SCIENTIFIC REPORTS

Chemoselective reduction and oxidation of ketones in water through control of the electron transfer pathway

Sun Min Kim[1], Ho Sung Yoo[1,2], Hideo Hosono[3,4], Jung Woon Yang[1] & Sung Wng Kim[1,2]

The selective synthesis of different products from the same starting materials in water, which is the most abundant solvent in nature, is a crucial issue as it maximizes the utilization of materials. Realizing such reactions for ketones is of considerable importance because numerous organic functionalities can be obtained via nucleophilic addition reactions. Herein, we report chemoselective reduction and oxidation reactions of 1,2-diketones in water, which initiates anionic electron transfer from the inorganic electride $[Ca_{24}Al_{28}O_{64}]^{4+} \cdot 4e^-$, through controlling the pathway of the electrons to substrates. The generation of different radical species for transient intermediates was the key process required to control the reaction selectivity, which was achieved by reacting the anionic electrons with either diketones or O_2, leading to the formation of ketyl dianion and superoxide radicals in the reduction and oxidation reactions, respectively. This methodology that utilizes electrides may provide an alternative to the pulse radiolysis of water in synthetic chemistry.

Water, which is the most versatile substance in nature, has attracted public and scientific interest in diverse fields, such as biology, physics, chemistry and materials science, because of its ecological and economic importance for life[1–4]. Following nature's chemical lead, considerable efforts have focused on using water as a solvent in synthetic organic chemistry for the development of practical reactions[5–8]. Although the use of water as the solvent in organic reactions has been restricted by hydrolysis reactions[9,10], the discovery of Diels-Alder reactions[11] triggered the widespread use of water as an alternative solvent for replacing typical organic solvents, such as THF, toluene and alcohols, and for enhancing the rates and selectivities of reactions[12–14]. The myriad of uses of water in organic chemistry is attributed to the characteristic features of water, including its hydrophobic, hydrogen bonding and polarity effects, which accelerate electron transfer as one of the key processes in water-mediated reactions[15,16].

The investigation of electron transfer in aqueous solutions was motivated by the discovery of solvated electrons during the pulse radiolysis of water, which is a well-established technique for the generation of electrons in water[17,18]. However, the short lifetime of solvated electrons and the generation of highly reactive radical species (e.g., $\cdot OH$, $\cdot O^{2-}$, $\cdot O_2H$, etc.) have hindered the widespread use of water in synthetic chemistry due to the degradation of both the reactivity and selectivity of the reactions[19]. Furthermore, the generation of excess electrons and radicals reduces selective electron transfer to organic substrates or induces over-reaction due to multiple electron transfer[20]. Thus, in water-mediated organic reactions, control over the electron transfer pathway is crucial for designing reactions with high yields and selectivities.

[1]Department of Energy Science, Sungkyunkwan University, Suwon 440-746, Republic of Korea. [2]IBS Centre for Integrated Nanostructure Physics, Institute for Basic Science, Suwon, Republic of Korea. [3]Materials Research Center for Element Strategy, Materials and Structures Laboratory, and Frontier Research Center, Tokyo Institute of Technology, 4259 Nagatsuta, Midori-ku, Yokohama 226-8503, Japan. [4]ACCEL Project, Japan Science and Technology Agency, 4-1-8 Honcho, Kawaguchi, Saitama 332-0012, Japan. Correspondence and requests for materials should be addressed to J.W.Y. (email: jwyang@skku.edu) or S.W.K. (email: kimsungwng@skku.edu)
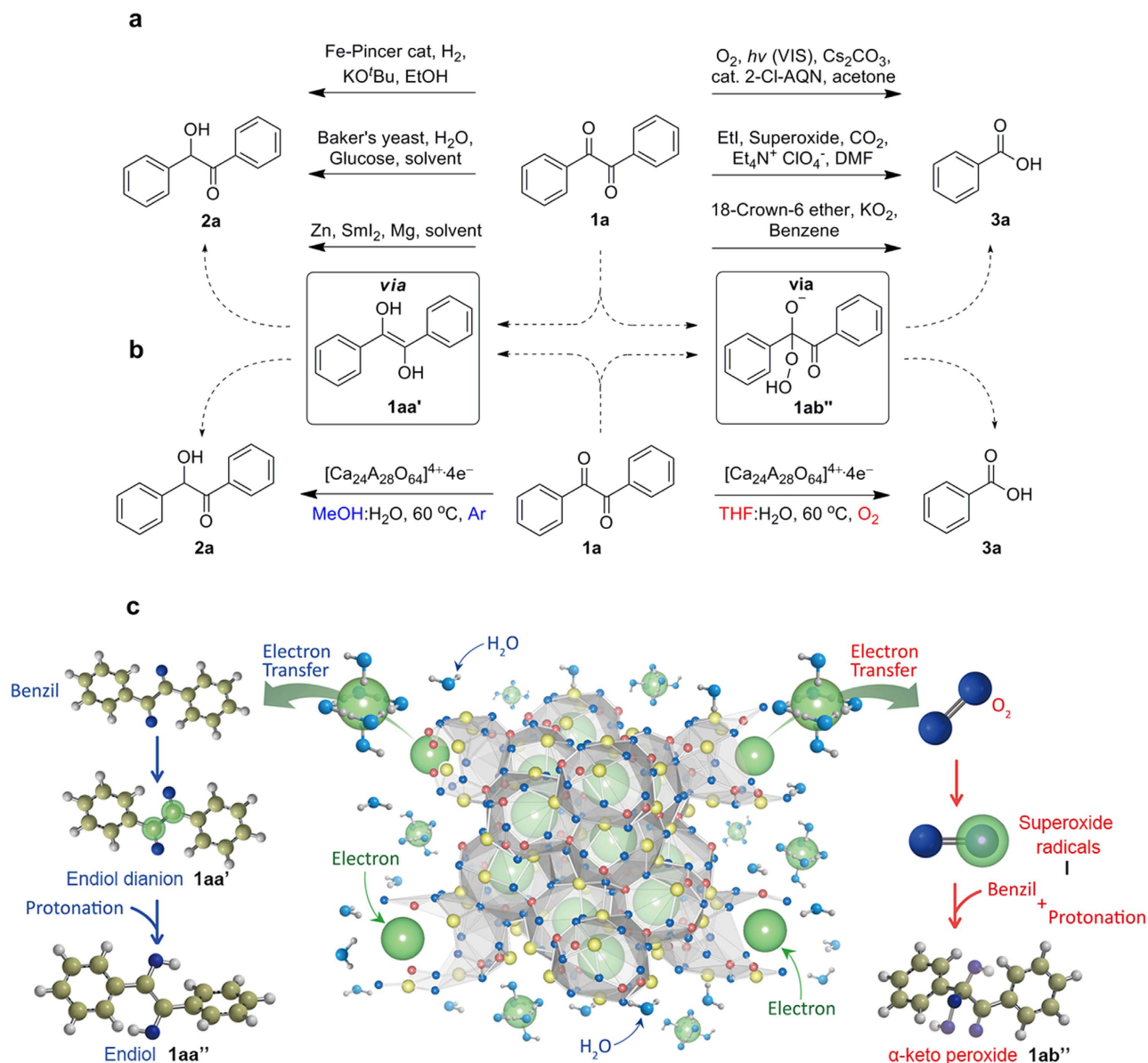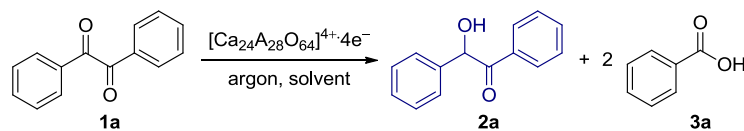
Figure 1. Strategies for the chemoselective reduction and oxidation of 1,2-diketones using the [Ca$_{24}$Al$_{28}$O$_{64}$]$^{4+}$·4e$^-$ electride. (**a**) Previous reports on reduction and oxidation reactions of benzil via the electron transfer process. (**b**) Present work on the chemoselective reduction and oxidation of benzil using the [Ca$_{24}$Al$_{28}$O$_{64}$]$^{4+}$·4e$^-$ electride. (**c**) Schematic illustration of the chemoselective reduction and oxidation of benzil by controlling the electron transfer pathway to benzil or O$_2$ via the release of electrons from the [Ca$_{24}$Al$_{28}$O$_{64}$]$^{4+}$·4e$^-$ electride via hydrolysis as well as the possible solvation of electrons by water molecules.

The development of chemoselective organic transformations is one of the most fundamental tasks in synthetic chemistry because it reduces material consumption, superfluous trimming and re-functionalization steps in reactions[21,22]. In particular, achieving chemoselectivity in water-mediated reactions by controlling the electron transfer pathway enables a single reactant to be transformed into structurally diverse products with different functionalities. However, the chemoselectivity of fundamental reactions in water, such as oxidation and reduction, has not been previously explored. Herein, we report chemoselective reactions both reduction and oxidation of 1,2-diketones in water by controlling the intermolecular electron transfer pathway with inorganic [Ca$_{24}$Al$_{28}$O$_{64}$]$^{4+}$·4e$^-$ electrides.

Electrides are ionic crystals with cavity-trapped electrons that act as anions[23]. The first electride was synthesized in 1983 using crown ethers and solvated electrons in alkali-ammonia solutions to provide precursors for anionic electrons[24]. Because the organic electrides were chemically and thermally unstable and decomposed in ambient conditions, their applications for synthetic chemistry were limited[25]. In 2003, the first electride stable at room temperature was synthesized using the inorganic complex oxide

Table 1. Optimization of the chemoselective reduction of **1a** using $[Ca_{24}Al_{28}O_{64}]^{4+} \cdot 4e^-$ electride[a]. [a]Performed with **1a** (0.2 mmol) in solvent (8 mL). [b]E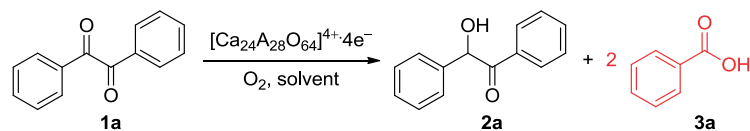quivalents of electride with respect to 1,2-diketone **1a**. [c]Isolated yields. [d]Partially oxygenated THF was used. [e]Using $[Ca_{24}Al_{28}O_{64}]^{4+} \cdot 2O^{2-}$.

$12CaO \cdot 7Al_2O_3$ to form $[Ca_{24}Al_{28}O_{64}]^{4+} \cdot 2O^{2-}$, which has a positively charged $[Ca_{24}Al_{28}O_{64}]^{4+}$ framework composed of 12 subnanometer-sized cages and two O^{2-} ions as counteranions[26]. Because of the anionic electrons, the $[Ca_{24}Al_{28}O_{64}]^{4+} \cdot 4e^-$ electride exhibited unique properties, such as improved electron transfer performance due to its low work function (~2.4 eV)[27] and transformation to a molten state at 1873 K while maintaining the solvated electrons[28]. This inorganic electride has recently appeared in a new class of reagents that serves as electron generators in aqueous solutions, facilitating the pinacol coupling reaction of aldehydes[29]. One consequence of the reaction between the $[Ca_{24}Al_{28}O_{64}]^{4+} \cdot 4e^-$ electride and water is that when electrides are dissolved in water, the anionic electrons that are loosely trapped in cavities can be released and directly transferred to the reactants, thus facilitating chemical reactions. Applying $[Ca_{24}Al_{28}O_{64}]^{4+} \cdot 4e^-$ electrides to water-mediated chemoselective reactions of ketones, which are ubiquitous functional groups, can provide important insights into the fundamental roles of electrons in water-mediated synthetic organic reactions and a broad opportunity for producing diverse functional molecules.

Results and Discussion

Figure 1 describes the strategy for realizing chemoselective oxidation and reduction reactions of ketones in water through controlling both the electron transfer pathway and the formation of different intermediates in each reaction. When the targeted electron acceptor is benzil **1a**, which is the model substrate selected for incorporating an electron acceptor (such as a carbonyl moiety), the path of the reaction is primarily dependent on the type of catalysts and reagents being used[30–37]. In fact, either the oxidation or reduction reaction of benzil **1a** can occur by using different reagents that completely alter the formation of intermediates to result in enediol **1aa"** in reduction reactions and α-keto peroxide **1ab"** in oxidation reactions (Fig. 1a). However, despite extensive research on the reaction of benzil with diverse electron transfer reagents and solvents, there was no success in utilizing both electron transfer pathways with one reagent in a highly selective manner. Furthermore, a selective reaction in the presence of water is difficult to achieve because of the vigorous water splitting reactions that occur between the excess electrons from the reagents and water. Nevertheless, as shown in Fig. 1b, it is hypothesized that the chemoselective reaction of benzil **1a** in the presence of water is possible if the electrons are smoothly generated through a moderate cage-opening rate by the robustness of the $[Ca_{24}Al_{28}O_{64}]^{4+} \cdot 4e^-$ electride in water, which diminishes the loss of electrons by water splitting. The solvated electrons would then react with different substances, such as benzil or O_2, to selectively form the transient radicals (**1aa'** or **I**). To realize our hypothesis, the $[Ca_{24}Al_{28}O_{64}]^{4+} \cdot 4e^-$ electride, which is an electron-donating reagent that possesses moderate reactivity in water, was used because of its smooth electron release and the possible solvation of anionic electrons by water molecules.

Figure 1c shows the details of our approach of using the $[Ca_{24}Al_{28}O_{64}]^{4+} \cdot 4e^-$ electride to realize chemoselective reactions of benzil in water. In water-mediated reactions with the $[Ca_{24}Al_{28}O_{64}]^{4+} \cdot 4e^-$ electride, water has two important roles: 1) releasing anionic electrons from the electrides and 2) acting as the medium for transferring the anionic electrons to electron acceptors. The cage structure of the

Table 2. Optimization of the oxidative cleavage of benzil **1a** using the $[Ca_{24}Al_{28}O_{64}]^{4+} \cdot 4e^-$ electride[a]. [a]Performed with **1a** (0.2 mmol) in solvent (8 mL). [b]Equivalents of electride with respect to 1,2-diketone **1a**. [c]Isolated yields.
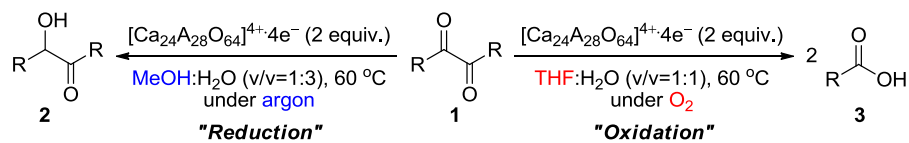
entry	solvent	electride (equiv)[b]	temp (°C)	time (h)	yield of **2a/3a**[c]
1	MeOH/H$_2$O (1:3)	2	60	2	0/36
2	DMSO/H$_2$O (1:3)	2	60	2	0/27
3	DMF/H$_2$O (1:3)	2	60	2	0/45
4	MeCN/H$_2$O (1:3)	2	60	2	0/53
5	THF/H$_2$O (1:3)	2	60	2	0/57
6	THF/H$_2$O (1:2)	2	60	7	0/80
7	**THF/H$_2$O (1:1)**	**2**	**60**	**20**	**0/96**

$[Ca_{24}Al_{28}O_{64}]^{4+} \cdot 4e^-$ electride slowly decomposes in water and forms a Ca-Al-O-OH gel as aluminous cement, leading to the release of anionic electrons. The released electrons are transferred to the appropriate electron acceptors, most likely through electron solvation by water molecules, which are aptly referred to as solvated electrons. During the reaction, we observed the evolution of hydrogen gas as a result of water splitting by electrons, which indicates that electrons are in proximity to water molecules. Because the formation of transient radicals is critical in determining the course of reactions and producing an intermediate, controlling the electron transfer pathway is the major concern. In the reduction reaction, benzil **1a** accepts two electrons and then transforms into the enediol dianion **1aa'**. In postulating the oxidation reaction, we intentionally involved oxygen molecules in the reaction to facilitate the formation of the superoxide radicals **I**.

Table 1 presents the results of the reduction reaction of benzil **1a**, which was conducted under an inert argon atmosphere to prevent the incorporation of oxygen molecules in the reactions. Benzil **1a** accepts two electrons from the $[Ca_{24}Al_{28}O_{64}]^{4+} \cdot 4e^-$ electride and then transforms into the enediol dianion **1aa'**. The resulting enediol dianion species may subsequently undergo protonation, affording an α-hydroxy ketone via keto-enol tautomerization. To identify the necessity of a proton source, we initially performed the reaction of benzil **1a** with 1.0 equivalent of electride in water alone. However, no reaction occurred, most likely due to the poor solubility of benzil **1a** in water (Table 1, entry 1), which prompted the use of co-solvent to improve the solubility of benzil **1a**. We observed the reaction progress when deoxygenated THF-H$_2$O (v/v = 1:1) was applied as a co-solvent to the reaction of benzil **1a** with 1.0 equivalent of $[Ca_{24}Al_{28}O_{64}]^{4+} \cdot 4e^-$ at 60 °C under an inert argon atmosphere. In this reaction, benzil **1a** was reduced to benzoin **2a** in low yield after 24 h (Table 1, entry 2). The use of an additional equivalent of electride led to a slight improvement in the reaction yield (Table 1, entry 3).

A significant enhancement in the yield of **2a** was achieved by replacing the THF-H$_2$O co-solvent with MeOH-H$_2$O co-solvent (Table 1, entry 4). This result is attributed to two reasons: 1) the difference in solvent polarity, which facilitates rapid electron transfer[38], and 2) the difference in solvent acidity, which accelerates protonation of the products. A more polar solvent is expected to facilitate electron transfer because of the stronger coupling between molecules and the faster solvation response. Although the two solvents, MeOH and H$_2$O, have similar pKa values (pKa of H$_2$O = 15.7 and pKa of MeOH = 15.5), the more acidic MeOH molecule donates a proton and becomes a $^-$OMe ion. Upon acid dissociation, the methoxide ion is stabilized by the solvation of H$_2$O molecules, in which the positively charged H atoms move toward the methoxide ion solutes. This process makes MeOH more acidic than H$_2$O, rendering MeOH a sufficient proton source in the reduction process.

When using alcohols in the co-solvent, the yield of product **2a** increased in the following order of acidity and electron transfer rates[39] (methanol > ethanol > isopropanol > *tert*-butanol) (Table 1, entries 4-7). Notably, the reaction time decreased as the MeOH-H$_2$O volume ratio was changed from 1:1 to 1:3 (Table 1, entry 8). It is hypothesized that the increased polarity from the greater amount of water contributed to the acceleration of cage opening and donation of electrons from the electrides. Finally, in contrast to deoxygenated THF-H$_2$O (v/v = 1:1) (Table 1, entry 3), the use of a partially oxygenated THF-H$_2$O co-solvent yielded a small amount of benzoic acid **3a** (Table 1, entry 9), which was identified by NMR spectroscopy. This result indicated that the oxidative cleavage reaction of benzil **1a** should be investigated by introducing oxygen molecules as electron acceptors into the reaction. To verify the necessity of electrons in the reaction, we examined the reaction using $[Ca_{24}Al_{28}O_{64}]^{4+} \cdot 2O^{2-}$ oxide, which is the precursor of the $[Ca_{24}Al_{28}O_{64}]^{4+} \cdot 4e^-$ electride (Table 1, entry 10). No reaction took place, which strongly

Scheme: $[Ca_{24}A_{28}O_{64}]^{4+}\cdot4e^-$ (2 equiv.), MeOH:H_2O (v/v=1:3), 60 °C under argon **"Reduction"** (2) ← (1) → **"Oxidation"** $[Ca_{24}A_{28}O_{64}]^{4+}\cdot4e^-$ (2 equiv.), THF:H_2O (v/v=1:1), 60 °C under O_2 (2 × 3)

R = Ph (**a**); 2-Naphthyl (**b**); 4-F-C_6H_4 (**c**); 4-Cl-C_6H_4 (**d**); 4-MeO-C_6H_4 (**e**); 4-MeO-C_6H_4 (**e**); 3-MeO-C_6H_4 (**f**); 4-Me-C_6H_4 (**g**)

Reduction				Oxidation			
entry	product	time (h)	yield (%)[b]	entry	product	time (h)	yield (%)[b]
1	**2a**	2	91	1	**3a**	20	96
2	**2b**	4	86	2	**3b**	7	85
3	**2c**	1	80	3	**3c**	22	>99
4	**2d**	6	82	4	**3d**	24	>99
5	**2e**	2	78	5	**3e**	22	83
6	**2f**	3	81	6	**3f**	20	70
7	**2g**	1	92	7	**3g**	22	70

Table 3. Reaction scopes of both the chemoselective reduction and oxidation reactions of 1,2-diketones using the $[Ca_{24}Al_{28}O_{64}]^{4+}\cdot4e^-$ electride[a]. [a]Performed with **1** (0.2 mmol) and $[Ca_{24}Al_{28}O_{64}]^{4+}\cdot4e^-$ electride (2 equiv.) in solvent (8 mL). [b]Isolated yields.

indicates that the electrons of the electride are essential for the reduction of 1,2-diketones. Furthermore, no reaction occurred in methanol, indicating that water is indispensable media to release and transfer the electrons via hydrolysis of cage structured $[Ca_{24}Al_{28}O_{64}]^{4+}\cdot4e^-$ electride (Table 1, entry 11).

Following the identification of benzoic acid **3a** after using the partially oxygenated THF-H_2O co-solvent, we changed the reaction atmosphere from inert argon gas to molecular oxygen as a terminal oxidant, which enabled an increase in the amount of oxygen molecules that was dependent upon the different solubilities of oxygen molecules in each solvent system. We initially performed the reaction of benzil **1a** with 2.0 equivalents of electride in MeOH-H_2O (v/v = 1:3) at 60 °C under an oxygen atmosphere and obtained benzoic acid **3a** in 36% yield (Table 2, entry 1). The use of DMF, DMSO and MeCN solvent in water afforded benzoic acid **3a** in moderate yields (up to 53%; Table 2, entries 2-4). The reaction was optimized using THF-H_2O co-solvent, which provided the best yield (96%; Table 2, entries 5-7).
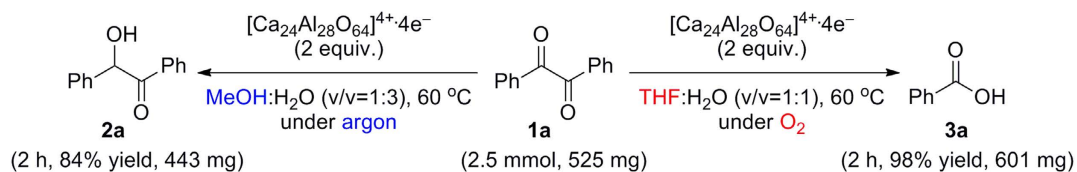
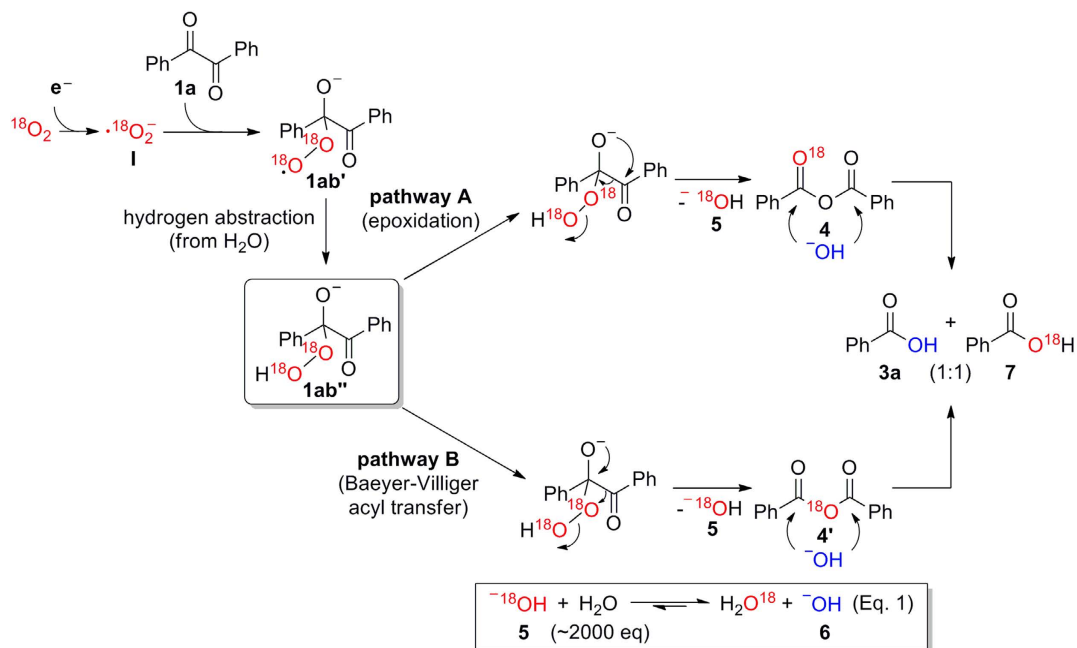**Figure 2.** Large-scale production of **2a** and **3a** using the $[Ca_{24}Al_{28}O_{64}]^{4+}\cdot 4e^{-}$ electride.

Figure 3. Proposed mechanism for the oxidative cleavage of 1,2-diketone utilizing using the $[Ca_{24}Al_{28}O_{64}]^{4+}\cdot 4e^{-}$ electride via ^{18}O isotopic labeling experiments.

Increasing the amount of THF in the co-solvent significantly improved the yield of benzoic acid **3a** (Table 2, entries 5-7), albeit with longer reaction times (20 h). This improvement may be explained by the following two reasons: i) due to the higher solubility of O_2 in THF (2.1 mM) compared to water (0.26 mM), the reaction is accomplished through an enhanced formation of superoxide radicals, or ii) decreasing the ratio of water in the co-solvent causes a reduction in polarity, which retards cage decomposition and electron release into the solvent. The slow generation of electrons and the reduced rate of molecular oxygen permeating into the co-solvent may minimize the probability of electron loss by reaction with O_2 rather than water.

Based on the chemoselective reactions established above, we expanded the reaction scope to the diverse set of 1,2-diketone molecules listed in Table 3. In the reactions of the unsubstituted aromatic 1,2-diketones, both the reduction and oxidation reactions afforded the corresponding products in high yields (Table 3, entries 1 and 2). Additionally, both the reduction and oxidation reactions proceeded not only for the 1,2-diketones bearing electron-withdrawing substituents on the aryl ring (Table 3, entries 3 and 4) but also for other substrates bearing strong electron-donating substituents, such as -Me or -OMe groups (Table 3, entries 5, 6 and 7). This result indicates that this electride, which possesses a low work function, has great potential for use as a powerful reducing agent in chemical reactions.

We also examined the feasibility of large-scale reactions using the $[Ca_{24}Al_{28}O_{64}]^{4+}\cdot 4e^{-}$ electride in water to address the potential limitations of utilizing the $[Ca_{24}Al_{28}O_{64}]^{4+}\cdot 4e^{-}$ electride in organic synthesis. For both the reduction and oxidation reactions, benzil **1a** was used as shown in Fig. 2 on a 2.5 mmol scale (525 mg of benzil), which was 12.5 times greater than the amount used for the optimization. Notably, benzoin **2a** and benzoic acid **3a** were obtained in yields of 84% and 98%, respectively.

Based on the experimental results, we propose mechanisms associated with electron transfer from the electrides in aqueous solutions. For the mechanism of the reduction process, two electrons from the $[Ca_{24}Al_{28}O_{64}]^{4+}\cdot 4e^{-}$ electride are transferred to 1,2-diketone **1a**. Consequently, two ketyl radical anions
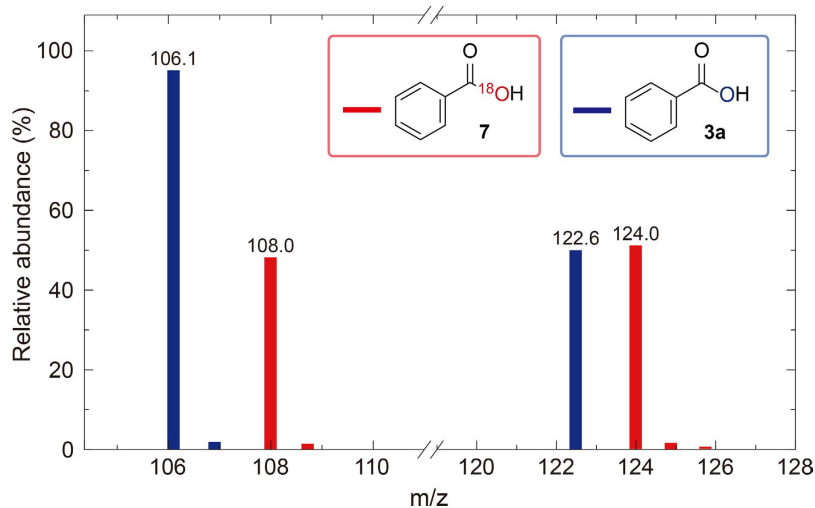
Figure 4. ^{18}O isotopic labeling results of the oxidative cleavage reaction of 1,2-diketone.
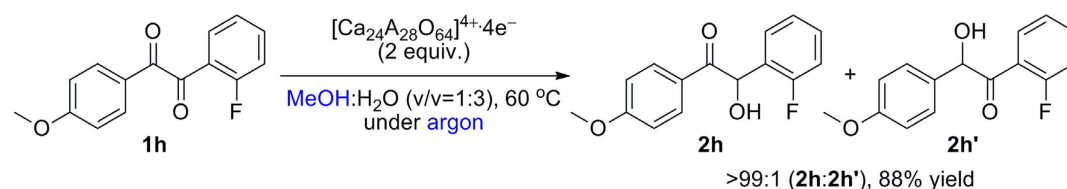

Figure 5. Regiospecific reduction of unsymmetrical 1,2-diketone.

of 1,2-diketone are generated and quickly converted to enediol dianion **1aa'** via radical dimerization[40]. The use of a protic solvent allowed the enediol dianion to be protonated, thereby forming enediol intermediate **1aa''** which undergoes tautomerization to form α-hydroxy ketone **2a**.

In contrast to reduction, the oxidation reaction was a rather complex process. The oxidative cleavage reaction occurs in a two-step process. In contrast to the reduction reaction that occurs via direct electron transfer to benzil **1a**, in the oxidation reaction, the electrons are firstly transferred to the oxygen molecule, generating superoxide radicals **I**[41]. These radical anions then react with benzil **1a**, leading to the formation of α-peroxy ketone intermediate **1ab''**.

To obtain insight into the reaction mechanism for oxidation, we conducted ^{18}O isotopic labeling experiments using $^{18}O_2$ gas, which provides an integral part of the electron transfer pathway for the formation of carboxylic acids, as shown in Fig. 3. The superoxide radicals **I** was initially generated by the reaction between $^{18}O_2$ and a single electron from the electride and then most likely transferred to **1a**, affording α-keto peroxy radical anion **1ab'**. Then, hydrogen abstraction from water occurred almost simultaneously to form α-keto peroxide **1ab''**. Subsequently, two different ^{18}O-labeled anhydrides, **4** and **4'**, were formed via either epoxidation (pathway A) or the Baeyer-Villiger reaction with acyl group migration from α-keto peroxide **1ab''**, with simultaneous release of ^{18}O-labeled hydroxide ion **5** (pathway B). Presumably, the $^{18}OH^-$ ions rapidly exchanged protons with an extremely large amount of water to produce hydroxide ion (OH^-) **6** according to Le Chatelier's principle (Eq. 1). The nucleophilic attack of a hydroxide ion on the carbonyl carbon of ^{18}O-labeled anhydrides **4** and **4'** produced ^{18}O-labeled benzoic acid **7** and ^{16}O-incorporated benzoic acid **3a** in equal quantities.

To support the proposed mechanism, the resulting products (3a and 7) were subjected to gas chromatography-mass spectrometry (GC-MS) for isotopic analysis. The ^{16}O and ^{18}O compositions of the individual carboxylic acids were determined based on the relative abundances of mass peaks at m/z = 122 for ^{16}O and m/z = 124 for ^{18}O. As shown in Fig. 4, it is clear that the relative abundances of the isotopic masses for each product are identical to those of the isotopic masses. This result strongly suggests that oxygen molecules are incorporated into 1,2-diketone, producing carboxylic acids, which is initiated by the formation of superoxide radicals **I**.

To expand the synthetic application of this selective fashion, we then investigated the regioselectivity in the reaction of unsymmetrical 1,2-diketone **1h** with the electride (Fig. 5). The most favourable

reduction site was the carbonyl adjacent to the electron-withdrawing substituted aromatic ring, showing the specific regioselectivity of the products in a >99: 1 ratio of **2h : 2h′**.

Summary

The use of the $[Ca_{24}Al_{28}O_{64}]^{4+}\cdot4e^-$ electride, an exceptional electron source, allowed the first demonstration of chemoselective oxidation and reduction reactions with ketones in water. Transient radical formation was integral to the chemoselective success of the reactions, and the formed radical was dependent on either the presence of a proton source or an oxygen molecule in each electron transfer process. This proposed mechanism explains why the electron transfer process in water, which is omnipresent but often goes unnoticed, should be regarded as a critical mechanistic step for the formation of intermediate substances in chemical reactions. Additionally, this new methodology using the $[Ca_{24}Al_{28}O_{64}]^{4+}\cdot4e^-$ electride as a solid-state reducing agent in water may provide an alternative to the high-energy pulse radiolysis of water, in which it is not possible to realize these selective chemical reactions. Finally, the solvated electrons, which are extremely potent reducing agents, can be used for oxidation reactions when the electron pathway is controlled to form the proper transient intermediates according to the desired reaction conditions.

Methods

Typical procedure for reduction of benzil using C12A7:e⁻. In 20 mL vial, C12A7:e⁻ (362 mg, 0.5 mmol) was added to solution of benzil (42 mg, 0.2 mmol) in 8 mL of EtOH:H₂O (v/v = 1:3) co-solvent at room temperature. The reaction was vigorously stirred for 2 h, then quenched with 5% HCl solution, and extracted with EtOAc (3 × 2 mL). The combined organic layers were dried over MgSO₄. The residue was purified by flash column chromatography on silica gel (hexanes/ethyl acetate = 4:1 to 2:1) to give benzoin (38 mg, 91% yield).

Typical procedure for oxidative cleavage reaction of benzil using C12A7:e⁻. In 20 mL vial, C12A7:e⁻ (362 mg, 0.5 mmol) was added to solution of benzil (42 mg, 0.2 mmol) in 8 mL of THF:H₂O (v/v = 1:1) co-solvent at room temperature. The reaction was vigorously stirred for 12 h, then quenched with 5% HCl solution, and extracted with EtOAc (3 × 2 mL). The combined organic layers were dried over MgSO₄. The residue was purified by flash column chromatography on silica gel (hexanes/ethyl acetate = 4:1 to 1:1) to give benzoic acid (46 mg, 96% yield).

^{18}O-labelling experiments by GC/MS. The ratios of $^{16}O^{16}O$, $^{16}O^{18}O$ and $^{18}O^{18}O$ were determined based on the intensities of mass peaks at m/z = 122, 124 and 126, analysed by a Varian GC-MS 4000 gas chromatograph equipped with mass spectrometer at room temperature.

References

1. Brownstein, K. R. & Tarr, C. Importance of classical diffusion in NMR studies of water in biological cells. *Phys. Rev. A* **19,** 2446 (1979).
2. Chaplin, M. Do we underestimate the importance of water in cell biology? *Nat. Rev. Mol. Cell Biol.* **7,** 861–866 (2006).
3. Conti Nibali, V. & Havenith, M. New Insights into the Role of Water in Biological Function: Studying Solvated Biomolecules Using Terahertz Absorption Spectroscopy in Conjunction with Molecular Dynamics Simulations. *J. Am. Chem. Soc.* **136,** 12800–12807 (2014).
4. Sun, T., Lin, F.-H., Campbell, R. L., Allingham, J. S. & Davies, P. L. An Antifreeze Protein Folds with an Interior Network of More Than 400 Semi-Clathrate Waters. *Science* **343,** 795–798 (2014).
5. Chanda, A. & Fokin, V. V. Organic synthesis "on water". *Chem. Rev.* **109,** 725–748 (2009).
6. Li, C.-J. & Chen, L. Organic chemistry in water. *Chem. Soc. Rev.* **35,** 68–82 (2006).
7. Butler, R. N. & Coyne, A. G. Water: Nature's Reaction Enforcer—Comparative Effects for Organic Synthesis "In-Water" and "On-Water". *Chem. Rev.* **110,** 6302–6337 (2010).
8. Simon, M.-O. & Li, C.-J. Green chemistry oriented organic synthesis in water. *Chem. Soc. Rev.* **41,** 1415–1427 (2012).
9. Kolb, H. C., VanNieuwenhze, M. S. & Sharpless, K. B. Catalytic Asymmetric Dihydroxylation. *Chem. Rev.* **94,** 2483–2547 (1994).
10. Tokunaga, M., Larrow, J. F., Kakiuchi, F. & Jacobsen, E. N. Asymmetric catalysis with water: efficient kinetic resolution of terminal epoxides by means of catalytic hydrolysis. *Science* **277,** 936–938 (1997).
11. Breslow, R., Maitra, U. & Rideout, D. Selective diels-alder reactions in aqueous solutions and suspensions. *Tetrahedron Lett.* **24,** 1901–1904 (1983).
12. Chen, G. M., Ramachandran, P. V. & Brown, H. C. The Critical Importance of Water in the Asymmetric Allylboration of N-Trimethylsilylbenzaldimines with B-Allyldiisopinocampheylborane. *Angew. Chem. Int. Ed.* **38,** 825–826 (1999).
13. Wu, X. *et al.* On Water and in Air: Fast and Highly Chemoselective Transfer Hydrogenation of Aldehydes with Iridium Catalysts. *Angew. Chem. Int. Ed.* **45,** 6718–6722 (2006).
14. Verma, A. K. *et al.* On Water: Silver-Catalyzed Domino Approach for the Synthesis of Benzoxazine/Oxazine-Fused Isoquinolines and Naphthyridines from o-Alkynyl Aldehydes. *J. Org. Chem.* **78,** 6657–6669 (2013).
15. Gray, H. B. & Winkler, J. R. Electron flow through proteins. *Chem. Phys. Lett.* **483,** 1–9 (2009).
16. Tezcan, F. A., Crane, B. R., Winkler, J. R. & Gray, H. B. Electron tunneling in protein crystals. *Proc. Natl. Acad. Sci. U. S. A.* **98,** 5002–5006 (2001).
17. Garrett, B. C. *et al.* Role of water in electron-initiated processes and radical chemistry: Issues and scientific advances. *Chem. Rev.* **105,** 355–390 (2005).
18. Bielski, B. H., Cabelli, D. E., Arudi, R. L. & Ross, A. B. Reactivity of HO₂/O₂⁻ radicals in aqueous solution. *J. Phys. Chem. Ref. Data* **14,** 1041–1100 (1985).
19. Garrison, W. M. Reaction mechanisms in the radiolysis of peptides, polypeptides, and proteins. *Chem. Rev.* **87,** 381–398 (1987).

20. Land, E. J., Mukherjee, T., Swallow, A. J. & Bruce, J. M. Reduction of the naphthazarin molecule as studied by pulse radiolysis. Part 1.-Addition of a single electron. *J. Chem. Soc., Faraday Trans. 1* **79,** 391–404 (1983).
21. Shenvi, R. A., O'Malley, D. P. & Baran, P. S. Chemoselectivity: The Mother of Invention in Total Synthesis. *Acc. Chem. Res.* **42,** 530–541 (2009).
22. Szostak, M., Spain, M. & Procter, D. J. Recent advances in the chemoselective reduction of functional groups mediated by samarium(ii) iodide: a single electron transfer approach. *Chem. Soc. Rev.* **42,** 9155–9183 (2013).
23. Dye, J. L. Electrides: Early Examples of Quantum Confinement. *Acc. Chem. Res.* **42,** 1564–1572 (2009).
24. Ellaboudy, A., Dye, J. L. & Smith, P. B. Cesium 18-crown-6 compounds. A crystalline ceside and a crystalline electride. *J. Am. Chem. Soc.* **105,** 6490–6491 (1983).
25. Kuchenmeister, M. E. & Dye, J. L. Synthesis and structures of two thermally stable sodides with the macrocyclic complexant hexamethyl hexacyclen. *J. Am. Chem. Soc.* **111,** 935–938 (1989).
26. Matsuishi, S. *et al.* High-Density Electron Anions in a Nanoporous Single Crystal: $[Ca_{24}Al_{28}O_{64}]^{4+}(4e^-)$. *Science* **301,** 626–629 (2003).
27. Toda, Y. *et al.* Work Function of a Room-Temperature, Stable Electride $[Ca_{24}Al_{28}O_{64}]^{4+}(e^-)_4$. *Adv. Mater.* **19,** 3564–3569 (2007).
28. Kim, S. W., Shimoyama, T. & Hosono, H. Solvated Electrons in High-Temperature Melts and Glasses of the Room-Temperature Stable Electride $[Ca_{24}Al_{28}O_{64}]^{4+}\cdot4e^-$. *Science* **333,** 71–74 (2011).
29. Buchammagari, *et al.* Room Temperature-Stable Electride as a Synthetic Organic Reagent: Application to Pinacol Coupling Reaction in Aqueous Media. *Org. Lett.* **9,** 4287–4289 (2007).
30. Langer, R., Leitus, G., Ben-David, Y. & Milstein, D. Efficient Hydrogenation of Ketones Catalyzed by an Iron Pincer Complex. *Angew. Chem. Int. Ed.* **50,** 2120–2124 (2011).
31. Yıldız, T., Çanta, N. & Yusufoğlu, A. Synthesis of new chiral keto alcohols by baker's yeast. *Tetrahedron: Asymmetry* **25,** 340–347 (2014).
32. Casadei, Maria A. Reactivity of the Electrogenerated O_2^-/CO_2 System Towards Alcohols. *Eur. J. Org. Chem.* **2001,** 1689–1693 (2001).
33. Sawyer, D. T., Stamp, J. J. & Menton, K. A. Reactivity of superoxide ion with ethyl pyruvate, .alpha.-diketones, and benzil in dimethylformamide. *J. Org. Chem.* **48,** 3733–3736 (1983).
34. Tachikawa, Y., *et al.* Aerobic photooxidative cleavage of 1,3-diketones to carboxylic acids using 2-chloroanthraquinone. *Tetrahedron Lett.* **54,** 6218–6221 (2013).
35. Bao, W., Zhang, Y. & Qi, S. SmI_2-Induced Asymmetric Reduction of Benzil in the Presence of Chiral Surfactant. *Synth. Commun.* **24,** 2437–2440 (1994).
36. Khurana, J. M., Bansal, G., Kukreja, G. & Pandey, R. R. Pinacol Formation and Reduction of Aromatic Carbonyls with Magnesium–Methanol at Ambient Temperature. *Monatsh. Chem./ Chem. Mon.* **134,** 1365–1371 (2003).
37. Lin, W. *et al.* Selective reduction of carbonyl groups in the presence of low-valent titanium reagents. *Tetrahedron Lett.* **55,** 2238–2242 (2014).
38. Maroncelli, M., Macinnis, J. & Fleming, G. R. Polar Solvent Dynamics and Electron-Transfer Reactions. *Science* **243,** 1674–1681 (1989).
39. Bietti, M., Baciocchi, E. & Engberts, J. B. F. N. Rate-determining electron-transfer reactions in highly aqueous alcohol-water mixtures. A quantitative analysis of solvent effects on the oxidation of 4-methoxyphenylacetate by potassium 12-tungstocobaltate(III). *Chem. Commun.* 1307–1308 (1996).
40. Meunier-Prest, R., Laviron, E., Gaspard, C. & Raveau, S. The reduction mechanism of the CO group.: Part 3. The electrochemical reduction of benzil in aqueous medium. *Electrochim. Acta* **46,** 1847–1861 (2001).
41. Saito, I., Matsuura, T. & Inoue, K. Formation of superoxide ion via one-electron transfer from electron donors to singlet oxygen. *J. Am. Chem. Soc.* **105,** 3200–3206 (1983).

Acknowledgements

Author Contributions

S.W.K. and J.W.Y. organized the research. S.M.K. and H.S.Y. carried out the experiments. All the authors contributed to the design of the experiments, the analysis of the data and editing of the manuscript.

Additional Information

Competing financial interests: The authors declare no competing financial interests.

How to cite this article: Kim, S. M. *et al.* Chemoselective reduction and oxidation of ketones in water through control of the electron transfer pathway. *Sci. Rep.* **5,** 10366; doi: 10.1038/srep10366 (2015).