Peroxytungstate anions in asymmetric ion pair catalyzed oxidations

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**NANYANG
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SINGAPORE

**Peroxytungstate Anions in Asymmetric Ion Pair Catalyzed
Oxidations**

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SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

2019

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SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

A thesis submitted to the Nanyang Technological
University in partial fulfilment of the requirement for the
degree of Doctor of Philosophy

2019

Statement of Originality

I hereby certify that the work embodied in this thesis is the result of original research done by me except where otherwise stated in this thesis. The thesis work has not been submitted for a degree or professional qualification to any other university or institution. I declare that this thesis is written by myself and is free of plagiarism and of sufficient grammatical clarity to be examined. I confirm that the investigations were conducted in accord with the ethics policies and integrity standards of Nanyang Technological University and that the research data are presented honestly and without prejudice.

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Authorship Attribution Statement

This thesis contains material from 1 paper published in the following peer-reviewed journal(s) and 1 paper in manuscript where I was the first or corresponding author.

Chapter 3 is published as X. Ye, A.M.P. Moeljadi, K.F. Chin, H. Hirao, L. Zong, and C.-H.Tan. Enantioselective sulfoxidation catalyzed by a bisguanidinium diphosphatobis(oxotungstate) ion pair. *Angew. Chem., Int. Ed.* 55, 7101-7105 (2016). DOI: 10.1002/ange.201601574.

The contributions of the co-authors are as follows:

- Prof Tan Choon-Hong provided the initial project direction and edited the manuscript drafts.
- I prepared the manuscript drafts. The manuscript was revised by Dr A.M.P. Moeljadi.
- I co-designed the computational study with A/Prof H. Hirao and performed all the laboratory work at the School of Physical and Mathematical Science. I also analyzed the data.
- All experiments, including sample preparation, was conducted by me in the Facility for Analysis, Characterization, Testing and Simulation.
- Dr K.F. Chin and Dr L. Zong assisted in the collecting optical rotation data and catalyst development.

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The contributions of the co-authors are as follows:

- Prof Tan Choon-Hong provided the initial project direction and edited the manuscript drafts.
- I prepared the manuscript drafts. The manuscript was revised by Dr K.F. Chin.
- I co-designed the IR and Raman study with Dr L. Richmond and A.M. Kabylda , and performed all the laboratory work at the School of Physical and Mathematical Science. I also analyzed the data.
- Most of experiments, including sample preparation, was conducted by Dr K.F. Chin and me in the Facility for Analysis, Characterization, Testing and Simulation.
- X. Zhang, E.C.X. Ang helped in part of substrates synthesis.
- Dr Yongxin Li assisted in the interpretation of the X-ray absorption spectroscopy data and carried out the spectral interpretation.

Note: If published materials are not inserted as thesis chapters, students must acknowledge co-worker contributions in the acknowledgement section of their thesis.

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Abstract

The aim of this study is to develop efficient asymmetric ion pair catalysis assisted by metal oxides to realize highly enantioselective oxidation reactions. In this thesis, two projects revealed the novel catalytic system as an excellent strategy in synthetic methodology. In each case, the essence of chemistry was studied mechanistically.

The first two chapters introduced the background from two aspects, which included the history of ion pair catalysis (Chapter 1) and application of tungstate salts in oxidation (Chapter 2). The following two chapters presented two projects utilizing the designed strategy.

Over the last few years, our group has developed a series of phase-transfer catalysts, which successfully solved problems in the enantioselective addition and substitution reaction under traditional base promoted conditions. Meanwhile, another precedent concept of ion pair catalysis was put forward as a branched subject in this field. Motivated by ion pair concept, the work discussed in this thesis proved the potential of the catalysts developed in our group under a novel working mode.

In Chapter 3, bisguanidinium diphosphatobisperoxotungstate $\text{BG}^{2+}[\{\text{PO}_2(\text{OH})_2\}_2\{\text{WO}(\text{O}_2)_2\}]^{2-}$ successfully catalyzed asymmetric sulfoxidation, which was applied in synthesis of (*S*)-Lansoprazole ultimately. The active species was characterized by Raman spectroscopy and supported by computational data. In Chapter 4, according to the success of oxidizing electron poor allylic and homoallylic amines, a further development was established. The real catalyst was a stable compound and demonstrated as bisguanidinium tetraperoxyditungstate $\text{BG}^{2+}[\text{W}_2\text{O}_2(\mu\text{-O})(\text{O}_2)_4]^{2-}$ by single crystal X-ray diffraction. Meanwhile, both experimental and computational data of Raman and IR were collected and compared for analysis and discussion. The perfectly matched spectra show the efficiency of information acquirability via Raman and IR, which has potential application in mechanism exploration in future work of this area.

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Chapter 1

Ion Pair Catalysis

1.1 Introduction

Ion pair catalysis was presented for the first time in 1926 by Bjerrum.¹ Eighty years later, this concept was defined officially in textbook by Anslyn and Dougherty.² It said, a cation and an anion are close enough, and the required dissociation energy is higher than the thermal energy (at room temperature) available for separating them. From the other perspective, the lifetime of ion pair is longer than the time required for forming non-interacting ions caused by *Brownian motion*.

The progress of industrial asymmetric synthesis calls for the breakthrough in developing ion pair catalysis. Currently, the asymmetric catalysis systems could be concluded as organometallic catalysis, chiral Lewis acid catalysis, chiral organocatalysis, chiral ion pair catalysis, chiral enzymatic catalysis, and chiral photoredox catalysis. The most traditional field is referred to organometallic chemistry. Covalent bonds between a reaction intermediate and a metal catalyst are formed, and then the enantioselectivity is directed by a chiral ligand on the metal catalyst.³ Chiral Lewis acid catalysis⁴ utilizes a broad range of main group and transition metal Lewis acids coordinated by chiral ligands, which is distinguished from organometallic catalysis by dative bond directing mechanism. Chiral organocatalysis⁵ has developed in recent few decades. It includes chiral enamine/iminium catalysis,⁶ chiral NHC catalysis,⁷ and chiral phosphine catalysis. Another field is ion pair catalysis, which could be subcategorized as chiral cationic and chiral anionic catalysis. The enantioselectivity can be induced through electrostatic or other noncovalent interactions between the charged intermediates and charged chiral ions.⁸ Chiral enzymatic catalysis⁹ also becomes a hot topic recently, which is human body benign and has large potential in application of drug modifications. The most novel field is different from the former in which free radicals are involved via chiral photoredox catalysts.¹⁰ It burgeons recently with the discovery and application of metallic chiral ligand photoredox catalysts. However, radical relay progresses without any covalent interaction

between the intermediates and catalysts, which distinguishes itself from the first traditional catalytic mode. Among these strategies, ion pair catalysis is good for both homogenous and heterogenous reactions, and has the advantages of low catalyst loading and large scalability, which guarantees the prospective application in productive engineering.

According to the structural characteristics of ion pair catalysts, four categories of ion pair catalysis are concluded: chiral cation-directed catalysis, chiral anion-directed catalysis, cation-binding catalysis, and anion-binding catalysis (Figure 1.1).⁸

Figure 1.1 Four typical ion pair catalysis

1.2 Chiral cation-directed catalysis

1.2.1 Ammonium cations

The earliest report of using chiral ammonium salt can be traced back to the 1984, which was utilized in *C*-methylation of indanones (Scheme 1.1).¹¹ The skeleton of quaternary ammonium salt **1** is derived from natural product, cinchonidine. Since then, researchers found it worked efficiently in base promoted reaction, and this strategy was successfully applied in a wide range of reactions, such as aldol, Michael, Mannich and so on.

Scheme 1.1 First chiral quaternary ammonium catalyzed alkylation

However, the natural alkaloid is very costly, and sometimes it has to be further modified to improve results. Thus, researchers started to develop artificial ammonium catalyst with different skeletons. New generations of ammonium catalysts are classified into two groups: one possesses sp^3 -nitrogen center, and another possesses sp^2 -nitrogen center (Figure 1.2). Maruoka and co-workers developed C_2 -symmetric bis-binaphthyl based sp^3 -nitrogen centered spirocyclic catalyst **2**.¹² Shibasaki and co-workers developed two centered sp^3 -nitrogen catalyst **3**.¹³ Our group has contributed to two sp^2 -nitrogen centered catalysts in recent decades. Pentanidinium (PN) **4** is the condensed product of one guanidine and one imidazole chloride.¹⁴ Bisguanidinium (BG) **5** is a two charged cation catalyst, which is the condensed product of two molecular imidazole chloride salts and piperazine.^{15,16}

Figure 1.2 Representative examples about sp^3 and sp^2 centered ammonium salts

As one of the most popular quaternary ammonium cations, Maruoka's catalyst was widely used in methodology (Scheme 1.2). In the first report,¹² they described the skeleton of bis-binaphthyl based spiro-ammonium, and examined a series of modified derivatives in Schiff base alkylation. They found **2a** showed best performance with basic aqueous solution among these catalysts, producing 90% yield and 99% *ee* in a model reaction.

Scheme 1.2 First application of Maruoka catalyst

Later, the combination of phase transfer catalyst and base became an efficient method to build quaternary carbon centers. Additionally, with the development of catalysts, a broader substrate scope was explored (Scheme 1.3), where alkylation of tertiary carbanion formed by deprotonation of β -keto esters proved.¹⁷

Scheme 1.3 C-H bond activation via Maruoka catalyst

Some other reactions involving similar deprotonation process were proved feasible with this catalytic system as well. The nucleophilic addition reactions were notable among them (Scheme 1.4). In the presence of **2c**, a direct aldol reaction^{18,19} between Schiff base and aliphatic aldehydes were achieved in both high yield and *ee*%.

Scheme 1.4 aldol reaction via Maruoka catalyst

Similar to the aldol reaction, Mannich reaction²⁰ was easy to realize in this way. By replacing aldehydes with α -imino esters (Scheme 1.5), the analogues of chiral diamines were constructed in one step in both high regio and enantioselectivity.

Scheme 1.5 Mannich reaction via Maruoka catalyst

When it comes to sp^2 -nitrogen centered ammonium, the systematic work was done in our group in recent decade. In 2009, the concept of chiral guanidinium salt²¹ was first put forward and used in phospho-Mannich reaction. Two years later, a landmark work of creating pentanidinium (**PN**) **4** was first demonstrated and applied to asymmetric Michael addition of Schiff base successfully.¹⁴ The key step of preparation of **4** was the condensation between imidazole salt and guanidine. In this Michael addition reaction, **4a** was characterized by single crystal X-ray diffraction (Scheme 1.6).

Scheme 1.6 First application of pentanidinium catalyst

On the basis of preliminary models of catalysts, a new generation of guanidinium-based ion pair catalyst was established,¹⁵ which was first reported and described as bisguanidinium (**BG**) **5** (Scheme 1.7). Motivated by the success of **PN** during 2011-2014, a strategy of changing the linker between the two guanidine units was attempted. In a series of catalyst derivatives, piperazine-linked **BG** was found to be the most potential catalyst for application in oxidation reaction. The main step to form **BG** was the condensation between two molecules of imidazole salts and one piperazine molecule in the presence of a base. In the first report of **BG**, trisubstituted enoates was chosen as the research object. The catalyst was modified with a specific side chain as **5b**. The terminal oxidant of dihydroxylation and oxohydroxylation was potassium permanganate. However, as potassium permanganate was so reactive, the reaction had to be conducted under extremely cold conditions. At the same time, potassium permanganate is not an ideal oxidant in industry. Thus, we work towards replacing the oxidant to hydrogen peroxide, which is widely used in practice.

Scheme 1.7 First application of bisguanidinium catalyst

The industrial method of asymmetric oxidation is Kagan's sulfoxidation, which is famous for its application in synthesizing Esomeprazole by utilizing Ti-tartaric acid complex and cumene hydroperoxide. To challenge the existing method, we began to research on sulfoxidation (see more details in chapter 3).²² Direct hydrogen peroxide transfer proved inefficient, but catalytic amount of metal oxide make the reaction work (Scheme 1.8). After

that, epoxidation was studied under the same catalytic system, and more information about ion pair catalysis was revealed during the mechanistic study (see more details in chapter 4).

Scheme 1.8 Bisguanidinium catalyzed oxidation reactions

On the other hand, **BG** showed ability to capture the hypervalent silicate intermediate. In 2016, an asymmetric alkylation using silylamide as pro-base (**pb**) was accomplished when catalyzed by **PN** or **BG**.²³ In the substrate scope of dihydrocoumarins and benzochromenones, **PN** was applied. However, in the substrate scope of α -benzyl-1-indanones, **BG** was preferred over **PN**. The configuration of the pro-base was attributed to the difference in the choices of catalyst. It was obvious that **pb2** was bigger than **pb1** in terms of the TBS group (Scheme 1.9). As **BG** has a larger space in its ionic center, it was able to capture a bulkier silicate intermediate.

Scheme 1.9 Hypervalent silicate intermediates and pro-base strategy

The same strategy was applied to 1,2-anionotropic rearrangement of acylsilane to produce chiral secondary alcohol. The intramolecular 1,2-Brook rearrangement occurred in the

presence of CsF, and the extra additive of silanol in system was to provide a proton to the acyl group (Scheme 1.10).²⁴

Scheme 1.10 1,2-Brook rearrangement activated by CsF

1.2.2 Phosphonium cations

Chiral quaternary phosphonium catalysts have been realized as another type of ion pair catalysts after the success of quaternary ammonium salts (Figure 1.3). In 2008, Maruoka and co-workers developed C_2 -symmetric tetraalkyl phosphonium salt **6**,^{25,26} with which they achieved enantioselective amination, Michael, and Mannich reactions. Ooi and co-workers developed *N*-benzylated D_2 -symmetric *P*-spiro tetraaminophosphonium salt **7**.²⁷ The working principle of quaternary phosphonium cation is similar to that of the quaternary ammonium cation.

Figure 1.3 Quaternary phosphonium cations

1.3 Cation-binding catalysis

Compared to cation-directed catalysis, cation-binding catalysis works as well in form of ion state. This type of ion pair catalyst follows the structural character of crown-ether chelated metal cation catalyst, such as 18-crown-6/ K^+ cation. Thus, a lot of modified crown polyethers were developed to improve their capability in terms of enantioselectivity.

The natural chiral-pool can be one of the most important motifs applied to polyethers. Akiyama and co-workers prepared chiral inositol derived crown ethers **8** to catalyze Michael addition reaction (Scheme 1.11).²⁸

Scheme 1.11 Polyether-binding potassium catalyzed Michael addition reaction

Another chiral source is artificial chiral compound. Cram and Sogah created BINOL-based chiral crown ether **9** to accomplish Michael addition in 1981 (Scheme 1.12), which was the first example of highly enantioselective Michael addition catalyzed by phase transfer catalyst.²⁹

Scheme 1.12 BINOL-based chiral crown ether/ K^+ catalyzed Michael addition reaction

1.4 Chiral anion-directed catalysis

1.4.1 Borate anions

Except for the Brønsted base deprotonated anion intermediates, the Brønsted acid activated cation intermediates also need to be controlled by chiral anion via ion-pairing. In 2000,

Arndtsen and co-workers reported the first application of chiral anion asymmetric catalysis (Scheme 1.13). A D_2 -symmetric BINOL-based chiral borate **10**³⁰ was synthesized with an achiral copper complex as counterion, which was used in aziridination. However, poor enantioselectivity was achieved under chiral borate catalyst. Later, they used the condensation product of tartaric acid and α -amino acid to prepare a new borate anion **11**, which was applied in cyclopropanation on styrene. The capability of the modified catalyst was still weak, and the *ee*% was 34%, a less than moderate result. Nelson and co-workers thought the problem lay in the copper complex counterion.³¹ It was assumed that the substrate formed a covalent bond with copper, thus weakening the directing effect of the borate. Thus, they used pure organocatalyst with achiral ammonium counterion. The substrate was dehalogenated³² by the counterion, then an intramolecular reaction happened to form a cation intermediate. From the results, it seemed that the problem could not be solved in this stage and more explorations should be done.

Scheme 1.13 Applications of borate anion

1.4.2 Phosphate anions

The BINOL-based phosphoric acid is an excellent hydrogen-bond directing asymmetric catalyst. Meanwhile, the conjugate base of acid proved to be an attractive candidate for ion pair catalyst as well. In 2006, List and co-workers reported chiral phosphate catalyzed reduction of citral to citronellal.³³ In previous work, both List³³ and MacMillan³⁴ gave their attention to chiral iminium ion strategy, and found the counterion affected the reactivity and enantioselectivity a lot. Then, List hypothesized the chiral inducing reagent could be a part of the counterion.³⁵ Thus, they used morpholine to activate aldehyde. At the same time, the Hantzsch ester was activated by phosphate ion **12** via hydrogen bonding. The whole species worked as a counterion pairing to the morpholine type iminium intermediate (Scheme 1.14). This strategy was a huge success, and this report became a landmark in phosphate catalyzed asymmetric catalysis.

Scheme 1.14 Iminium intermediate controlled by chiral phosphate

Subsequently, List's group applied this strategy to other types of reactions. For instance, they achieved epoxidation of α,β -unsaturated aldehydes (Scheme 1.15).³⁶ The oxidant, *tert*-butyl hydroperoxide (TBHP) was associated to phosphate anion via hydrogen bonding. The

ammonium counterion reacted with aldehyde to form the iminium cation intermediate, through which, the oxidation was realized with chiral-inducing process.

Scheme 1.15 Chiral phosphate catalyzed epoxidation

In 2010, Dixon and co-workers reported a condensation reaction between tryptamines and keto acid derivatives via 3-triphenyl silyl substituted BINOL-based phosphoric acid **13** (Scheme 1.16). The initial step of the reaction was formation of a pair of diastereomeric *N*-acyliminium phosphate salts. One of the diastereomers had a higher reactivity in cycloaddition, which led to the major product.^{37,38}

Scheme 1.16 Chiral phosphate catalyzed cyclo-addition

In 2011, Huang and co-workers reported *N*-alkylation between indole and α,β -unsaturated γ -lactams (Scheme 1.17).³⁹ Initially, α,β -unsaturated γ -lactam was protonated by

chiral phosphoric acid catalyst **12-H**. Once the *N*-acyliminium ions formed, it would pair with chiral anion. At last, a nucleophilic addition to benzopyrrole ring to give the alkylated product.

Scheme 1.17 Chiral phosphate catalyzed *N*-alkylation

Above mentioned efficient strategy was continuously studied in more reaction mechanisms. For example, the carbocation intermediates are easy to be controlled by phosphate catalysts. Thus, Antilla and co-workers provided the first report of intramolecular pinacol rearrangement reaction (Scheme 1.18).⁴⁰ However, low enantioselectivity was observed in non-aryl group migration. They assumed that not only the hydrogen-bonding but also electrostatic interactions existed in catalytic process.

Scheme 1.18 Chiral phosphate catalyzed Pinacol rearrangement

Motivated by the success with carbocations, oxocarbenium was considered as the next target to be controlled by phosphate anion. In 2009, Tu and co-workers accomplished a ring expansion semi-Pinacol rearrangement to produce spiroethers in high yield and *ee*% (Scheme

1.19).⁴¹ The protonation on cyclohexylallylic ether led to form oxocarbenium intermediate. Then deprotonation on the alcohol pushed the rearrangement progress.

Scheme 1.19 Chiral phosphate catalyzed semi-Pinacol rearrangement

In the previous discussion, the application of a borate anion catalyst in S_N2 reaction was introduced, and the results were unsatisfying. Thus, by keeping the reaction under the same pathway, the ammonium intermediates were controlled by phosphate catalyst excellently. Later, Toste and co-workers applied the same strategy in the same type of reaction via episulfonium intermediates (Scheme 1.20).⁴² In addition, the reaction condition was milder than the reaction with borate.

Scheme 1.20 Chiral phosphate catalyzed S_N2 reaction

Other than the cation intermediates, the cationic reagents could be controlled. For example, selectfluor⁴³⁻⁴⁵ is a salt with two nitrogen centered cation of two charges (Scheme 1.21). The reagent itself can be captured by anion catalyst **15**, then passes the fluorine atom to the substrates.

Scheme 1.21 Chiral phosphate catalyzed fluorination

The last classical category is metallated intermediate. In this kind of catalytic cycle, the chiral anion catalyst **12-Ag** works as a dual catalyst with metal complex. In 2007, Toste and co-workers reported Au-catalyzed intramolecular cyclization reaction (Scheme 1.22).⁴⁶ Due to the linear geometry of allene, the ligand on gold catalyst was far from the reaction site, which made it difficult to induce enantioselectivity by chiral ligand on metal. Hence, they hypothesized that the counterion of Au-complex could approach the reaction site. Finally, they proved the design of the strategy, in which the hydrogen bonding effect helped in achieving excellent results.

Scheme 1.22 Dual catalysis of chiral phosphate and gold catalyst

1.4.3 *N*-Triflylphosphoramidate anions

In 2008, Yamamoto and co-workers developed a *N*-Triflylphosphoramidate anion **16** by replacing one oxo-group on phosphate (Scheme 1.23), which was an excellent chiral Brønsted

acid catalyst in application of asymmetric protonation reaction. In presence of this novel Brønsted acid catalyst, the phenol substrate was protonated and paired with the chiral anion. A rapid proton transfer from achiral phenyl oxonium to silyl ether enolate substrate occurred, and it was followed by a desilylation with phenol to form the product. However, being the first generation of amide centered catalyst, the enantiomeric excess value was 90% at maximum in specific substrate.⁴⁷

Scheme 1.23 *N*-Triflylphosphoramidate anion catalyst

List and co-workers continued to work on amide anion catalyst. They discovered binaphthyl disulfonimide catalyst **17** to activate aldehyde in Mukaiyama aldol reaction (Scheme 1.24).^{48,49} The chiral amide salt paired with oxocarbenium, and both yield was up to 98%, and ee% was up to 94%.

Scheme 1.24 Binaphthyl disulfonimide catalyzed Mukaiyama aldol reaction

To broaden the scope of the reactions, they further developed a novel catalyst called imidodiphosphate anion **18** (Scheme 1.25). The structure of imidodiphosphate anion was constructed by two molecules of BINOL-based phosphate condensed with a mono amide group. They described it as a chiral pocket capturing the substrate and releasing the product after inducing the chiral center.⁵⁰ It successfully catalyzed the 5-, 6-, 7-membered cyclic enol ethers in spiroacetalization reaction.

Scheme 1.25 Imidodiphosphate anion catalyzed spiroacetalization reaction

1.5 Anion-binding catalysis

Anion-binding catalysis was first recognized in achiral applications. It was discovered by Schreiner and co-workers in a thiourea catalyzed acetalization reaction (Scheme 1.26).⁵¹ They

put forward two modes of catalytic behaviors. One mode was aldehyde carbonyl group binding to thiourea catalyst **19** via hydrogen bonding. The other mode involved orthoester in the mechanism where the incipient anion was generated by the reaction between thiourea catalyst and orthoester, which attacked rapidly on aldehyde. Until the hemiacetal oxocarbenium intermediate formed, it would be attacked by another molecule of the incipient anion in S_N2-like pathway. The evidence of this mechanism was provided when they applied thiols in the reaction. In principle, the thiol was a strong nucleophile and could achieve formal substitution on carbonyl and thiourea binding complex in priority. However, the product was only the normal ether from the orthoester.

Scheme 1.26 Thiourea catalyzed acetalization reaction via anion-binding mechanism

Subsequently, the same group used this catalytic mode in tetrahydropyranylation of alcohols (Scheme 1.27). The protonation of hydropyran olefin was followed by alkoxylation.⁵²

The intermediate was a thiourea chelated alkoxide anion, which worked as nucleophile when attacking the protonated pyran ring.

Scheme 1.27 Thiourea catalyzed tetrahydropyranylation reaction

The earliest application of a thiourea catalyst in asymmetric synthesis was reported by Jacobsen and co-workers (Scheme 1.28).⁵³ They found the cyanide anion was binding to the catalyst **20** and promoted an addition reaction to imine substrates. The yield was up to 99%, and the *ee*% was up to 93%.

Scheme 1.28 Thiourea hydroxide-binding catalyzed cyanidation

Similarly, the halide anion could be a potential object to be discussed. In 2008, Jacobsen group continued in this area and used 1-chloroisochromans and silyl ketene acetals to furnish addition reaction (Scheme 1.29).⁵⁴ Initially, 1-chloroisochroman was dehalogenated by catalyst **21**, then a halide binding anion and an oxocarbenium cation were formed. Furthermore, the silyl ketene acetal was attacked by ion pair in specific direction to achieve high enantioselectivity.

Scheme 1.29 Thiourea halide-binding catalyzed addition reaction

During 2009-2011, Seidel and co-workers accomplished a series of reactions utilizing carboxylate bound chiral thiourea anion (Scheme 1.30).⁵⁵⁻⁵⁷ The 4-(dimethylamino)pyridine (DMAP) accepted one acyl group, then it paired with the chiral anion to attack the free amine.⁵⁸ The last step of this reaction was deprotonation to produce the chiral secondary amine. Since the starting material, free amine, was a racemic chiral reagent, the result was described by *s*-factor for the kinetic resolution progress. It was the first time that a dual catalyst system led ion pair complex worked as both donor and acceptor in the presence of thiourea **22** and DMAP at the same time.

Scheme 1.30 Carboxylate bound chiral thiourea anion catalyzed *N*-alkylation

Inspired by the design of the dual catalytic mode, Jacobsen and co-workers applied it to enolate anion intermediates in 2011 (Scheme 1.31).⁵⁹ Initially, the benzoyl fluoride released fluoride, which bound to thiourea catalyst **23** to form the chiral anion. Immediately, the acyl group connected to DMAP to form the cation. The fluoride in ion pair cleaved the TMS-protected enol and was replaced by enolate anion. At last, the two components in ion pair reacted with each other, and the acylation product was obtained.

Scheme 1.31 Application of enolate bound chiral thiourea anion

In 2010, their group kept discovering new anion intermediate, and this time, they found *N*-iodophthalimide as a successful case (Scheme 1.32).⁶⁰ The iodonium source *N*-iodophthalimide was initiated by I₂. After forming the triiodide cation, it activated the carboxylic olefin to form iodonium cation. At the same time, the phthalimide anion bound to amino-urea catalyst **24**, and the I₂ regenerated to produce triiodide cation again.

Scheme 1.32 Application of iodide bound chiral thiourea anion

In the same year, they did some work of sulfonated anion. They chose *ortho*-nitrobenzenesulfonic acid as proton source in Povarov reaction (Scheme 1.33).⁶¹ The protonated imine underwent a [4+2] cycloaddition assisted by sulfonate-binding urea anion catalyst. They also modified the amino group on the catalyst **25**. The sulfinyl substituted chiral amine stabilized the protonated imine substrate via hydrogen bonding.

Scheme 1.33 Application of triflate bound chiral thiourea anion

1.6 Summary

In this chapter, the concept of ion pair catalysis was introduced from the beginning, and four types of ion pair catalysis were listed and illustrated using various examples. Since the new century, an explosion of related reports was contributed by researchers worldwide, which illustrated novelty of our research as well. In the section of chiral cation-directed catalysis, the recent development of our phase-transfer catalyst was reviewed, which includes the main content of this thesis.

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Chapter 2

Tungstate Anion and Derivatives in Oxidation

2.1 Introduction

Tungsten is a transition metal with elemental symbol W.¹ Its atomic number is 74, which is in period 6, group 6. The electron configuration is $[\text{Xe}]4f^{14}5d^46s^2$, so it can exhibit oxidation states from -2 to 6. Molybdenum and tungsten are in the same group, which show the similar reactivity in many applications. Therefore, these two metals are usually compared, studied and discussed at the same time, and in most cases, they show the same principles. The most common oxidized product of tungsten is WO_3 , which can further dissolve in alkaline water to form WO_4^{2-} . Molybdenum oxide is often used as an oxidant in organic synthesis. The tungsten catalysts with coordination of various ligands have also been studied a lot in oxidation reactions.^{2,3} Due to the structural feature of chiral cation catalyst developed in our group, we focused on anionic form of tungstate to start our research. We aim to utilize the oxidative property of tungstate, and have accomplished some asymmetric oxidation reaction via ion pair catalysis.

Tungstates and congeners are known to polymerize in aqueous solutions in different forms according to the miscellaneous additives, pH and concentrations. The most famous example is Keggin's structure, which represented a series of anions with a general formula of $[\text{XM}_{12}\text{O}_{40}]^{n-}$. The first α -Keggin structure was $(\text{NH}_3)_3[\text{PMo}_{12}\text{O}_{40}]$, reported by Berzelius in 1826.⁴

In this chapter, in-depth introductions to tungstate are constructed according to the active species, and there will be three categories: tungstate monomer, tungstate oligomer, and tungstate polymer. All selected applications are organic oxidation reactions, including epoxidation, cleavage of double-bond (to carboxylic acids, aldehydes or ketones), oxidation of alcohols, oxidation of amines, sulfoxidation, and oxidation of imines.

2.2 Tungstate monomer in oxidation

The pioneering work of using tungstate as a catalyst in oxidation was demonstrated by Payne in 1959.⁵ They used 2-10 mole % of tungstate catalyst and 1.2 equivalent of hydrogen peroxide solution (30%, w/w) to oxidize α,β -unsaturated acids to epoxy acids in heated water (Scheme 2.1). Before their study, other groups tried to use tungstic acid to catalyze the epoxidation, but they obtained a lot of hydroxylated side product. They assumed the epoxide was easily hydrolyzed under extremely acidic conditions. Thus, Payne hypothesized to restrict the pH of the system, by which they could prevent the side reaction happening. Owing to the mild condition established by replacing the tungstic acid to sodium tungstate salts, they avoided hydroxylation of the substrates successfully.

Scheme 2.1 First example of catalytic tungstate in oxidation

In 1985, Sharpless and co-workers improved the procedure and substrate scope based on the work done by Payne (Scheme 2.2).⁶ First of all, they expanded the scope of substrates and concluded the differences of reactivities of olefins with different substitutions. They found tri-substitution substrates performed better under Payne's condition, even when it was conducted at room temperature. Later, they compared Payne's strategy with their Ti-complex oxidation system, and thought the tungstate anion might be chelated to some acid, by which the capability of catalyst was increased significantly. They tried to prove it by tuning additive and checking the relative reaction rate of a model substrate. The experimental data supported their assumptions.

entry	additive	ratio additive/catalyst	relative rate
1	picolinic acid	1.19	3.0
2	no additive		5.1
3	ethylene glycol	1.19	14.9
4	D-(-)-butanediol	1.21	23.2
5	<i>d</i> -lactic acid	1.20	25.0
6	L-(+)-tartaric acid	1.19	28.9

Scheme 2.2 More explorations contributed by Sharpless

In 1996, Noyori and co-workers used phase transfer catalyst with sodium tungstate in epoxidation of terminal olefins (Scheme 2.3).⁷ They overcame the problem of substrate scope limitation and promoted the efficiency of the reaction, achieving excellent yields. However, they pointed out that styrene could not be converted to epoxide in high yield, which was due to the hydrolytic decomposition at the interface. About the additive (aminomethyl)phosphonic acid, they gave an explanation as follows: the conjugated base of phosphonic acid became a ligand coordinating to tungstate anion, which improved the activity of the catalyst.

Scheme 2.3 Tungstate catalyst assisted by phase transfer catalyst

In 1997, Noyori group applied this phase transfer catalyzed strategy to the oxidation of alcohols, secondary alcohols to ketones and primary alcohols to aldehydes or to acids when over-oxidized (Scheme 2.4).^{8,9} As alcohols were more easily oxidized than olefins, they found the tungstate anion along with the phase transfer catalyst was active enough. Hence, they proposed the active species was a tungstate with a hydroxyl group. By controlling the loading of the oxidant and adjusting the concentration of the reaction, over-oxidation could be promoted or inhibited.

Scheme 2.4 More types of oxidation under Noyori's system

A huge success of phase transfer tungstate catalyst was achieved in producing the adipic acid from cyclohexene in 1999 by Noyori group (Scheme 2.5).¹⁰ In their previous work, they had already proposed the catalyst structure. This time, they described the mechanism of the over-oxidation reaction. Cyclohexene was oxidized to an epoxide first, then the epoxide was hydrolyzed to a diol. The diol was further oxidized to give α -hydroxy ketone product, which continuously underwent the Baeyer-Villiger oxidation to form seven-membered ring. After one step of oxidation followed by a hydrolysis, adipic acid was obtained ultimately.

Scheme 2.5 Mechanism study of over-oxidized reaction catalyzed by phase transfer catalyst with tungstate

In 2001, the Noyori group complemented the tungstate catalytic system by investigating the sulfide oxidation.¹¹ A tungstate anion coordinated with a phenylphosphoric acid in 1 to 1 ratio, pairing with a phase transfer cation (Scheme 2.6). The starting material could be oxidized to sulfoxide, or over-oxidized to sulfone. Even though the dominant product was determined by the amount of the oxidant, the sulfone could not be excluded when producing the sulfoxide. Hence, the chemoselectivity was one main problem in this reaction.

Scheme 2.6 Tungstate monomer with phosphate ligand

Besides, the oxidation of nitrogen atom was researched using tungstate catalyst. In 1990, Murahashi and co-workers established simple reaction conditions for the oxidation of secondary amines (Scheme 2.7).¹² Only a catalytic amount of tungstate and stoichiometric

hydrogen peroxide were applied to the substrate in water or methanol. As a result, acyclic and cyclic nitrones were obtained in good to excellent yield.

Scheme 2.7 Oxidation of nitrogen atom via tungstate

In 2001, Varlamov and co-workers complemented the cyclic nitrones synthesis with the same strategy (Scheme 2.8).¹³ 2-Benzazepine derivatives was an important building block of drug moieties for Alzheimer's disease.

Scheme 2.8 Cyclic nitrone synthesis via tungstate

In 2005, Aslanzadeh reported an oxidation of primary amines by using sodium tungstate as a catalyst and hydrogen peroxide in urea (UHP) as an oxidant (Scheme 2.9).¹⁴ This method was applied to a large scope of substrates including benzylic amines and α -amino esters, in which the yields ranged from 65% to 80%.

Scheme 2.9 Oxidation of primary amines via tungstate

In 2011, Leonard and co-workers discovered a new method to oxidize diamines to directly produce unstable nitro-compounds (Scheme 2.10).¹⁵ The reaction conditions were harsh and dangerous, as the hydrogen peroxide was used with concentrated sulfuric acid. The procedure demanded researchers with rich experiences.

Scheme 2.10 Tungstate oxidized amines to nitro-compounds

The oxidation N-alkyl imine was also studied under the catalysis of tungstate salts (Scheme 2.11). The imine was oxidized to oxaziridine in the presence of 10 mol% tungstate, and the yield of reaction was up to 96%.¹⁶

Scheme 2.11 Tungstate oxidized imines to oxaziridines

2.3 Tungstate oligomer in oxidation

In 1983, Venturello and co-workers reported an epoxidation reaction catalyzed by tungstate and phosphoric acid under phase transfer conditions.¹⁷ Initially, they found the effectiveness of the reaction depended highly on the pH of the reaction solution, where the rate of the reaction increased drastically as the pH decreased. Later, they recognized that the buffer solution of $\text{H}_3\text{PO}_4/\text{NaH}_2\text{PO}_4$ was effective in producing the acid-sensitive epoxides. Thus, they considered that the reactivity was not merely influenced by pH. Two years later, they successfully prepared and isolated the catalyst using the previously reported conditions.¹⁸ They had strong evidence through single crystal X-ray crystallography and examined the activity in the reported reaction (Scheme 2.12). The fundamental structure was phosphorus centered salt with four coordinated tungstates $[\text{PW}_4\text{O}_{24}]^{3-}$, and the overall charge of the anion was -3. Almost at the same time, Ishii group was studying the oxidation application of Keggin's structure. They realized a novel catalyst was generated in the presence of a phase transfer catalyst in hydrogen peroxide solutions, which was called PCWP. In 1990, they compared the IR data with Venturello's crystal and confirmed the structure.¹⁹

Scheme 2.12 Ishii-Venturello anion application

In Ishii's report, they described the catalyst was with three tetrahexylammonium cations, and they tried to oxidize various alkynes by PCWP (Scheme 2.13). During their research, they found several products. Except for the main product α,β -epoxy ketones, there were other side products, such as α,β -epoxy ketones and acids.

Scheme 2.13 Alkyne oxidation catalyzed by PCWP

Inspired by the interesting discovery and motivated by more challenging reactions, Ishii's group reported a diol oxidation in 1991.²⁰ Only 1.6 mol% of PCWP catalyst and 6 equivalents of hydrogen peroxide were used for acyclic aliphatic diols, benzylic diols, and cyclic diols. They found that a secondary alcohol is specifically oxidized in the presence of a primary alcohol. Additionally, the cyclic diols could be hydrolyzed to acids. In 1995, Ishii group supplemented this work by studying the chemoselectivity among the α -hydroxy ketone, diketone and acid products.²¹ They found using stoichiometric amount of PCWP resulted in highly specific oxidation to diketones. Meanwhile, in the presence of a catalytic amount of PCWP, adding the hydrogen peroxide dropwise could lead to efficient oxidation to diketones

as well. With the same catalytic amount of PCWP, the adding of hydrogen peroxide in one portion afforded the α -hydroxy ketone as a main product. This study clearly revealed the oxidative efficiency of PCWP was much higher than the common oxidant (Scheme 2.14).

Scheme 2.14 Diol oxidation catalyzed by PCWP

Meanwhile, Ishii group also applied the system to the oxidation of primary amines (Scheme 2.15).²² Non-aromatic amines were oxidized to oximes, and some of the products could be dried over and dehydrolyzed to N-oxides. Aromatic amines were oxidized to the corresponding nitroso compounds.

Scheme 2.15 N-oxidation catalyzed by PCWP

Likewise, the direct oxidation of olefins to α -hydroxy ketones was realized by this strategy. Ishii's group continued their study on the application of PCWP, and reported this result in 1992 (Scheme 2.16).²³ As shown below, sulfuric acid was a crucial component in this reaction. Without sulfuric acid, the olefins would be oxidized to epoxides (see Scheme 2.12). However, in the presence of the sulfuric acid, the reaction led to the formation of the α -hydroxy ketone as the dominant product.

Scheme 2.16 Alkene oxidation catalyzed by PCWP

In 1964, inorganic chemists Einstein and Penfold identified the potassium dihydrated tetraperoxyditungstate $[\{\text{W}(=\text{O})(\text{O}_2)_2(\text{H}_2\text{O})\}_2(\mu\text{-O})]^{2-}\text{K}_2^+$ by X-ray analysis (Figure 2.1).²⁴ The typical dinuclear tungstate was isolated from a cold aqueous solution, which crystalized colorlessly in shape of blade. The article focused on discussing the fundamental parameters of this inorganic compound, and no application of this novel species was explored.

Figure 2.1 X-ray of $[\{\text{W}(=\text{O})(\text{O}_2)_2(\text{H}_2\text{O})\}_2(\mu\text{-O})]^{2-}\text{K}_2^+$

In 2003, Mizuno and co-workers occasionally found the potassium dinuclear dihydrated tetraperoxyditungstate was effective in epoxidation of α,β -unsaturated alcohols (Scheme 2.17).²⁵ By utilizing this catalyst, the utilization rate of hydrogen peroxide reached 97%, and the yield of epoxides were from 83-98%.

Scheme 2.17 Epoxidation of α,β -unsaturated alcohols via $[\{\text{W}(=\text{O})(\text{O}_2)_2(\text{H}_2\text{O})\}_2(\mu\text{-O})]^{2-}\text{K}_2^+$

In 2004, they continued this work and concluded that the neutral solution of the catalyst promoted highly selective epoxidation of allylic alcohols. The reactivity of the whole reaction decreased by replacing the catalyst with K_2WO_4 . (Scheme 2.18).²⁶ As a result, the conversion

of the reaction was terminated at 30%. On the other hand, if the catalyst directly replaced with H_2WO_4 , they observed triols as products in high selectivity and yield. It was obvious that the triols was formed from the epoxy alcohol via hydrolysis in acid solution. Nonetheless, it could not be claimed that H_2WO_4 could transform to dinuclear dihydrated tetraperoxyditungstate automatically in acid solution, because hydrolysis step could break the equilibrium of epoxide progress in the first step.

Scheme 2.18 Comparison of catalytic differences among $[\{\text{W}(=\text{O})(\text{O}_2)_2(\text{H}_2\text{O})\}_2(\mu\text{-O})]^{2-}\text{K}_2^+$, K_2WO_4 , and H_2WO_4

In 2007, Mizuno's group successfully synthesized $\mu\text{-}\eta^1\text{:}\eta^1\text{-peoxo-bridging}$ dinuclear tetraperoxyditungstate and dehydrate tetraperoxyditungstate (Figure 2.2).²⁷ They took both to oxidize alkyl olefins, benzylic alcohols, allylic alcohols, and phosphines. Interestingly, these two catalysts showed the same performance in these reactions. As early as 1989, Griffith and co-workers predicted the structure of dehydrate tetraperoxyditungstate accurately by analyzing the IR and Raman data of those ionic compounds with different counterions.²⁸

Figure 2.2 X-ray of $\mu\text{-}\eta^1\text{:}\eta^1\text{-peoxo-bridging dinuclear tetraperoxyditungstate and dehydrate tetraperoxyditungstate}$

2.4 Tungstate polymer in oxidation

The most famous tungstate polymeric structure is Keggin's structure, which was first reported by Berzelius in 1826.⁴ They proposed the configuration as chain or ring. Until 1934, James Fargher Keggin determined the α -Keggin's anion by X-ray diffraction (Figure 2.3), since then the Keggin's structure has been deeply researched, and 5 types of isomers have been identified (α -, β -, γ -, δ -, ϵ -).²⁹

Figure 2.3 Keggin's structure

Ishii and co-workers synthesized tris(cetylpyridinium)12-tungstophosphate (CWP), which was an ion exchanged product between cetylpyridinium chloride and α -Keggin acid. They reported some reactions using CWP as a catalyst. In 1987, they achieved a facile lactonization of α,ω -diols in the presence of CWP.³⁰ One year later, a carboxylation reaction of pinacols was realized with the use of CWP.³¹ In 1989, CWP was applied to epoxidation of allylic alcohols.³² They discussed the influence of the solvent, the phase transfer catalyst, the pH, and the difference between tungstate and molybdenum on reactions (Scheme 2.19).

Scheme 2.19 CWP applications developed by Ishii's group

Another famous tungstate polymeric catalyst is tetra-*n*-butylammonium decatungstate ($[(\text{C}_4\text{H}_9)_4\text{N}]_4^+\text{W}_{10}\text{O}_{32}^{4-}$, TBADT, Figure 2.4). Moreover, TBADT is a photoredox catalyst, and it can promote single electron transfer process in oxidation.

Figure 2.4 Structure of TBADT

For example, Craig and co-workers described the preparation, application, and kinetic study of TBADT in 1990 (Scheme 2.20).³³ The catalyst was activated by UV-light to form a radical anion. Then the radical anion worked as an oxidant in dehydrogenation homocoupling reaction, which obtained one electron from thioethers. Consequently, the thioether radical cation dissociated to one proton and one free neutral radical for the homocoupling step.

Scheme 2.20 Photocatalytic capability of TBADT

2.5 Summary

Tungstate salts have worked as oxidants in organic reactions for more than 70 years. Initially, it worked merely as an oxidant in stoichiometric amount. Later, it was developed into a catalyst by bringing the oxygen atom from a terminal oxidant, such as hydrogen peroxide, to the target molecules. The structures of catalytically active tungstate salts can be classified into monomer, oligomer, and polymer. Thus, pairing tungstate with a chiral cation catalyst is a plausible strategy for asymmetric oxidation. Exploration of this concept would not only lead to novel asymmetric oxidation reactions but also provide new insight into the structure and reactivity of tungstate.

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Chapter 3

Bisguanidinium Diphosphatobisperoxotungstate

Catalyzed Sulfoxidation

3.1 Introduction

Chiral sulfoxides are a vital moiety of enantioenriched drugs, such as Esomeprazole, Lansoprazole, and Armodafinil. Therefore, we are interested in the practical preparation of enantiopure chiral sulfoxides.¹⁻⁴ Kagan oxidation has been widely adopted for asymmetric sulfoxidation in industry for a long time (Figure 3.1, Eqn. 1),⁵ which utilizing $\text{Ti}(\text{O-}i\text{Pr})_4$ and chiral diethyl tartrate in extra mole equivalent of water to produce a homogeneous reagent to get clean chiral sulfoxide. There are emerging methods⁶⁻⁹ to prepare chiral sulfoxides including some recent breakthroughs utilizing imidodiphosphoric acid (Figure 3.1, Eqn. 2),¹⁰ or binuclear titanium chiral complex (Figure 3.1, Eqn. 3).¹¹

Figure 3.1 Some representative work of asymmetric sulfoxidation

Chiral cationic ion-pairing catalysis using inorganic salts is well known. The oxidizing anionic salts can be stoichiometric as in the epoxidation of chalcone with sodium hypochlorite using Maruoka catalyst (Figure 3.2, Eqn. 1).¹²⁻¹⁴ Alternatively, the actual oxidant, (hypo)iodite, can be generated *in situ* through the use of iodide and stoichiometric oxidant such as cumene

hydroperoxide (CHP) (Figure 3.2, Eqn. 2). Ishihara demonstrated that enantioselective oxidative cycloetherification can be accomplished with this approach.¹⁵⁻¹⁶ We recently demonstrated that by using potassium permanganate salt in the presence of a chiral dicationic bisguanidinium, highly enantioselective dihydroxylation and oxohydroxylation of α,β -unsaturated esters can be achieved (Figure 3.2, Eqn. 3).¹⁷ This strategy is highly complementary to the chiral anion ion-pairing catalysis that was demonstrated to be compatible with a variety of cationic metal species.¹⁸⁻²⁰ Herein, we wish to report the enantioselective sulfoxidation using a catalytic amount of silver tungstate in the presence of chiral dicationic bisguanidinium (Figure 3.2, Eqn. 4).

A. Non-metallic anion salts

1. Epoxidation (stoichiometric - hypochlorite)

2. Oxidative Cyclization (catalytic - iodide)

B. Metallic anion salts

3. Dihydroxylation/Oxohydroxylation (stoichiometric - permanganate)

4. Sulfoxidation (catalytic - tungstate) *This Work*

Figure 3.2 Enantioselective chiral cation ion-pairing oxidations.

3.2 Results and discussion

3.2.1 Reaction development

Initially, we mimicked the structures of target medicines, which was with heterocyclic substituted sulfoxides. Therefore, we prepared some heterocyclic substituted sulfides as model precursors. The first set of experiments we did were used to exclude the possibility of background reaction in presence of tungstate. As it showed in Table 3.1, either without tungstate or without **5a**, reaction did not work at all.

Table 3.1 Oxidative activity test of tungstate ^a

Entry	5a (mol%)	Na ₂ WO ₄ (mol%)	Result ^{b,c}
1	2	-	N.R
2	-	5	N.R
3	2	5	isolated yield % = 79 ee % = 0

^aReaction conditions: substrate (0.05 mmol), H₂O₂ (0.0525 mmol, 1.05 equiv, 35%w/w), 0.5 mL DCM at room temperature. ^bYield of isolated product. ^cDetermined by HPLC analysis on a chiral stationary phase.

Because solvent is one of the most important factors to produce enantioselectivity, we changed the solvent and observed ee% for the first time (see in Table 3.2). It seemed the reaction working in toluene (entry 2) could give best reaction in these conditions.

Table 3.2 Screening of solvent ^a

Entry	Temp (°C)	Solvent	yield (%) ^b	ee (%) ^c
1	0	Et ₂ O	42	17
2	0	Tol	41	32
3	0	CPME	35	19
4	-20	CPME	-	30

^aReaction conditions: substrate (0.05 mmol), H₂O₂ (0.0525 mmol, 1.05 equiv, 35%w/w), **5a** (0.001 mmol, 2.0 mol%), Na₂WO₄ (0.0025 mmol, 5.0 mol%), 0.5 mL solvent. ^bYield of isolated product. ^cDetermined by HPLC analysis on a chiral stationary phase.

With current condition in hand, we tried to apply it in different substrates. Among these structures, we found sulphide with aromatic tetrazole ring could be oxidized to corresponding sulfoxide in 27% yield, 30% ee (Table 3.3, entry 3).

Table 3.3 Exploration of heterocyclic compounds scope ^a

Entry	Het	yield (%) ^b	ee (%) ^c
1		Trace	8
2		17	8
3		27	30
4		Trace	6

^aReaction conditions: substrate (0.05 mmol), H₂O₂ (0.0525 mmol, 1.05 equiv, 35%w/w), **5a** (0.001 mmol, 2.0 mol%), Na₂WO₄ (0.0025 mmol, 5.0 mol%), 0.5 mL toluene at 0°C. ^bYield of isolated product. ^cDetermined by HPLC analysis on a chiral stationary phase.

Thus, we used the tetrazole compound as model reactant and put extra additive to improve reaction. Some Brønsted acid and Lewis acid were examined. Obviously, the

enantioselectivities under the reaction conditions with weak Brønsted acid were improved a lot (Table 3.4, entry 1-4). Under the basic and neutral conditions, the reactions were inhibited (entry 5-8).

Table 3.4 Screening of additive ^a

Entry	Additive (10 mol%)	Solvent	yield (%) ^b	ee (%) ^c
1	NaH ₂ PO ₄	Tol	60	42
2	KH ₂ PO ₄	Tol	60	41
3	LiH ₂ PO ₄	Tol	66	42
4	LiH ₂ PO ₄	<i>p</i> -CF ₃ Tol	74	38
5	K ₂ HPO ₄	Tol	Trace	-
6	LiOAc	Tol	N.R	-
7	LiCl	Tol	N.R	-
8	LiBr	Tol	N.R	-

^aReaction conditions: substrate (0.05 mmol), H₂O₂ (0.0525 mmol, 1.05 equiv, 35%w/w), **5a** (0.001 mmol, 2.0 mol%), Na₂WO₄ (0.0025 mmol, 5.0 mol%), additive (0.005 mmol, 10.0 mol%), 0.5 mL solvent at room temperature. ^bYield of isolated product. ^cDetermined by HPLC analysis on a chiral stationary phase.

Because the condition was changed a lot after deciding to use additive, the tungstate should be rescreened on the same reaction model (Table 3.5). The results showed (NH₄)₂WO₄ might be the best choice (entry 2). Yield of product reached to 85%, and ee% reached to 56% at 0 °C. Furthermore, we lowered the temperature to -20 °C (entry 4) and -40 °C (entry 5). Yield of reaction reached as high as 98%, and ee% was more than moderate.

Table 3.5 Further screening of tungstate in presence of additive ^a

Entry	Temp (°C)	M _x (WO ₄) _y (5 mol%)	Time (h)	yield (%) ^b	ee (%) ^c
1	0	Na ₂ WO ₄	24	28	40
2	0	(NH ₄) ₂ WO ₄	48	85	56
3	0	Bi ₂ (WO ₄) ₃	48	70	17
4	-20	(NH ₄) ₂ WO ₄	72	83	62
5	-40	(NH ₄) ₂ WO ₄	90	98	70

^aReaction conditions: substrate (0.05 mmol), H₂O₂ (0.0525 mmol, 1.05 equiv, 35%w/w), **5a** (0.001 mmol, 2.0 mol%), M_x(WO₄)_y (0.0025 mmol, 5.0 mol%), LiH₂PO₄ (0.005 mmol, 10.0 mol%), 0.5 mL toluene at room temperature. ^bYield of isolated product. ^cDetermined by HPLC analysis on a chiral stationary phase.

Based on the current condition, sulphide with *N*-methylbenzimidazole ring was oxidized. It was very disappointing that only trace amount of product was obtained (Table 3.6, entry 1). Hence, the solvent was switched to ether. Fortunately, unexpected results were obtained in diisopropyl ether (entry 2) and diethyl ether (entry 3).

Table 3.6 Condition test on drug analogues ^a

Entry	Solvent	yield (%) ^b	ee (%) ^c
1	Tol	trace	18
2	<i>i</i> -Pr ₂ O	60	88
3	Et ₂ O	75	90

^aReaction conditions: substrate (0.05 mmol), H₂O₂ (0.0525 mmol, 1.05 equiv, 35%w/w), **5a** (0.001 mmol, 2.0 mol%), (NH₄)₂WO₄ (0.0025 mmol, 5.0 mol%), LiH₂PO₄ (0.005 mmol, 10.0 mol%), 0.5 mL solvent at 0°C. ^bYield of isolated product. ^cDetermined by HPLC analysis on a chiral stationary phase.

After a period of condition tuning, we concluded all factors and applied them in one substrate **26a** to determine the final condition. The systematic and general information was as shown in Table 3.7 below.

Table 3.7 Final optimization of the reaction conditions

Entry	BG	$M_x(WO_4)_y$	Additive	Solvent	yield (%) ^b	ee (%) ^c
1 ^d	(S,S)- 5a	--	--	Et ₂ O	N.R.	N.A.
2	(S,S)- 5a	Na ₂ WO ₄	--	Et ₂ O	20	-5
3	(S,S)- 5a	Na ₂ WO ₄	NaH ₂ PO ₄	Et ₂ O	36	20
4	(S,S)- 5a	K ₂ WO ₄	NaH ₂ PO ₄	Et ₂ O	18	-2
5	(S,S)- 5a	(NH ₄) ₂ WO ₄	NaH ₂ PO ₄	Et ₂ O	48	42
6	(S,S)- 5a	Ag₂WO₄	NaH₂PO₄	Et₂O	83	88
7	(R,R)- 5a	Ag₂WO₄	NaH₂PO₄	Et₂O	90	-89
8	(S,S)- 5a	Ag ₂ WO ₄	LiH ₂ PO ₄	Et ₂ O	70	90
9	(S,S)- 5a	Ag ₂ WO ₄	KH ₂ PO ₄	Et ₂ O	83	84
10	(S,S)- 5a	Ag ₂ WO ₄	NH ₄ H ₂ PO ₄	Et ₂ O	82	82
11	(S,S)- 5a	Ag ₂ WO ₄	NaHSO ₄	Et ₂ O	52	80
12	(S,S)- 5a	Ag ₂ WO ₄	NaH ₂ PO ₄	Tol	60	74
13	(S,S)- 5a	Ag ₂ WO ₄	NaH ₂ PO ₄	DCM	68	20
14	(S,S)- 5a	Ag ₂ WO ₄ ^e	NaH ₂ PO ₄	Et ₂ O	55	50
15	(S,S)- 5a	Ag₂WO₄^e	NaH₂PO₄	<i>i</i>-Pr₂O	96	92
16	(S,S)- 5b	Ag ₂ WO ₄ ^e	NaH ₂ PO ₄	<i>i</i> -Pr ₂ O	63	50
17	(S,S)- 5c	Ag ₂ WO ₄ ^e	NaH ₂ PO ₄	<i>i</i> -Pr ₂ O	52	32
18	(S,S)- 5d	Ag ₂ WO ₄ ^e	NaH ₂ PO ₄	<i>i</i> -Pr ₂ O	84	8
19	(S,S)- 5e	Ag ₂ WO ₄ ^e	NaH ₂ PO ₄	<i>i</i> -Pr ₂ O	65	63
20	(S,S)- 5a	--	NaH ₂ PO ₄	<i>i</i> -Pr ₂ O	19	N.A.

^aReaction conditions: **26a** (0.05 mmol), H₂O₂ (0.0525 mmol, 1.05 equiv, 35%w/w), **5** (0.001 mmol, 2.0 mol%), M_x(WO₄)_y (0.0025 mmol, 5.0 mol%), 1.0 mL Et₂O at 0 °C. ^bYield of isolated product. ^cDetermined by HPLC analysis on a chiral stationary phase. ^dNo reaction was also observed at room temperature. ^e2.0 mol% of Ag₂WO₄ was used.

At the outset, benzimidazole-derived benzyl sulfide **26a** was chosen as the model substrate to investigate the reaction conditions (Table 3.7). In the presence of 2.0 mol% of bisguanidinium (*S,S*)-**5a** with Et₂O as solvent, no reaction was found when only H₂O₂ was used (Table 3.7, entry 1); indicating that (*S,S*)-**5a** alone cannot catalyze the reaction. When 5.0 mol% of Na₂WO₄ was added, the reaction gave sulfoxide **27a** in poor yield and low enantioselectivity (entry 2). When 10 mol% NaH₂PO₄ was added, the yield of sulfoxide **27a** improved significantly to 36% and its *ee* value improved to 20% (entry 3). When Na₂HPO₄ and Na₃PO₄ were used instead, the reactions were inhibited. Next, a range of commercially available tungstate salts, such as K₂WO₄, (NH₄)₂WO₄ and Ag₂WO₄ were evaluated (entries 4-6). Sulfoxide **27a** was obtained in 83% yield with 88% *ee* value when Ag₂WO₄ was used (entry 6). We assumed that Ag⁺ forced the Cl⁻ to be exchanged from **BG**, forming precipitate of AgCl, which decreased the competition between the counter ions of **BG**. Moreover, *ent*-**5a** afforded the antipode with similar efficiency and enantioselectivity (entry 7). Various additives were tested, and both yield and *ee*% were compared to Na₂HPO₄ (entry 8-11). Above all, solvent was examined (entry 6,12,13). When the catalyst loading of Ag₂WO₄ was decreased to 2.0 mol%, it is necessary to change the solvent to diisopropyl ether to provide the best results (entry 15). the best solvent was Et₂O in previous conclusions, hence, the Et₂O was re-examined under the same condition (entry 14). Other bisguanidiniums (*S,S*)-**5b-5e** featuring different benzyl groups was unable to improve the results obtained with (*S,S*)-**5a** (entries 16-19). We also confirm that NaH₂PO₄ in the absence of Ag₂WO₄ did not promote the sulfoxidation reaction (entry 20).

With the optimized reaction conditions in hand, the substrate scope of benzimidazole-derived sulfides was examined (Scheme 3.1, **27a-27i**). The benzimidazole group does not seem

to act as a ligand and inhibit the reaction. Both electron donating and electron withdrawing substitutions on the benzyl group worked well, affording the corresponding sulfoxidation products in good to excellent yields with good levels of enantioselectivities. The oxidation ability of the catalyst is able to override even highly electron withdrawing group such as pentafluorobenzyl (**27g**). Besides benzyl groups, simple alkyl groups or esters are also tolerated in this reaction (**27h-1**). Other heterocyclic systems such as benzothiazole (**27m-r**), pyridine (**27s-t**) and thiophene (**27u**) also worked well providing products with excellent *ee* values. However, thiophene heterocyclic sulfides gave lower yields with significant amount of sulfone detected. We were also able to scale the reaction to gram scale (3.5 mmol) to give **27q** in 91% yield and 92% *ee*. The established strategy was also successfully applied to the preparation of (*S*)-Lansoprazole **29**, a commercial proton-pump inhibitor (Scheme 3.2).

Reactions were carried out on 0.2 mmol scale in 4.0 mL solvent for 36 hours unless otherwise noted; yield values refer to isolated yields after purification and *ee* was determined by chiral HPLC. ^a 5.0 mol% of Ag₂WO₄ was used.

^b Et₂O as the solvent. ^c 8.0 mL *i*Pr₂O was used.

Scheme 3.1 Enantioselective sulfoxidation of heterocyclic sulfides.

Scheme 3.2 Enantioselective synthesis of (*S*)-Lansoprazole.

Simple phenyl substituent sulfoxides were also created (Table 3.8, **6a-6d**). Due to the activity differences existing among the substrates, the concentration and solvent can influence the results. When using *i*Pr₂O as the sole solvent, the conventional sulphide was over-oxidized to sulfone. In Et₂O, the conversion was limited. In DMC (dimethyl carbonate), it terminated in 4 hours under 5 °C, while only moderate yield and ee were obtained. Surprisingly, when the mixed solvent system was examined, both chemoselectivity and enantioselectivity increased.

Table 3.8 Other conventional substrates of sulphides^[a]

[a] Reactions were carried out on 0.2 mmol scale in a solvent mixture of DMC (4.0 mL)/Et₂O (4.0 mL). (DMC=dimethyl carbonate) [b] Reactions were carried out in a solvent mixture of DMC (4.0 mL)/*i*Pr₂O (4.0 mL).

3.2.2 Mechanism study

During optimization of the reaction conditions, we realized that the ratio of Ag_2WO_4 to NaH_2PO_4 is crucial in obtaining good yields and enantioselectivities (Scheme 3.3). The most significant improvement was achieved when the ratio of phosphate to tungstate reached 1:2. As the amount of phosphate in this current methodology is in excess over tungstate, we speculated that the Ishii-Venturello catalyst, $[\text{PO}_4\{\text{WO}(\text{O}_2)_2\}_4]^{3-}$, is not the active catalyst in this methodology. When we replaced the $\text{Ag}_2\text{WO}_4/\text{NaH}_2\text{PO}_4$ with $\text{H}_3\text{PW}_{12}\text{O}_{40}$ (Keggin's reagent) as in Ishii's protocol, the reaction provided sulfoxides in 40% yield and 30% *ee*.

Scheme 3.3 Influence of phosphate loading.

Ligand coordination or substitution has been previously shown to be an important factor that can influence the catalytic activities of peroxotungstates. Under the current experimental condition, monomeric and oligomeric dihydroxide species **i** (Figure 3.3) should exist and in the presence of phosphate additive, form substituted phosphate species **ii-iv**.²¹⁻²³ These complexes assume distorted pentagonal bipyramid geometry and obey the 18-electron rule. As a result, coordination of three or more phosphates to the tungstate center can be considered to be unlikely. It is also important to note that due to the short O-O bond distances (1.45 to 1.47 Å)²⁴ in the peroxo group, the oxygen atoms will most likely lie in the equatorial plane, instead of occupying both axial and equatorial positions in the complex. Based on these premises, the four possible configurations of substituted peroxotungstate species are presented (Figure 3.3).

Figure 3.3 Four possible peroxotungstate species.

Raman spectra was computed for candidate structure **i-iv** by performing vibrational frequency analysis on stationary points optimized at the B3LYP/B1 theory level in gas phase. The result is shown in Figure 3.4. The peak at 1014 cm^{-1} in experimental Raman spectra was found to be the peak with the highest intensity, which corresponds to the W=O bond stretching vibrations. Computed Raman spectra showed this peak at 920-1000 cm^{-1} region. Additionally, characteristic bands from W(O₂) group appear in 500-600 cm^{-1} region, while bands above 1000 cm^{-1} generally correspond to vibrational modes from phosphate group.

Figure 3.4 Predicted Raman spectra of active species candidates, computed at B3LYP/B1 theory level for (A) dihydroxide **i**, (B) equatorial monophosphate **ii**, (C) axial monophosphate **iii**, (D) diphosphate **iv**.

	P=O	W=O	O-O	P-O-H	P-O-H	W(O ₂)
Calc.	1014	1001	940	840, 802	713	643 _{asym} , 564 _{sym}
Expt. ^{a,b}	1042	1014	943	872, 825	711	631 _{asym} , 564 _{sym}

^a Preparation: In a 4mL sample vial, BG-1 (0.01 mmol, 1.0 equiv), tungstate oxide (0.01 mmol, 1.0 equiv), phosphate monobasic (0.05 mmol, 5.0 equiv), hydrogen peroxide (0.1 mmol, 10.0 equiv, 35%, w/w) and diethyl ether in a proper amount were added at room temperature. Keep stirring for 6 hours, and filtrate the precipitate. Blow drying the mixture, then remove water on vacuo. ^b Raman setting: 2mW, 532 laser power, 30 seconds.

Figure 3.5 Experimental Raman spectrum and vibration diagram of $[\mathbf{P2W}]^{2-}$,

Raman spectra of the active species were obtained and compared with predicted Raman spectra of the four possible intermediates. Computed Raman spectra were obtained by performing vibrational frequency analysis on stationary points optimized at the B3LYP/B1 level of theory in gas phase, where B1 is a combination of LANL2DZ effective core potential basis set for W and the 6-31g* basis set for remaining atoms. A peak was observed experimentally at 711 cm^{-1} , which corresponds to the twisting of P-O-H group in the phosphate ligand (Figure 3.5). This same peak was found only in the computed spectra of $[\mathbf{P2W}]^{2-}$ (713 cm^{-1}).

Figure 3.6 Vector representations of the vibrational mode corresponding to the band at 713 cm^{-1} in the computed Raman spectra of diphosphate **4**. Dotted lines represent hydrogen bond interactions.

A more thorough analysis of the $[\text{P2W}]^{2-}$ structures revealed that intramolecular hydrogen bond interaction between the two phosphate ligands is important for this peak (Figure 3.6); absence of such interaction will shift the vibrational frequency towards 800 cm^{-1} . We thus propose that the active anion of this enantioselective sulfoxidation is diphosphatobis(oxotungstate), $[\{\text{PO}_2(\text{OH})_2\}_2\{\text{WO}(\text{O}_2)_2\}]^{2-}$.

Figure 3.7 Representation of $[\text{BG}]^{2+}[\text{P2W}]^{2-}$ ion pair.

(a) ONIOM optimization result, color coded as grey: C, blue: N, white: H, orange: P, red: O. (b) Atoms in close distance to $[\text{P2W}]^{2-}$ core is highlighted. (c) Surface of $[\text{BG}]^{2+}$ structure is displayed.

Preliminary computational studies of the complete $[\text{BG}]^{2+}[\text{P2W}]^{2-}$ structure using two-layer ONIOM (QM:QM')² method revealed a stable ion-pair interaction, where $[\text{P2W}]^{2-}$ is buried in the chiral cavity of $[\text{BG}]^{2+}$ (Figure 3.7).

Figure 3.8 Representation of $[\text{BG}]^{2+}[\text{P2W}]^{2-}$ ion-pair from ONIOM optimization result, color-coded as grey: C, blue: N, white: H, orange: P, red: O, pink: W. NCI surface of BG1 structure is displayed: green indicates attractive non-covalent interactions.

This configuration results in only one of the peroxo-oxygen (marked as **Oc** in Figure 3.8) being exposed, leaving it as the only possible reaction site. This will restrict the direction of approach of the sulfide, thereby providing fertile condition for an enantioselective reaction. We thus propose a simple working model, which includes the initial formation of $[\text{P2W}]^{2-}$ in the aqueous phase through the interactions of silver tungstate, phosphate and hydrogen peroxide (Figure 3.9). The formation of the ion-pair $[\text{BG}]^{2+}[\text{P2W}]^{2-}$ in the organic phase is facilitated by $[\text{BG}]^{2+}$. After oxidation, $[\text{P2W}]^{2-}$ is regenerated in the aqueous phase by H_2O_2 .

Figure 3.9 Working Model.

3.3 Summary

In summary, we report the first enantioselective tungstate-catalyzed oxidation reaction. Especially, with the aid of a chiral bisguanidinium diphosphatobisperoxotungstate ion pairing catalyst, high enantioselectivities were achieved for a variety of drug-like heterocyclic sulfides under mild condition with H_2O_2 , a cheap and environmentally friendly oxidant. Except for Kagan-Sharpless Ti-complex catalysis, heterocyclic sulfides were less investigated in the research history of enantioselective sulfoxidations. In addition, the ion-pair catalysis was also applied to conventional sulfides successfully. With the advantage of low-catalyst loading and large-scale producing, synthetic utility was demonstrated through the preparation of (*S*)-Lansoprazole, a commercial proton-pump inhibitor. The active ion-pair catalyst was identified to be bisguanidinium diphosphatobisperoxotungstate using Raman spectroscopy and computational studies.

3.4 Experimental

3.4.1 Experimental procedure

Scheme 3.4 Preparation and characterization of bisguanidinium catalysts (**5a** as the representative example)

1,4-Bis((4*S*,5*S*)-1,3-bis(3,5-di-*tert*-butylbenzyl)-4,5-diphenylimidazolidin-2-

ylidene)piperazine-1,4-diium chloride (5a**):** Thiourea **32** was prepared according to literature procedure¹. A 25 mL RBF was charged with a solution of thiourea (1.59 g, 2.41 mmol, 1.0 equiv) in toluene (8 mL) with a condenser under N₂ atmosphere. (COCl)₂ (1.66 mL, 19.3 mmol, 8.0 equiv) was added via syringe in one portion. The mixture was heated to 90 °C for about 12 h, and then refluxed for 1 h. Toluene was removed under reduced pressure and solid imidazoline salt **33** was obtained directly for the next step without any purification. The imidazoline salt was dissolved in dry MeCN (2 mL) under nitrogen atmosphere, and then piperazine (62 mg, 0.72 mmol, 0.3 equiv) was added, followed by the addition of Et₃N (1 mL, 7.23 mmol, 3.0 equiv). Then the whole solution was heated to reflux for 12 h and cooled to rt. Add 1M HCl (20 mL) to the reaction solution and the mixture was extracted by CH₂Cl₂ (20 mL × 3). Solvent was removed under reduced pressure and bis-guanidinium salt **5a** was obtained by flash chromatography (silica gel, DCM-Methanol 100:1-30:1), as a beige powder, 695 mg, 68% yield. **5a**²⁺: ¹H NMR (400 MHz, CDCl₃) δ 7.30 (dd, *J* = 5.0, 1.5 Hz, 12H), 7.20 (s, 4H), 7.05 (dd, *J* = 6.5, 2.8 Hz, 8H), 6.96 (d, *J* = 1.5 Hz, 8H), 5.19 (d, *J* = 14.7 Hz, 4H), 4.82 (d, *J* = 14.7 Hz, 4H), 4.73 (d, *J* = 9.5 Hz, 4H), 4.48 (d, *J* = 9.5 Hz, 4H), 4.32 (s, 1H), 1.14 (s, 72H); ¹³C NMR (100 MHz, CDCl₃) δ 162.68, 151.30, 137.67, 131.89, 129.58, 129.16, 126.51, 123.37, 122.26, 70.39, 54.52, 48.99, 34.69, 31.37, 31.28; HRMS (ESI) calc. for C₉₄H₁₂₄Cl₂N₆ m/z [M-2Cl]²⁺: 668.4944; found: 668.4941.

Scheme 3.5 Preparation of **5a** catalyzed sulfoxidation of heterocyclic sulfides

In a 4 mL sample vial, sulfides **26** (0.2 mmol, 1.0 equiv), bisguanidium chloride (0.004 mmol, 0.02 equiv), silver tungstate oxide (0.004 mmol, 0.02 equiv), sodium phosphate monobasic (0.02 mmol, 0.1 equiv) and solvent were added. Then lower the solution to the presupposed temperature. After stabilizing, H₂O₂ (1.05 equiv, 35% w/w) was injected in one portion into the system. The mixture was stirred for 24 hours to 48 hours, and the termination of reaction was monitored by TLC. The resulting suspension was quenched by saturated Na₂S₂O₃ (sat.). EtOAc (0.5 mL×3) was used for extraction, and the organic layers was combined and dried over anhydrous Na₂SO₄. The organic solvent was removed in rotary evaporator (the water-bathing temperature is under 38 °C), and the residues was purified by chromatography on silica gel to afford the desired products **27**.

Scheme 3.6 Preparation of **5a** catalyzed sulfoxidation of phenyl sulfides

In a 10 mL sample vial, sulfides **30** (0.2 mmol, 1.0 equiv), bisguanidium chloride (0.004 mmol, 0.02 equiv), silver tungstate oxide (0.004 mmol, 0.02 equiv), ammonium phosphate monobasic (0.02 mmol, 0.1 equiv) and 8mL mixed solvent were added. The solvent mixture was consisted of 4 mL dimethyl carbonate and 4 mL diethyl ether (diisopropyl ether in **5a**). Then lower the solution to the presupposed temperature. After stabilizing, H₂O₂ (1.05 equiv, 3% w/w) was injected in one portion into the system. The mixture was stirred for 18hours, and the termination of reaction was monitored by TLC. The resulting suspension was quenched by saturated

$\text{Na}_2\text{S}_2\text{O}_3$ (sat.). EtOAc (0.5 mL $\times$ 3) was used for extraction, and the organic layers was combined and dried over anhydrous Na_2SO_4 . The organic solvent was removed in rotary evaporator (the water-bathing temperature is under 38 °C), and the residues was purified by chromatography on silica gel to afford the desired products **31**.

Scheme 3.7 Application of Lansoprazole

In a 25 mL RBF, sulfides **28** (0.2 mmol, 1.0 equiv), bisguanidium chloride **5a** (0.004 mmol, 0.02 equiv), silver tungstate oxide (0.004 mmol, 0.02 equiv), ammonium phosphate monobasic (0.02 mmol, 0.1 equiv) and 8 mL solvent were added. Then lower the solution to the presupposed temperature in a constant incubator. After stabilizing, H_2O_2 (1.05 equiv, 3% w/w) was injected in one portion into the system. The mixture was stirred for 48hours, and the termination of reaction was monitored by TLC. The resulting suspension was quenched by saturated $\text{Na}_2\text{S}_2\text{O}_3$ (sat.). Use NaHCO_3 to wash, and then EtOAc (0.5 mL $\times$ 3) was used for extraction, and the organic layers was combined and dried over anhydrous Na_2SO_4 . The organic solvent was removed in rotary evaporator (the water-bathing temperature is under 38 °C), and the residues was purified by chromatography on silica gel to afford the desired products **29**.

3.4.2 Characterization of asymmetric products

(S)-2-(Benzylsulfinyl)-1-methyl-1H-benzo[d]imidazole (27a): 96% yield; white solid; ^1H NMR (400 MHz, CDCl_3) δ 7.87–7.82 (m, 1H), 7.38–7.35 (m, 2H), 7.32–7.26 (m, 2H), 7.21 (td, $J = 10.4, 4.7$ Hz, 2H), 7.03 (dd, 2H), 4.64 (d, $J = 12.9$ Hz, 1H), 4.50 (d, $J = 12.9$ Hz, 1H), 3.45 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 150.01, 141.54, 136.47, 130.61, 128.89, 128.77, 124.68, 123.77, 120.59, 109.83, 60.96, 29.97; HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{14}\text{N}_2\text{OS}$ m/z $[\text{M}+\text{H}]^+$: 271.0905; found: 271.0904; $[\alpha]_D^{22} = -29.16$ (c 3.8, CH_2Cl_2); HPLC analysis: Chiralcel OJ-H (Hex/IPA = 70/30, 1.0 mL/min, 254 nm, 22°C), 17.1, 29.0 (major) min, 92% ee.

(S)-1-Methyl-2-((4-methylbenzyl)sulfinyl)-1H-benzo[d]imidazole (27b): 94% yield; white solid; ^1H NMR (400 MHz, CDCl_3) δ 7.89–7.78 (m, 1H), 7.38–7.33 (m, 2H), 7.32–7.27 (m, 1H), 7.03 (d, $J = 7.9$ Hz, 2H), 6.93 (d, $J = 8.0$ Hz, 2H), 4.62 (d, $J = 12.9$ Hz, 1H), 4.45 (d, $J = 12.9$ Hz, 1H), 3.49 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 150.38, 142.01, 138.80, 136.58, 130.50, 129.45, 125.73, 124.51, 123.53, 120.78, 109.78, 60.62, 30.03, 21.27; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{16}\text{N}_2\text{OS}$ m/z $[\text{M}+\text{H}]^+$: 285.1062; found: 285.1056; $[\alpha]_D^{22} = -29.41$ (c 2.2, CH_2Cl_2); HPLC analysis: Daicel Corporation IB3 (Hex/IPA = 70/30, 1.0 mL/min, 254 nm, 22°C), 8.4, 15.4 (major) min, 94% ee.

(S)-2-((4-Chlorobenzyl)sulfinyl)-1-methyl-1H-benzo[d]imidazole (27c): 81% yield; white solid; ^1H NMR (400 MHz, CDCl_3) δ 7.82 (dd, $J = 8.0, 6.6$ Hz, 1H), 7.36 (qd, $J = 12.8, 8.0$ Hz, 3H), 7.22 (d, $J = 8.3$ Hz, 2H), 7.01 (d, $J = 8.3$ Hz, 2H), 4.63 (d, $J = 13.0$ Hz, 1H), 4.47 (d, $J = 13.0$ Hz, 1H), 3.59 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 149.73, 141.95, 136.67, 135.11,

131.96, 128.97, 127.55, 124.75, 123.74, 120.80, 109.88, 59.90, 30.23; HRMS (ESI) calcd for $C_{15}H_{13}ClN_2OS$ m/z $[M+H]^+$: 305.0515; found: 305.0518; $[\alpha]_D^{22} = -41.21$ (c 3.2, CH_2Cl_2); HPLC analysis: Daicel Corporation IB3 (Hex/IPA = 70/30, 1.0 mL/min, 254 nm, 22°C), 9.3, 30.4 (major) min, 97% ee.

(S)-2-((4-Fluorobenzyl)sulfinyl)-1-methyl-1H-benzo[d]imidazole (27d): 78% yield; white solid; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87–7.78 (m, 1H), 7.43–7.29 (m, 3H), 7.04 (dd, $J = 8.4, 5.5$ Hz, 2H), 6.91 (t, $J = 8.6$ Hz, 2H), 4.60 (dd, $J = 30.8, 13.2$ Hz, 2H), 3.56 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.47, 162.00, 149.54, 140.37, 136.17, 132.38, 132.30, 125.06, 124.75, 124.71, 124.30, 120.10, 115.91, 115.70, 110.00, 59.95, 30.23; HRMS (ESI) calcd for $C_{15}H_{13}FN_2OS$ m/z $[M+H]^+$: 289.0811; found: 289.0808; $[\alpha]_D^{22} = -33.38$ (c 4.3, CH_2Cl_2); HPLC analysis: Daicel Corporation IB3 (Hex/IPA = 70/30, 1.0 mL/min, 254 nm, 22°C), 8.9, 29.7 (major) min, 88% ee.

(S)-1-Methyl-2-((4-nitrobenzyl)sulfinyl)-1H-benzo[d]imidazole (27e): 74% yield; yellow solid; ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, $J = 8.3$ Hz, 1H), 7.82 (d, $J = 7.4$ Hz, 1H), 7.60–7.27 (m, 2H), 4.72 (dd, $J = 42.3, 12.9$ Hz, 1H), 3.69 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.17, 148.18, 141.87, 136.73, 136.60, 131.66, 124.99, 123.91, 123.72, 120.84, 109.96, 59.48, 30.46; HRMS (ESI) calcd for $C_{15}H_{13}N_3O_3S$ m/z $[M+H]^+$: 316.0756; found: 316.0761; $[\alpha]_D^{22} = -$

213.88 (*c* 2.3, CH₂Cl₂); HPLC analysis: Daicel Corporation IA3 (Hex/IPA = 70/30, 1.0 mL/min, 254 nm, 22°C), 14.3, 25.0 (major) min, 88% ee.

(S)-1-Methyl-2-((naphthalen-2-ylmethyl)sulfinyl)-1H-benzo[d]imidazole (27f): 95% yield; white solid; ¹H NMR (400 MHz, CDCl₃) δ 7.92–7.85 (m, 1H), 7.77 (d, *J* = 7.8 Hz, 1H), 7.66 (d, *J* = 8.4 Hz, 1H), 7.62 (dd, 1H), 7.58 (s, 1H), 7.50–7.34 (m, 4H), 7.23–7.17 (m, 1H), 7.06 (dd, *J* = 8.4, 1.7 Hz, 1H), 4.82 (d, *J* = 12.9 Hz, 1H), 4.69 (d, *J* = 12.9 Hz, 1H), 3.35 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 149.98, 141.18, 136.34, 133.09, 133.08, 130.23, 128.35, 127.90, 127.65, 127.51, 126.67, 126.54, 126.18, 124.70, 123.83, 120.40, 109.79, 61.21, 30.00; HRMS (ESI) calcd for C₁₉H₁₆N₂OS *m/z* [M+H]⁺: 321.1062; found: 321.1062; [α]_D²² = -222.58 (*c* 2.2, CH₂Cl₂); HPLC analysis: Daicel Corporation IB3 (Hex/IPA = 70/30, 1.0 mL/min, 254 nm, 22°C), 10.7, 38.0 (major) min, 99% ee.

(S)-1-Methyl-2-(((perfluorophenyl)methyl)sulfinyl)-1H-benzo[d]imidazole (27g): 84% yield; white solid; ¹H NMR (400 MHz, CDCl₃) δ 7.80 (d, *J* = 8.1 Hz, 1H), 7.48–7.33 (m, 3H), 4.88 (d, *J* = 13.2 Hz, 1H), 4.71 (d, *J* = 13.1 Hz, 1H), 4.09 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 149.60, 141.96, 137.04, 125.30, 123.95, 121.11, 109.99, 47.47, 30.92; HRMS (ESI) calcd for C₁₅H₉F₅N₂OS *m/z* [M+H]⁺: 361.0434; found: 361.0435; [α]_D²² = -141.82 (*c* 2.2, CH₂Cl₂); HPLC analysis: Daicel Corporation IB3 (Hex/IPA = 70/30, 1.0 mL/min, 254 nm, 22°C), 10.2, 15.6 (major) min, 92% ee.

(S)-2-((2-(1,3-Dioxolan-2-yl)ethyl)sulfinyl)-1-methyl-1H-benzo[d]imidazole (27h): 72% yield; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ 7.81 (d, $J = 7.9$ Hz, 1H), 7.45–7.36 (m, 2H), 7.34 (ddd, $J = 8.3, 6.6, 1.8$ Hz, 1H), 5.04 (t, $J = 3.9$ Hz, 1H), 4.11 (s, 3H), 4.01–3.92 (m, 2H), 3.89–3.80 (m, 2H), 3.59 (ddd, $J = 8.3, 6.8, 1.8$ Hz, 2H), 2.28 (dddd, $J = 14.8, 8.0, 6.9, 4.0$ Hz, 1H), 2.14 (dddd, $J = 9.9, 7.5, 6.6, 3.5$ Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 151.13, 141.62, 136.73, 124.84, 123.71, 120.85, 109.98, 102.46, 65.26, 47.86, 31.01, 26.58; HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{16}\text{N}_2\text{O}_3\text{S}$ m/z $[\text{M}+\text{H}]^+$: 281.0960; found: 281.0959; $[\alpha]_D^{22} = +8.45$ (c 0.9, CHCl_3); HPLC analysis: Daicel Corporation IB3 (Hex/IPA = 70/30, 1.0 mL/min, 254 nm, 22°C), 15.1, 19.3 (major) min, 95% ee.

(S)-6-((1-Methyl-1H-benzo[d]imidazol-2-yl)sulfinyl)hexanenitrile (27i): 71% yield; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ 7.84–7.78 (m, 1H), 7.47–7.39 (m, 2H), 7.37 (ddd, 1H), 4.14 (s, 3H), 3.57 (ddd, $J = 13.2, 9.4, 5.6$ Hz, 1H), 3.45 (ddd, $J = 13.2, 9.5, 6.3$ Hz, 1H), 2.36 (t, $J = 6.8$ Hz, 2H), 2.05–1.81 (m, 2H), 1.79–1.63 (m, 4H); ^{13}C NMR (101 MHz, CDCl_3) δ 150.80, 141.27, 136.74, 125.02, 123.96, 120.68, 119.40, 110.09, 52.84, 31.13, 27.71, 25.06, 21.66, 17.05; HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{17}\text{N}_3\text{OS}$ m/z $[\text{M}+\text{Na}]^+$: 298.0990; found: 298.0996; $[\alpha]_D^{22} = +7.71$ (c 0.7, CHCl_3); HPLC analysis: Daicel Corporation IB3 (Hex/IPA = 70/30, 1.0 mL/min, 254 nm, 22°C), 24.6, 41.0 (major) min, 82% ee.

(S)-Methyl-2-((1-methyl-1*H*-benzo[*d*]imidazol-2-yl)sulfinyl)acetate (27j): 85% yield; white solid; ^1H NMR (400 MHz, CDCl_3) δ 7.84–7.77 (m, 1H), 7.46–7.39 (m, 2H), 7.36 (ddd, $J = 8.3, 6.4, 2.0$ Hz, 1H), 4.69 (d, $J = 15.1$ Hz, 1H), 4.44 (d, $J = 15.1$ Hz, 1H), 4.11 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 165.45, 165.43, 150.83, 141.38, 136.67, 125.25, 125.18, 123.97, 121.01, 120.92, 110.20, 57.21, 53.12, 31.04; HRMS (ESI) calcd for $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}_3\text{S}$ m/z $[\text{M}+\text{H}]^+$: 253.0647; found: 253.0645; $[\alpha]_D^{22} = +5.25$ (c 1.2, CH_2Cl_2); HPLC analysis: Daicel Corporation IB3 (Hex/IPA = 70/30, 1.0 mL/min, 254 nm, 22°C), 15.6, 22.0 (major) min, 89% ee.

(S)-Ethyl-2-((1-methyl-1*H*-benzo[*d*]imidazol-2-yl)sulfinyl)acetate (27k): 92% yield; white solid; ^1H NMR (400 MHz, CDCl_3) δ 7.80 (d, $J = 8.0$ Hz, 1H), 7.46–7.38 (m, 2H), 7.35 (ddd, $J = 8.2, 6.5, 1.9$ Hz, 1H), 4.65 (t, $J = 14.3$ Hz, 1H), 4.41 (d, $J = 15.0$ Hz, 1H), 4.18 (q, $J = 7.1$ Hz, 2H), 4.10 (s, 3H), 1.21 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 164.92, 150.95, 141.46, 136.66, 125.11, 123.89, 120.93, 110.16, 62.39, 57.45, 31.01, 14.05; HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}_3\text{S}$ m/z $[\text{M}+\text{H}]^+$: 267.0803; found: 267.0807; $[\alpha]_D^{22} = +4.62$ (c 1.2, CH_2Cl_2); HPLC analysis: Daicel Corporation IB3 (Hex/IPA = 70/30, 1.0 mL/min, 254 nm, 22°C), 11.4, 16.6 (major) min, 90% ee.

(S)-tert-Butyl-2-((1-methyl-1H-benzo[d]imidazol-2-yl)sulfinyl)acetate (27l): 86% yield; white solid; ^1H NMR (400 MHz, CDCl_3) δ 7.83–7.75 (m, 1H), 7.46–7.38 (m, 2H), 7.35 (ddd, J = 8.3, 6.5, 1.9 Hz, 1H), 4.57 (d, J = 14.8 Hz, 1H), 4.34 (d, J = 14.8 Hz, 1H), 4.11 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3) δ 163.93, 151.09, 141.45, 136.64, 125.06, 123.86, 120.89, 110.13, 83.86, 58.46, 31.01, 27.97; HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}_3\text{S}$ m/z $[\text{M}+\text{Na}]^+$: 317.0936; found: 317.0937; $[\alpha]_D^{22}$ = +13.78 (c 1.1, CHCl_3); HPLC analysis: Daicel Corporation IB3 (Hex/IPA = 70/30, 1.0 mL/min, 254 nm, 22°C), 7.3, 8.6 (major) min, 80% ee.

(S)-2-(Benzylsulfinyl)benzo[d]thiazole (27m): 78% yield; white solid; ^1H NMR (400 MHz, CDCl_3) δ 8.09 (d, J = 8.2 Hz, 1H), 7.93 (d, J = 8.1 Hz, 1H), 7.57 (t, J = 7.3 Hz, 1H), 7.47 (t, J = 7.6 Hz, 1H), 7.34–7.23 (m, 3H), 7.17 (d, J = 6.8 Hz, 2H), 4.51 (d, J = 13.1 Hz, 1H), 4.33 (d, J = 13.1 Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 176.99, 153.74, 136.04, 130.47, 128.75, 128.71, 128.39, 126.93, 126.16, 123.93, 122.26, 118.61, 62.85; HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{11}\text{NOS}_2$ m/z $[\text{M}+\text{H}]^+$: 274.0360; found: 274.0356; $[\alpha]_D^{22}$ = -47.99 (c 3.3, CH_2Cl_2); HPLC analysis: Chiralcel OD-H (Hex/IPA = 90/10, 1.0 mL/min, 254 nm, 22°C), 13.4 (major), 16.4 min, 93% ee.

(S)-2-((4-Methylbenzyl)sulfinyl)benzo[d]thiazole (27n): 70% yield; white solid; ^1H NMR (400 MHz, CDCl_3) δ 8.10 (d, J = 8.2 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.57 (ddd, J = 8.3, 7.3, 1.2 Hz, 1H), 7.48 (ddd, 1H), 7.15–7.01 (m, 4H), 4.48 (d, J = 13.1 Hz, 1H), 4.31 (d, J = 13.1 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 177.27, 153.84, 138.80, 136.13, 130.46,

129.56, 127.00, 126.22, 125.37, 124.00, 122.37, 62.82, 21.32; HRMS (ESI) calcd for $C_{15}H_{13}NOS_2$ m/z $[M+Na]^+$: 310.0336; found: 310.0333; $[\alpha]_D^{22} = -74.52$ (c 1.6, CH_2Cl_2); HPLC analysis: Chiralcel OD-H (Hex/IPA = 90/10, 1.0 mL/min, 254 nm, 22°C), 12.4 (major), 15.9 min, 90% ee.

(S)-2-((3-Methoxybenzyl)sulfinyl)benzo[d]thiazole (27o): 94% yield; white solid; ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, $J = 8.2$ Hz, 1H), 7.95 (d, $J = 8.1$ Hz, 1H), 7.57 (ddd, 1H), 7.48 (ddd, 1H), 7.18 (t, $J = 7.9$ Hz, 1H), 6.84 (dd, $J = 8.2, 2.3$ Hz, 1H), 6.79 (d, $J = 7.5$ Hz, 1H), 6.66 (d, $J = 1.8$ Hz, 1H), 4.48 (d, $J = 13.1$ Hz, 1H), 4.30 (d, $J = 13.1$ Hz, 1H), 3.60 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.19, 159.82, 153.84, 136.17, 129.86, 129.82, 127.05, 126.29, 124.00, 122.95, 122.39, 115.26, 115.21, 63.17, 55.18, 25.48; HRMS (ESI) calcd for $C_{15}H_{13}NO_2S_2$ m/z $[M+H]^+$: 304.0466; found: 304.0467; $[\alpha]_D^{22} = -59.08$ (c 3.1, CH_2Cl_2); HPLC analysis: Daicel Corporation IB3 (Hex/IPA = 70/30, 1.0 mL/min, 254 nm, 22°C), 7.3 (major), 7.6 min, 91% ee.

(S)-2-((3,5-Dimethoxybenzyl)sulfinyl)benzo[d]thiazole (27p): 86% yield; white solid; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, $J = 8.2$ Hz, 1H), 7.96 (d, $J = 8.1$ Hz, 1H), 7.56 (ddd, 1H), 7.48 (ddd, $J = 11.2, 4.1$ Hz, 1H), 6.41–6.35 (m, 1H), 6.31 (d, $J = 2.2$ Hz, 2H), 4.43 (d, $J = 13.0$ Hz, 1H), 4.26 (d, $J = 13.0$ Hz, 1H), 3.60 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.30, 160.97, 153.85, 136.20, 130.55, 127.07, 126.32, 124.00, 122.41, 108.22, 101.57, 63.57, 55.35; HRMS

(ESI) calcd for $C_{16}H_{15}NO_3S_2$ m/z $[M+H]^+$: 334.0572; found: 334.0574; $[\alpha]_D^{22} = -166.21$ (c 3.1, $CHCl_3$); HPLC analysis: Chiralcel OD-H (Hex/IPA = 90/10, 0.5 mL/min, 254 nm, 22°C), 37.8 (major), 42.4 min, 92% ee.

(S)-2-((Naphthalen-2-ylmethyl)sulfinyl)benzo[d]thiazole (27q): 85% yield; white solid; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, $J = 8.2$ Hz, 1H), 7.90 (d, $J = 8.1$ Hz, 1H), 7.83–7.76 (m, 1H), 7.72 (dd, $J = 8.7, 4.9$ Hz, 3H), 7.58 (ddd, 1H), 7.51–7.41 (m, 3H), 7.25 (dd, $J = 8.5, 1.7$ Hz, 1H), 4.68 (d, $J = 13.1$ Hz, 1H), 4.50 (d, $J = 13.1$ Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.12, 153.87, 136.14, 133.27, 133.26, 130.36, 128.59, 128.10, 127.79, 127.58, 127.05, 126.66, 126.51, 126.26, 124.02, 122.38, 63.41.; HRMS (ESI) calcd for $C_{18}H_{13}NOS_2$ m/z $[M+H]^+$: 324.0517; found: 324.0523; $[\alpha]_D^{22} = -78.47$ (c 2.2, CH_2Cl_2); HPLC analysis: Chiralcel AS-H (Hex/IPA = 90/10, 1.0 mL/min, 254 nm, 22°C), 36.1, 43.4 (major) min, 91% ee.

(S)-2-(Propylsulfinyl)benzo[d]thiazole (27r): 70% yield; colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, $J = 8.2$ Hz, 1H), 7.98 (d, $J = 8.0$ Hz, 1H), 7.54 (t, $J = 7.7$ Hz, 1H), 7.47 (t, $J = 7.6$ Hz, 1H), 3.26–3.11 (m, 2H), 1.99 (tq, $J = 14.8, 7.4$ Hz, 1H), 1.76 (tq, 1H), 1.08 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.86, 153.99, 136.02, 126.99, 126.21, 123.97, 122.36, 116.21, 58.61, 15.53, 13.24; HRMS (ESI) calcd for $C_{10}H_{11}NOS_2$ m/z $[M+Na]^+$: 248.0180; found: 248.0176; $[\alpha]_D^{22} = -1.15$ (c 2.0, CH_2Cl_2); HPLC analysis: Chiralcel OB-H (Hex/IPA = 90/10, 1.0 mL/min, 254 nm, 22°C), 12.3 (major), 14.5 min, 91% ee.

(S)-2-(Benzylsulfinyl)pyridine (27s): 76% yield; white solid; ^1H NMR (400 MHz, CDCl_3) δ 8.69 (d, $J = 4.3$ Hz, 1H), 7.80 (td, $J = 7.7, 1.7$ Hz, 1H), 7.63 (d, $J = 7.9$ Hz, 1H), 7.37 (ddd, $J = 7.6, 4.7, 1.1$ Hz, 1H), 7.31 – 7.21 (m, 3H), 7.04 (dd, $J = 7.7, 1.6$ Hz, 2H), 4.40 (d, $J = 13.1$ Hz, 1H), 4.10 (d, $J = 13.1$ Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 163.64, 149.11, 137.86, 130.27, 129.31, 128.31, 128.17, 124.67, 120.73, 59.97; HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{11}\text{NOS}$ m/z $[\text{M}+\text{H}]^+$: 218.0640; found: 218.0639; $[\alpha]_D^{22} = -205.63$ (c 2.6, CHCl_3); HPLC analysis: Chiralcel OD-H (Hex/IPA = 90/10, 1.0 mL/min, 254 nm, 22°C), 17.7 (major), 21.9 min, 80% ee.

(S)-2-((4-Methylbenzyl)sulfinyl)pyridine (27t): 96% yield; white solid; ^1H NMR (400 MHz, CDCl_3) δ 8.71–8.51 (m, 1H), 7.78 (td, $J = 7.7, 1.7$ Hz, 1H), 7.62 (dt, $J = 7.9, 0.9$ Hz, 1H), 7.33 (ddd, $J = 7.6, 4.7, 1.2$ Hz, 1H), 7.02 (d, $J = 7.8$ Hz, 2H), 6.89 (d, $J = 8.0$ Hz, 2H), 4.33 (d, $J = 13.1$ Hz, 1H), 4.03 (d, $J = 13.1$ Hz, 1H), 2.28 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 163.90, 149.26, 138.08, 137.84, 130.25, 129.14, 126.26, 124.67, 120.77, 59.87, 21.24; HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{13}\text{NOS}$ m/z $[\text{M}+\text{Na}]^+$: 254.0616; found: 254.0620; $[\alpha]_D^{22} = -253.06$ (c 3.4, CHCl_3); HPLC analysis: Chiralcel OB-H (Hex/IPA = 90/10, 0.5 mL/min, 254 nm, 22°C), 21.7 (major), 25.5 min, 85% ee.

(S)-2-(Benzylsulfinyl)thiophene (27u): 53% yield; white solid; ^1H NMR (400 MHz, CDCl_3) δ 7.62 (d, $J = 4.9$ Hz, 1H), 7.32–7.24 (m, 3H), 7.13 (t, $J = 4.1$ Hz, 1H), 7.08 (dd, $J = 7.2, 1.9$ Hz, 2H), 7.05–6.98 (m, 1H), 4.36 (d, $J = 12.4$ Hz, 1H), 4.15 (d, $J = 12.4$ Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 144.93, 131.19, 130.33, 129.89, 129.34, 128.80, 128.58, 127.28, 65.14; HRMS (ESI) calcd for $\text{C}_{11}\text{H}_{10}\text{OS}_2$ m/z $[\text{M}+\text{H}]^+$: 245.0071; found: 245.0071; $[\alpha]_D^{22} = +73.96$ (c 1.0, CHCl_3); HPLC analysis: Chiralcel OD-H (Hex/IPA = 90/10, 1.0 mL/min, 254 nm, 22°C), 18.5, 25.0 (major) min, 95% ee.

(S)-2-(((3-Methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methyl)sulfinyl)-1H-

benzo[d]imidazole or (S)-Lansoprazole (29): 81% yield; white solid; ^1H NMR (400 MHz, Acetone) δ 8.38 (d, $J = 5.6$ Hz, 1H), 7.75 (d, $J = 3.1$ Hz, 2H), 7.40 (dd, $J = 6.1, 3.2$ Hz, 2H), 7.13 (d, $J = 5.7$ Hz, 1H), 4.93–4.90 (AB-system, $J = 13.5$ Hz, 2H), 4.89–4.84 (q, $J = 7.8$ Hz, 2H), 2.33 (s, 3H); ^{13}C NMR (101 MHz, Acetone) δ 162.69, 155.37, 152.14, 149.15, 126.02, 124.16, 123.71, 123.27, 107.52, 66.50, 66.15, 65.80, 65.44, 61.80, 61.75, 11.07; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{14}\text{F}_3\text{N}_3\text{O}_2\text{S}$ m/z $[\text{M}+\text{H}]^+$: 370.0837; found: 370.0838; $[\alpha]_D^{22} = -253.8$ (c 0.5, Acetone); HPLC analysis: Chiralcel OD-H (Hex/IPA = 80/20, 0.7 mL/min, 254 nm, 22°C), 22.9 (major), 33.3min, 90% ee.

31a

(S)-(Butylsulfinyl)benzene (31a): 79% yield; colorless oil; ^1H NMR (400 MHz, CDCl_3) δ 7.63–7.58 (m, 2H), 7.52–7.45 (m, 3H), 2.77 (dt, 2H), 1.79–1.65 (m, 1H), 1.64–1.51 (m, 1H), 1.50–1.34 (m, 2H), 0.89 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 143.97, 130.91,

129.18, 124.04, 57.01, 24.13, 21.87, 13.62; HRMS (ESI) calcd for $C_{10}H_{14}OS$ m/z $[M+H]^+$: 183.0844; found: 183.0849; $[\alpha]_D^{22} = -165.82$ (c 0.73, CH_2Cl_2); HPLC analysis: Chiralcel OB-H (Hex/IPA = 50/50, 0.5 mL/min, 254 nm, 22°C), 9.5 (major), 12.2 min, 90% ee.

31b

(S)-2-((Phenylsulfinyl)methyl)naphthalene (31b): 93% yield; white solid; ^1H NMR (400 MHz, $CDCl_3$) δ 7.83–7.76 (m, 2H), 7.71 (dd, $J = 8.6, 5.9$ Hz, 2H), 7.50–7.42 (m, 4H), 7.39 (d, $J = 4.3$ Hz, 4H), 7.08 (dd, $J = 8.4, 1.7$ Hz, 1H), 4.25 (d, $J = 12.6$ Hz, 1H), 4.16 (d, $J = 12.6$ Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.88, 133.18, 133.02, 131.30, 129.93, 128.98, 128.23, 127.95, 127.81, 127.75, 126.71, 126.44, 126.41, 124.56, 64.00; HRMS (ESI) calcd for $C_{17}H_{14}OS$ m/z $[M+H]^+$: 267.0844; found: 267.0850; $[\alpha]_D^{22} = -41.85$ (c 1.3, CH_2Cl_2); HPLC analysis: Chiralcel OD-H (Hex/IPA = 90/10, 1.0 mL/min, 254 nm, 22°C), 18.7, 22.2 (major) min, 86% ee.

31c

(S)-1,2,3,4,5-Pentafluoro-6-((phenylsulfinyl)methyl)benzene (31c): 82% yield; white solid; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63–7.38 (m, 5H), 4.19 (d, $J = 13.0$ Hz, 1H), 4.09 (d, $J = 13.0$ Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.57, 132.14, 129.45, 124.05, 50.40; HRMS (ESI) calcd for $C_{13}H_7F_5OS$ m/z $[M+H]^+$: 307.0216; found: 307.0221; $[\alpha]_D^{22} = -102.15$ (c 1.5, CH_2Cl_2); HPLC analysis: Chiralcel OD-H (Hex/IPA = 90/10, 1.0 mL/min, 254 nm, 22°C), 10.7, 12.1 (major) min, 90% ee.

31d

(S)-1-((Phenylsulfinyl)methyl)-4-(trifluoromethyl)benzene (31d): 99% yield; white solid; ^1H NMR (400 MHz, CDCl_3) δ 7.56–7.30 (m, 7H), 7.07 (d, J = 8.0 Hz, 2H), 4.10 (d, J = 12.7 Hz, 1H), 4.01 (d, J = 12.7 Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 142.36, 133.18, 131.55, 130.81, 129.15, 125.37, 125.33, 124.39, 62.60; HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{11}\text{F}_3\text{OS}$ m/z $[\text{M}+\text{H}]^+$: 285.0561; found: 285.0555; $[\alpha]_D^{22}$ = -88.63 (c 1.5, CH_2Cl_2); HPLC analysis: Chiralcel OD-H (Hex/IPA = 90/10, 1.0 mL/min, 254 nm, 22°C), 12.7, 14.0 (major) min, 88% ee.

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Chapter 4

Bisguanidinium Tetraperoxyditungstate

Catalyzed Epoxidation

4.1 Introduction

Asymmetric epoxidation of allylic amines is one of the most versatile reactions, as the chiral amino-epoxides obtained can be further derivatized to amino alcohols, which are present in the scaffold of many drugs and natural products.¹⁻² Due to the competitive *N*-oxidation of amines,³ there are only few reports on peracid-mediated epoxidations of allylic amines.⁴⁻⁸ Chemo- and diastereoselective epoxidation of allylic amines have been developed either through *N*-oxide⁹⁻¹² or protonated ammonium cation.¹³ For similar reasons, there are also few reports on chiral ligand mediated metal-catalyzed asymmetric epoxidation of allylic amines.¹⁴⁻¹⁵ The few examples included Yamamoto's report on the use of Hf(IV)-bishydroxamic acid complex-catalyzed asymmetric epoxidation that was successful for a wide range of substrates including allylic sulfonamides, homoallylic sulfonamides, aldimine and ketimine (Figure 4.1).¹⁴ Separately, he utilized chiral Schiff base/titanium(IV) catalyst for asymmetric epoxidation of the *N*-alkenyl sulfonamides and homoallylic sulfonamides.¹⁵

Figure 4.1 Highly enantioselective epoxidation of allylic and homoallylic amines using chiral ligand-mediated metal-catalyzed reactions.

We recently demonstrated that ion pair catalyst consisting of a chiral cationic and an inorganic anionic salt can catalyze several reactions with high stereoselectivity.¹⁶⁻²⁰ We demonstrated that bisguanidinium permanganate can mediate enantioselective dihydroxylation and oxohydroxylation¹⁷ of α,β -unsaturated esters. We have also developed highly efficient and highly enantioselective bisguanidinium-catalyzed sulfoxidation^{18,21} of heterocyclic sulfides and alkyl aryl sulfides using aqueous hydrogen peroxide as oxidant. Diphosphatobis(permanganate)²¹ and dinuclear oxodiperoxomolybdatesulfate¹⁸ were identified to be the active anionic species respectively (Figure 4.2).

Figure 4.2 Our previous studies of highly enantioselective sulfoxidations using ion pair catalysts.

Thus, we like to expand the scope of ion pair catalysis of anionic metal oxides to include asymmetric epoxidation of challenging olefin substrates (Figure 4.3).

Figure 4.3 This work using chiral cationic ion pair strategy for asymmetric epoxidation of allylic and homoallylic amines.

In this report, we disclose a highly enantioselective epoxidation of allylic amines using a new ion pair catalyst that consists of a chiral cationic bisguanidinium $[BG]^{2+}$ and achiral tetraperoxyditungstate anion $[W_2O_2(\mu-O)(O_2)_4]^{2-}$ (Figure 4.4).

Figure 4.4 X-Ray crystallographic structure of $[\text{BG}]^{2+}[\text{W}_2\text{O}_2(\mu\text{-O})(\text{O}_2)_4]^{2-}$ **5g** (ellipsoids at 50% probability).

4.2 Results and discussion

4.2.1 Reaction development

As amines are more prone to be oxidized than olefin, protecting groups were added to the amines to circumvent this chemoselectivity issue. Initially, we chose a series of 1,1'-allylic amides as reactant. It was obvious that the substrates with tosyl group led to better results than others (Table 4.1, entry 1,5). Thus, in the following work, we applied tosyl group in most substrates to established the epoxidation reaction.

Table 4.1 Exploration of substrate scope ^a

Entry	Substrate	yield (%) ^b	ee (%) ^c
1		77	63
2		22	40
3		10	11
4		45	11
5		83	54

^aReaction conditions: **substrate** (0.05 mmol), H₂O₂ (0.06 mmol, 1.20 equiv., 35%w/w), **5a** (0.0025 mmol, 2.5 mol%), Ag₂WO₄ (0.002 mmol, 2.0 mol%), NaHSO₄ (0.015mmol, 30.0 mol%), 500 μ L solvent at 0 °C.

^bYield of isolated product. ^cDetermined with HPLC analysis using a chiral stationary phase.

We have previously shown that a highly efficient and highly enantioselective bisguanidinium-catalyzed sulfoxidation was achieved using bisguanidinium diphosphatobisperoxotungstate as the catalyst.²¹ Using this catalyst, we tested tosyl and phenyl di-protected allylic amine **34a** and found that low yield (5%) of allylic epoxide **35a** was isolated (Table 4.2, entry 3). We then tested conditions without any additive (entry 1), with acetic acid (entry 2) and with sodium hydrogen sulfate, NaHSO₄ (entry 4). We found that moderate yield (52%) and good *ee* value (60%) were obtained for allylic epoxide **35a**, when NaHSO₄ was used as the additive in a sub-stoichiometric amount (0.3 equiv.) (entry 4). No side products from the oxidation of nitrogen was observed. When the reaction temperature was carried out at 0 °C, *ee* value of allylic epoxide **35a** improved to 67%; however, the yield

decreased to 16% (entry 5). The counterion effect of the tungstate was also examined (entries 5-8) and Ag_2WO_4 was found to give the best results. We propose that the efficient formation of AgCl from Ag_2WO_4 and bisguanidinium chloride allows the complete formation of the ion pair catalyst and this was important to improve the reactivity and selectivity of the reaction (entry 8). Solvent also play a vital role in determining the reactivity and stereoselectivity of this reaction (entry 8-11). After screening a large number of solvents, it was revealed that 4-*tert*-butyltoluene proved to give the best yield (89%) and best enantioselectivity (94% *ee*) (entry 11). We also examined the additives, and NaHSO_4 promoted the reaction best (entry 11-14). Later, we found a premade catalyst **5g** could work in the system alone and give high *ee* value. If NaHSO_4 is used as an additive (entry 16), both the yield and *ee* value reached to the same level as the *in situ* condition (entry 11).

Table 4.2 Optimization of Asymmetric Epoxidation of Protected 1,2-Allylic Amine^a

34a + 35% aq. H_2O_2 $\xrightarrow[\text{additives, solvent, T}]{[\text{BG}]^{2+}[\text{X}]^{2-}, [\text{W}]}$ **35a**

$[\text{BG}]^{2+}$: R = 3, 5-di-*t*-Bu- $\text{C}_6\text{H}_3\text{CH}$
5a = $[\text{BG}]^{2+} \cdot 2[\text{Cl}]^-$
5g = $[\text{BG}]^{2+} [\text{W}_2\text{O}_7(\mu\text{-O})(\text{O}_2)_4]^{2-}$

Entr	$[\text{BG}]^{2+}[\text{X}]^{2-}$	[W]	Additive	Solvent	T (°C)	yield (%) ^b	<i>ee</i> (%) ^c
1	5a	Na_2WO_4	-	toluene	r.t.	N.R.	N.A.
2	5a	Na_2WO_4	$\text{CH}_3\text{CO}_2\text{H}$	toluene	r.t.	<5	10
3	5a	Na_2WO_4	$\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$	toluene	r.t.	5	-13
4	5a	Na_2WO_4	NaHSO_4	toluene	r.t.	52 ^d	60
5	5a	Na_2WO_4	NaHSO_4	toluene	0	16	67
6	5a	Cs_2WO_4	NaHSO_4	toluene	0	50	70
7	5a	CaWO_4	NaHSO_4	toluene	0	15	60
8	5a	Ag_2WO_4	NaHSO_4	toluene	0	38	75
9	5a	Ag_2WO_4	NaHSO_4	CH_2Cl_2	0	13	20
10	5a	Ag_2WO_4	NaHSO_4	<i>i</i> -Pr ₂ O	0	47	86
11	5a	Ag_2WO_4	NaHSO_4	4- <i>t</i> -butyltoluene	0	89	94
12	5a	Ag_2WO_4	KHSO_4	4- <i>t</i> -butyltoluene	0	89	90
13	5a	Ag_2WO_4	TBAHSO ₄	4- <i>t</i> -butyltoluene	0	10	90
14	5a	Ag_2WO_4	$\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$	4- <i>t</i> -butyltoluene	0	17	-28

15 ^e	5g	-	-	4- <i>t</i> -butyltoluene	0	57	92
16 ^f	5g	-	NaHSO ₄	4- <i>t</i> -butyltoluene	0	>99	94

^aReaction conditions: **34a** (0.05 mmol), H₂O₂ (0.06 mmol, 1.20 equiv., 35%w/w), [**BG**]²⁺[**X**]²⁻ (0.0025 mmol, 2.5 mol%), M_x(WO₄)_y (0.002 mmol, 2.0 mol%), additive (0.015mmol, 30.0 mol%), 500 μL solvent at 0 °C.

^bYield of isolated product. ^cDetermined with HPLC analysis using a chiral stationary phase. ^d39% of **34a** was recovered. ^eThe ion pair catalyst **5g** (0.0025 mmol, 2.5 mol%) was premade and used directly with substrate (0.05 mmol) and H₂O₂ (0.06 mmol, 1.20 equiv., 35%w/w) in 500 μL solvent. ^fBased on the condition with premade catalyst **5g** (0.0025 mmol, 2.5 mol%), add extra NaHSO₄ (0.005 mol, 10.0 mol%) at the beginning of the experiment.

With the optimized conditions in hand, we are keen to know how the protecting groups on the amine and substitution pattern of the olefin affect the reactivity and enantioselectivity of the epoxidation. We used **5g** along with NaHSO₄ as the additive (condition of Table 4.2, entry 16) to explore the substrates scope of 1,2-allylic amines, and the results showed moderate to excellent yields (71 to 99% yield) and good to excellent enantioselectivities (68 to 97% *ee*). Compared to **35a**, increasing the alkyl chain length at 1-position to two carbons saw a drop in enantioselectivity of the epoxide **35b** (89% *ee*). However, when the 1- and 2-position were linked to form cyclic allylic amines, the *ee* values increased to 92% and 97% respectively for epoxides **35c** and **35d**. Next, the effect of the aromatic protecting groups on nitrogen was investigated. 1-Naphthyl (abbreviated as 1-Np in Scheme 4.1) protected cyclic epoxide **35e** and *para*-methoxyphenyl protected cyclic epoxide **35f** were obtained in excellent enantioselectivities (90-95% *ee*). The effect of other protecting groups was also evaluated; *para*-methoxybenzyl, 1-naphthyl, *para*-methoxyphenyl, and *para*-bromophenyl protected acyclic epoxide **35g-j** were obtained in 94-96% *ee*. From these results, it was observed that aryl-protecting group on nitrogen does not affect the enantioselectivity of the epoxides significantly. When a phenyl group was added to the terminal position of alkene on 1-position, both yields and *ee* values remained unaffected; but when the length of alkyl chain on 2-position was increased to 3-carbons, the yields are slightly decreased (**35k-m**). When we lengthen the alkyl chain on position-1 with silyl-protected alcohol group, acyclic epoxide **35n** was obtained

in good yield but slightly lower *ee* value. A single crystal of amino-epoxide **35e**, suitable for X-ray structural analysis, was obtained and the absolute stereochemistry was determined to be (*R,R*).

^aReaction conditions: **34** (0.1 mmol), H₂O₂ (0.12 mmol, 1.20 equiv, 35%w/w), **5g** (0.0025 mmol, 2.5 mol%), NaHSO₄ (0.01 mmol, 10.0 mol%), 1.0 mL solvent at 0 °C. Yields were obtained by chromatographic purification. Enantiomeric excess was determined using chiral HPLC. ^bReaction was conducted at R.T. 1-Np is 1-naphthyl.

Scheme 4.1 Asymmetric epoxidation of protected 1,2-allylic amine **34**^a

The ability of this methodology to be carried out on a larger scale was demonstrated with the formation of epoxide **35g** on a 3.0 mmol-scale with an *ee* value of 92% and yield of 91% (Scheme 4.2). Deprotection of the tosyl-group was achieved using sodium in liquid ammonia, with epoxide **8** obtained without losing much *ee* value. It is interesting to note that the epoxide was retained intact under the basic reaction conditions.

Scheme 4.2 Scale-up experiment and deprotection

4.2.2 Identification of catalyst

We were able to prepare the ion pair catalyst **5g** as a white powder and NaHSO₄ has a crucial role in the formation of the catalyst (Figure 4.4). When NaHSO₄ was not added or replaced with NaH₂PO₄, the preparation of the ion pair catalyst was not successful. We initially speculated that the structure of the ion pair to be an analogue of dinuclear oxodiperoxomolybdatesulfate ion pair, containing a bridging sulfate between two tungsten atoms (Figure 4.3)¹⁸. After several attempts, we were able to obtain a single crystal suitable for X-ray diffraction, grown from DMF at room temperature. While we did indeed obtain a bimetallic anion, there was no sulfate bridge. The achiral tetraperoxyditungstate anion²² species [W₂O₂(μ-O)(O₂)₄]²⁻ is found to fit nicely into the central cavity of the chiral dication. Each tungsten is coordinated to two peroxo-groups and a terminal oxo ligand, and both tungsten atoms in the anion are linked by a non-linear oxygen bridge [W₁-O₆-W₂: 103.4(4)°]. Thus, the coordination number is 6 on tungsten and in a distorted octahedral arrangement of oxygen atoms. It is

interesting to note that the bond length of O₆-W₂ (1.962(10) Å) is slightly longer than O₆-W₁ (1.942(11) Å). Both O₁-W₁ (1.761(10) Å) and O₁₁-W₂ (1.690(10) Å) bonds fall in the typical range for the W=O bond. Influenced by the adjacent metal, the bond lengths of O₅-W₁ (2.003(10) Å) and O₇-W₂ (1.942(10) Å) are longer than the other bond lengths between peroxo-group and tungsten (Fig. 1d). The crystal was added in catalytic amount (2.5 mol%) into a solution containing di-protected allylic amine **34a**, and epoxide **35a** was obtained in 92% *ee* and moderate yield (Table 4.2, entry 15), demonstrating that the crystal is the active catalyst of the epoxidation. If we repeat the same experiment in the presence of NaHSO₄, the yield improved significantly (entry 16). While NaHSO₄ is not part of the active catalyst, we speculate that it is important for maintaining the structure of the active catalyst and allowing the catalyst to be re-oxidized by hydrogen peroxide.

4.2.3 Characterization of catalyst

Einstein and Penfold identified the hydrated tetraperoxyditungstate [W₂O₁₁(H₂O)₂]²⁻·K₂⁺ using X-ray crystallography and showed that each tungstate has a pentagonal bipyramidal arrangement. Each tungstate is 7-coordinated with 2 peroxy groups, a bridging oxo between the two tungstate and the apical positions are occupied by an oxo group and water²³. The structure of dehydrated tetraperoxyditungstate [$\{W(=O)(O_2)_2\}_2(\mu-O)$]²⁻ or [W₂O₂(μ-O)(O₂)₄]²⁻ (anion of our ion pair catalyst) was first proposed by Griffith in 1995.²⁴ Without an X-ray crystal structure, the catalyst was characterized through IR and Raman analysis. By changing the counterion for [$\{W(=O)(O_2)_2\}_2(\mu-O)$]²⁻, several useful sets of data were obtained, and characteristic IR and Raman spectroscopic peaks were identified.²⁵ In this regard, we conducted spectroscopic studies with FT-IR and FT-Raman for our ion pair catalyst, **5g** [BG]²⁺[W₂O₂(μ-O)(O₂)₄]²⁻. This is followed by density functional theory (DFT) calculation to provide qualitative simulated frequencies in a bid to understand the experimental spectra. Based on the

spectra overlay for **5a** $[\text{BG}]^{2+} \cdot 2[\text{Cl}]^-$ and the ion pair catalyst **5g** $[\text{BG}]^{2+}[\text{W}_2\text{O}_2(\mu\text{-O})(\text{O}_2)_4]^{2-}$ (Figure 4.5), the appearance of new peaks could be attributed to the tetraperoxyditungstate, $[\text{W}_2\text{O}_2(\mu\text{-O})(\text{O}_2)_4]^{2-}$. Frequency analysis of the optimized electronic structure of **5g** shows that there are two $\nu_{\text{sym}}[\text{W}(\text{O}_2)]$, one $\nu_{\text{asym}}[\text{W}(\text{O}_2)]$, one $\nu(\text{W}=\text{O})$ and one $\nu_{\text{asym}}(\text{W}_2\text{O})$ stretching. These vibrations were assigned to the new peaks attributed to the tungstate anion for Raman and IR. The $\nu_{\text{asym}}(\text{W}_2\text{O})$ stretching has a strong absorbance peak in IR but is very weak in Raman. In general, the experimental and theoretical spectra are overall a good fit, with difference in wavenumber of up to 40 cm^{-1} for IR. The calculated scaled values for Raman spectra are in excellent agreement with the experimentally observed data and are consisted with previously reported tungstate vibrational wavelengths⁴⁹. As a result, we have demonstrated the reliability of the B3LYP method in predicting Raman spectra of the ion pair catalyst and suggest that it can be more accurate to estimate experimental data. Meanwhile, the IR can supplement information, which may be lost in Raman.

Figure 4.5 Experimental (in blue) and computational (in khaki) characters of **5g**, and **5a** was set as blank control (in black). **a**, Infrared spectra of **5a**, **5g** and **5g** (calc.). **b**, Raman spectra of **5g** (calc.), **5g** and **5a**.

With the elucidation of the active catalytic species, we propose a plausible mechanism (Figure 4.6). Firstly, the tungstate anion was oxidized and dimerized in the presence of NaHSO_4 and oxidant. The solubility of Na_2WO_4 and NaHSO_4 were initially poor in water but after the addition of hydrogen peroxide, a clear homogeneous solution was formed. This indicated that the tetraperoxyditungstate $[\text{W}_2\text{O}_2(\mu\text{-O})(\text{O}_2)_4]^{2-}$ anion is highly soluble and it is then carried into the organic phase by the bisguanidinium $[\text{BG}]^{2+}$, forming the ion pair catalyst **5g**. After the epoxidation reaction, the reduced form of tetraperoxyditungstate is regenerated by hydrogen peroxide at the interphase region between the organic solvent and water.

Figure 4.6 Proposed reaction pathway of ion pair phase transfer catalysis.

4.3 Summary

In summary, we have developed an ion pair strategy for epoxidation of allylic amines in high enantioselectivity using bisguanidinium tetraperoxyditungstate as a catalyst. Environmentally benign aqueous hydrogen peroxide is used as the terminal oxidant in stoichiometric amount. The catalytic oxidation process provided excellent yields and enantioselectivities for 1,1'-allylic protected amines. Low catalyst loading, ease of operation (under air), scalability, and tolerance to functional groups demonstrate the versatility of this method. The structure of the ion pair catalyst $[\text{BG}]^{2+}[\text{W}_2\text{O}_2(\mu\text{-O})(\text{O}_2)_4]^{2-}$ was elucidated by using X-ray crystallography and further characterized with IR and Raman spectroscopies. Analysis of the IR and Raman spectra allow to identify specific structures on the anion, which will be useful for the identification of related anions in the absence of X-ray crystallography.

4.4 Experimental

4.4.1 Experimental procedure

Premixed catalyst: To a 4 mL glass vial, **substrate** (1.0 mmol, 1.0 equiv.), **5g** (0.025 mmol, 0.025 equiv.), sodium hydrogen sulfate (0.1 mmol, 0.1 equiv.) were added, followed by addition of *t*-butyltoluene (1 mL). The mixture was then cooled in a 0 °C incubator with stirring for 15 minutes. 35% aq. H₂O₂ (1.2 mmol, 1.2 equiv.) was then added in one portion into reaction at 0°C. The mixture was left to stir at 0°C for 48 h.

In situ catalyst: To a 4 mL glass vial, **substrate** (1.0 mmol, 1.0 equiv.), Ag₂WO₄ (0.02 mmol, 0.02 equiv.), **5a** (0.025 mmol, 0.025 equiv.), sodium hydrogen sulfate (0.3 mmol, 0.3 equiv.) were added, followed by addition of *t*-butyltoluene (1 mL). The mixture was then cooled in a 0 °C incubator with stirring for 15 minutes. 35% aq. H₂O₂ (1.2 mmol, 1.2 equiv.) was then added in one portion into reaction at 0 °C. The mixture was continue to stir at 0 °C for 48 h.

Work-up: After the reaction was complete (monitored by TLC), sat. Na₂S₂O₃ (aq.) was added into reaction to quench any unreacted oxidant. The aq. layer was extracted with Ethyl Acetate 3 times. The combined organic extracts was dried over anhydrous Na₂SO₄, concentrated under reduced pressure to get crude. Purification by flash column chromatography on silica gel (Eluent: Hexane-Ethyl Acetate 20:1 to 4:1) to obtain desired product.

To a 50 mL Schlenk flask, sodium(washed by distilled hexane for twice) and magnetic stir-bar was added, followed equipped with a cold-finger condenser. The cold-finger condenser was connected to ammonia gas cylinder. After the gas condensed to liquid, the mixture in flask turned to dark blue. Then the cold-finger condenser was removed and replaced by rubber stopper with balloon. A solution of **3g** (2 mmol) in THF (5.0 mL) was injected into flask. The reaction was quenched by solid ammonium chloride after 2 h. The work-up step was terminated until the blue disappeared. A filtration separation followed and the filter residue was washed by DCM. Combine the THF solution and DCM solution, and remove the organic solvent under reduced pressure to get crude. Purification by flash column chromatography on silica gel (Eluent: DCM-Ethyl Acetate 1:1) to obtain desired product.

4.4.2 Characterization of asymmetric products

***N*-((2,3-dimethyloxiran-2-yl)methyl)-4-methyl-*N*-phenylbenzenesulfonamide (35a):** >99% yield, white solid, ^1H NMR (500 MHz, CDCl_3) δ 7.48 (d, $J = 8.0$ Hz, 2H), 7.33 (d, $J = 4.4$ Hz, 3H), 7.27 (t, $J = 7.3$ Hz, 2H), 7.09 – 7.00 (m, 2H), 3.92 (d, $J = 13.6$ Hz, 1H), 3.31 (d, $J = 13.6$ Hz, 1H), 2.57 (q, $J = 5.3$ Hz, 1H), 2.44 (s, 3H), 1.40 (s, 3H), 1.08 (d, $J = 5.4$ Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 143.74, 139.92, 135.37, 129.60, 129.19, 128.95, 128.31, 127.82, 59.02, 58.41, 58.39, 21.68, 14.79, 13.75. HRMS: (ESI) $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{18}\text{H}_{21}\text{NNaO}_3\text{S}$, 354.1140, found 354.1130. HPLC analysis: Chiralcel OD-H (Hex/IPA = 95/05, 1.0 mL/min, 254 nm, 23°C), 9.4min (major), 11.6 min, 94% ee. $[\alpha]^{22.4}_{\text{D}} +3.4^\circ$ (c 0.58, CHCl_3).

***N*-((3-ethyl-2-methyloxiran-2-yl)methyl)-4-methyl-*N*-phenylbenzenesulfonamide**

(35b): >99% yield, white solid, ^1H NMR (500 MHz, CDCl_3) δ 7.45 (d, $J = 8.0$ Hz, 2H), 7.30 (d, $J = 5.0$ Hz, 3H), 7.25 (t, $J = 7.8$ Hz, 2H), 7.10 – 6.94 (m, 2H), 3.97 (d, $J = 13.4$ Hz, 1H), 3.20 (d, $J = 13.4$ Hz, 1H), 2.42 (s, 3H), 2.35 (t, $J = 6.4$ Hz, 1H), 1.46 (dt, $J = 14.0, 7.1$ Hz, 1H), 1.38 (s, 3H), 1.22 (td, $J = 14.5, 7.3$ Hz, 1H), 0.66 (t, $J = 7.5$ Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 143.74, 139.62, 135.20, 129.59, 129.18, 128.95, 128.30, 127.84, 64.23, 58.99, 58.25, 21.67, 21.65, 14.77, 9.84. HRMS: (ESI) $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{19}\text{H}_{23}\text{NNaO}_3\text{S}$, 368.1296, found 368.1301. HPLC analysis: Chiralcel OD-H (Hex/IPA = 95/05, 1.0 mL/min, 254 nm, 23°C), 9.8.min (major), 13.6 min, 89% ee. $[\alpha]^{22.6}_{\text{D}} +4.8^\circ$ (c 0.75, CHCl_3).

***N*-(6-oxabicyclo[3.1.0]hexan-1-ylmethyl)-4-methyl-*N*-phenylbenzenesulfonamide (35c):**

71% yield, white solid, ^1H NMR (400 MHz, CDCl_3) δ 7.43 (d, $J = 8.3$ Hz, 2H), 7.32 – 7.24 (m, 3H), 7.24 – 7.16 (m, 2H), 7.08 – 6.91 (m, 2H), 4.01 (d, $J = 14.1$ Hz, 1H), 3.70 (d, $J = 14.1$ Hz, 1H), 2.97 (s, 1H), 2.39 (s, 3H), 1.92 – 1.73 (m, 3H), 1.56 – 1.31 (m, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 143.73, 139.96, 135.34, 129.60, 129.15, 128.89, 128.25, 127.84, 65.96, 62.09, 52.92, 27.79, 27.38, 21.69, 19.40. HRMS: (ESI) $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{19}\text{H}_{21}\text{NNaO}_3\text{S}$, 366.1140, found 366.1145. HPLC analysis: Chiralcel OD-H (Hex/IPA = 95/05, 1.0 mL/min, 254 nm, 23°C), 10.2min (major), 12.1 min, 92% ee. $[\alpha]^{22.4}_{\text{D}} +2.3^\circ$ (c 0.49, CHCl_3).

***N*-(7-oxabicyclo[4.1.0]heptan-1-ylmethyl)-4-methyl-*N*-phenylbenzenesulfonamide (35d):**

83% yield, white solid, ^1H NMR (400 MHz, CDCl_3) δ 7.42 (d, $J = 8.3$ Hz, 2H), 7.31 – 7.24 (m, 3H), 7.24 – 7.16 (m, 2H), 6.98 (dd, $J = 6.7, 3.0$ Hz, 2H), 3.88 (d, $J = 13.5$ Hz, 1H), 3.23 (d, $J = 13.5$ Hz, 1H), 2.57 (d, $J = 2.9$ Hz, 1H), 2.38 (s, 3H), 2.29 – 2.02 (m, 1H), 1.74 (ddd, $J = 21.3, 14.6, 6.9$ Hz, 2H), 1.46 – 0.97 (m, 5H). ^{13}C NMR (101 MHz, CDCl_3) δ 143.72, 139.86, 135.38, 129.60, 129.14, 129.09, 128.33, 127.84, 58.11, 58.04, 57.55, 25.49, 24.60, 21.68, 20.16, 19.14. HRMS: (ESI) $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{20}\text{H}_{23}\text{NNaO}_3\text{S}$, 380.1296, found 380.1300. HPLC analysis: Chiralcel AD-H (Hex/IPA = 95/05, 1.0 mL/min, 254 nm, 23°C), 15.8min (major), 19.2 min, 97% ee. $[\alpha]^{22.4}_{\text{D}} +3.4^\circ$ (c 0.52, CHCl_3).

***N*-((7-oxabicyclo[4.1.0]heptan-1-yl)methyl)-4-methyl-*N*-(naphthalen-1-yl)benzenesulfonamide (35e):**

>99% yield, white solid ^1H NMR (400 MHz, CDCl_3) δ 8.13 (dd, $J = 191.9, 8.4$ Hz, 1H), 7.86 – 7.21 (m, 8H), 6.88 (dd, $J = 138.7, 7.1$ Hz, 1H), 4.43 (d, $J = 13.0$ Hz, 1H), 3.76 (dd, $J = 78.6, 13.9$ Hz, 1H), 2.91 (d, $J = 13.0$ Hz, 1H), 2.45 (t, $J = 10.1$ Hz, 2H), 2.03 – 1.62 (m, 1H), 1.53 – 0.51 (m, 5H). ^{13}C NMR (101 MHz, CDCl_3) δ 143.97, 143.80, 137.39, 136.50, 135.74, 134.94, 134.85, 134.69, 133.35, 132.09, 129.70, 129.64, 129.32, 129.28, 128.45, 128.30, 128.08, 127.72, 127.00, 126.81, 126.69, 126.46, 125.37, 125.08, 124.94, 124.63, 124.11, 60.30, 58.98, 58.42, 58.30, 57.71, 57.37, 25.97, 25.46, 24.52, 24.39, 21.72, 21.68, 20.15, 20.09, 19.00, 18.37. HRMS: (ESI) $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{24}\text{H}_{25}\text{NO}_3\text{S}$,

407.1555, found 407.1558. HPLC analysis: Chiralcel AD-H (Hex/IPA = 95/5, 1.0 mL/min, 254 nm, 23°C), 22.7 min, 26.5 min (major), 95% ee. $[\alpha]^{22.4}_D +51.6^\circ$ (c 1.72, CH₂Cl₂).

***N*-(7-oxabicyclo[4.1.0]heptan-1-ylmethyl)-*N*-(4-methoxyphenyl)-4-**

methylbenzenesulfonamide (35f): 98% yield, white solid ¹H NMR (500 MHz, CDCl₃) δ 7.46 (d, J = 8.3 Hz, 2H), 7.30 – 7.19 (m, 2H), 6.96 – 6.88 (m, 2H), 6.86 – 6.72 (m, 2H), 3.86 (d, J = 13.4 Hz, 1H), 3.79 (s, 3H), 3.22 (d, J = 13.4 Hz, 1H), 2.60 (d, J = 2.6 Hz, 1H), 2.42 (s, 3H), 2.19 (dt, J = 14.9, 6.0 Hz, 1H), 1.96 – 1.69 (m, 2H), 1.54 – 1.36 (m, 2H), 1.28 (ddd, J = 15.0, 8.7, 5.1 Hz, 1H), 1.22 – 1.07 (m, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 159.30, 143.63, 135.42, 132.29, 130.20, 129.58, 127.85, 114.31, 58.12, 57.91, 57.79, 55.52, 25.48, 24.64, 21.68, 20.20, 19.16. HRMS: (ESI) $[M+Na]^+$ calcd. for C₂₁H₂₅NNaO₄S, 410.1402, found 410.1413. HPLC analysis: Chiralcel IB-3 (Hex/IPA = 97/03, 0.8 mL/min, 254 nm, 23°C), 16.0min (major), 17.7 min, 90% ee. $[\alpha]^{21.4}_D -0.46^\circ$ (c 0.71, CHCl₃).

***N*-(((2*S*,3*S*)-2,3-dimethyloxiran-2-yl)methyl)-*N*-(4-methoxybenzyl)-4-**

methylbenzenesulfonamide (35g): 95% yield, white solid ¹H NMR (400 MHz, CDCl₃) δ 7.68 (d, J = 8.3 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 8.7 Hz, 2H), 6.80 (d, J = 8.7 Hz, 2H), 4.46 (d, J = 14.9 Hz, 1H), 4.11 (d, J = 14.9 Hz, 1H), 3.78 (s, 3H), 3.38 (d, J = 14.6 Hz, 1H), 2.91 (d, J = 14.6 Hz, 1H), 2.61 (q, J = 5.4 Hz, 1H), 2.42 (s, 3H), 1.13 (s, 3H), 1.02 (d, J = 5.5 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 159.37, 143.52, 136.94, 130.14, 129.84, 128.08,

127.31, 113.92, 59.49, 58.34, 55.39, 55.37, 54.89, 52.70, 21.62, 14.61, 13.65. HRMS: (ESI) $[M+H]^+$ calcd. for $C_{20}H_{26}NO_4S$, 376.1583, found 376.1581. HPLC analysis: Chiralcel AD-H (Hex/IPA = 95/05, 1.0 mL/min, 254 nm, 23°C), 32.0 min (major), 42.9 min, 96% ee. $[\alpha]^{22.4}_D +10.48^\circ$ (c 0.84, CH_2Cl_2).

35h

***N*-((2,3-dimethyloxiran-2-yl)methyl)-4-methyl-*N*-(naphthalen-1-yl)benzenesulfonamide**

(35h): 99% yield, white solid ^1H NMR (300 MHz, $CDCl_3$) δ 8.30 – 7.88 (m, 1H), 7.84 (dd, J = 8.5, 4.8 Hz, 2H), 7.62 – 7.17 (m, 7H), 6.90 (dd, J = 74.1, 7.4 Hz, 1H), 4.39 (d, J = 13.2 Hz, 1H), 3.90 (d, J = 13.9 Hz, 1H), 3.62 (d, J = 13.9 Hz, 1H), 3.00 (d, J = 13.2 Hz, 1H), 2.51 (q, J = 5.5 Hz, 1H), 2.43 (d, J = 6.9 Hz, 3H), 2.05 (q, J = 5.4 Hz, 1H), 1.38 (d, J = 65.1 Hz, 3H), 0.85 (dd, J = 129.3, 5.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 129.70, 129.64, 129.31, 128.24, 128.10, 126.92, 126.49, 125.02, 124.29, 123.99, 61.19, 58.57, 58.31, 58.24, 21.72, 15.29, 13.72, 13.52, 6.71. HRMS: (ESI) $[M+Na]^+$ calcd. for $C_{22}H_{23}NaNO_3S$, 381.1399, found 381.1400. HPLC analysis: Chiralcel OJ-H (Hex/IPA = 95/5, 1.5 mL/min, 254 nm, 23°C), 19.2 min, 28.3 min (major), 94% ee. $[\alpha]^{22.4}_D +35.6^\circ$ (c 1.28, CH_2Cl_2).

35i

***N*-((2,3-dimethyloxiran-2-yl)methyl)-*N*-(4-methoxyphenyl)-4-**

methylbenzenesulfonamide (35i): 97% yield, colorless oil, ^1H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, J = 8.0 Hz, 2H), 7.27 (t, J = 6.8 Hz, 2H), 6.94 (d, J = 8.7 Hz, 2H), 6.83 (d, J = 8.7 Hz, 2H), 3.86 (d, J = 13.5 Hz, 1H), 3.82 (s, 3H), 3.28 (d, J = 13.5 Hz, 1H), 2.57 (q, J = 5.4 Hz, 1H),

2.44 (s, 3H), 1.41 (s, 3H), 1.11 (d, $J = 5.4$ Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 159.17, 143.51, 135.32, 132.24, 129.96, 129.45, 127.72, 114.24, 58.90, 58.52, 58.11, 55.39, 21.55, 14.64, 13.67. HRMS: (ESI) $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{21}\text{H}_{23}\text{NNaO}_4\text{S}$, 384.1245, found 384.1237; HPLC analysis: Chiralcel AS-H (Hex/IPA = 95/05, 1.0 mL/min, 254 nm, 23°C), 26.7 min, 33.6 min (major), 95% ee. $[\alpha]^{21.4}_{\text{D}} +2.7^\circ$ (c 0.51, CHCl_3)

***N*-(4-bromophenyl)-*N*-((2,3-dimethyloxiran-2-yl)methyl)-4-methylbenzenesulfonamide**

(35j): 96% yield, white solid, ^1H NMR (500 MHz, CDCl_3) δ 7.45 (dt, $J = 9.6, 2.5$ Hz, 4H), 7.27 (s, 2H), 7.00 – 6.84 (m, 2H), 3.75 (d, $J = 13.8$ Hz, 1H), 3.42 (d, $J = 13.8$ Hz, 1H), 2.64 (q, $J = 5.5$ Hz, 1H), 2.44 (s, 3H), 1.58 (s, 3H), 1.37 (s, 3H), 1.13 (d, $J = 5.5$ Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 144.06, 144.04, 135.01, 135.00, 132.43, 132.41, 130.50, 130.49, 129.76, 129.75, 127.80, 127.78, 122.25, 77.41, 77.16, 76.91, 59.12, 58.06, 57.90, 21.72, 21.70, 14.79, 14.78, 13.78, 13.76. HRMS: (ESI) $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{18}\text{H}_{20}\text{BrNNaO}_3\text{S}$, 432.0245, found 432.0247. HPLC analysis: Chiralcel OD-H (Hex/IPA = 90/10, 1.0 mL/min, 254 nm, 23°C), 9.1 min (major), 10.8 min, 95% ee. $[\alpha]^{22.4}_{\text{D}} +36.0^\circ$ (c 0.53, CH_2Cl_2).

***N*-((3-benzyl-2-methyloxiran-2-yl)methyl)-*N*-phenylbenzenesulfonamide**

(35k): >99% yield, white solid, ^1H NMR (500 MHz, CDCl_3) δ 7.42 (d, $J = 8.3$ Hz, 2H), 7.29 – 7.17 (m, 9H), 7.03 – 6.98 (m, 2H), 6.98 – 6.92 (m, 2H), 3.91 (d, $J = 13.7$ Hz, 1H), 3.31 (d, $J = 13.7$ Hz, 1H), 2.75 (dd, $J = 14.4, 6.0$ Hz, 1H), 2.67 (t, $J = 6.0$ Hz, 1H), 2.59 (dd, $J = 14.4, 5.9$

Hz, 1H), 2.41 (s, 3H), 1.53 (s, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 143.76, 139.55, 137.36, 135.18, 129.59, 129.18, 128.78, 128.74, 128.72, 128.28, 127.82, 126.59, 62.93, 59.49, 58.23, 35.00, 21.67, 15.28. HRMS: (ESI) $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{24}\text{H}_{25}\text{NO}_3\text{SNa}$, 430.1453, found 430.1462; HPLC analysis: Chiralcel OD-H (Hex/IPA = 95/05, 1.0 mL/min, 254 nm, 23°C), 19.2 min (major), 24.1 min, 93% ee. $[\alpha]^{21.2}_{\text{D}} + 5.5^\circ$ (c 0.76, CHCl_3)

***N*-((3-benzyl-2-ethyloxiran-2-yl)methyl)-4-methyl-*N*-phenylbenzenesulfonamide**

(35l): >99% yield, white solid, ^1H NMR (400 MHz, CDCl_3) δ 7.41 (d, J = 8.1 Hz, 2H), 7.28 – 7.15 (m, 9H), 7.02 – 6.90 (m, 4H), 4.06 (d, J = 13.7 Hz, 1H), 3.20 (d, J = 13.7 Hz, 1H), 2.69 (dd, J = 14.1, 10.1 Hz, 2H), 2.59 (dd, J = 12.6, 3.4 Hz, 1H), 2.41 (s, 3H), 1.92 (dd, J = 14.3, 7.4 Hz, 1H), 1.69 (dd, J = 14.4, 7.3 Hz, 1H), 1.16 (t, J = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 143.78, 139.49, 137.58, 134.83, 129.56, 129.09, 128.75, 128.73, 128.66, 128.27, 127.88, 126.52, 77.48, 77.16, 76.84, 63.86, 62.66, 54.72, 34.65, 21.67, 21.12, 8.93. HRMS: (ESI) $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{25}\text{H}_{27}\text{NNaO}_3\text{S}$, 444.1609, found 444.1620; HPLC analysis: Chiralcel AD-H (Hex/IPA = 95/05, 1.0 mL/min, 254 nm, 23°C), 13.4 min (major), 14.9 min, 92% ee. $[\alpha]^{21.2}_{\text{D}} + 4.3^\circ$ (c 0.72, CHCl_3)

***N*-((3-benzyl-2-propyloxiran-2-yl)methyl)-4-methyl-*N*-phenylbenzenesulfonamide (35m):**

74% yield, white solid, ^1H NMR (400 MHz, CDCl_3) δ 7.41 (d, J = 8.0 Hz, 2H), 7.21 (dd, J = 15.1, 7.9 Hz, 8H), 6.96 (dd, J = 10.5, 7.6 Hz, 4H), 4.08 (d, J = 13.7 Hz, 1H), 3.16 (d, J = 13.7 Hz, 1H), 2.74 – 2.54 (m, 3H), 2.41 (s, 3H), 1.94 – 1.81 (m, 1H), 1.66 – 1.49 (m, 4H), 1.01 (t, J

= 7.1 Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 143.78, 139.52, 137.62, 134.84, 129.56, 129.09, 128.75, 128.66, 128.28, 127.90, 126.51, 63.57, 61.89, 55.29, 34.71, 30.25, 21.68, 18.03, 14.67. HRMS: (ESI) $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{26}\text{H}_{29}\text{NNaO}_3\text{S}$, 458.1766, found 458.1763. HPLC analysis: Chiralcel OD-H (Hex/IPA = 95/05, 1.0 mL/min, 254 nm, 23°C), 10.6 min, 13.0 min (major), 68% ee. $[\alpha]^{22.7}_{\text{D}} +3.5^\circ$ (c 0.57, CHCl_3).

35n

***N*-((3-(3-((*tert*-butyldiphenylsilyl)oxy)propyl)-2-methyloxiran-2-yl)methyl)-4-methyl-*N*-phenylbenzenesulfonamide (35n):** 94% yield, colourless oil, ^1H NMR (500 MHz, CD_3CN) δ 7.57 (dt, J = 8.1, 1.6 Hz, 4H), 7.45 – 7.32 (m, 9H), 7.28 (d, J = 8.1 Hz, 2H), 7.26 – 7.18 (m, 3H), 7.02 – 6.89 (m, 2H), 3.82 (d, J = 13.6 Hz, 1H), 3.46 (ddd, J = 10.3, 8.3, 4.2 Hz, 2H), 3.21 (d, J = 13.6 Hz, 1H), 2.37 (s, 3H), 2.31 (t, J = 6.2 Hz, 1H), 1.23 (s, 7H), 0.95 (s, 9H). ^{13}C NMR (126 MHz, CDCl_3) δ 143.74, 139.57, 135.66, 135.17, 133.98, 129.74, 129.59, 129.18, 128.90, 128.30, 127.84, 127.75, 63.28, 62.83, 58.95, 58.19, 28.74, 26.97, 24.90, 21.68, 19.31, 14.81. HRMS: (ESI) $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{36}\text{H}_{43}\text{NNaO}_4\text{SSi}$, 636.2580, found 636.2584. HPLC analysis: Chiralcel OD-H (Hex/IPA = 95/5, 0.5 mL/min, 254 nm, 23°C), 16.7min (major), 20.8 min, 86% ee. $[\alpha]^{22.4}_{\text{D}} +35.3^\circ$ (c 2.31, CH_2Cl_2).

36

1-((2*S*,3*S*)-2,3-dimethyloxiran-2-yl)-*N*-(4-methoxybenzyl)methanamine (36): 72% yield, colorless oil, ^1H NMR (400 MHz, CDCl_3) δ 7.22 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 3.79 (s, 3H), 3.71 (s, 2H), 3.05 (q, J = 5.5 Hz, 1H), 2.80 – 2.59 (q, 2H), 1.30 (s, 3H), 1.28 (d, J = 5.5 Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 158.72, 132.55, 129.29, 113.86, 60.50, 57.22, 55.36, 55.20, 53.34, 15.63, 13.91. HRMS: (ESI) $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{13}\text{H}_{20}\text{NO}_2$, 222.1494,

found 222.1502. HPLC analysis: Chiralcel AS-H (Hex/IPA = 80/20, 1.0 mL/min, 254 nm, 23°C), 7.2 min, 10.7 min (major), 92% ee. $[\alpha]^{23}_{\text{D}} -5.2^{\circ}$ (c 2.16, CH_2Cl_2).

4.3.3 Single crystal

35% H_2O_2 (3.45 mL, 40.0 mmol) was added dropwise to a mixture of $\text{Na}_2\text{WO}_4 \cdot 2\text{H}_2\text{O}$ (330 mg, 1.13 mmol) and NaHSO_4 (1.8 g, 15.0 mmol) in 10 mL deionized water. Before adding the H_2O_2 , the $\text{Na}_2\text{WO}_4 \cdot 2\text{H}_2\text{O}$ and NaHSO_4 were partially dissolved. After finishing the dropping, all components were dissolved, giving a colorless solution at room temperature. Then the above solution was added dropwise to a turbid solution of (*S,S*)-**5a**⁴ (564 mg, 0.4 mmol) in Et_2O (20 mL). After vigorously stirring for 15 min, the Et_2O layer turned to a yellow solution. After further stirring for 2 h and removal of Et_2O by evaporation, (*S,S*)-**5g** precipitated from organic phase. 4.0 mL deionized water was added and the resulting heterogeneous mixture was submitted to ultra sonicator for 1 min. Then the pale white solid was filtered off and washed with deionized water (20 mL). After drying under vacuum at room temperature, (*S,S*)-**5g** was obtained as a pale white powder (731.5 mg, 97% yield) and its structure was characterized and determined by X-ray single-crystal diffraction. ^1H NMR (400 MHz, CDCl_3) δ 7.46 – 6.65 (m, 32H), 5.28 – 4.63 (dd, 8H), 4.58 – 4.03 (d, 8H), 3.32 (s, 4H), 1.15 (s, 72H).

Fig. 2 X-ray structure of (*S,S*)-**5g**. (CCDC: 1868566)

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Appendix

YXY3174B-OJH3010254230-50 XY3174B-OJH3010254230-50.lcd
uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	17.383	11828226	384055	67.514	51.004
2	30.211	11362426	184801	32.486	48.996
Total		23190652	568856	100.000	100.000

YXY3164A-OJH3010254230-50 XY3164A-OJH3010254230-50.lcd
uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	17.144	258746	8918	7.707	4.049
2	28.965	6131967	106799	92.293	95.951
Total		6390713	115718	100.000	100.000

YZY1083A-IB3-3010254230-100-R YZY1083A-IB3-3010254230-100-R.lcd
uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	8.582	7605917	468032	61.694	50.142
2	17.375	7562819	290606	38.306	49.858
Total		15168736	758638	100.000	100.000

YXY3098A-IB3-3010254230-25 YXY3098A-IB3-3010254230-25.lcd

uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	8.368	181149	12725	4.412	2.960
2	15.495	5939401	275660	95.588	97.040
Total		6120550	288385	100.000	100.000

YZY1083C-IB3-3010254230-100-R YZY1083C-IB3-3010254230-100-R.lcd
uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	9.513	9270799	652125	76.174	50.018
2	32.256	9264079	203976	23.826	49.982
Total		18534878	856101	100.000	100.000

YXY3132A-IB3-3010254230-40 YXY3132A-IB3-3010254230-40.lcd
uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	9.264	130431	8985	3.706	1.207
2	30.422	10673637	233449	96.294	98.793
Total		10804068	242434	100.000	100.000

YXY3154A-IB3-3010254230-100-R XYX3154A-IB3-3010254230-100-R.lcd
uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	8.840	9031234	568421	75.153	49.912
2	30.318	9062975	187934	24.847	50.088
Total		18094209	756355	100.000	100.000

YXY3154B-IB3-3010254230-40 XYX3154B-IB3-3010254230-40.lcd
uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	8.892	456992	28775	14.998	5.777
2	29.656	7453577	163083	85.002	94.223
Total		7910569	191859	100.000	100.000

YXY3172A-IA3-3010254230-100-R XYX3172A-IA3-3010254230-100-R.lcd
uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	14.271	5209509	193648	60.479	50.325
2	25.334	5142280	126542	39.521	49.675
Total		10351789	320190	100.000	100.000

YXY3184-IA3-3010254230-40 XYX3184-IA3-3010254230-40.lcd

uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	14.306	1018531	40008	9.311	5.933
2	24.972	16149837	389671	90.689	94.067
Total		17168368	429679	100.000	100.000

YXY3192A-IB3-3010254230-100-R XYX3192A-IB3-3010254230-100-R.lcd
uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	10.561	14573807	761242	76.291	49.966
2	38.322	14593517	236572	23.709	50.034
Total		29167324	997813	100.000	100.000

YXY3192B-IB3-3010254230-50 XYX3192B-IB3-3010254230-50.lcd

uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	10.720	57575	3142	1.554	0.497
2	37.968	11525223	198996	98.446	99.503
Total		11582798	202138	100.000	100.000

YXY3172B-IB3-3010254230-100-R XYX3172B-IB3-3010254230-100-R.lcd
uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	10.281	3775097	254634	60.014	50.158
2	16.312	3751267	169654	39.986	49.842
Total		7526363	424288	100.000	100.000

YXY3182-IB3-3010254230-25 XYX3182-IB3-3010254230-25.lcd

uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	10.183	614364	40590	6.038	3.838
2	15.582	15393442	631604	93.962	96.162
Total		16007806	672195	100.000	100.000

YXY3248A-IB3-3010254230-100-R XYX3248A-IB3-3010254230-100-R.lcd
uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	15.147	4189489	133053	53.288	49.991
2	19.903	4191050	116633	46.712	50.009
Total		8380539	249686	100.000	100.000

YXY3248B-IB3-3010254230-30 XYX3248B-IB3-3010254230-30.lcd

uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	15.132	145996	5147	2.694	2.246
2	19.265	6353557	185876	97.306	97.754
Total		6499554	191023	100.000	100.000

YXY3250A-IB3-3010254230-100-R XYX3250A-IB3-3010254230-100-R.lcd
uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	24.752	8728851	152023	56.608	50.045
2	43.534	8713116	116533	43.392	49.955
Total		17441967	268557	100.000	100.000

YXY3250B-IB3-3010254230-60 XYX3250B-IB3-3010254230-60.lcd

uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	24.603	2099469	42298	14.042	9.041
2	40.983	21122932	258922	85.958	90.959
Total		23222401	301220	100.000	100.000

YXY3232A-IB3-3010254230-100-R XY3232A-IB3-3010254230-100-R.lcd
uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	15.593	11563134	380259	57.169	49.952
2	23.077	11585415	284892	42.831	50.048
Total		23148549	665152	100.000	100.000

YXY3232B-IB3-3010254230-35 XY3232B-IB3-3010254230-35.lcd

uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	15.603	2152543	74999	8.822	5.411
2	22.046	37628485	775177	91.178	94.589
Total		39781028	850176	100.000	100.000

YXY3234A-IB3-3010254230-100-R XYX3234A-IB3-3010254230-100-R.lcd
uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	11.308	8811903	458927	57.063	49.972
2	16.858	8821841	345322	42.937	50.028
Total		17633744	804249	100.000	100.000

YXY3234B-IB3-3010254230-25 XYX3234B-IB3-3010254230-25.lcd

uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	11.375	547635	28354	6.965	5.384
2	16.616	9623172	378755	93.035	94.616
Total		10170807	407110	100.000	100.000

YXY3246A-IB3-3010254230-100-R XY3246A-IB3-3010254230-100-R.lcd
uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	7.310	10861827	879418	52.428	49.926
2	8.808	10894095	797954	47.572	50.074
Total		21755923	1677371	100.000	100.000

YXY3246B-IB3-3010254230-12 XY3246B-IB3-3010254230-12.lcd

uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	7.261	2898886	253488	11.597	9.896
2	8.573	26394966	1932382	88.403	90.104
Total		29293852	2185869	100.000	100.000

YXY2134B-ODH1010254230-25 XYX2134B-ODH1010254230-25.lcd
uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	14.201	9833400	342482	54.577	48.942
2	17.502	10258342	285041	45.423	51.058
Total		20091743	627523	100.000	100.000

YXY3148A-ODH1010254230-25 XYX3148A-ODH1010254230-25.lcd

uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	13.373	7249159	280279	96.840	96.580
2	16.444	256698	9145	3.160	3.420
Total		7505857	289424	100.000	100.000

YXY2206A-ODH1010254230-100-R XYX2206A-ODH1010254230-100-R.lcd
uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	13.190	12618341	409443	58.119	50.020
2	16.639	12608245	295050	41.881	49.980
Total		25226586	704492	100.000	100.000

YXY3114A-ODH1010254230-25 XYX3114A-ODH1010254230-25.lcd

uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	12.436	17192185	634067	95.734	94.653
2	15.909	971142	28258	4.266	5.347
Total		18163327	662325	100.000	100.000

YXY2210A-IB3-3010254230-100-R XY2210A-IB3-3010254230-100-R.lcd
uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	7.480	18799954	1806037	51.611	49.646
2	7.910	19068028	1693317	48.389	50.354
Total		37867981	3499354	100.000	100.000

YXY3102B-IB3-3010254230-12 XY3102B-IB3-3010254230-12.lcd
uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	7.256	27730115	2963615	95.303	95.391
2	7.625	1339867	146074	4.697	4.609
Total		29069982	3109689	100.000	100.000

YZY1153A-ODH10005254230-100-R YZY1153A-ODH10005254230-100-R.lcd
uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	39.276	30473496	398999	50.865	49.414
2	42.646	31196694	385430	49.135	50.586
Total		61670189	784429	100.000	100.000

YXY3094B-ODH1005254230-55 YXY3094B-ODH1005254230-55.lcd

uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	37.830	50760652	609872	94.897	95.751
2	42.363	2252274	32793	5.103	4.249
Total		53012927	642665	100.000	100.000

YXY2218A-ASH-1010254230-100-R XYX2218A-ASH-1010254230-100-R.lcd
uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	38.059	15179463	98870	55.246	50.077
2	47.454	15132551	80095	44.754	49.923
Total		30312013	178965	100.000	100.000

YXY3116A-ASH1010254230-60 XYX3116A-ASH1010254230-60.lcd
uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	36.139	341816	2351	4.945	4.301
2	43.425	7604799	45202	95.055	95.699
Total		7946615	47553	100.000	100.000

YZY1025B-OBH-1010254230-100-R YZY1025B-OBH-1010254230-100-R.lcd
uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	11.229	109380403	2015071	46.509	49.700
2	13.948	110703080	2317622	53.491	50.300
Total		220083484	4332693	100.000	100.000

YXY3148B-OBH1010254230-20 YXY3148B-OBH1010254230-20.lcd

uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	12.339	7775143	202177	94.505	95.653
2	14.477	353365	11756	5.495	4.347
Total		8128507	213933	100.000	100.000

YZY1097A-ODH-1010254230-100-R YZY1097A-ODH-1010254230-100-R.lcd
uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	15.896	714147	19682	52.692	50.024
2	18.853	713458	17671	47.308	49.976
Total		1427605	37352	100.000	100.000

YXY3166B-ODH1010254230-25 YXY3166B-ODH1010254230-25.lcd

uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	17.666	6039043	164809	90.714	90.289
2	21.881	649548	16870	9.286	9.711
Total		6688591	181679	100.000	100.000

YZY1125A-OBH-1005254230-100-R YZY1125A-OBH-1005254230-100-R.lcd
uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	22.783	9843428	164241	53.895	50.326
2	26.210	9716080	140501	46.105	49.674
Total		19559508	304742	100.000	100.000

YXY3220A-OBH1005254230-35 YXY3220A-OBH1005254230-35.lcd

uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	21.707	51586183	820459	92.856	92.475
2	25.502	4197800	63125	7.144	7.525
Total		55783983	883584	100.000	100.000

27u

YZY1097C-ODH-1010254230-100-R YZY1097C-ODH-1010254230-100-R.lcd
uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	16.330	43376051	977905	55.697	50.163
2	22.587	43094210	777860	44.303	49.837
Total		86470261	1755765	100.000	100.000

YXY3276B-ODH1010254230-35 YXY3276B-ODH1010254230-35.lcd
uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	18.488	485581	14792	3.022	2.297
2	24.944	20658780	474650	96.978	97.703
Total		21144361	489442	100.000	100.000

YXY4016A-ODH2007254230-100 XYX4016A-ODH2007254230-100.lcd
uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	20.990	11936319	116253	59.153	50.365
2	30.258	11763522	80275	40.847	49.635
Total		23699840	196528	100.000	100.000

YXY4072B-ODH2007254230-50-2 XYX4072B-ODH2007254230-50-2.lcd

uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	22.965	1169991	7727	95.430	95.200
2	33.280	58986	370	4.570	4.800
Total		1228977	8097	100.000	100.000

31a

YZY1095B-OBH-5005254230-100-R1 YZY1095B-OBH-5005254230-100-R1.lcd
uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	9.502	1214636	52574	59.776	50.405
2	12.258	1195128	35378	40.224	49.595
Total		2409763	87952	100.000	100.000

YXY4144-OBH5005254230-15 YXY4144-OBH5005254230-15.lcd

uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	9.509	473982	17664	95.641	95.204
2	12.223	23878	805	4.359	4.796
Total		497860	18469	100.000	100.000

31b

YXY4118A-ODH1010254230-100-R XYX4118A-ODH1010254230-100-R.lcd
uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	18.688	1479821	34615	52.795	49.730
2	22.237	1495906	30950	47.205	50.270
Total		2975727	65565	100.000	100.000

YXY4118B-ODH1010254230-30 XYX4118B-ODH1010254230-30.lcd

uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	18.719	192003	4376	8.219	7.204
2	22.168	2473312	48864	91.781	92.796
Total		2665315	53240	100.000	100.000

31c

YXY4114A-ODH1010254230-100-R XYX4114A-ODH1010254230-100-R.lcd
uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	10.800	1795146	73946	52.826	49.963
2	12.167	1797818	66035	47.174	50.037
Total		3592964	139981	100.000	100.000

YXY4114D-ODH1010254230-15 XYX4114D-ODH1010254230-15.lcd

uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	10.706	62851	2680	5.818	5.045
2	12.147	1183008	43379	94.182	94.955
Total		1245859	46059	100.000	100.000

31d

YXY4136A-ODH1010254230-100-R XY4136A-ODH1010254230-100-R.lcd
uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	12.340	613612	19755	50.426	49.943
2	13.807	615006	19421	49.574	50.057
Total		1228618	39176	100.000	100.000

YXY4136B-ODH1010254230-20 XY4136B-ODH1010254230-20.lcd

uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	12.714	83661	3250	7.141	6.202
2	14.039	1265356	42266	92.859	93.798
Total		1349016	45516	100.000	100.000

35a

Detector A Channel 2 254nm

Peak#	Ret. Time	Area	Area%
1	9.559	5424617	49.544
2	11.515	5524374	50.456
Total		10948991	100.000

Detector A Channel 2 254nm

Peak#	Ret. Time	Area	Area%
1	9.422	2274822	96.820
2	11.607	74711	3.180
Total		2349533	100.000

35b

Detector A Channel 2 254nm

Peak#	Ret. Time	Area	Area%
1	9.740	1147201	50.036
2	13.132	1145558	49.964
Total		2292759	100.000

Detector A Channel 2 254nm

Peak#	Ret. Time	Area	Area%
1	9.777	6024082	94.110
2	13.557	376998	5.890
Total		6401080	100.000

35c

mV

Detector A Channel 2 254nm

Peak#	Ret. Time	Area	Area%
1	10.203	1054717	50.284
2	11.988	1042790	49.716
Total		2097507	100.000

mV

YXY6246A-ODH0510254230-20 XY6246A-ODH0510254230-20.lcd
uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	10.191	4520916	174374	96.419	95.938
2	12.482	191401	6476	3.581	4.062
Total		4712318	180850	100.000	100.000

35d

mV

Detector A Channel 2 254nm

Peak#	Ret. Time	Area	Area%
1	15.441	1492532	49.874
2	18.728	1500053	50.126
Total		2992585	100.000

mV

YXY6246B-ADH0510254230-30 XY6246B-ADH0510254230-30.lcd

uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	14.941	6553186	175176	98.009	98.421
2	18.225	105149	3558	1.991	1.579
Total		6658336	178734	100.000	100.000

35e

Detector A Channel 2 254nm

Peak#	Ret. Time	Area	Area%
1	23.032	702549	50.125
2	27.028	699043	49.875
Total		1401591	100.000

Detector A Channel 2 254nm

Peak#	Ret. Time	Area	Area%
1	22.740	10360614	97.431
2	26.524	273177	2.569
Total		10633791	100.000

Detector A Channel 2 254nm

Peak#	Ret. Time	Area	Area%
1	15.927	7539694	48.737
2	17.028	7930587	51.263
Total		15470281	100.000

Detector A Channel 2 254nm

Peak#	Ret. Time	Area	Area%
1	16.027	24610266	94.764
2	17.686	1359757	5.236
Total		25970024	100.000

35g

YXY7008A-ADH0510254230-60 XY7008A-ADH0510254230-60.lcd
uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	32.003	7085578	87921	97.630	97.823
2	42.926	157689	2135	2.370	2.177
Total		7243267	90056	100.000	100.000

YXY7008B-ADH0510254230-60 XY7008B-ADH0510254230-60.lcd
uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	32.003	7085578	87921	97.630	97.823
2	42.926	157689	2135	2.370	2.177
Total		7243267	90056	100.000	100.000

35h

Detector A Channel 2 254nm

Peak#	Ret. Time	Area	Area%
1	20.280	4916144	50.136
2	29.172	4889389	49.864
Total		9805533	100.000

Detector A Channel 2 254nm

Peak#	Ret. Time	Area	Area%
1	19.223	14713412	96.475
2	28.299	537664	3.525
Total		15251076	100.000

35i

mV

Detector A Channel 2 254nm

Peak#	Ret. Time	Area	Area%
1	31.852	5097901	49.824
2	41.288	5133853	50.176
Total		10231755	100.000

mV

YXY6252B-ASH0510254230-60 XY6262B-ASH0510254230-60.lcd
uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	28.015	548236	5690	3.691	2.278
2	35.680	23523156	148491	96.309	97.722
Total		24071392	154181	100.000	100.000

mV

Detector A Channel 2 254nm

Peak#	Ret. Time	Area	Area%
1	8.807	21017769	49.548
2	10.001	21401614	50.452
Total		42419383	100.000

uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	8.391	40408448	1517216	97.558	97.644
2	10.321	975037	37975	2.442	2.356
Total		41383485	1555191	100.000	100.000

35k

mV

Detector A Channel 2 254nm

Peak#	Ret. Time	Area	Area%
1	18.936	147254	50.716
2	23.327	143094	49.284
Total		290348	100.000

mV

Detector A Channel 2 254nm

Peak#	Ret. Time	Area	Area%
1	19.233	667911	96.360
2	24.127	25233	3.640
Total		693144	100.000

351

mV

Detector A Channel 2 254nm

Peak#	Ret. Time	Area	Area%
1	13.471	1440308	51.524
2	15.004	1355111	48.476
Total		2795419	100.000

mV

YXY6268B-ADH0510254230-20 XY6268B-ADH0510254230-20.lcd

uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	12.767	9871535	293559	95.020	95.903
2	14.319	421679	15385	4.980	4.097
Total		10293213	308943	100.000	100.000

35m

mV

Detector A Channel 2 254nm

Peak#	Ret. Time	Area	Area%
1	9.312	807678	53.510
2	11.158	701718	46.490
Total		1509396	100.000

mV

Detector A Channel 2 254nm

Peak#	Ret. Time	Area	Area%
1	10.644	160983	16.178
2	13.029	834083	83.822
Total		995066	100.000

35n

mV

Detector A Channel 2 254nm

Peak#	Ret. Time	Area	Area%
1	15.071	9224248	49.501
2	17.882	9410313	50.499
Total		18634562	100.000

mV

Detector A Channel 2 254nm

Peak#	Ret. Time	Area	Area%
1	16.746	9331885	93.424
2	20.832	656883	6.576
Total		9988768	100.000

YXY7104-2-ASH2010254230-30R XYX7104-2-ASH2010254230-30R.lcd
uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	7.154	777228	25027	58.188	50.615
2	10.746	758327	17984	41.812	49.385
Total		1535555	43010	100.000	100.000

YXY7102-2-ASH1510254230-20redo XYX7102-2-ASH2010254230-20redo.lcd
uV

Detector A Channel 1 254nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	7.208	69656	2701	7.237	4.431
2	10.663	1502231	34617	92.763	95.569
Total		1571886	37318	100.000	100.000