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# Metal-free selective alcohol oxidation *via* quinazolinone: mechanistic insights and sustainable applications†

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The oxidation of alcohols has been extensively studied over the years; however, the development of metal-free, selective methods for alcohol oxidation—particularly those enabling precise transformation into aldehydes or ketones—remains a significant challenge. Herein, we report a new organic oxidant that facilitates alcohol oxidation *via* acid-catalyzed transfer hydrogenation of quinazolin-2(1*H*)-one (HDQ). This eco-friendly and scalable process offers high selectivity, a straightforward workup, and broad substrate scope. Mechanistic studies, supported by isotope labeling and density functional theory (DFT) calculations, were conducted to elucidate the reaction pathway. Notably, this approach provides a dual-function pathway, directly yielding a diverse array of aldehydes and ketones while simultaneously producing 3,4-dihydroquinazolin-2(1*H*)-one (DHQZ), a privileged scaffold in small-molecule drug design. This novel alternative to conventional oxidation methods offers a sustainable solution suitable for large-scale chemical production.

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## Introduction

The oxidation of alcohols to aldehydes or ketones is a cornerstone reaction in both academia and industrial chemistry, playing a crucial role in pharmaceutical chemistry, fine chemicals, and organic synthesis. However, traditional stoichiometric oxidants,<sup>1–3</sup> such as chromium-based reagents and Dess–Martin Periodinane are associated with several drawbacks including their narrow substrate scope or environmental impact. In contrast, chemists are increasingly turning to cleaner oxidants, such as molecular oxygen and peroxides, due to their environmental benefits. However, the continuous supply of oxygen to the reaction system inevitably results in undesired over-oxidation. Moreover, the reliance on complex metal catalysts introduces the risk of metal residues contaminating

high-value products, which can limit the scalability of these approaches, particularly in the manufacturing of certain pharmaceuticals.<sup>4–11</sup>

Compared to the methods described above, the classical Oppenauer oxidation,<sup>12</sup> a well-known transfer hydrogenation method, is also employed to convert alcohols into aldehydes or ketones. This straightforward transformation is unfortunately impeded by the intrinsic reversibility of the reaction, and progress in developing novel hydrogen transfer receptors for alcohol oxidation has largely stagnated. Although recent studies have investigated the inter-conversion of alcohols and carbonyl compounds through metal-catalytic, photocatalytic, or electrochemically induced transfer hydrogenation reactions,<sup>13–16</sup> eco-friendly approaches that avoid metal catalysts or complex reaction systems remain underexplored. Specifically, the development of a simple, efficient hydrogen acceptor capable of acting as a selective oxidizing agent for large-scale industrial conversion of alcohols to aldehydes or ketones represents a promising direction for future research.

In recent years, quinoline and its derivatives, such as 3,4-dihydroquinazolin-2(1*H*)-one (DHQZ), have garnered attention in medicinal chemistry as versatile scaffolds<sup>17–19</sup> due to their broad range of biological activities, including anti-inflammatory, anti-cancer, and anti-viral properties.<sup>20,21</sup> Traditionally, DHQZ has been synthesized *via* cyclocarbonylation, a method often limited by its complex and demanding reaction conditions.<sup>22–24</sup> More recently, an efficient strategy for the preparation of hydroquinolinone analogs

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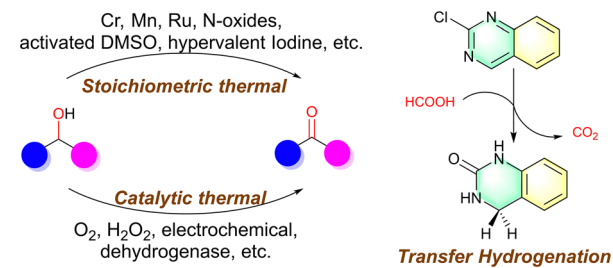
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## a. Previous work



## b. This work

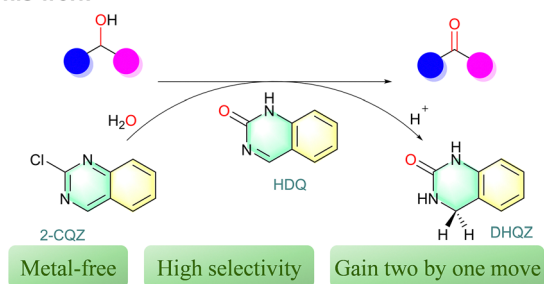


Fig. 1 (a) Landscape of alcohol oxidation approaches and transfer hydrogenation of the 2-CQZ to DHQZ. (b) Alcohol oxidation via HDQ-mediated hydrogen transfer.

has been reported, involving successive hydrolysis and transfer hydrogenation<sup>25</sup> (Fig. 1a). This approach, which employs formic acid as a hydrogen source and produces carbon dioxide as the sole by-product, highlights the potential of N-aromatic heterocyclic compounds to act as effective dehydrogenating agents in redox-related applications. In this study, we demonstrate that a specific aromatic heterocyclic compound, quinazolin-2(1H)-one (HDQ), can selectively oxidize alcohols to aldehydes or ketones. This new methodology not only provides a greener and more sustainable alternative to established oxidation methods but also delivers a versatile scaffold for drug development via a straightforward reaction. Our findings advance the understanding of quinazoline-based oxidants and pave the way for their application in large-scale industrial processes.

## Results and discussion

Initially, a series of N-aromatic heterocyclic compounds were screened for their reactivity on potential substrates. Unexpectedly, when evaluating potential oxidants using 1-phenylethanol as the model substrate (Fig. 2), we identified a subset of compounds capable of mediating the selective oxidation to acetophenone. Among these, compound 4A (2-chloroquinazoline, 2-CQZ) demonstrated exceptional substrate conversion (95%). Subsequent analysis of the reaction mixture revealed the formation of DHQZ, presumably generated through the successive hydrolysis and transfer hydrogenation of 2-CQZ.

This observation prompted further investigation of the hydrolysis mechanism. We confirmed that 2-CQZ undergoes stepwise hydrolysis to yield HDQ as the key oxidative intermediate. Furthermore, HDQ exhibits robust oxidant capability

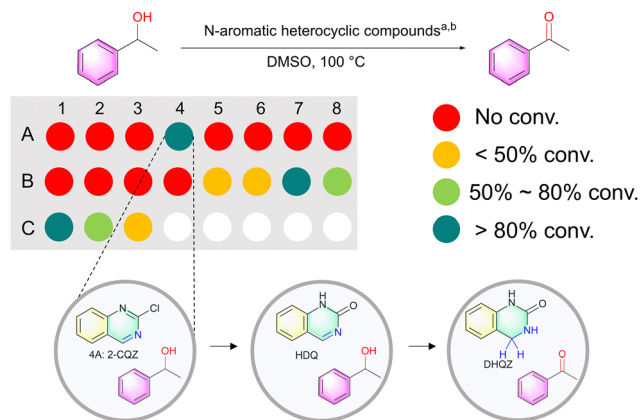


Fig. 2 Alcohol oxidation screening with 19 N-heteroaromatics. <sup>a</sup> Experimental details in ESI†. <sup>b</sup> Conversion quantified by LC-MS. As the reaction formulas in the figure are labeled.

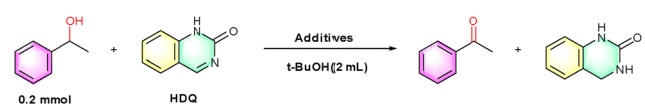
under mild acid catalysis at ambient temperature (ESI† Section S3). Notably, the development of a practical process utilizing HDQ as a novel oxidizing agent for alcohols would be both metal-free and cost-effective, as HDQ can be directly synthesized through the cyclization of 2-aminobenzaldehyde with urea.<sup>26</sup>

To optimize the conditions for oxidation using HDQ, various solvents were screened, with primary and secondary alcohols deliberately excluded to avoid their potential interference as reactive substrates. Most of the tested solvents yielded high oxidation efficiencies (Table S2, ESI†), and tert-butanol was ultimately chosen as the preferred solvent due to its alignment with green chemistry principles.<sup>27,28</sup> In some cases, protonic acids are unsuitable for acid-sensitive alcohol substrates; therefore, we investigated several Lewis acids as alternatives (Table 1). At room temperature, catalytic amounts of Lewis acids were insufficient to achieve high oxidation efficiency. Complete oxidation was only observed when the reaction temperature was raised to 60 °C. Among the tested Lewis acids, TiCl<sub>4</sub> and Sn(OTf)<sub>2</sub> demonstrated superior performance, delivering yields exceeding 90%, whereas ZnCl<sub>2</sub> and InBr<sub>3</sub> proved less effective.

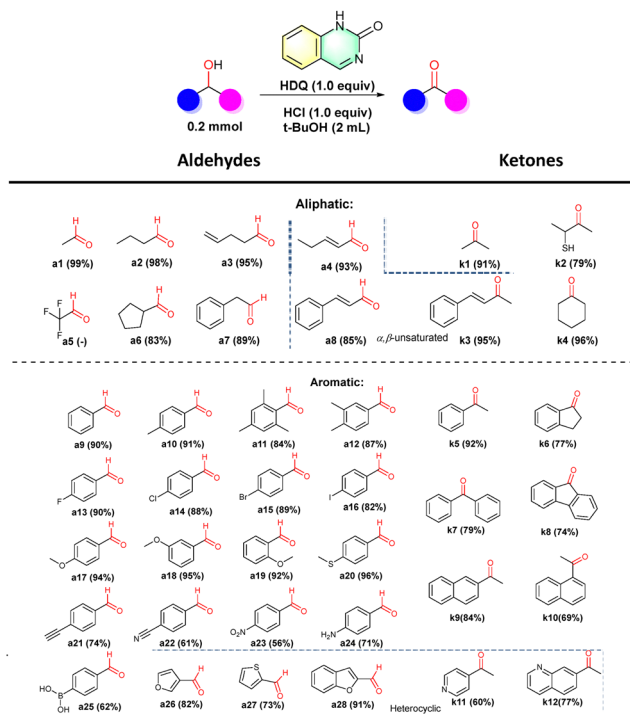
The substrate tolerance of various alcohols was further evaluated. Under optimized reaction conditions, a broad range of aliphatic alcohols were efficiently oxidized (Table 2). Alcohols containing alkenyl groups were also well-tolerated under these conditions, allowing for the preparation of α,β-unsaturated aldehydes or ketones (a4, a8, k3). For aromatic alcohols, the position of substituents on the aromatic ring did not significantly affect the yields (a17–a19). However, benzyl alcohols with strong electron-withdrawing groups, such as cyanide (a22) or nitro (a23), showed lower conversion rates to aldehydes. Notably, alcohols containing acetylene group (a21) and easily oxidized groups like the methylthio group (a20) were well-tolerated, indicating selective oxidation of primary and secondary alcohols without affecting other functional groups. Furthermore, some aromatic heteroalcohols also performed well under these conditions, achieving high oxidation yields.

Conventional oxidation methods often face challenges in controlling the selectivity of oxidation sites in polyols. To address



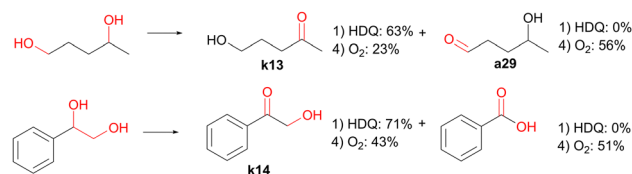
Table 1 Optimization of reaction conditions<sup>a</sup>


Entry	HDQ (equiv.)	Additives	Temp. (°C)	Yield <sup>b</sup> (%)	Yield <sup>c</sup> (%)
1	1.0	—	25	n.d.	n.d.
2	1.0	HCl(1.0 equiv.)	25	96	90
3	2.0	HCl(1.0 equiv.)	25	97	75
4	0.5	HCl(1.0 equiv.)	25	49	88
5	1.0	HCl(0.2 equiv.)	25	39	44
6	1.0	HCl(0.2 equiv.)	60	94	89
7	1.0	HCl(0.05 equiv.)	60	83	80
8	1.0.	AcOH(1.0 equiv.)	25	91	88
9	1.0.	NaOH(1.0 equiv.)	25	n.d.	n.d.
10	1.0.	K <sub>2</sub> CO <sub>3</sub> (1.0 equiv.)	25	n.d.	n.d.
11	1.0.	Et <sub>3</sub> N(1.0 equiv.)	25	n.d.	n.d.
12	1.0.	AlCl <sub>3</sub> (0.2 equiv.)	60	89	75
13	1.0.	ZnCl <sub>2</sub> (0.2 equiv.)	60	27	<10
14	1.0.	BF <sub>3</sub> (0.2 equiv.)	60	84	70
15	1.0.	InBr <sub>3</sub> (0.2 equiv.)	60	37	19
16	1.0.	Sn(OTf) <sub>2</sub> (0.2 equiv.)	60	93	81
17	1.0.	TMSOTf(0.2 equiv.)	60	58	40
18	1.0.	TiCl <sub>4</sub> (0.2 equiv.)	60	97	80
19	1.0.	TiCl <sub>4</sub> (1.0 equiv.)	25	94	81
20	1.0.	TiCl <sub>4</sub> (0.05 equiv.)	60	71	79

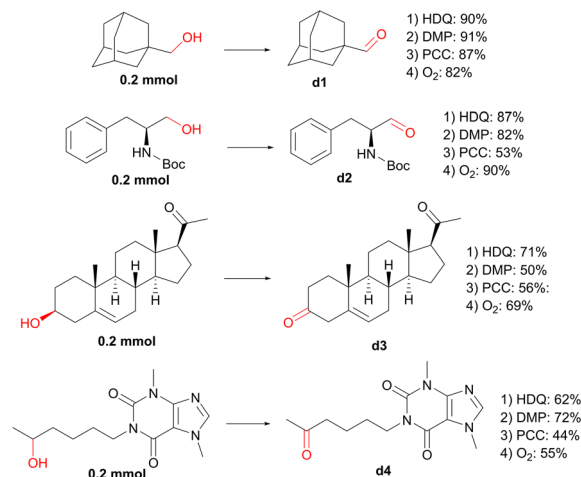
<sup>a</sup> 1-Phenethylalcohol (0.2 mmol) in *t*-BuOH (2 mL), reaction time 1.5 h.<sup>b</sup> Isolated yields of acetophenone. <sup>c</sup> Isolated yields of DHQZ.Table 2 Scope of alcohol oxidation<sup>ab</sup><sup>a</sup> Reaction conditions: alcohol (0.2 mmol), HDQ (1.0 equiv.), HCl (1.0 equiv.), *t*-BuOH (2 mL), 25 °C for 1.5 h. <sup>b</sup> Yields are isolated.

this, further investigations were conducted to explore the selective oxidation of primary *versus* secondary alcohols using 1,4-pentanediol and 1-phenyl-1,2-ethanediol as substrates (Scheme 1a). The results

## Selective oxidation of primary and secondary alcohols.



## Oxidative synthesis of pharmaceutical intermediates.



**Scheme 1** Scope of additional substrate. Reaction conditions: (1) HDQ (1 equiv.), HCl (1.0 equiv.), *t*-BuOH (2 mL), 25 °C for 3 h. (2) DMP (1.0 equiv.), pyridine (1 equiv.), *t*-BuOH (2 mL), 25 °C for 3 h. (3) PCC (1.0 equiv.), *t*-BuOH (2 mL), 25 °C for 3 h. (4) CuI (0.05 equiv.), *L*-proline (0.05 equiv.), TEMPO (0.05 equiv.), *t*-BuOK (1 equiv.), MeCN (2 mL), 25 °C for 5 h. Yields are isolated.

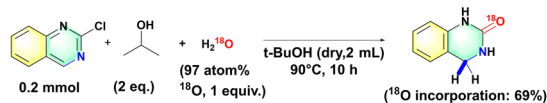
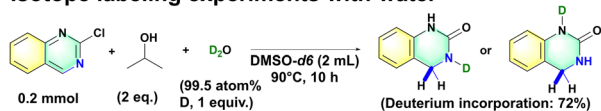
demonstrated higher selectivity for secondary alcohols oxidation compared to primary alcohols, as no aldehyde formation was detected in the reaction mixture. The hydroxyl group at the benzyl position was preferentially oxidized over the terminal hydroxyl group. The application of this method to the synthesis of drug fragments is equally advantageous compared to established reactions (Scheme 1b). Alcohols derived from adamantane, amino acids, steroids, and alkaloids were efficiently oxidized by HDQ, and importantly, the stereochemistry of chiral molecules was preserved.

The broad substrate scope and high yields make this reaction readily scalable from milligram to gram quantities. To evaluate its scalability, we performed the oxidation of a template substrate on a gram scale and compared it to other strategies (Table S3, ESI<sup>†</sup>). Our method demonstrated high efficiency, achieving satisfactory conversions (>90% yield for both acetophenone and DHQZ), while offering a dual-function process: it enables direct access to a wide range of aldehydes and ketones, along with the efficient production of DHQZ. Furthermore, the poor solubility of DHQZ allows for its easy recovery *via* simple filtration, significantly streamlining the post-processing steps.

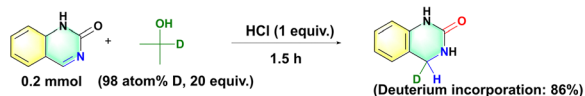
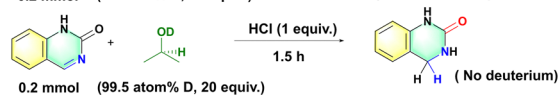
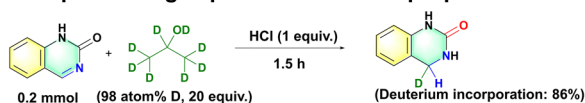
Mechanistic studies were conducted using isotope labeling experiments. When D<sub>2</sub>O was added to the oxidation system containing 2-CQZ (Scheme 2a), a specific N–H signal of the reduction product DHQZ was absent in <sup>1</sup>H-NMR spectra, indicating the substitution of active hydrogen atoms. Further confirmation came from using oxygen-18 labeled water, which traced the oxygen



## Isotope labeling experiments with water



## Isotope labeling experiments with isopropanol



Scheme 2 Controlled experimental schemes for mechanistic analysis.

source in the reduction product. High-resolution mass spectrometry (HRMS) confirmed the incorporation of oxygen-18, thereby demonstrating that hydrolysis of 2-CQZ generates both HDQ and HCl as essential components for the subsequent oxidation. To further investigate the hydrogen transfer between the alcohol substrate and HDQ, we examined various deuterated isopropanol substrates: 2-propanol- $d_8$ , 2-propanol- $O-d_1$ , and 2-propanol- $2-d_1$  (Scheme 2b). The results showed that only the hydrogen at the 4-position was deuterated in the reduction products derived from 2-propanol- $d_8$  and 2-propanol- $2-d_1$ , while no deuterium incorporation was observed in the reduction products from 2-propanol- $O-d_1$ . This indicates that the hydrogen at the  $\alpha$ -position of the alcohol is specifically transferred to the 4-position of the HDQ during the reaction.

Encouraged by these findings, we propose a plausible acid-catalyzed addition mechanism for the oxidation process: 2-CQZ undergoes partial hydrolysis upon exposure to heat, producing HDQ and a molecule of hydrogen chloride. This reaction generates protonated HDQ, featuring a highly reactive  $\alpha,\beta$ -unsaturated ring system. The feasibility of the  $\alpha$ -H migration of isopropanol as a pivotal step in the reaction was meticulously verified using advanced density functional theory (DFT) calculations. After exploring various protonation scenarios and electron transfer pathways, we determined that the most favorable process involves the 3,4-addition of HDQ with alcohols. During this process, the  $\alpha$ -hydrogen of the alcohol is abstracted by the 4-position of HDQ, triggering an electronic rearrangement that yields the corresponding aldehyde or ketone, while HDQ is transformed into DHQZ. The resulting Gibbs free energy profiles reveal the energy barrier, underscoring the reaction's susceptibility to oxidation under acid catalysis (Fig. 3). Notably, the activation of HDQ by a protonated or Lewis acid is critical for the oxidation, consistent with the observed failure of oxidation in basic conditions.

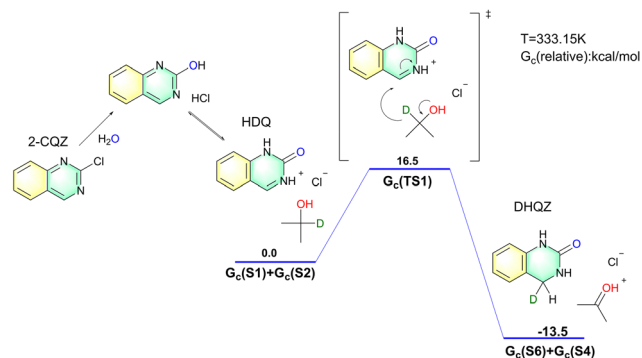


Fig. 3 Proposed mechanism of alcohol oxidation via ionic addition.

## Conclusions

In summary, we have developed a cost-effective, one-step method for synthesizing aldehydes and ketones from alcohols *via* acid-catalyzed transfer hydrogenation of HDQ. This highly selective strategy accommodates a broad substrate scope of alcohols with a simplified post-reaction process. Additionally, it produces the pharmaceutically valuable reduction product DHQZ, a privileged scaffold for drug development targeting NMDA antagonists, KRAS inhibitors, M1 regulators, and other bioactive compounds. Mechanistic studies revealed an ionic addition mechanism involving the transfer of the  $\alpha$ -hydrogen to the quinazoline ring. Aligned with green chemistry principles, this approach offers significant potential for applications in chemical synthesis and pharmaceutical innovation.

## Author contributions

Boheng Wan: writing – original draft, investigation, formal analysis, validation. Kairan Cui: software. Jie Xu: data curation. Shaohua Xing: formal analysis. Zimo Zhu: investigation. Yang Lai: validation. Sheng Wu: supervision. Jiaxuan Guo: validation. Yadong Chen: funding acquisition. Tao Lu: project administration. Jie Feng: methodology. Yong Zhu: conceptualization.

## Data availability

Crystallographic data are freely available from the Cambridge Crystallographic Data Centre (CCDC 2381048).<sup>†</sup> Additional experimental details, including experimental procedures, crystal structures, compound characterization, NMR spectra of all new compounds, ligand datasets and computational details are available in the ESI.<sup>†</sup> Further data are available upon request from the authors. Source data are provided with this paper.

## Conflicts of interest

There are no conflicts to declare.

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