetric amination of β-keto esters under mild basic phase-transfer reaction conditions, giving the products **13** with very good yields and ees (Scheme 2). The electronic properties of the substituents on the



Scheme 1 Manabe's phosphonium salts as PTCs.



Scheme 2 Maruoka's phosphonium salts catalyzed asymmetric amination.



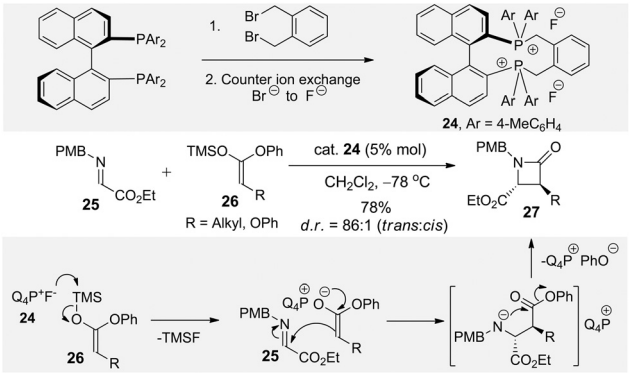
Scheme 3 Maruoka's phosphonium salts catalyzed asymmetric Mannich and Michael addition reactions.

aromatic ring of *tert*-butyl indanecarboxylate **12** showed an insignificant effect on the enantioselectivity of the amination reactions. The scope of the reaction was successfully expanded to the acyclic β-keto ester **14** and the six-membered cyclic β-diketone **15**. The product derived from substrate **16** is a key intermediate for the synthesis of the aldose reductase inhibitor AS-3201 (Ranirestat).[10]

Following the successful asymmetric amination, Maruoka and co-workers continued to employ the chiral quaternary phosphonium salt (*S*)-**11b** in asymmetric Mannich and Michael addition reactions of 3-aryloxindoles (Scheme 3).[11] They aimed to stereoselectively construct quaternary carbon centers at the 3-positions of these substrates, a transformation leading to an important structural pattern of various bioactive compounds.[11] Prior to this study, the Mannich reaction on this type of substrate has proven to be very challenging while the asymmetric Michael addition reaction has never been reported in the literature before.[11] Under the optimal reaction conditions, the asymmetric Mannich reactions between 3-arylindoles **17** and activated imines **18** catalyzed by (*S*)-**11b** worked smoothly to form the Mannich adduct **19** with excellent diastereoselectivity and high enantioselectivity. Furthermore, the Michael addition reactions between 3-arylindoles **17** and alkylvinyl ketones **20** also worked very well with outstanding enantioselectivity. Maruoka and co-workers had also taken the chance to convert the unsubstituted Michael adduct **21** to tricyclic diamines **22** and **23** within a few steps. These compounds possess the tricyclic skeletons of pharmaceutically important natural products such as CPC-1, (–)-physostigmine and (–)-pseudophrynaminol.[12]

2.2. Phosphonium salts as organocatalysts for homogeneous base-free asymmetric reactions

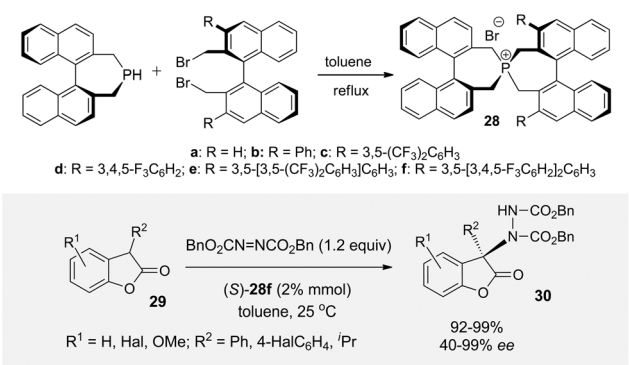
In their aforementioned studies Maruoka and co-workers investigated the use of numerous bases and found out that they have significant impact on the stereoselectivity of the reactions. Given that these bases are not sufficiently strong to form the ylides of the phosphonium salts, Maruoka and co-workers had yet to try these reactions under base-free reaction conditions, similar to what they have done with chiral quaternary ammonium phase-



Scheme 4 Lectka's [2 + 2] cycloaddition.

transfer catalysts **3** (Scheme 1).[9] Meanwhile, other groups have recently published their investigations of utilizing analogous chiral tetraalkyl phosphonium salts as asymmetric organocatalysts in homogeneous reaction media. In 2009 Lectka and co-workers described the use of phosphonium fluoride **24** as a multifunctional Lewis-acid precatalyst for the [2 + 2] cycloaddition of ketene acetals **26** and activated imines **25** to form disubstituted β-lactams **27** (Scheme 4).[13] β-Lactams are valuable compounds for a range of purposes from antibiotics to inhibitors of prostate-specific antigen and cytomegalovirus protease.[14] Presumably, the fluoride anion first does a nucleophilic attack on the ketene acetal silyl ether to create the enolate as a better nucleophile. The quaternary phosphonium cation then acts as the stereo-controlling counter-ion in the [2 + 2] transition state. The eventual catalyst, the quaternary phosphonium phenoxide, proceeds further to catalyze the reaction as observed from earlier examples of β-lactam formations.[15] The employment of this chiral quaternary phosphonium fluoride facilitated a high-yielding reaction with excellent diastereoselectivity, whereas several ammonium fluorides were investigated without any satisfactory results. However, the enantioselectivity of this reaction was not reported in this study. The catalytic activity of **24** in this reaction expands the scope of quaternary phosphonium catalysis, as this is a rare example of [2 + 2] cycloaddition reaction catalyzed by phosphonium salts.

In 2011 Ma and co-workers published their study on utilizing spiro quaternary phosphonium bromides very similarly to Maruoka's catalysts **2** (Scheme 1) and **11** (Scheme 2) to catalyze unprecedented asymmetric amination reactions of 3-substituted benzofuranones **29** (Scheme 5).[16] Mechanistic studies revealed

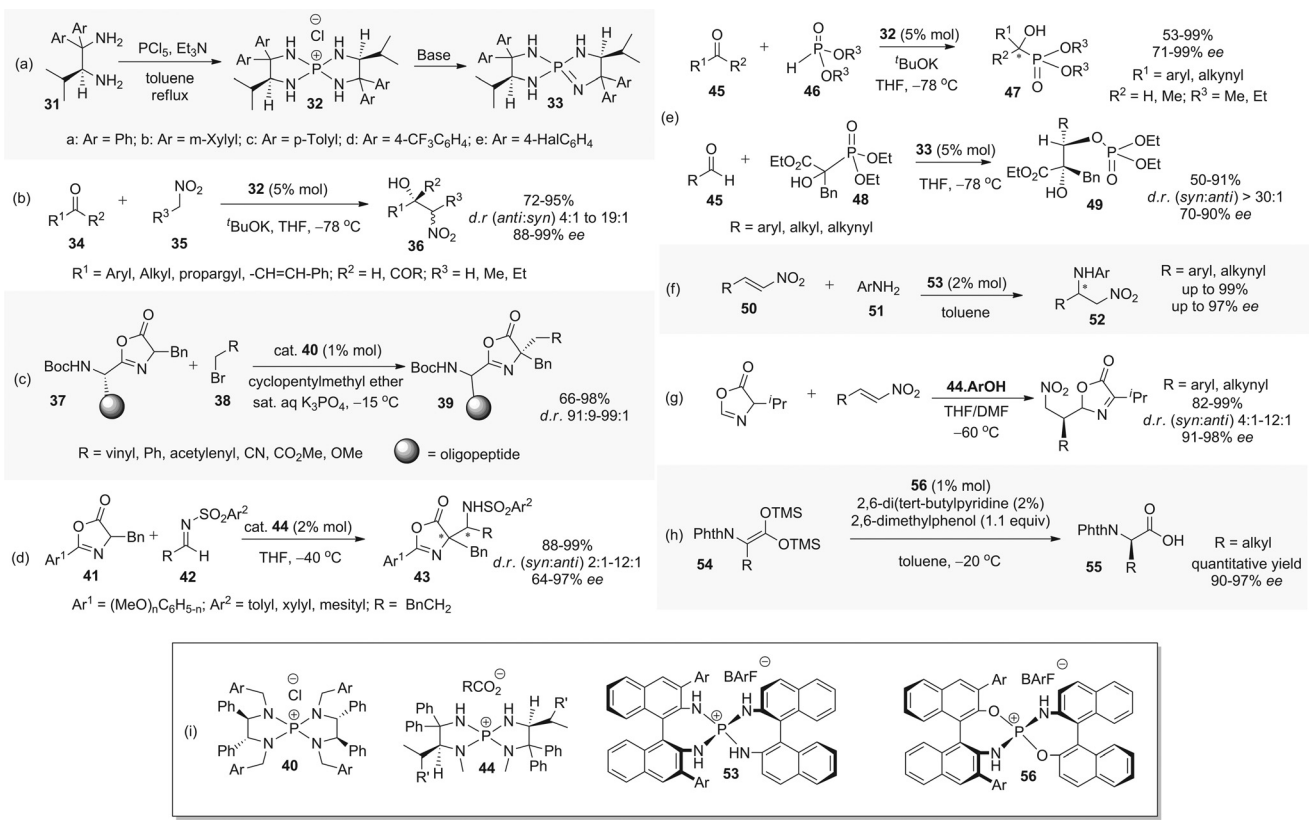


Scheme 5 Ma's asymmetric amination of benzofuranones.

that the reactions were likely to proceed *via* the enol forms of benzofuranones, which are undetectable by NMR spectroscopy but can be identified by HPLC/MS (ESI) methods. These enols are present in equilibrium with the benzofuranones and presumably stabilized by the induced-fit π–π stacking of the substrates and the binaphthyl moiety of the catalyst, which are in agreement with DFT calculations. The phosphonium cation is also acting as a Lewis acid to coordinate to the azocarboxylate compound (**30**, Scheme 5) for electrophilic activation of the nitrogen-donor in the transition state of the reaction, which is crucial for the reactivity of this chemical process. In these *homogeneous base-free* reactions, the polarity of solvent has a strong impact on the enantioselectivity, with the best ee obtained in the non-polar toluene. Catalysts **28a–f** generally gave good to high yields with the enantioselectivity increasing from **28a** to **28f**, as bulky substituents on the binaphthyl moiety of the catalyst have a strong effect on both the reactivity and the stereoselectivity of the reaction.

3. Tetraaminophosphonium salts as a new class of organocatalysts

In a different approach, Ooi and co-workers introduced the design and preliminary catalytic applications of *P*-spiro tetraamino phosphonium salts **32** (Scheme 6a) in 2007.[8] This special type of quaternary phosphonium salts can be readily accessed from chiral diamines **31**. The orientation of alkyl and geminal aryl substituents on the two nearly-perpendicular diazaphosphacycles could be manipulated to control the steric effect of the phosphonium cation. The abundant amino groups for H-bonding interactions equip the phosphonium cation with the capacity for anion recognition, which is an important feature in catalysis. In this preliminary study, tetraamino phosphonium salts **32** were found to have excellent catalytic activity on the direct Henry reactions between the aromatic aldehydes **34** (R^2 = H) and nitroalkanes **35** (Scheme 6b) in the presence of a strong base. Based on mechanistic studies,[17] tetraamino phosphonium salts **32** are deprotonated *in situ* to form triaminoimino phosphoranes **33**, which act as the basic reagent to deprotonate the nitroalkanes. Tetraamino phosphonium salts **32** could also form hydrogen-bonding bidentate ion pairs with nitronate anions, allowing the highly stereoselective addition to the aldehydes. The electronic properties of aryl substituents on the diazaphosphacycles of the catalysts have a significant effect on the stereoselectivity of the reactions, with **32d** inducing the best enantioselectivity.[8] The scope of this reaction type was successfully extended to α,β-unsaturated and aliphatic aldehydes as well as 1,2-diketones[18b] and propargyl aldehydes[18a] in subsequent studies. This work has opened a new direction for the application of chiral quaternary phosphonium salts in organocatalysis. Indeed, the succeeding investigations of the Ooi group have demonstrated that this type of tetraamino phosphonium salts and their analogues (Scheme 6i) can catalyze a wide range of asymmetric chemical transformations. These include alkylation reactions catalyzed by phosphonium salt **40** (Scheme 6c),[19] Mannich reactions catalyzed by phosphonium salt **44** (Scheme 6d),[20] aldol-type phosphonylation reactions catalyzed by phosphonium salt **32** or its imino form **33** (Scheme 6e),[21] aza-Michael addition



Scheme 6 *P*-Spiro tetraamino phosphonium salts as catalysts.

reactions catalyzed by phosphonium salt **53** (Scheme 6f)[22] and Michael-type conjugated addition reactions catalyzed by solvated phosphonium salt **44** oligomers (Scheme 6g),[23] generally with excellent yields and outstanding stereoselectivity. The diamino-dioxaphosphonium salt analogues **56** can be used as chiral sources of protons for deprotection of silyl ethers, offering unprecedented opportunities for the development of related applications (Scheme 6h).[24]

4. Conclusion and outlook

In conclusion, rapid developments during the last few years have demonstrated that chiral quaternary phosphonium salts can work as versatile catalysts for numerous types of asymmetric chemical transformations. The hypervalent capacity and electronic properties of the phosphonium unit offer the opportunities to design and construct a wider range of quaternary salts, which is not just limited to tetraalkyl onium salts. Taking advantage of the abundant structural and stereochemical diversity of the structurally well-defined phosphorus compounds already available, especially in the field of transition-metal catalysis, there is an enormous potential for the future development of this field based on the pioneering investigations discussed in this article.

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