

Zwitterion-Induced Organic–Metal Hybrid Catalysis in Aerobic Oxidation

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1. INTRODUCTION

Zwitterionic compounds are a class of molecules that contain site-isolated positive and negative ions while the molecules are overall neutral.¹ Zwitterions have emerged as a new class of bifunctional organocatalysts that exhibit unusual reactivity and selectivity in various reactions.² The ion pairs in zwitterions can operate synergistically without self-neutralization through charge delocalization.³ Some important developments have been made using zwitterions to enhance catalytic performance in transition metal catalysis, although the cases are sporadic. For instance, Gessner and co-workers reported a class of phosphonium ylides as zwitterionic ligands for hydroamination and Buchwald coupling reactions.⁴ In addition, Albrecht and co-workers developed donor-flexible $N_{,N'}$ -bis(pyridylidene)oxalamide (bisPYA) zwitterionic ligands, which were found to be highly effective in the ruthenium-catalyzed Lemieux-Johnson-type oxidative cleavage of olefins.⁵ Compared with traditional neutral ligands, the application of zwitterions in transition metal catalysis remains largely under-exploited, partly due to lacking of efficient methods for the preparation of useful zwitterions. Therefore, it is important to explore the applications of zwitterions in transition metal catalysis, which could unveil new reactivities and bring new opportunities in tuning catalysts' properties.⁶

Recently, our group has developed a new class of aziridinederived $[N^+-N^-]$ **ZW1** and $[P^+-N^-]$ **ZW2** zwitterions, which were found to be highly effective in catalyzing (trans)esterification reactions, deacylative dihalogenation of β -oxo amides, intermolecular bromoesterification of alkenes, and isomerization of maleic acid esters.⁷ Mechanistic studies suggest that zwitterion-catalyzed reactions involve a synergistic activation mode involving the following: (1) the basic sulfonamide anion interacts with the electrophilies (H or Br); (2) the cationic moiety interacts with the carbonyl groups via a nonclassical hydrogen bond (NCHB),⁸ which involves the C-H···O noncovalent interaction between the α -C-H of the cation of zwitterion and the carbonyl oxygen of the substrate (Figure 1A). These structurally stable zwitterions were prepared simply by treating suitable aziridines with amine/phosphine bases.⁹ A library of zwitterionic catalysts can be accessed quickly, which is highly beneficial to reaction optimization. In addition, the structural rigidity of these zwitterions allows for effective site-isolation of the ion pairs for highly efficient catalysis. To our own quest to explore the application of these zwitterions in other catalytic transformations, herein we report the use of ZW2 in activating ruthenium trichloride for aerobic oxidation.

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Figure 1. (A, B) Applications of zwitterions in organo- and metal catalysis.

2. RESULTS AND DISCUSSION

2.1. Generation of Active Catalyst Species. Initially, we attempted to use zwitterion (\pm) -ZW2 as a bifunctional ligand to explore different metal-catalyzed reactions. After some screenings, interestingly, a white solid was obtained when ZW2 was mixed with hydrated ruthenium trichloride ($RuCl_3 xH_2O$) in wet 1,2-dichloroethane (DCE) at room temperature. A single crystal was successfully obtained and studied by X-ray crystallography (Figure 1B). It was found that ZW2 cocrystallized with a molecule of HCl and water (i.e., $ZW2 \cdot HCl \cdot H_2O$) potentially via multiple hydrogen bonds. Based on the position of the chlorine atom, it appears that the Brønsted basic amide anion interacts with a molecule of HCl via a hydrogen bond $(Cl-H^{c} = 2.398 \text{ Å}, \text{ assuming } N-H^{c} = 0.861 \text{ Å})$. The chloride also appears interacting weakly with the α -proton of the phosphonium cation and the proton of water. In addition, an NCHB interaction $(O-H^b = 2.565 \text{ Å})$ was observed between H_2O and the α -proton of the phosphonium cation in ZW2.

The oxygen positioned on top of $C-H^b$ with $C-H^b-O$ almost linear $(C-H^b-O = 162^\circ)$. The crystal sample was also studied by ¹H NMR in a solution phase (CDCl₃). Compared with pure ZW2, the downfield shifts of H^b (α -C-H of phosphonium, 3.46 ppm) and the existence of N-H^c (9.24 ppm) indicate that the ZW2·HCl complex remains stable in a solution phase. Besides the formation of ZW2·HCl complex, we believe that ruthenium oxide species (see Figure S4 in the Supporting Information) might be formed concurrently in this system because they were commonly synthesized under basic conditions.¹⁰ When compared with pure ZW2·HCl, the N-H NMR signal in the inorganic/organic catalyst mixture is more downfield shifted, indicating that there might be a hydrogen bond interaction between the inorganic and organic catalyst components (see Figure S5 in the Supporting Information). Generally, Ru-O species could be deposited on solid materials such as Al₂O₃ and Fe₃O₄ and further applied to heterogeneous catalysis.¹⁰ Thus, our method can be pubs.acs.org/acscatalysis

Research Article



Figure 2. Oxidation with $RuCl_3$ and various ligands.

considered as a new approach to generate Ru–O species via homogeneous systems.

Ruthenium trichloride is known to be relatively inert compared with other ruthenium complexes due to the strongly coordinating chloride anion.¹¹ Aerobic oxidation of benzyl alcohol catalyzed by RuCl₃ under 1 atm oxygen resulted in very low conversion.¹² Harsh reaction conditions are typically required for the oxidation reactions catalyzed by RuCl₃. For instance, it was reported that RuCl₃ catalyzed the oxidation of alcohols under high pressure (2-20 atm oxygen) at high temperature (100 °C) in the presence of amine ligands (e.g., Et_3N).^{13a,b} Similar oxidation could be proceeded at room temperature, but stoichiometric amount of dicyclohexylamine and much longer reaction time (2-4 days) were needed.^{13c} On the other hand, silver salts have been applied in order to remove the strongly coordinating chloride anion and provide more active ruthenium species.¹⁴ However, this process is expensive and AgCl is generated irreversibly as waste. Since

ZW2 can capture the chloride from ruthenium trichloride via noncovalent interactions under mild conditions, the protocol can potentially be used to activate the inert ruthenium trichloride for catalytic reactions.

2.2. Reaction Studies. Oxidation of alcohols to carbonyl compounds is a ubiquitous and pivotal reaction in both academic research and chemical industry, and the resulting compounds are important building blocks for medicines, agricultural chemicals, and fragrances.¹⁵ Thus, this transformation was chosen as a benchmark reaction to examine the performance of the catalytic protocol. Molecular oxygen (1 atm) was used as the terminal oxidant, which is highly desired in industrial processes because water molecules are the only byproduct. Alcohol **2a** was used as the model substrate with RuCl₃·xH₂O as the metal source, and the reaction was carried out under 1 atm oxygen at 23 °C. The background reaction was sluggish in the absence of an external additive (Figure 2). To our delight, the oxidation proceeded smoothly with



Conditions: reactions were carried out with substrate (0.3 mmol), RuCl₃•xH₂O (n mol%) and **ZW2** (3n mol%) in (CH₂Cl)₂ (0.2 M) in a sealed tube (10 mL capacity) under O₂ (1 atm) at the indicated time and temperature. The yields are isolated yields.





Figure 4. Catalyst recycling and chemoselective oxidation.

catalytic amount of zwitterion (\pm) -ZW1. The phosphonium zwitterion (\pm) -ZW2 showed better performance; the desired aldehyde 3a was obtained in 97% yield, and no side product 4a was detected. Fifty-five percent of 3a was obtained when the loading of RuCl₃ was reduced to 2.5 mol %. Optimum results were obtained when ruthenium trichloride and ZW2 were used in a 1:3 ratio. Generally, Lewis bases were used to enhance the activity or selectivity of metal catalysts. Therefore, typical neutral Lewis bases such as phosphines PL1–PL4 (PPh₃, PCy₃, DPPE, and DPPF), amines NL1–NL4 (TEA, TMEDA, DMAP, and Bpy), and *N*-heterocyclic carbene IPr were also evaluated but poor yields of 3a were observed. In particular, PL1 and PL2 gave significant amount of side product 4a.

Other zwitterions with different substituents or skeletons were also investigated. For (\pm) -ZW3 that is derived from an acyclic skeleton, the yield of 3a was unsatisfactory. Zwitterions



Figure 5. (A–D) Mechanistic studies.

derived from DMAP, DABCO, Me₃N, or PMe₃ [(\pm) -ZW4– (\pm) -ZW7] were examined but their catalytic performances were inferior to ZW2. Zwitterions derived from phenyl rings instead of cyclohexane were also studied; poor yields of 3a were observed with zwitterions ZW8–ZW10. These results indicate that both the cationic partner and the distance between the ion pairs are crucial for superior catalytic effects.

2.3. Reaction Scope. Catalytic performance was examined with various alcohol substrates (Figure 3). Benzyl alcohols with electron-donating (methyl, methoxy, and dimethylamine) or electron-withdrawing (halogen, nitro, methyl ester, and sulfonamide) substituents were successfully oxidized to the corresponding aldehydes in good yields (3a-3i). Alcohols with naphthyl, pyridinyl, and furanyl substituents were also found to be compatible with the catalytic protocol (3j-3l). Various secondary alcohols 2m-2r were also studied. Similar to the cases in the aldehyde synthesis, the desired aryl- and alkyl-substituted ketones 3m-3r were obtained smoothly. Gratefully, the catalytic system was also compatible with the oxidation of allylic alcohols 2s-2v to give the corresponding unsaturated carbonyl compounds 3s-3v. Notably, the olefin functionality in the substrates remained intact under the mild reaction conditions. The stereochemistry of the Z-olefin in Z-3s was also retained. Aliphatic and cyclic alcohols were subjected to investigation, and the desired carbonyl products were obtained smoothly (3w-3z and 3aa-3ad). The reaction

temperature was increased to compensate the slower reaction as a result of the less reactive alcohol substrates. Oxidation of tropine that contains an amine substituent gave no reaction and the substrate was recovered quantitatively, potentially due to the poisoning of the metal center or neutralization of **ZW2**· HCl by the amine.

We also explored the application of the catalytic protocol to other class of substrates. Delightedly, oxidative dehydrogenation of hydroquinone **5a** gave 1,4-benzoquinone **6a** in 86% yield using 2.5 mol % of RuCl₃ catalyst. In addition, substituted hydroquinones **5b**–**5d** were converted into 1,4-benzoquinones **6b**–**6d** in excellent yields. Moreover, 1,4-naphthoquinone **6e** was furnished successfully starting from 1,4-dihydroxylnaphthalene **5e**. A brief examination on other oxidation reactions was conducted. Interestingly, the reaction could also be applied to the oxidative dehydrogenation of indolines 7 to indoles **8**. Quinoxaline **10** was also obtained through the double oxidation of 1,2,3,4-tetrahydroquinoxaline **9**.

Practicality of the oxidation was demonstrated by conducting the reaction under ambient air at a gram scale (Figure 4). Gratefully, the oxidation reaction of **2a** proceeded smoothly to give aldehyde **3a** in 95% yield under the optimal conditions. In addition, the catalyst could be recovered simply by precipitation and the recycled catalyst could promote the same reaction without observable loss of catalytic efficiency. The catalytic protocol could also be applied to the chemo-



Figure 6. (A-C) Studies on the role of zwitterion.

selective oxidation of diol **2ae**, and the mono-oxidized product **3ae** was obtained exclusively.

2.4. Mechanistic Studies. Several control experiments were conducted to shed light on the mechanism. Kinetic isotopic effect (KIE) experiments were performed to reveal the process of C-H cleavage (Figure 5A). Mono-deuterated substrate **2a-D** was subjected under the standard oxidation conditions, and the ratio of $k_{\rm H}/k_{\rm D}$ of product **3a** was found to be 5.75, indicating that the C-H abstraction of substrate **2a** might be the rate-determining step.¹² Radical clock experiments were conducted with substrate **2af** under the standard conditions (Figure 5B). The desired ketone product **3af** was obtained quantitatively and no cyclopropane ring-opening product **12** was detected, suggesting that the reaction is unlikely to go through the putative benzylic radical intermediate **11**. Furthermore, no signal relevant to the redox of Ru was observed in the cyclic voltammetry study,

suggesting that the reaction might not undergo via redox of the Ru center (see Figure S6 in the Supporting Information). Next, the di-deuterated substrate $2a-D_2$ together with the unsaturated ketone 13 was subjected to the reaction conditions under N₂ (Figure 5C). Interestingly, appreciable amount of deuterated compound 14 was detected. Thus, we speculated that the deuterium in substrate $2a-D_2$ might be captured to form the Ru-D species, which could reduce unsaturated ketone 13 through Michael addition.¹⁶ We also conducted a control experiment by carefully measuring the amount of oxygen used in the reaction in a sealed tube (Figure 5D). It was found that 0.5 equiv of molecular oxygen (i.e., 1 equiv of oxygen atom) was sufficient to drive the reaction to completion.

In order to understand the role of chloride anions, various silver salts including $AgSbF_6$, $AgBF_4$, and AgOTf were added in order to displace the chloride counteranion (Figure 6A).¹⁷ It was found that the reaction efficiency was affected by the basicity of the counteranions and chloride showed the better catalytic activity than other less coordinating anions. In the absence of **ZW2**, the silver salts alone were also tested to displace the chloride from $RuCl_3 \cdot xH_2O$ and only trace amount of oxidized product was observed. These results suggest that the catalytic efficiency of the protocol was not done by simply removing the strongly coordinating chloride counterion from the ruthenium center.

Next, we attempted to probe the role of ZW2 in the reaction. Phosphonium salt PBr and tosyl amide NLi, which are the segmented catalysts of ZW2, were also evaluated (Figure 6B). A sluggish reaction was observed when either of these components or their 1:1 mixture was used, indicating that the site-isolated cation and anion in ZW2 might work synergistically. The ZW2·HCl complex was used instead of ZW2 in the reaction, and the oxidation gave no conversion, suggesting that the basicity of ZW2 is pivotal to activate ruthenium trichloride at the initial stage in order to achieve high catalytic performance. Another set of experiment was carried out with ZW2 or ZW2·HCl alone as the catalyst, and no reaction was observed. This result reveals that the organic (ZW2) and inorganic (Ru-O species) components are both necessary in the catalytic system. Potassium carbonate was added to the reaction in order to capture the acidic proton on ZW2·HCl that was in situ generated in the reaction. Reaction yield of the desired product dropped dramatically, implying that the acidic proton is also playing a crucial role. When 4 Å molecule sieves were added to remove moisture, the catalytic performance diminished significantly, which indicates the important role of water.

We suspected that the N–H–Cl moiety in the **ZW2**·HCl complex might interact with the alcohol substrate via a hydrogen bond.¹⁸ Indeed, after adding 4-methylbenzyl alcohol (**2b**) to a solution of **ZW2**·HCl in CDCl₃, it was found that protons of the TsN–H moiety of **ZW2**·HCl (both the N–H and the aromatic region) shifted upfield significantly while the α -H of phosphonium (H^a) shifted downfield (Figure 6C). At the same time, protons at the benzyl group (H^c and H^d) of the substrate shifted upfield. These chemical shifts could be corresponding to the putative complex **A** that contains hydrogen bonds between O–H in the substrate and H–Cl in **ZW2**·HCl.

A plausible mechanism was established by piecing the abovementioned experimental results (Figure 7). First, the amide anion in **ZW2** might coordinate with the ruthenium center of ruthenium trichloride, causing the dissociation of



Figure 7. Plausible mechanism.



Figure 8. Catalytic transfer semi-hydrogenation.

chloride to give ZW2·HCl. We speculate that the NCHB originating from the phosphonium cation might assist the dissociation of the strongly coordinating chloride anion from the ruthenium center (Figure 1B) and the cooperative effect of the amide anion and phosphonium cation appears to be crucial (Figure 6B). Hydrolysis might take place concurrently, giving Ru-O species as the metal catalyst component in the reaction system. This degradation of ruthenium trichloride could be suppressed when the basicity of ZW2 was neutralized or the water was removed (Figure 6B). Then, the alcohol substrates might be activated by the ZW2·HCl complex via hydrogen bonds to give species A (Figure 6C). We believe that such interaction might be interrupted by removing the chloride anion (Figure 6A) and the acidic proton (Figure 6B). Subsequently, the Ru-O species might oxidize the alcohol together with the generation of Ru–H species (Figure 5C) via β -H elimination. In the presence of molecular oxygen, the ruthenium hydride species might give the Ru-OOH species via insertion (Figure 5D). Since 0.5 equiv of molecular oxygen is sufficient for the reaction, we suspect that Ru-OOH species might eliminate $1/2O_2$ to give Ru–O species, which could be used in the next catalytic cycle.^{12,13a,19}

2.5. Transfer Hydrogenation. Since ruthenium hydride intermediates might be involved in the catalytic cycle, we speculated that the zwitterion might be applicable to the transfer hydrogenation reaction of alkyne **15** (Figure 8). Preliminary studies showed that the RuCl₃ (4 mol %)/**ZW2** (8 mol %) catalytic protocol gave small amount (c.a. 5%) of *trans*-1,2-diphenylethylene (**16**). Further optimization revealed that using [Ru(cymen)Cl₂]₂ together with **ZW2** effectively catalyzed the transfer semi-hydrogenation of diphenylacetylene (**15**) into *trans*-1,2-diphenylethylene (**16**) in 80% yield. More importantly, excellent stereoselectivity (**16**:17 = 40:1) was

observed. In contrast, Lewis bases such as triphenylphosphine **PL1** and NHC carbene **IPr** gave only moderate yield and stereoselectivity.

3. CONCLUSIONS

In summary, we report a new strategy of capturing chloride anions from RuCl_3 catalysts using a novel organic $[P^+\cdot N^-]$ zwitterion compound via multiple hydrogen bond interaction (classical and nonclassical hydrogen bonds). The organic (**ZW2**·HCl) and inorganic (Ru–O species) catalytic components were in situ generated, which were found to be useful in catalytic aerobic oxidation of alcohols, hydroquinolines, and indolines under mild conditions. Mechanism studies revealed that the chloride anion was pivotal for catalytic efficiency. A more detailed mechanistic study is currently underway to elucidate a clearer picture on role of the zwitterionic compounds in the reactions. This proof-of-concept study opens a new avenue for catalyst design in metal catalysis chemistry.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.0c05684.

Experimental details and spectroscopic and analytical data for new compounds (PDF) Crystallographic data of **ZW2**·HCl (CIF)

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Notes

The authors declare no competing financial interest.

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