




 Cite this: *New J. Chem.*, 2025, **49**, 7314

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

 Boheng Wan,^a Kairan Cui,^a Jie Xu,^a Shaohua Xing,^a Zimo Zhu,^a Yang Lai,^a Sheng Wu,^{ab} Jiakuan Guo,^d Yadong Chen,^a Tao Lu,^{*ac} Jie Feng ^{*a} and Yong Zhu ^{*a}

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.

 Received 27th February 2025,
 Accepted 8th April 2025

DOI: 10.1039/d5nj00893j

rsc.li/njc

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,^{1–3} 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.^{4–11}

Compared to the methods described above, the classical Oppenauer oxidation,¹² 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,^{13–16} 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^{17–19} due to their broad range of biological activities, including anti-inflammatory, anti-cancer, and anti-viral properties.^{20,21} Traditionally, DHQZ has been synthesized *via* cyclocarbonylation, a method often limited by its complex and demanding reaction conditions.^{22–24} More recently, an efficient strategy for the preparation of hydroquinolinone analogs

^a School of Science, China Pharmaceutical University, No. 639 Longmian Avenue, Nanjing 211198, P. R. China. E-mail: lutao@cpu.edu.cn, 1020162519@cpu.edu.cn, zhuyong@cpu.edu.cn

^b School of Pharmacy, AnHui College of Traditional Chinese Medicine, No. 18 Wuxia West Road, Wuhu City 241002, P. R. China

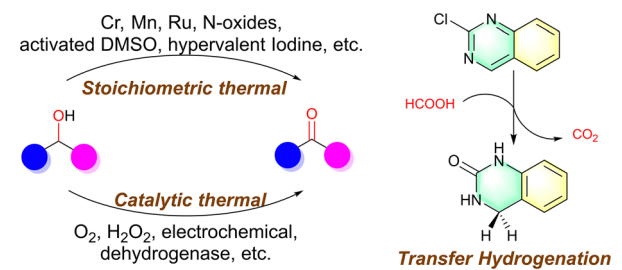
^c State Key Laboratory of Natural Medicines, China Pharmaceutical University, No. 639 Longmian Avenue, Nanjing 211198, P. R. China

^d Sir Run Run Hospital, Nanjing Medical University, No. 109 Longmian Avenue, Nanjing 211198, P. R. China

† Electronic supplementary information (ESI) available: Experimental procedures, characterization data of products, and copies of NMR spectra. CCDC 2381048. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d5nj00893j>



a. Previous work



b. This work

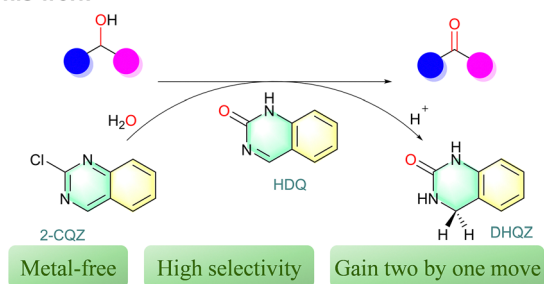


Fig. 1 (a) Landscape of alcohol oxidation approaches and transfer hydrogenation of the 2-CQZ to DHQZ. (b) Alcohol oxidation *via* HDQ-mediated hydrogen transfer.

has been reported, involving successive hydrolysis and transfer hydrogenation²⁵ (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(1*H*)-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

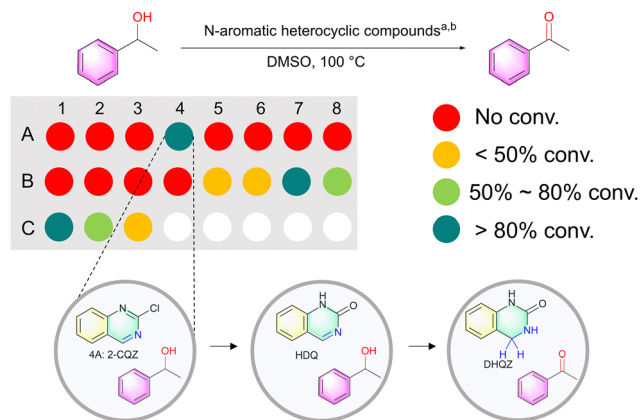


Fig. 2 Alcohol oxidation screening with 19 N-heteroaromatics. ^a Experimental details in ESI†. ^b Conversion quantified by LC-MS. As the reaction formulas in the figure are labeled.

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.²⁶

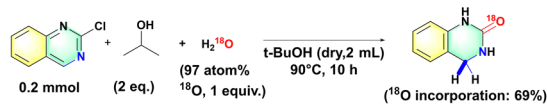
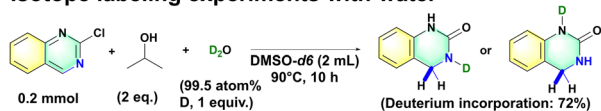
To optimize the conditions for oxidation using HDQ, various solvents were screened, with primary and secondary alcohols deliberately excluded to avoid their potential interference as reactive substrates. Most of the tested solvents yielded high oxidation efficiencies (Table S2, ESI†), and tert-butanol was ultimately chosen as the preferred solvent due to its alignment with green chemistry principles.^{27,28} 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, TiCl₄ and Sn(OTf)₂ demonstrated superior performance, delivering yields exceeding 90%, whereas ZnCl₂ and InBr₃ 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.

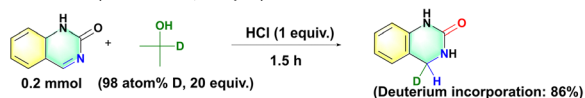
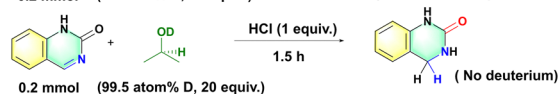
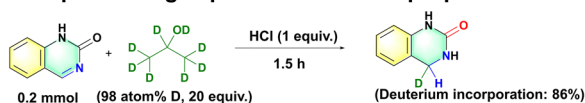
Conventional oxidation methods often face challenges in controlling the selectivity of oxidation sites in polyols. To address



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 α -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 α,β -unsaturated ring system. The feasibility of the α -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 α -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.

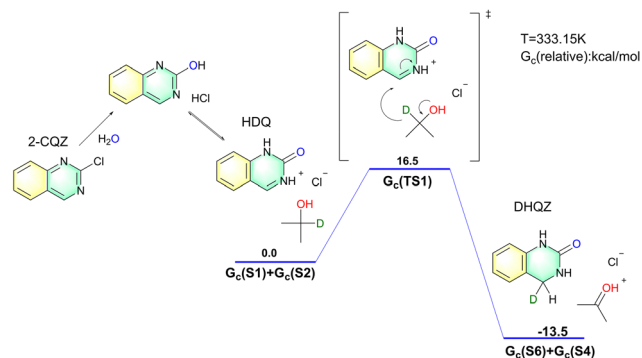


Fig. 3 Proposed mechanism of alcohol oxidation via ionic addition.

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 α -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).[†] 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.[†] 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.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (Grant No. 82473895 and 82473786) and



the Academic Funding Program for Top Talents in Disciplines (Majors) of Higher Education Institutions in Anhui (Grant No. gxbjZD2022103). We would like to thank Ms Qian Zhao and the Science Compass research platform for supporting our crystallography research. We also express our gratitude to Dr Haichun Liu from China Pharmaceutical University, and Dr Bin Wang from Lingnan Normal University for their guidance on our computational chemistry research.

References

- S. Chandrasekaran and V. Ganesh, in *Comprehensive Organic Synthesis*, ed. P. Knochel, Elsevier, Amsterdam, 2nd edn, 2014, pp. 277–294.
- G. Tojo and M. Fernandez, *Oxidation of Alcohols to Aldehydes and Ketones: A Guide to Current Common Practice*, 2006.
- W. Gou, P. Dai, M. Wang, Y. Wang, N. Ma, X. Zhou, Y. Xu, L. Zhang and C. Li, *Synthesis of Diverse Ureas from Amines and CO₂ at Atmospheric Pressure and Room Temperature*, *J. Org. Chem.*, 2024, **89**, 12498–12507.
- R. H. Crabtree, *Homogeneous Transition Metal Catalysis of Acceptorless Dehydrogenative Alcohol Oxidation: Applications in Hydrogen Storage and to Heterocycle Synthesis*, *Chem. Rev.*, 2017, **117**, 9228–9246.
- K. Alfonsi, J. Colberg, P. J. Dunn, T. Fevig, S. Jennings, T. A. Johnson, H. P. Kleine, C. Knight, M. A. Nagy, D. A. Perry and M. Stefaniak, *Green chemistry tools to influence a medicinal chemistry and research chemistry based organisation*, *Green Chem.*, 2008, **10**, 31–36.
- C. P. Vinod, K. Wilson and A. F. Lee, *Recent advances in the heterogeneously catalysed aerobic selective oxidation of alcohols*, *J. Chem. Technol. Biotechnol.*, 2011, **86**, 161–171.
- B. L. Ryland and S. S. Stahl, *Practical Aerobic Oxidations of Alcohols and Amines with Homogeneous Copper/TEMPO and Related Catalyst Systems*, *Angew. Chem., Int. Ed.*, 2014, **53**, 8824–8838.
- S. E. Davis, M. S. Ide and R. J. Davis, *Selective oxidation of alcohols and aldehydes over supported metal nanoparticles*, *Green Chem.*, 2013, **15**, 17–45.
- C. Parmeggiani and F. Cardona, *Transition metal based catalysts in the aerobic oxidation of alcohols*, *Green Chem.*, 2012, **14**, 547–564.
- C. Parmeggiani, C. Matassini and F. Cardona, *A step forward towards sustainable aerobic alcohol oxidation: new and revised catalysts based on transition metals on solid supports*, *Green Chem.*, 2017, **19**, 2030–2050.
- C. D. F. Milagre and H. M. S. Milagre, *Alcohol dehydrogenase-catalyzed oxidation*, *Curr. Opin. Green Sustainable Chem.*, 2022, **38**, 100694.
- J. J. Li, in *Name Reactions: A Collection of Detailed Mechanisms and Synthetic Applications*, ed. J. J. Li, Springer International Publishing, Cham, 5th edn, 2014, pp. 447–448.
- I. Yamada and R. Noyori, *Asymmetric Transfer Hydrogenation of Benzaldehydes*, *Org. Lett.*, 2000, **2**, 3425–3427.
- D. Šterk, M. Stephan and B. Mohar, *Highly Enantioselective Transfer Hydrogenation of Fluoroalkyl Ketones*, *Org. Lett.*, 2006, **8**, 5935–5938.
- M. Buonaiuto, A. G. De Crisci, T. F. Jaramillo and R. M. Waymouth, *Electrooxidation of Alcohols with Electrode-Supported Transfer Hydrogenation Catalysts*, *ACS Catal.*, 2015, **5**, 7343–7349.
- E. Zhao, W. Zhang, L. Dong, R. Zbořil and Z. Chen, *Photocatalytic Transfer Hydrogenation Reactions Using Water as the Proton Source*, *ACS Catal.*, 2023, **13**, 7557–7567.
- M. Kawai, K. Ando, Y. Matsumoto, I. Sakurada, M. Hirota, H. Nakamura, A. Ohta, M. Sudo, K. Hattori, T. Takashima, M. Hizue, S. Watanabe, I. Fujita, M. Mizutani and M. Kawamura, *Discovery of (–)-6-[2-[4-(3-fluorophenyl)-4-hydroxy-1-piperidinyl]-1-hydroxyethyl]-3,4-dihydro-2(1H)-quinolinone—A potent NR2B-selective N-methyl D-aspartate (NMDA) antagonist for the treatment of pain*, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 5558–5562.
- C. W. Lindsley, P. J. Conn, M. R. Wood, B. J. Melancon, M. S. Poslusney and J. C. Tarr, *WO Pat.*, WO2013106795, 2013.
- S. Rabizadeh, N. Kayvan, S. Buzko, P. Weingarten, H. McFarlane, A. Juncker-Jensen, J. Golovato, P. Soon-Shiong, C. Tao and D. Ho, *WO Pat.*, WO2016161361, 2016.
- V. Alagarsamy, K. Chitra, G. Saravanan, V. R. Solomon, M. T. Sulthana and B. Narendhar, *An overview of quinazolines: Pharmacological significance and recent developments*, *Eur. J. Med. Chem.*, 2018, **151**, 628–685.
- H. A. M. Gomaa, *A comprehensive review of recent advances in the biological activities of quinazolines*, *Chem. Biol. Drug Des.*, 2022, **100**, 639–655.
- J. Paz, C. Pérez-Balado, B. Iglesias and L. Muñoz, *Carbon Dioxide as a Carbonylating Agent in the Synthesis of 2-Oxazolidinones, 2-Oxazinones, and Cyclic Ureas: Scope and Limitations*, *J. Org. Chem.*, 2010, **75**, 3037–3046.
- M. Wang, J. Han, X. Si, Y. Hu, J. Zhu and X. Sun, *Effective approach to ureas through organocatalyzed one-pot process*, *Tetrahedron Lett.*, 2018, **59**, 1614–1618.
- H. Matsuo, J.-C. Choi, T. Fujitani and K.-I. Fujita, *Carbonylation of o-phenylenediamines with CO₂ to 2-benzimidazolones catalyzed by alumina*, *Tetrahedron Lett.*, 2022, **96**, 153772.
- R. Luo, S. Wang, Y. Liang, J. Liao and L. Ouyang, *Successive hydrolysis and transfer hydrogenation of 2-chloroquinolines to 3,4-dihydroquinolones*, *New J. Chem.*, 2024, **48**, 17700–17705.
- Y. Yamamoto and S. Shinkai, *Category 2, Hetarenes and Related Ring Systems*, 2004.
- F. Zhou, Z. Hearne and C.-J. Li, *Water—the greenest solvent overall*, *Curr. Opin. Green Sustainable Chem.*, 2019, **18**, 118–123.
- V. Hessel, N. N. Tran, M. R. Asrami, Q. D. Tran, N. Van Duc Long, M. Escrivà-Gelonch, J. O. Tejada, S. Linke and K. Sundmacher, *Sustainability of green solvents – review and perspective*, *Green Chem.*, 2022, **24**, 410–437.

