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Zong, Lili; Tan, Choon-Hong

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Phase transfer and ion pairing catalysis of pentanidiums and bisguanidiniums

*Lili Zong and Choon-Hong Tan**

Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences,
Nanyang Technological University, 21 Nanyang Link, Singapore 637371

CONSPECTUS: Catalysts accelerate biological processes and organic reactions in a controlled and selective fashion. There are continuing efforts in asymmetric catalysis to develop efficient catalysts with broad reaction scope and industrial practicability. Amongst the various modes of asymmetric catalysis, phase transfer catalysis has attracted intense interest due to its ease to scale up and low catalyst loading. Chiral quaternary ammonium and phosphonium salts are well-studied classes of chiral phase transfer catalysts and they typically are comprised of sp^3 -hybridized quaternary onium salts. In this Account, we describe our recent attempts to develop N - sp^2 hybridized guanidinium-type salts as efficient phase transfer catalysts as well as ion pair catalysis based on N - sp^2 hybridized bisguanidinium-type salts.

The sp^2 -quaternized ammonium salts, pentanidiums, which contain five nitrogen atoms in conjugation, displayed remarkable phase transfer catalytic efficiency. We have shown that pentanidium can catalyze Michael additions of *tert*-butyl glycinate-benzophenone Schiff base with various α,β -unsaturated acceptors, such as vinyl ketones, acrylates and chalcones in high

enantioselectivities. The structurally amendable pentanidium phase transfer catalysts supply diverse reactivity and selectivity to various other organic transformations, such as α -hydroxylation of 3-substituted-2-oxindoles, Michael addition of 3-alkyloxindoles with vinyl sulfone and alkylation reactions of sulfenate anions and dihydrocoumarins. Pentanidium salts are applicable to enantioselective transformations on a preparative scale at low catalyst loading, allowing for the synthesis of a broad range of enantiopure compounds. From computational and experimental results, we also proposed that halogenated pentanidium catalysts participated in halogen bonding and this contributed to the excellent stereocontrol in alkylation reactions.

Subsequently, we articulated that chiral cations can direct functional anions besides basic anions in traditional Brønsted basic phase transfer reactions, including metal-centered anions. We identified dicationic bisguanidinium as an excellent ion pairing catalyst, first demonstrating that bisguanidinium formed an ion pair with permanganate and directed the anion in enantioselective dihydroxylation and oxohydroxylation of α,β -unsaturated esters. This initial success led us to explore chiral cationic ion pairing catalysis as a general mode of catalysis. This mode of catalysis is at the interphase between organocatalysis, phase transfer catalysis and organometallic catalysis. We then identified bisguanidinium diphosphatobis(oxotungstate) and bisguanidinium dinuclear oxodiperoxomolybdatesulfate ion pairs as the active catalysts in enantioselective sulfoxidations using aqueous H_2O_2 as oxidant. The structure of bisguanidinium dinuclear oxodiperoxomolybdatesulfate ion pair was elucidated using single crystal *X*-ray analysis. Bisguanidinium-catalyzed sulfoxidations emerged as a practical methodology for the synthesis of enantioenriched sulfoxides including armodafinil and lansoprazole, which are commercial drugs. Finally, we are also able to show that pentanidium and bisguanidinium hypervalent silicates are intermediates in enantioselective alkylations using silylamide as Brønsted probase.

1. INTRODUCTION

Guanidine, the functional group on the side chain of arginine, is a strong base and is protonated over a wide pH range. Thus, in physiological conditions, it usually exists as guanidinium. The guanidinium motif is known to play crucial roles in substrate recognition at the active site of enzymes through non-covalent interactions such as hydrogen bonding.¹ Interactions between guanidinium and functional groups such as phosphates, carboxylates and enolates are also of considerable interest in bioorganic chemistry and host-guest macromolecular chemistry.² Since the pioneering works of Chinchilla,³ Lipton⁴ and Corey⁵ in the 1990s, numerous exciting outcomes have been achieved by utilizing chiral guanidines as general Brønsted base catalysts.⁶ Our group has reported a variety of chiral guanidine-catalyzed asymmetric reactions and these results have been summarized in several reviews.⁷ This Account will emphasize our recent efforts in using guanidinium-type and bisguanidinium-type salts **1**, **2** and **3** as phase transfer⁸ and ion pairing catalysts (Figure 1).

Figure 1. Guanidinium-type salts as phase transfer and ion pairing catalysts.

2. PENTANIDIUM-CATALYZED ENANTIOSELECTIVE PHASE TRANSFER REACTIONS

In our attempt to enhance the basicity of the guanidine catalyst **1**, structurally novel pentanidine containing five nitrogen atoms in conjugation was designed. The hypothesis was that with

increased conjugation, it might render pentanidine with increased basicity and less acidic nucleophiles can be activated. Although the pentanidine did not exhibit enhanced basicity, serendipitously, we found that its fully alkylated salt, pentanidium salts **2**, is an excellent phase transfer catalyst (Figure 1). We prepared the pentanidium salts **2** from commercially available chiral diamines and tetra-methylated pentanidium **2a** can be obtained in five steps with good chemical yield. Generally, pentanidium salts **2** can be synthesized through the coupling between imidazolinium chloride and a guanidine partner under basic conditions (Scheme 1). Single-crystal *X*-ray diffraction analysis of pentanidium **2a** reveals that the five nitrogen atoms are not coplanar and the resulting two five-membered rings are in a twisted spatial arrangement (Figure 2).⁹

Scheme 1. Synthesis of pentanidium salts **2** through imidazolinium chloride.

Figure 2. Crystal structure of tetra-methylated pentanidium **2a**.

2.1 Pentanidium-catalyzed Michael addition of *tert*-butylglycinate Schiff base

Scheme 2. Pentanidium **2a**-catalyzed Michael addition of Schiff base.

When we investigated the propensity for pentanidium to function as phase transfer catalyst, we found that pentanidium **2a** is an excellent catalyst for the Michael addition of *tert*-butylglycinate-benzophenone Schiff base **4**.⁹ Pentanidium **2a** displayed excellent reactivity; with only 2.0 mol% of catalyst, the reaction with methyl vinyl ketone **5a** was completed within 3 h, providing the

adduct **6a** in 86% yield and in 91% *ee* (Scheme 2). The generality of the method was successfully demonstrated using different Michael addition acceptors such as vinyl ketones, acrylates and chalcones. It was found that loading of the catalyst could be further lowered to 0.05 mol% for a gram-scale reaction (Scheme 3). The Michael addition between Schiff base **4** and chalcone **5m** proceeded with high stereoselectivity providing the adduct **6m** in 90% *ee* and as a single diastereomer; it was transformed to pyrrolidine derivative **7** in simple steps.

Scheme 3. Preparative-scale reaction with low catalyst loading.

Figure 3. Pentanidium-catalyzed reactions using prochiral intermediates.

The aforementioned result indicates that chiral pentanidium cation can discriminate efficiently between the two enantiotopic faces of prochiral ester enolate. Further investigations reveal that amide enolate, sulfenate anion and cyclic ester enolate are also suitable prochiral nucleophiles (Figure 3).

2.2 Pentanidium-catalyzed α -hydroxylation of 3-substituted-2-oxindoles

The amide enolate (Figure 3b) generated from 3-substituted 2-oxindole has been widely employed as key intermediate for the synthesis of enantioenriched 3,3-disubstituted oxindoles. These oxindoles are frequently observed as the core structure in natural products and extensively investigated in drug discovery programs due to their potent antibacterial and anticancer activities.¹⁰ Catalytic enantioselective α -oxidation of 3-substituted-2-oxindole is a direct and attractive approach to access 3-substituted-3-hydroxy-2-oxindole core structures.¹¹ In 2008, Itoh reported the preparation of α -hydroxyoxindoles using a *Cinchonidinium* catalyst under phase transfer conditions.¹² The product was obtained with moderate enantioselectivity and triethyl phosphite was required to reduce the peroxide intermediate. Encouraged by the efficiency and excellent stereocontrol of pentanidium, we investigated the α -hydroxylation of 3-substituted-2-oxindole **7** with air as oxidant (Scheme 4a).¹³ Pentanidium **2b**, bearing bulkier side arms was developed for this reaction (Scheme 1). Initially, we were perplexed that no reductant such as triethyl phosphite was required and α -hydroxyoxindoles were obtained directly with high enantioselectivities. Using isotope labelling experiments with 0.55 equivalent of $^{18}\text{O}_2$, the role of molecular oxygen was verified (Scheme 4b). Mass spectrometry was employed to characterize the isolated hydroxyloxindole [^{18}O]-**8a** and 84% level of ^{18}O incorporation was observed.

Scheme 4. a) Pentanidium **2b**-catalyzed α -hydroxylation of 3-substituted-2-oxindoles, b) isotope labelling experiment and c) effect of the amount of oxygen on chemoselectivity.

We found that the amount of molecular oxygen in the reaction affects the amount of hydroperoxide oxindole formed (Scheme 4c). When the reaction was conducted with excess oxidant by using an O_2 balloon, hydroperoxide oxindole **9a** was obtained in 85% yield with good enantioselectivity. Hydroperoxide oxindole **9a** and hydroxyloxindole **8a** were found to have the same absolute configuration (*R*). To gain insights into the reaction, racemic hydroperoxide oxindole **9a** was prepared and used as oxidant in the α -hydroxylation of oxindole **7a** in the absence of air (Scheme 5a). With 5 mol % of pentanidium **2b** and two equivalents of racemic **9a** as oxidant, the α -hydroxylated product (*R*)-**8a** was achieved with 76% ee, while the remained hydroperoxide oxindole was determined to be (*S*)-**9a** with 51% ee. On the basis of the experimental results (Scheme 4c and Scheme 5a), we proposed a two-step reaction that includes a kinetic resolution step (Scheme 5b). In the first step, in the presence of pentanidium **2b** and base, the enolate generated from 3-substituted-2-oxindole **7a**, adds to O_2 in an enantioselective fashion to give hydroperoxide oxindole (*R*)-**9a**. This is followed by a kinetic resolution step, in

which hydroperoxide oxindole (*R*)-**9a** is reduced by a second enolate of 3-substituted-2-oxindole **7a**, furnishing hydroxyoxindole product (*R*)-**8a** with improved enantiopurity.

Scheme 5. a) Racemic hydroperoxide **9a** as oxidant and b) proposed reaction pathway involving a kinetic resolution process.

2.3 Pentaniidum-catalyzed Michael addition of 3-alkylsubstituted oxindoles

The direct Michael addition of 3-substituted oxindole to activate alkenes is an attractive approach to prepare 3,3-disubstituted oxindoles containing a quaternary carbon stereocenter. Recently, successful attempts using commercially available vinyl sulfones as Michael acceptors have been reported using organocatalysis.¹⁴ However, only limited examples of highly enantioenriched 3,3-dialkyl oxindoles have been obtained.¹⁵ We found that pentaniidum **2** are efficient phase transfer catalysts for Michael addition of 3-alkyloxindoles **7** to phenyl vinyl sulfone **10** at low catalyst loading (Scheme 6).

Scheme 6. Effect on enantioselectivities using halogenated pentanidiums.

Scheme 7. Pentanidium **2f**-catalyzed Michael addition of 3-alkylsubstituted oxindoles.

Pentanidium **2c**, with four 3,5-di-*tert*-butylbenzyl side-arms, was first tested and a moderate level of enantioselectivity was obtained (Scheme 6).¹⁶ Further modification, by installing different halogens to the two benzyl groups, led to an enhancement in enantioselectivity and a high level of enantiocontrol was achieved with brominated-pentanidium **2f** or iodinated-

pentanidium **2g**. With 0.25 mol% of pentanidium **2f**, the reaction between a series of 3-alkylsubstituted oxindoles **7** and phenyl vinyl sulfone **10** proceeded in a highly enantioselective manner to furnish corresponding Michael adducts **11** with high functional group tolerance (Scheme 7). Gram quantity of oxindole **11g** can be easily obtained from scale-up experiments. The adduct **11g** then underwent simple transformations to provide pyrroloindoline derivative **12**, an analogue of the natural product precursor esermethole.¹⁷

2.4 Pentanidium-catalyzed alkylation of sulfenate

Sulfenate anion¹⁸ is an unstable reaction intermediate but it can be generated *in situ*; it has a nucleophilic sulfur center, which can be used for the construction of S-C bond. This intermediate can be used to prepare sulfoxide in a complementary way to the classical Andersen method and direct sulfoxidation method. There are a few methods to generate sulfenate anion *in situ*, including the use of base, fluoride or heat (Scheme 8).¹⁹ Perrio and co-workers reported a phase transfer alkylation of sulfonate using *Cinchonidinium* catalyst and it provided chiral sulfoxides with moderate enantioselectivity.²⁰ Using pentanidium **2c** as catalyst, we investigated the enantioselective benzylation of 2-thienyl sulfenate generated *in situ* from sulfinyl methyl esters **13a** (Scheme 9).²¹ After optimization of reaction parameters, such as sulfenate anion precursors, solvent, inorganic base and temperature, the enantioselectivities remained moderate. Several pentanidiums with different steric or electronic patterns were prepared and it was found that levels of enantioselectivities significantly increases with the introduction of halogen to the pentanidiums (**2h-2j**). On the contrary, pentanidium **2k**, containing OMe substituted side arms, results in significant deterioration of enantioselectivity.

a) **Base-mediated retro-Michael elimination**

b) **Fluoride-mediated retro-Michael elimination**

c) **Heat-mediated elimination**

Scheme 8. Methods for the *in situ* generation of sulfenate.

Scheme 9. Development of halogenated pentanidiums for sulfenate alkylation.

The generality of this reaction was systematically evaluated with a variety of sulfenate precursor **13** and alkyl halides using halogenated pentanidiums **2i** or **2j**. By trapping 2-thienyl sulfenate with various alkyl bromides, various sulfoxides **14a-i** bearing benzyl, alkyl, allylic, propargylic, 2-naphthylmethyl groups were produced in good enantioselectivities. When thienyl or benzothienyl sulfenates were utilized, sulfoxides **14j-o** were obtained in high yields and excellent enantioselectivities (Scheme 10). It is noteworthy that the reaction between sulfenate and *m*-xylene dibromide furnished *bis*-sulfoxide **14k** in good yield (87%, *dl/meso* = 4.75:1) and excellent enantioselectivity. Sulfenates functionalized with furyl, benzofuryl and benzimidazole moieties were also smoothly converted to their corresponding heterocyclic sulfoxides **14p-s**.

Remarkably, benzimidazole sulfoxide **14s**, reminiscent to the drug esomeprazole,²² was obtained in excellent enantioselectivity.

Scheme 10. Halogenated pentanidium **2i** or **2j**-catalyzed alkylation of sulfenate anion.

Preliminary mechanistic studies on the retro-Michael/alkylation reaction found that the base-promoted *in situ* generated sulfenate anion, could undergo sulfur alkylation, oxygen Michael addition or alkaline hydrolysis, depending on reaction conditions (Figure 4a). When a less active alkylating reagent, benzyl chloride, was used, only oxa-Michael adduct **15** was obtained even in the presence of pentanidium **2c**. On the contrary, sulfoxide **14a** was produced through sulfur alkylation using iodinated-pentanidium **2j**. These experimental studies indicated that iodinated-

pentanidium **2j** activated and stabilized both the electrophilic alkylating reagents and the sulfenate.

Figure 4. a) Diverse reaction pathways of sulfenate anion, b) optimized most *R*-TS and c) proposed mechanistic model.

Computational studies were performed to obtain the most stable transition state (TS) structure for the *R*- and *S*-sets of the TS at M06/BS1:UFF calculated with ONIOM method in Gaussian09A2. It was found that the *R*-TS, which leads to the experimental product **14a** with *R* configuration, is more stable than the *S*-TS by 1.2 kcal mol⁻¹ in terms of the Gibbs free energy (Figure 4b). Theoretical study on stereoselectivity is consistent with experimental observations. Further analysis of the non-covalent interactions between iodinated-pentanidium **2j** and the substrates revealed that Br-I halogen bonding²³ between the leaving Br of benzyl bromide and iodide on the iodinated-pentanidium **2j**, plays a key role to stabilize the TS (Figure 4c).

2.5 Pentanidium-catalyzed alkylation of dihydrocoumarins

Scheme 11. a) Silylamide **BSA** as a probase, b) effect of halogenated pentanidiums and c) identification of silyl ketene acetal **18** as an intermediate.

We found that halogenated pentanidiums **2h-j** exhibited excellent stereocontrol in the alkylation of dihydrocoumarins **16**, using silylamide as the probase (Scheme 11).²⁴ In this strategy, a base with strong basicity but weak nucleophilicity would be generated *in situ* and consumed immediately for the formation of an enolate (Scheme 11a).²⁵ The potential background and side reactions are thus suppressed when employing this transient strong base. The approach will allow the utilization of base-sensitive substrates and reagents, consequently expanding the scope of asymmetric phase transfer reactions. For instance, dihydrocoumarins **16a**, which will undergo alkaline hydrolysis in the presence of alkali metal alkoxides or

hydroxides, due to the labile lactone moiety, was smoothly converted to the alkylated product **17a** in high yield and excellent enantioselectivity. Silyl ketene acetal **18** was identified as a key intermediate *via* NMR analysis of the crude reaction mixture. This was further verified by the direct benzylation of pre-prepared silyl ketene acetal **18** (Scheme 11c). This reaction is suitable for lactones including dihydrocoumarins, 3,4-dihydro-2H-benzo[h]chromen-2-ones and 1,2-dihydro-3H-benzo[f]chromen-3-ones (Scheme 12).

Scheme 12. Halogenated pentanidium **2i**-catalyzed enantioselective alkylation of lactones.

3. BISGUANIDIINIUM-CATALYZED ION PAIRING ENANTIOSELECTIVE REACTIONS

In 2013, we found that bicyclic guanidinium salt **1·HI** can operate under phase transfer conditions for the alkylation of 3-substituted 2-oxindoles (Scheme 13).²⁶ Recently, we

developed dicationic bisguanidinium **3**, which was initially designed with the intention to work with dianions or multiple anions. Bisguanidinium salts²⁷ (**BG**) **3** features two guanidinium moieties linked with various spacers (Scheme 14). For ease of synthesis, commercially available cyclic secondary diamines such as piperazine were examined as spacers between the two chiral imidazolinium salts. The dicationic bisguanidinium salts **3** were thus achieved in excellent yields and are amenable to modification. We hope that the dicationic moiety will lead us to discover new chemistries.

Scheme 13. Guanidinium **1·HI**-catalyzed phase-transfer alkylation reaction.

Scheme 14. General route to bisguanidinium salts **3** with piperazine as spacer.

In conventional cationic phase transfer catalysis, most reactions are Brønsted base reactions, which the functional anion is usually either hydroxide or carbonate. Occasionally, other functional anions such as cyanide (CN^-) and hypochlorite (ClO^-) are used in phase transfer Strecker or oxidation reactions respectively. An innovative example is the use of (hypo)iodite

(IO⁻), generated *in situ* from iodide, by Ishihara for the phase transfer oxidative cycloetherification.²⁸ However, these reactions are but a subset of a more general strategy of chiral cationic ion pairing catalysis, which is defined as reactions using a catalyst composed of an organic chiral cation and an inorganic anionic salt (Figure 5).²⁹ In theory, all functional inorganic anions are possible counterparts to the chiral cations including organometallic anions. This mode of catalysis is complementary to the anion-directed catalysis using chiral phosphates.³⁰ Motivated by the desire to exploit more cation-directed anionic inorganic reagents, we began to systematically investigate metal-centered anions, beginning with metal oxides.

Figure 5. Chiral cationic ion pairing catalysis.

3.1 Bisguanidinium-catalyzed dihydroxylation and oxohydroxylation of α -aryl acrylates

Permanganate (MnO₄⁻) oxidation of alkenes under phase transfer condition was first reported using stoichiometric amount of a *Cinchonidinium* salt.³¹ Moderate enantioselectivities and low yields were reported. The lack of catalytic activity of *Cinchonidinium* phase transfer catalyst is ascribed to its decomposition under the oxidation conditions. In the early stage of our research,

we conducted simple experiments to determine the stability of dicationic bisguanidiniums in the presence of large excess KMnO_4 ; we found that bisguanidiniums **3a-d** (Scheme 14) were compatible with the oxidation conditions and were recoverable after the reactions. With 2.0 mol% **BG** (*S,S*)-**3d** and 20 wt% aqueous potassium iodide (KI), the oxidation of the α,β -unsaturated ester **21a** proceeded smoothly to afford diol **22a** with excellent enantioselectivity.³² The yield is moderate as a side product **23a** is formed due to C-C cleavage (Scheme 15). Generally, substrates bearing electron-rich aryl groups results in higher enantioselectivities than electron-deficient ones. We were surprised that thioether group is well tolerated in this methodology. We also demonstrated that this methodology is highly selective for α,β -unsaturated esters over simple alkenes.

Scheme 15. Bisguanidinium **3d**-catalyzed dihydroxylation of α -aryl acrylates.

Trisubstituted enoates were also investigated for the permanganate-mediated alkene oxidation (Scheme 16). With 2.0 mol% of **BG** (*S,S*)-**3c**, a mixture of *Z,E*-trisubstituted enoates **24a** provided two diastereoisomers, diols **25a** and **25a'** in high enantioselectivities with a significant

amount of the cleavage product observed. In an attempt to improve the yield of the desired diols, various additives were examined. When the pH of the reaction was lowered through the addition of acetic acid, 2-hydroxy-3-oxocarboxylic ester **26a** was unexpectedly obtained exclusively in high yield and high enantioselectivity (Scheme 16). The observed high enantioselectivity indicates that both *Z*- and *E*-trisubstituted enoates **24a** were transformed to the same enantiomer **26a** under these conditions. The reaction pathways to diols and C-C cleavage products were efficiently suppressed and we named this transformation, oxohydroxylation. Substrates bearing alkyl, thienyl, furyl, alkene moieties are well tolerated and a series of 2-hydroxy-3-oxocarboxylic esters **26a-n** with high levels of enantioselectivities were achieved. Enantioenriched α -hydroxymalonates **26o-p** were prepared using methoxy-substituted enoates *E*-**24o-p** as starting materials.

Scheme 16. Bisguanidinium **3c**-catalyzed oxohydroxylation of trisubstituted enoates.

Scheme 17. a) Selectivity between $\text{TBA}^+\text{MnO}_4^-$ and KMnO_4 , b) cyclic manganate diester **27** as an intermediate and c) proposed ion pairing working model.

A control reaction was attempted using 1.5 equivalent of tetrabutylammonium permanganate, an oxidant soluble in organic solvent (Scheme 17a). The reaction provided high level of chiral induction, which led us to propose that rate acceleration through ion pairing rather than the phase transfer step is crucial for asymmetric induction. Cyclic manganate diester **27**³³ is widely recognized as the common intermediate in permanganate reaction and we proposed that it is

through this intermediate that different products are obtained, *via* diverse pathways (Scheme 17b). We found that the isolated diols **25** were not further oxidized to **26** under oxohydroxylation conditions, indicating that the diols are not intermediates in oxohydroxylation.

The absolute configuration of the α -chiral center of oxidation products **26**, derived from both *Z*- and *E*-trisubstituted enoates **24**, is identical. On the basis of Lee's prior work³⁴ and our experimental results, a working model of reaction acceleration through the formation of an intimate ion pair between bisguanidinium and enolate anion in the transition states was proposed (Scheme 17c). The results reveal that rate acceleration is mainly attributed to transition state stabilization through strong electrostatic interaction between dicationic **BG** and enolate anion. The disclosure of this catalytic asymmetric permanganate oxidation opens up new paradigms for chiral cation-directed catalysis. Exploration of other functional anions will undoubtedly lead to the discovery of interesting new transformations for asymmetric synthesis.

3.2 Bisguanidinium diphosphatobisperoxotungstate-catalyzed sulfoxidation

Peroxtungstate species have been reported to serve as catalyst for oxidation reactions such as epoxidation³⁵ and sulfoxidation.³⁶ Since peroxotungstate are anionic species, we hypothesized that their reactions can be accelerated and modulated using chiral cations. We found that with 2.0 mol% of **BG** (*S,S*)-**3a** and 2.0 mol% of Ag₂WO₄, oxidation of heterocyclic sulfides **28a** went smoothly to produce sulfoxides **29a** with excellent enantioselectivities (Scheme 18).³⁷ Notably, the amount of additive, NaH₂PO₄ or NH₄H₂PO₄ is crucial to achieve high yield and high stereoinduction. A series of enantioenriched sulfoxides **29a-q** bearing benzimidazole, benzothiazole, pyridine, thiophene moieties were obtained, which are of potential interest for

drug development. The practical utility was further illustrated in the preparation of proton-pump inhibitor (*S*)-Lansoprazole **29l**.

Scheme 18. Bisguanidinium diphosphatobisperoxotungstate-catalyzed sulfoxidation.

Experimentally, we found that a ratio of greater than 2 equivalent of dihydrogen phosphate (H_2PO_4^-) with respect to tungstate is essential for achieving high enantioselectivity. Raman spectra of the active catalyst was obtained (Figure 6) and an experimentally peak observed at 711 cm^{-1} corresponds well to a peak at 713 cm^{-1} in the computed Raman spectra of

$[\{\text{PO}_2(\text{OH})_2\}_2\{\text{WO}(\text{O}_2)_2\}]^{2-}$. This peak is attributed to the twisting of P-O-H group in the phosphate ligand. A more thorough analysis of the $[\{\text{PO}_2(\text{OH})_2\}_2\{\text{WO}(\text{O}_2)_2\}]^{2-}$ revealed that an intramolecular hydrogen bond interaction between the two phosphate ligands is important for this peak; absence of such interaction will shift the vibrational frequency towards 800 cm^{-1} . We thus proposed that the active anion is diphosphatobispermoxotungstate $[\{\text{PO}_2(\text{OH})_2\}_2\{\text{WO}(\text{O}_2)_2\}]^{2-}$ (Scheme 19a). Based on both computational and experimental results, a simple working model is proposed detailing the formation of diphosphatobispermoxotungstate and its transport from the aqueous to the organic phase (Scheme 19b).

Figure 6. Experimental Raman spectrum of $[\{\text{PO}_2(\text{OH})_2\}_2\{\text{WO}(\text{O}_2)_2\}]^{2-}$.

Scheme 19. a) Diphosphatobis(oxotungstate) **30** and b) proposed working model.

3.3 Bisguanidinium dinuclear oxodiperoxomolybdates-catalyzed sulfoxidation

Similar to peroxotungstates, peroxomolybdates³⁸ are well-known catalysts for oxidation reactions.³⁹ However, they are typically complex mixtures and it is widely recognized as the challenging obstacle for elaborating them into highly enantioselective catalyst. In the attempt to prepare enantiopure sulfoxides of 2-sulfinyl esters through alkylation of sulfenate anions using α -halogenated carboxylate, an unsatisfactory outcome was observed. Thus, direct sulfoxidation strategy was adopted to gain access to 2-sulfinyl ester sulfoxides **31a**, which can be further elaborated to a commercial drug armodafinil. We found that with 2.5 mol % $\text{Na}_2\text{MoO}_4 \cdot 2\text{H}_2\text{O}$ and potassium hydrogen sulfate (KHSO_4), the oxidation proceeded efficiently with 1.0 mol% of **BG** (*S,S*)-**3a** and H_2O_2 as oxidant (Scheme 20a).⁴⁰ Its practical utility was successfully demonstrated in the gram-scale synthesis of (*R*)-modafinil (armodafinil) using a 0.25 mol% loading of (*R,R*)-**3a** (Scheme 20b).

Scheme 20. a) Catalytic molybdate-mediated sulfoxidation and b) preparative scale synthesis of armodafinil.

The reactive catalytic species can be prepared by mimicking the reaction conditions in the absence of sulfide substrate (Scheme 21). The active catalyst was collected as a pale-yellow precipitate through filtration and the structure of the catalyst, $(R,R)\text{-3a-[Mo]}$, was confirmed using *X*-ray analysis (Figure 7)⁴¹ and ⁹⁵Mo NMR.⁴² The achiral anionic molybdenum species $[(\mu_2\text{-SO}_4)\{\text{Mo}_2\text{O}_2(\mu_2\text{-O}_2)_2(\text{O}_2)_2\}]^{2-}$ is revealed by *X*-ray crystallography to be embedded within the chiral cavity formed by two side arms of the chiral bisguanidinium dication.

Scheme 21. Identification of the active catalyst.

Figure 7. X-Ray crystallographic structure of $[\text{BG}]^{2+}[(\mu_2\text{-SO}_4)\{\text{Mo}_2\text{O}_2(\mu_2\text{-O}_2)_2(\text{O}_2)_2\}]^{2-}$ (*R,R*)-**3a**-[Mo](ellipsoids at 50% probability)

The catalyst (*R,R*)-**3a**-[Mo] displayed excellent catalytic activity in sulfoxidation with H_2O_2 as oxidant (Scheme 22). (*R,R*)-**3a**-[Mo] was used directly as a stoichiometric oxidant and it provided sulfoxide **ent-31a** in 90% yield and 80% *ee*. This result confirm that (*R,R*)-**3a**-[Mo] is the actual oxidant and high level of enantiodiscrimination can be achieved. However, using just 0.25 equivalent of (*R,R*)-**3a**-[Mo] led to the formation of **ent-31a** in 50% yield with 31% *ee*; demonstrating that two out of four peroxo moieties on (*R,R*)-**3a**-[Mo] are active oxygen donors as two equivalents of active oxygen from (*R,R*)-**3a**-[Mo] are transferred to the sulfides. On the basis of the experimental results, a possible mechanistic model was proposed (Scheme 23).⁴³ It is proposed that the second oxygen transfer is slower and less enantioselective than the first. In the presence of H_2O_2 , the dimeric structure of the catalyst will be maintained and it is this structure that provides the highly effective enantiofacial discrimination.

Scheme 22. Mechanistic studies by using $[\text{BG}]^{2+}[(\mu\text{-SO}_4)\text{Mo}_2\text{O}_2(\mu\text{-O}_2)_2(\text{O}_2)_2]^2(R,R)\text{-3a-[Mo]}$.

Scheme 23. Proposed catalytic cycle of bisguanidinium dinuclear oxodiperoxomolybdsulfate.

3.4 Bisguanidinium-catalyzed alkylation of cyclic ketones

Previously, we used the silylamide probase strategy with pentanidium as catalyst, to achieve the highly enantioselective alkylation of lactones²⁴. For cyclic and linear ketones, we found that bisguanidiniums are more suitable. The probase can act as a silylation reagent to generate silyl enol ether, which is a key intermediate for the alkylation. With 10 mol% of **BG** (*S,S*)-**3a** and 2 equivalent of probase, bis(*tert*-butyldimethylsilyl)acetamide (**BTBSA**), a variety of α -benzyl-1-indanones and α -benzyl-tetralones **32a-i** can be smoothly converted to alkylation product **33a-i** in high yields and enantioselectivities (Scheme 24a).²⁴ TBS enol ether **34** was prepared from α -benzyl-1-indanone **32a** and submitted to the alkylation condition (Scheme 24b). The enantioselectivity and yield obtained were similar to the conditions using probase directly, demonstrating that TBS enol ether is an intermediate in the reaction. For the alkylation of linear

ketones, such as simple phenyl ethyl ketone, due to their low reactivity, the corresponding alkylation reaction can only be achieved *via* the preparation of their silyl enol ethers.

Scheme 24. a) Bisguanidinium **3a**-catalyzed enantioselective alkylation of cyclic ketones using probase strategy and b) identification of silyl enol ether as an intermediate.

Scheme 25. Proposed working model with **BG** hypervalent silicates ion pair.

Based on the experimental results, a working model for enantioselective alkylation using silylamide as probase is putatively proposed (Scheme 25). When the probase is activated with fluoride, **BG** silylamide is first formed followed by **BG** enolate **A**. Silyl enol ether **B** is subsequently formed *via* silylation with another silylamide. We found that the steric features of the probase affects strongly the enantioselectivities and bis(*tert*-butyldimethylsilyl)acetamide (**BTBSA**) afforded better results than bis(trimethylsilyl)acetamide (**BSA**). A **BG** hypervalent silicates ion pair **C** is proposed to be the key intermediate, which is responsible for the enantiofacial differentiation of the incoming electrophiles.

4. CONCLUSION AND PERSPECTIVES

Over the past few years, we have developed *N*-sp² hybridized guanidinium-type salts as efficient phase transfer catalysts. We have shown that these are general catalysts for a variety of transformations and reactions can be performed at a preparative scale with low loading of catalyst. In some cases, commercially important compounds are prepared as a demonstration of

industrial applicability. We have also articulated a new mode of catalysis at the interface of phase transfer catalysis, organocatalysis and organometallic catalysis. We describe the possibility of activating and modulating organometallic catalysts through ionic interactions and not through the use of ligands. Chiral cationic ion pairing catalysis is in its infancy and we hope that more colleagues will find this approach refreshing and join us in exploring and defining its scope.

AUTHOR INFORMATION

Corresponding Author

*E-mail: choonhong@ntu.edu.sg

Notes

The authors declare no competing financial interest.

Biographical Information

Lili Zong was born in Henan (China) in 1985. She received her B.S. in engineering from Harbin Institute of Technology (China) in 2006. She studied organic chemistry under the supervision of Professor Yixiang Cheng during her M.Sc. in Nanjing University (China). In 2010, she started her graduate studies at National University of Singapore under the tutelage of Professor Choon-Hong Tan. She is currently a postdoctoral fellow in the laboratory of Professor Stefan Matile at University of Geneva.

Choon-Hong Tan was born in Singapore in 1971. He received his BSc(Hons) First Class from the National University of Singapore in 1995. He obtained financial support from Trinity College (Cambridge), the Cambridge Commonwealth Trust and Tan Kah Kee Postgraduate Scholarship to pursue his PhD and he graduated from the University of Cambridge in 1999. Following that, he carried out postdoctoral training at Harvard University. He was a Research Associate at Harvard Medical School before joining the National University of Singapore in 2003 to start his

independent career. He joined Nanyang Technological University (Singapore) in 2012 and was promoted to Full Professor in 2016.

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