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Highly Selective Aerobic Oxygenation of Tertiary Allylic Alcohols with Molecular Oxygen

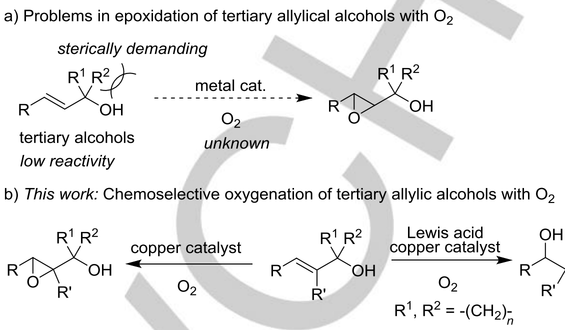
Bencong Zhu, Tao Shen, Xiaoqiang Huang, Yuchao Zhu, Song Song, Ning Jiao*

Abstract: Aerobic epoxidation of tertiary allylic alcohols remains a significant challenge. Herein, we report an efficient and highly chemoselective copper-catalyzed epoxidation and semipinacol rearrangement reaction of tertiary allylic alcohols with molecular oxygen. The solvent 1,4-dioxane activates dioxygen, thereby avoiding the addition of sacrificial reductant.

Epoxidation of allylic alcohols plays an important role in organic synthesis,[1] since it provides a straightforward approach to epoxy alcohols that are widely used as building blocks for the synthesis of natural products and pharmaceuticals.[2] Significantly, the groups of Sharpless,[3] Katsuki,[4] Yamamoto,[5] among others,[6] independently have developed asymmetric variants of this transformation through the use of transition metal catalysts. These reactions rely on Ti, Nb, V, Mo, or Hf species in conjunction with a stoichiometric oxidant including peracids, organic and inorganic peroxides, and H_2O_2. Nevertheless, the stoichiometric use and disposal of such peroxides raise problems from safe and environmental viewpoints. In addition, the application of H_2O_2 sometimes results in poor chemoselectivity owing to the ring expansion of epoxy alcohols to triols.

Molecular oxygen represents a clean, cheap and abundant oxidant,[7, 8] and could be a more desirable choice for epoxidations.[9] However, efficient oxygenation reactions with O_2 are considered difficult.[10] To achieve the epoxidation of allylic alcohols with O_2, sacrificial reducing reagents,[11] such as aldehydes, are required to activate O_2 and generate peroxides *in situ*. Another yet-unsolved problem is the epoxidation of tertiary allylic alcohols with molecular oxygen. This is likely due to a lack of coordinating ability resulting from the steric bulk of the substrate (Scheme 1a).[5d]. Therefore, developing efficient epoxidations of tertiary allylic alcohols with O_2 is highly desirable.

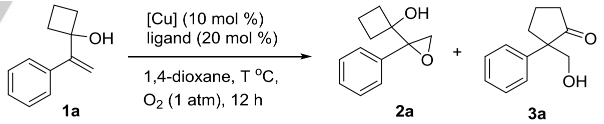
Herein, we report a novel Cu-catalyzed aerobic oxygenation of sterically demanding allylic tertiary alcohols. (Scheme 1b). The following significance exists in this report: (1) Inexpensive copper catalysts and environmentally friendly molecular oxygen are employed; (2) To the best of our knowledge, this presents a novel epoxidation of tertiary allylic alcohols with O_2; (3) 1,4-Dioxane was disclosed as both solvent and a new oxygen atom transmitter, thereby avoiding the employment of sacrificial aldehydes in the reported aerobic epoxidations; (4) The selectivity is very high without the triols byproducts formation.



Scheme 1. Epoxidation of tertiary allylic alcohols with O_2.

With our continued interests in copper catalytic system, we began our investigation of this transformation by attempting the oxidation of 1-(1-phenylvinyl) cyclobutanol **1a** (Table 1) Initially, when $CuBr_2$ and pyridine severed as the catalyst and ligand respectively, epoxide **2a** was obtained in 38% yield (entry 1). The screening of various copper catalysts showed that $Cu(OAc)_2$ delivered **2a** with superior efficiency (entry 2, also see SI). Replacing pyridine with other nitrogen-based ligands including 1, 10-phenanthroline, bipyridine and TMEDA didn't improve the outcome of epoxides (see SI). Interestingly, the reaction without ligand yielded **2a** in 78% NMR yield and 72% isolated yield, which was the optimized conditions for epoxidation (entry 3). Other solvents including THF, toluene, DCE, and MeCN failed to generate any product (see SI).

Table 1. Reaction Conditions Investigation[a]



Entry	[Cu]	Ligand	T °C	2a[b]	3a[b]
1	$CuBr_2$	pyridine	90	38%	trace
2	$Cu(OAc)_2$	pyridine	90	65%	trace
3	$Cu(OAc)_2$	--	90	78%(72%[f])	trace
4	$Cu(CH_3CN)_4PF_4$	pyridine	90	54%	11%
5	$Cu(OTf)_2$	TMEDA	90	trace	53%
6[c]	$Cu(OTf)_2$	TMEDA	80	trace	58%
7[c, d]	$Cu(OTf)_2$	TMEDA	80	trace	63%
8[c, d, e]	$Cu(OTf)_2$	TMEDA	80	trace	74%

[a] Reaction conditions: 1a (0.2 mmol), Cu catalyst (10 mol %), ligand (20 mol %), 1,4-dioxane (2 mL) stirred under O_2 for 12 h. [b] 1H NMR yields using $Cl_2CHCHCl_2$ as internal standard. [c] Reaction time was 18 h. [d] $Mg(OTf)_2$ (10 mol %) was added. [e] H_2O (0.5 equiv) was added. [f] Isolated yields. TMEDA = tetramethylethylenediamine.

It is noteworthy that a same trace amount of byproduct was detected in the above conditions screening reactions. Further careful characterization experiments demonstrated **3a** was a semipinacol rearrangement [12] product. This attracted our attention, because this kind of α-hydroxymethyl cyclopentanones are useful synthons. We then turned to optimize the conditions for semipinacol rearrangement. When $Cu(CH_3CN)PF_6$ was employed as the catalyst, **3a** was obtained

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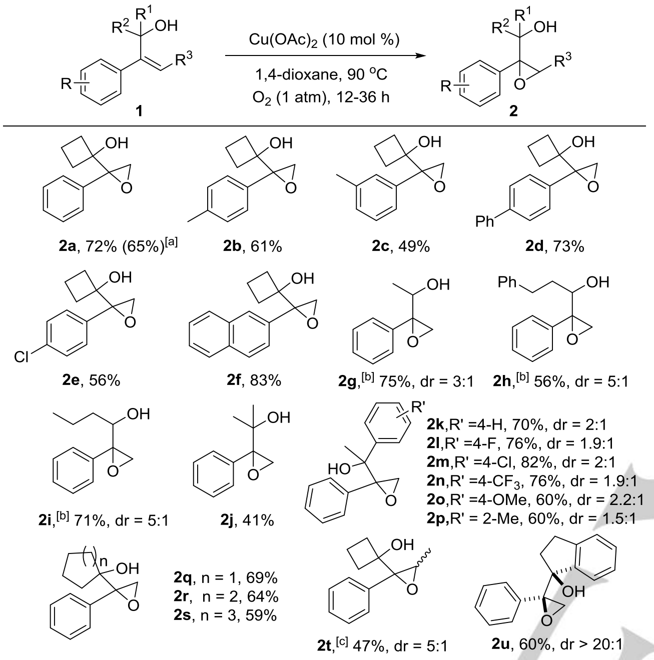
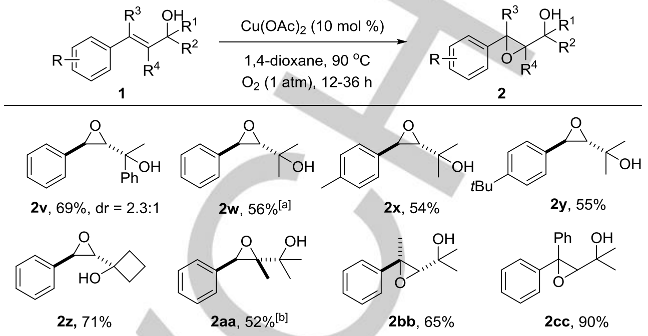
in 11% yield with the formation of **2a** in 54% yield (entry 4). The employment of strongly Lewis acidic $Cu(OTf)_2$ performed well in the presence of nitrogen-base ligands, among which TMEDA was the most effective (entry 5, slso see SI). The addition of catalytic amount of Lewis acid $Mg(OTf)_2$ and 0.5 equivalent of H_2O, intended to accelerate the rearrangement process, further improved the reaction outcome, delivering **3a** in 74% yield (entries 7 and 8). Therefore, excellent chemoselectivity could be achieved by simply altering the copper salt employed.



Scheme 2. Reaction conditions: see entry 3, Table 1. Isolated yields. [a] The reaction was conducted in gram-scale (8.0 mmol). [b] CuO (10 mol %) was used as the catalyst. [c] The allylic alcohol was used as a mixture of isomers with a E/Z ratio of 4:1.

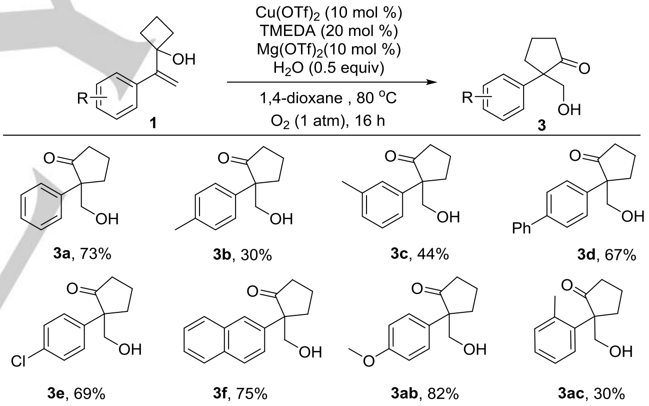
The substrate scope of aerobic epoxidation was evaluated under the optimized conditions (Scheme 2). A series of aryl-substituted allylic alcohols (**2b**-**f**) were sufficiently reactive under the chosen conditions, leading to the products in moderate to good yields. Secondary and tertiary alcohols bearing different substituents in R^1 and R^2 positions reacted to generate epoxide products with high efficiencies, but diastereoselectivity was low (**2g**-**2i**, **2k**-**2p**) Substrates with five, six or seven-membered rings worked smoothly, providing epoxides in moderate yields (**2q**-**2s**). In addition, a methyl group at the R^3 position was demonstrated to be tolerated (**2t**). Notably, epoxidation of the substrate with high steric hindrance at α position of the hydroxyl group was found to be highly diastereoselectivity (**2u**).

In addition, 3-aryl propenols were then investigated (Scheme 3). Substituents at the R^1 and R^2 position were well tolerated (**2v-2z**). In the case of tertiary allylic alcohols with polysubstituted carbon-carbon double bond, epoxy alcohols were obtained in moderate to good yields (52-90% yields, **2aa-2cc**). The *E*-olefins afforded the *trans*-epoxides (**2v**-**2bb**), while the *Z*-olefins afforded the *cis*-epoxides (see Eq. S13), indicating that the epoxidation is stereospecific. The structures of epoxides were determined by the ^3J (H,H) coupling constants (see SI).



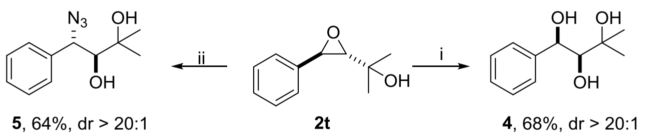
Scheme 3. Reaction conditions: see entry 3, Table 1. Isolated yields. [a] $Cu(OAc)_2$ (20 mol %) was used as the catalyst. [b] $Cu(acac)_2$ (10 mol %) was used as the catalyst.

Furthermore, the substrate scope of semipinacol rearrangement reaction was explored (Scheme 4). The methyl group at the *ortho*, *meta* or *para* position of the phenyl ring was compatible, albeit with relatively lower yields (**3b**, **3c**, **3ac**). Other cyclobutanol derivatives with substituents on aromatic ring went smoothly, affording products in good yields (**3d**-**3f**, **3ab**).



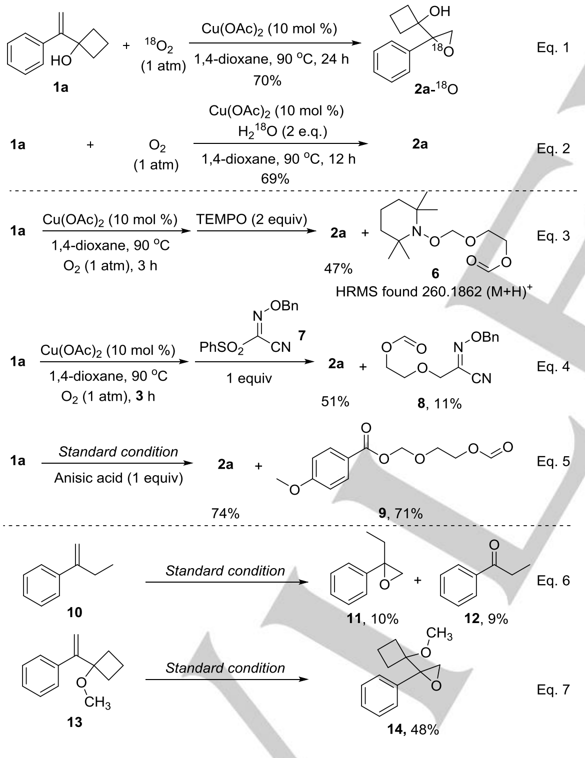
Scheme 4. Reaction conditions: see entry 8, Table 1. Isolated yields.

Epoxy alcohols are highly useful intermediates and building blocks in synthesis. This aerobic epoxidation transformation could be performed in gram-scale (**2a**, Scheme 2), revealing the great potential for further applications. Nucleophilic additions of **2t** by water or sodium azide in water, opened the ring to afford triols **4** or azido-substituted diols **5**, which map well onto many natural products and pharmaceuticals, including antibiotics (Scheme 5).[13]



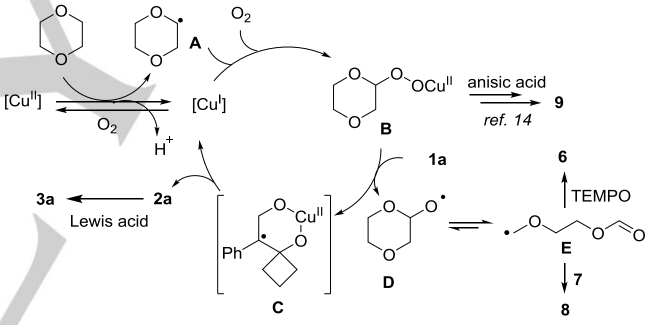
Scheme 5. Synthetic application. (i) H_2O, 60 °C; (ii) 2 equiv NaN_3, H_2O, 60 °C.

To explore the mechanism, several control experiments were conducted. The ^{18}O label experiments indicated that the oxygen atom in the epoxides is derived from molecular oxygen instead of water (Eqs. 1 and 2). In addition, this epoxidation was completely inhibited by the addition of radical scavenger such as TEMPO or BHT, suggesting that a radical process might be involved (see SI). Moreover, when TEMPO was added after 3 hours, an adduct **6** derived from TEMPO, O_2 and 1,4-dioxane was detected by HRMS (Eq. 3). Inspiringly, an adduct **8** was obtained though separation when a sulfonyl oxime ether reagent **7** was added as the radical trap (Eq. 4). Furthermore, compound **9** was observed in 71% yield in the presence of 4-methoxybenzoic acid through a reported β-scission ring-opening process[14] (Eq. 5). These results indicate that 1,4-dioxane was involved in the molecular oxygen activation and underwent further fragmentation process as reported.[14] When substrate **10** without the hydroxyl group was subjected to the standard conditions, desired epoxide **11** was only obtained in 10% yield together with the formation of 9% of ketone **12** (Eq. 6). Notably, the *o*-methylated derivatives could also produce epoxide in 48% yields (Eq. 7, also see Eq. S11, SI). These data highlight that the oxygen atom plays a significant role in promoting reactivity and preventing undesirable overoxidation.



To verify the possibility of epoxide **2a** as the intermediate for the formation of the rearrangement product **3a**, a kinetic diagram was conducted under standard conditions for the generation of **3a**. As displayed in Figure S2 (see SI), epoxide **2a** was firstly detected and was consumed after an initial increase, while **3a** appeared and gradually increased after a certain reaction time. This clearly demonstrates that epoxides are the key intermediates for the seminal rearrangement.[12]

Based on these results, a plausible mechanism is proposed (Scheme 6). Initially, oxidation of 1, 4-dioxane by copper(II) via single-electron transfer (SET) process occurs to generate radical-cation which furnishes radical intermediate **A** through further deprotonation process.[15] **A** is then trapped by O_2 and Cu(I) resulting in copper(II) peroxide intermediate **B** stabilized by anomeric effect .[8c, 16] Subsequent O-O bond homolysis followed by directed radical addition to substrate **1a** forms intermediate **C** with the formation of oxygen-centered radical species **D**. Then, radical epoxidation gives product **2a** with the regeneration of copper(I) species. In the presence of Lewis acid, product **2a** would undergo rearrangement delivering product **3a**.[12] In line with literature report and our mechanistic studies, intermediate **B** could undergo further fragmentation and reaction with anisic acid to afford compound **9**[14]. In the final step, the Cu(I) could be reoxidized to Cu(II) by O_2. We cannot rule out the pathway that species **D** abstract the hydrogen from the solvent and regenerated radical **A** for the chain reaction. In addition, intermediate **D** undergoes β-scission ring-opening process[17a] driven by stabilizing the three-electron “half-bond” transition state,[17b] to produce intermediate **E** which could be trapped by TEMPO or sulfonyl oxime ether reagent **7** leading to the detection of adduct **6** or **8** respectively.



Scheme 6. Proposed Mechanism

In conclusion, we report a novel copper-catalyzed oxygenation of tertiary allyl alcohols with molecular oxygen which previously posed a significant challenge. A wide range of epoxides and α-hydroxymethyl cyclopentanones are synthesized in good to excellent yield (up to 90%) with catalyst-dependent chemoselectivities. Mechanistic studies demonstrate that 1,4-dioxane serves as the solvent and the oxygen atom transmitter, thereby avoiding the requirement of additional sacrificial agents in the present aerobic epoxidation chemistry. Further exploration of aerobic oxygenation reaction through the activation of O_2 by 1,4-dioxane are ongoing in our laboratory.

Acknowledgements

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Keywords: Molecular oxygen • Oxygenation• Allylic alcohols • Rearrangement • Chemoselectivity

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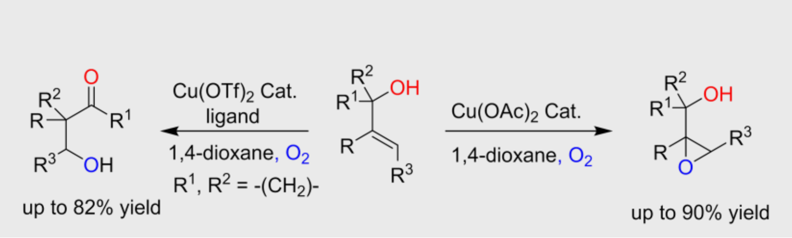

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Highly Selective Aerobic Oxygenation of Tertiary Allylic Alcohols with Molecular Oxygen

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This work realized a novel and highly chemoselective copper-catalyzed epoxidations and semipinacol rearrangement reactions of tertiary allylic alcohols with molecular oxygen, which are previously difficult to be achieved. 1,4-dioxane was proved as the solvent and an oxygen atom transmitter, thereby avoiding the requirement of additional sacrificial agents.