JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

pubs.acs.org/JACS
Communication

Catalytic Enantioselective Hydrogen Atom Abstraction Enables the Asymmetric Oxidation of *Meso* Diols

Nelson Y. S. Lam, Jyoti Dhankhar, Antti S. K. Lahdenperä, and Robert J. Phipps*

Cite This: *J. Am. Chem. Soc.* 2024, 146, 33302−33308
Read Online

ABSTRACT: Desymmetrization of *meso* diols is an important strategy for the synthesis of chiral oxygen-containing building blocks. Oxidative desymmetrization is an important subclass, but existing methods are often constrained by the need for activated alcohol substrates. We disclose a conceptually distinct strategy toward oxidative diol desymmetrization that is enabled by catalytic enantioselective hydrogen atom abstraction. Following single electron oxidation of a cinchona alkaloid-derived catalyst, enantiodetermining hydrogen atom abstraction generates a desymmetrized ketyl radical intermediate which reacts with either DIAD or O_2 before *in situ* elimination to form valuable hydroxyketone products. A range of cyclic and acyclic *meso* diols are competent, defining the absolute configuration of up to four stereocenters in a single operation. As well as providing rapid access to complex hydroxyketones, this work emphasizes the broad synthetic potential of harnessing hydrogen atom abstraction in an enantioselective manner.

Alcohol oxidation is among the most commonly used transformations in organic synthesis.[1] Classically carried out with stoichiometric oxidative reagents, recent developments have led to a suite of catalytic methods that permit the use of less activated oxidants.[2] The inclusion of a catalyst provides opportunities to perform enantioselective oxidation in a practical manner without requiring stoichiometric chiral oxidants,[3] and has been widely applied to the kinetic resolution of racemic chiral secondary alcohols.[4,5] Alternatively, catalytic enantioselective alcohol oxidation can be used to desymmetrize *meso* diols. This requires a chiral catalyst to selectively oxidize one of two enantiotopic hydroxyl groups, generating a single chiral product. Several important advances have been made toward the enantioselective oxidation of *meso* primary diols, spanning a range of catalytic approaches (Figure 1A, left).[6] In contrast, enantioselective oxidation protocols for *meso* secondary diols[7] are largely limited to activated (*e.g.* benzylic) alcohols (Figure 1A, right).[3c,8] To the best of our knowledge, there is only a single example demonstrated on nonactivated *meso* secondary alcohols: Hua and co-workers in 2016 utilized chiral Pd/Au nanoclusters as catalysts to give excellent enantioselectivities in the oxidation of simple carbocyclic *meso* diols.[9] However, this method has not been extended to acyclic and more complex diol substrates, in which other functional groups or prochiral stereocenters were present.

By taking advantage of structural parallels between cinchona alkaloids and the established hydrogen atom abstraction (HAA) catalyst quinuclidine,[10] we recently developed a series of chiral catalysts capable of performing enantioselective HAA from *meso* diols (Figure 1B).[11−14] After single electron oxidation of a modified cinchona alkaloid, the resulting chiral quinuclidinium radical cation selectively abstracts one of the two enantiotopic hydrogen atoms from the achiral diol substrate, setting the adjacent hydroxyl stereocenter in the process. Inspired by the prior work of Wendlandt,[15] we demonstrated that the resulting ketyl radical can be intercepted with a thiol hydrogen atom donor to afford enantioenriched *trans* diols or trapped with electron deficient olefins in Giese addition. In addition to introducing a chiral catalyst for HAA, our work represented a rare example of an asymmetric diol desymmetrization which takes place at carbon rather than oxygen, an outcome achieved by harnessing a radical mechanism involving hydrogen atom transfer.[16,17]

Leveraging the known nucleophilic character of the enantioenriched ketyl radical intermediate,[18] we speculated whether this may be trapped with a suitable oxidant which, upon *in situ* elimination, would deliver enantioenriched hydroxyketone-containing products. These are prevalent in bioactive molecules and synthetic intermediates[19] and extensive literature precedent exists for their elaboration.[20] Most approaches for asymmetric oxidation are initiated by enantiodetermining *O*-functionalization.[21] In contrast, this process would offer a conceptually distinct strategy, where enantioselection is initiated by desymmetrization at carbon rather than oxygen. Herein we report the realization of this approach using either diisopropyl azodicarboxylate (DIAD) or oxygen as mild oxidants to intercept the desymmetrized ketyl radical (Figure 1C). Enantioselective oxidation of a range of cyclic and linear *meso* secondary diols is possible, in many cases allowing the absolute configuration of multiple stereocenters to be defined in a single operation.

Received: October 4, 2024
Revised: November 14, 2024
Accepted: November 18, 2024
Published: November 26, 2024

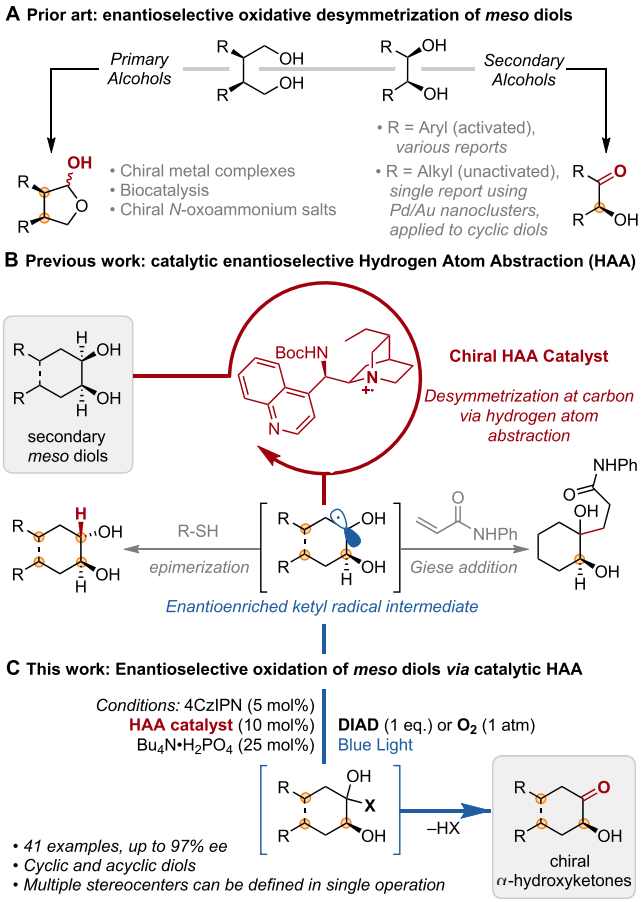
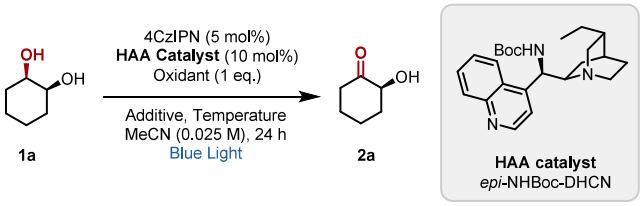


Figure 1. Prior art relating to enantioselective oxidative desymmetrization of *meso* diols and enantioselective hydrogen atom abstraction.

We commenced our optimization using *meso* cyclohexane-1,2-diol (**1a**) as the model substrate, using the optimal chiral HAA catalyst from our previous work[11] (*epi*-NHBoc-DHCN, 10 mol %), 4CzIPN as photocatalyst (5 mol %) and the additive $Bu_4N{\cdot}H_2PO_4$ (25 mol %) at +10 °C (Table 1). An evaluation of oxidants (entries 1−4) identified diisopropyl azodicarboxylate (DIAD) as the best performer and acetonitrile as the optimal solvent (entry 4, 54% yield, 82% ee; see SI for full details).[22,23] Interestingly, omission of the $Bu_4N{\cdot}H_2PO_4$ additive resulted in negligible reactivity (entry 5),[10] its importance here contrasting with our reported enantioselective epimerization reaction where its impact was minimal on the same substrate.[11] Yield and enantioselectivity markedly improved when the reaction was conducted at −35 °C (entry 6, 91% ee), and a minor yield improvement was obtained on addition of 4 Å molecular sieves (entry 7).[24] Control experiments varying the conditions from entry 7 were conducted to establish the importance of each component. Omission of blue light (entry 8), photocatalyst (entry 9) or HAA catalyst (entry 10) resulted in no product formation. Finally, conducting the reaction in the absence of DIAD gave minimal product formation (entry 11), indicating its key role.

With optimized conditions, we proceeded to examine the scope of *meso* cyclic diols (Scheme 1A; see SI for ineffective examples). Six, seven and eight-membered carbocyclic *meso* diols were competent (**2a−c**). Reduced yield due to product volatility and lower enantioselectivities was observed for five-membered diol **2d**, which required a telescoped derivatization to the corresponding benzoate ester for isolation. A fused

Table 1. Selected Reaction Optimization and Controls



	Oxidant	Conditions	Yield[a]	ee[b]
1.	TCCA	$Bu_4N{\cdot}H_2PO_4$ (25 mol %), +10 °C	45%	8%
2.	BzOO*t*Bu	$Bu_4N{\cdot}H_2PO_4$ (25 mol %), +10 °C	18%	76%
3.	O_2 (1 atm)	$Bu_4N{\cdot}H_2PO_4$ (25 mol %), +10 °C	20%	82%
4.	**DIAD**	$Bu_4N{\cdot}H_2PO_4$ (25 mol %), +10 °C	54%	82%
5.	**DIAD**	No $Bu_4N{\cdot}H_2PO_4$, +10 °C	2%	n.d.
6.	**DIAD**	$Bu_4N{\cdot}H_2PO_4$ (25 mol %), **−35 °C**	78%	91%
7.	**DIAD**	$Bu_4N{\cdot}H_2PO_4$ (25 mol %), **4 Å MS, −35 °C**	**92%**[c]	**91%**
8.		No Light	0%	n.d.
9.		No 4CzIPN (Photocatalyst)	0%	n.d.
10.		No HAA catalyst	0%	n.d.
11.		No DIAD	8%	n.d.

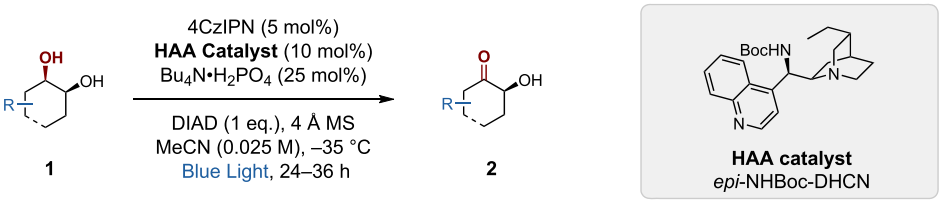
[a]Yields determined by ^{1}H NMR using CH_2Br_2 as internal standard. [b]Enantiomeric excess (ee) determined by chiral SFC analysis from the benzoate ester derivative of **2a**. [c]Isolated yield of **2a** prior to derivatization. TCCA: Trichloroisocyanuric Acid.

benzene ring (**2e**), cyclic protected amine (**2f**), esters (**2g−h**) and acetals (**2i−j**) were effective, showing no cross-reactivity at other C−H bonds potentially liable to HAA. Remarkably, alkenes (**2k−l**), motifs which may interfere in radical processes, were highly effective; no evidence of alkene isomerization, radical addition or competitive HAA at allylic sites was observed. We evaluated the corresponding *meso*-1,3 isomer of **1a** which underwent oxidation but gave low ee (see SI). We next explored a series of more elaborate *meso* cyclic diols and functionalized 5,6-fused bicycles were first examined (**2m−2s**). Notably, cyclic ethers (**2m**), protected amines (**2n**), acetonides (**2o**), esters (**2p−s**) and nitriles (**2q−s**) were tolerated. Extension to 7,6-bicycles (**2t−u**), as well as more strained 4,6- (**2v**) and 3,6-fused bicycles (**2w−x**), and monocyclic tetrasubstituted substrate **2y** was also amenable. In the case of **2w**, in which the starting diol contains an epoxide, the hydroxyketone product was unstable. This underwent *in situ* elimination to afford the dihydroxyenone **2w′** as a single diastereomer in good yield and excellent enantioselectivity. While diminished enantioselectivity was observed for substrates containing bulky substituents (*e.g.* **2x** and **2z**), the success of **2x** attests to the mildness of this method as it contains both cyclopropyl and alkyl chloride motifs. Finally, 3,8-fused (**2z-2aa**) and 5,8-fused (**2ab-2ac**) bicycles were also highly effective. In the above cases, our enantioselective oxidation can set the absolute configuration of up to four stereocenters in a single operation, generating stereodefined hydroxyketones that would be challenging to access using conventional methods.[19b]

A series of linear *meso* alcohols were next examined (Scheme 1B). Simple diols bearing alkyl chains were highly effective, giving the corresponding hydroxyketone products (**4a−c**) with high ee values. The reaction was tolerant of phenyl substituents (**4d−4e**), affording the products in high ee with no evidence of deleterious HAA at the benzylic position. Diesters (**4f**) and silyl ethers (**4g−h**) proved amenable. In these cases, we

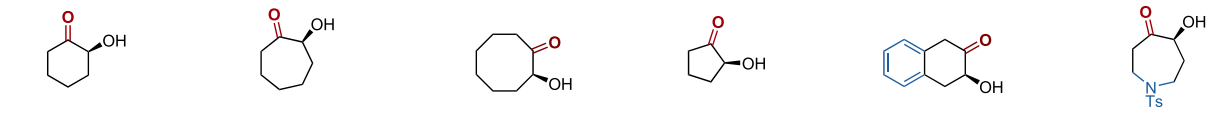
https://doi.org/10.1021/jacs.4c13919
J. Am. Chem. Soc. 2024, 146, 33302−33308

Scheme 1. Scope of Enantioselective Oxidation for (A) Cyclic and (B) Linear *Meso* Diols



A Cyclic *meso* diols

Setting a single stereocenter:



2a 92%, 91% ee

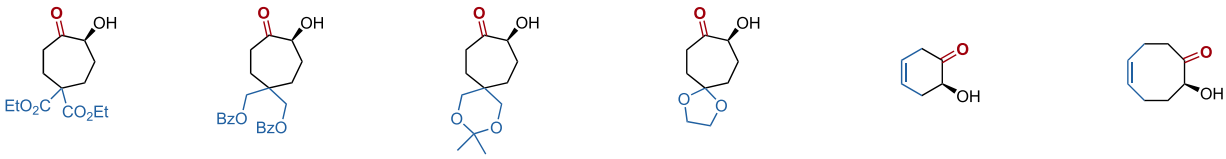
2b 92%, 92% ee

2c 82%[a], 82% ee

2d 47%[b], 75% ee

2e 51%, 93% ee

2f 78%, 93% ee



2g 70%, 89% ee

2h 70%, 79% ee

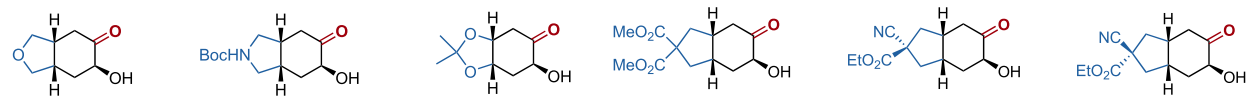
2i 78%, 82% ee

2j 87%, 90% ee

2k 77%, 90% ee

2l 72%[a], 94% ee

Setting multiple stereocenters: (reaction time: 36 h)



2m 74%, 84% ee

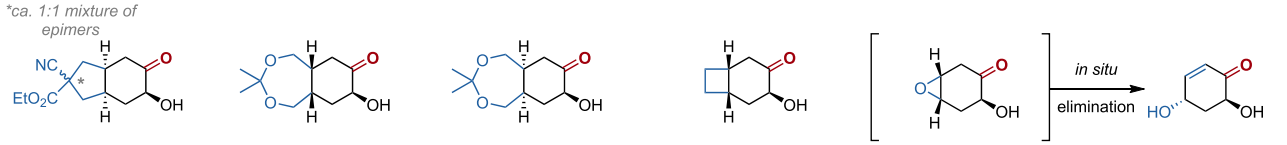
2n 47%, 80% ee

2o 75%, 84% ee

2p 75%, 89% ee

2q 56%, 78% ee

2r 38%, 89% ee



2s 61%, Diast. 1: 88% ee, Diast. 2: 93% ee

2t 75%, 84% ee

2u 88%, 90% ee

2v 93%, 87% ee

2w

2w' 84%,[c] 94% ee

2x 58%, 72% ee

2y 38%, 72% ee

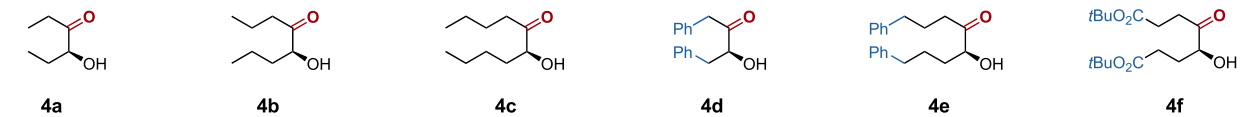
2z 87%, 93% ee

2aa 90%, Diast. 1: 94% ee, Dlast. 2: 91% ee

2ab 97%, 93% ee

2ac 53%, 94% ee

B Linear *meso* diols



4a 81%, 96% ee

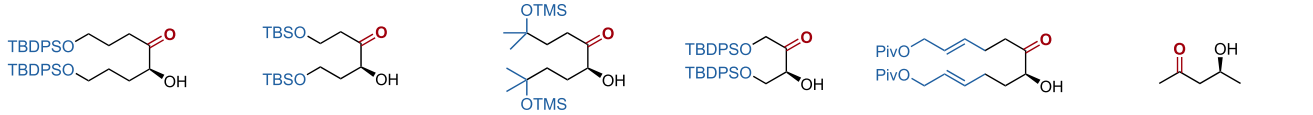
4b 88%, 96% ee

4c 73%, 88% ee

4d 46%, 90% ee

4e 68%, 97% ee

4f 35%, 84% ee



4g 21%, 94% ee

4h 22%, 85% ee

4i 81%, 95% ee

4j 0% (95% SM)

4k 34%, 85% ee

4l 66%[d] (86%)[e], 94% ee

[a]Isolated yields of hydroxyketone. Enantiomeric excess (ee) determined after *O*-benzoylation for products without a chromophore. 36 h reaction time, [b]Isolated as *O*-Bz ester, [c]Fifteen mol % HAA catalyst loading, [d]Isolated as TBDPS ether, [e]NMR yield in parentheses.

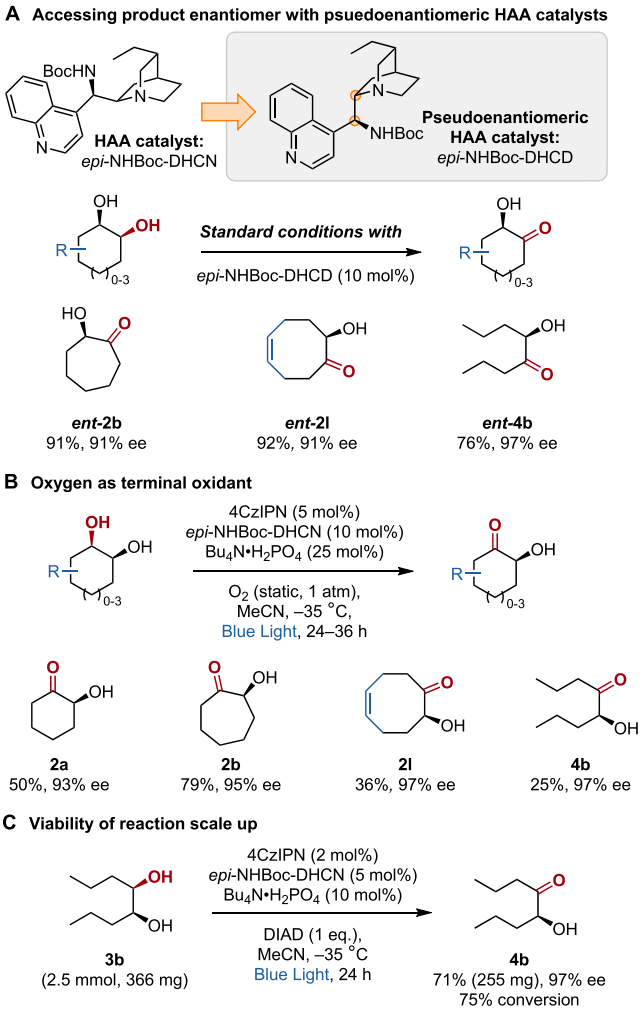
https://doi.org/10.1021/jacs.4c13919
J. Am. Chem. Soc. 2024, 146, 33302−33308

attribute the low yields to electronic deactivation toward HAA resulting in moderate conversions; an effect that could apparently be counteracted by inclusion of extra alkyl groups in **4i**. As may be expected, moving the ether motif even closer to the site of HAA shut down the reaction completely (**4j**). In another example of tolerance to alkene functionality, a pivalate-protected diallylic alcohol (**4k**) gave modest yield of the product but in good enantioselectivity. We also demonstrate that enantioselective oxidation of an acyclic *meso* 1,3-diol could also be achieved; *meso*-pentane-2,4-diol underwent oxidation with high yield and enantioselectivity (**4l**). A reduced yield was obtained due to product volatility, and preparative isolation required telescoping to the corresponding TBDPS ether (a known intermediate for the total synthesis of altohyrtin A).[25] This result indicates potential applications toward accessing chiral β-hydroxyketones distinct from a classical aldol-type disconnection. Comparison with literature optical rotation values for cyclic hydroxyketones **2a–d**, linear α-hydroxyketones **4a–4d** and TBDPS-protected β-hydroxyketone **4l′** indicated that the major enantiomer for newly set hydroxyl stereocenter was *S*-configured across all substrate classes. This observation was consistent with our enantioselective diol epimerization, in line with a common mechanism involving enantiodetermining HAA by the cinchona alkaloid derived catalyst. For modest-yielding reactions that gave nonvolatile products, the remaining mass balance typically consists of recovered starting material; overoxidation was not observed, indicating that enantioselectivity was not enhanced by downstream resolution processes. It is desirable that both product enantiomers can be readily accessed.

Gratifyingly, subjecting a sample of substrates with pseudoenantiomeric dihydrocinchonidine-derived HAA catalyst (*epi*-NHBoc-DHCD) afforded the antipodal cyclic (*ent*-**2b** and *ent*-**2l**) and linear (*ent*-**4b**) hydroxyketones with excellent yields and ees (Scheme 2A). During reaction optimization, we observed that oxygen gas could be used as the terminal oxidant, maintaining good enantioselectivity albeit with reduced product conversion (Table 1, entry 3, see SI for further optimization).[24] To explore this further, we subjected diols **1a**, **1b**, **1l** and **3b** to the enantioselective oxidation under a static atmosphere of O_2 in the absence of DIAD. In all cases, the desired product was obtained in high enantioselectivities, albeit with modestly reduced yields (Scheme 2B). This demonstrates that use of molecular oxygen in this protocol is viable and may find applications in reaction scale up with further development, potentially in a flow setting.[26] We also investigated a modestly scaled up reaction, which was successfully achieved on 2.5 mmol of **3b** (corresponding to a 25-fold increase in reaction scale compared to Scheme 1), employing slightly modified conditions to conserve photocatalyst, HAA catalyst and additives (Scheme 2C). This afforded the target hydroxyketone **4b** in 71% yield and 97% ee.

Regarding the photoredox aspect of the mechanism, one possibility involves reductive quenching of the photocatalyst by *epi*-NHBoc-DHCN (typically proposed with quinuclidine[10]), HAA from the diol, followed by quenching of the intermediate ketyl radical with DIAD prior to reduction and elimination (see SI for complete depiction). However, Stern Volmer fluorescence quenching experiments revealed that DIAD is a faster (1.5x) quencher of the excited state photocatalyst than *epi*-NHBoc-DHCN, presumably through oxidative quenching to form $4CzIPN^{\bullet+}$ and $DIAD^{\bullet-}$ (Figure 2B, see SI for discussion). The 10-fold greater concentration of DIAD at

Scheme 2. Further Experiments to Expand Method



the start of the reaction would suggest that photocatalytic oxidation of the HAA catalyst may be minimal under these conditions.[27] Studies suggest that initially formed $DIAD^{\bullet-}$ radical anion may be protonated by catalytic amounts of $Bu_4N\cdot H_2PO_4$ to afford the neutral $DIAD^{\bullet}$ radical and it is plausible that the photocatalytic cycle (blue) could close through single electron oxidation of the HAA catalyst (Figure 2A). Enantiodetermining HAA from *meso* diol ***I*** would ensue to generate an enantioenriched ketyl radical in ***II***. This could potentially combine with $DIAD^{\bullet}$ to afford ***III***, which eliminates *in situ* to afford H_2DIAD ***IV*** and hydroxyketone ***V*** (*shown*). Alternatively, electron transfer between $DIAD^{\bullet}$ and ***II*** followed by proton transfer (*not shown*) is also a possibility at this point.

In summary, we report a conceptually distinct strategy to achieve the enantioselective oxidation of *meso* secondary diols through catalytic hydrogen atom abstraction. A desymmetrized ketyl radical intermediate could be trapped by either DIAD or molecular oxygen to furnish hydroxyketones with very high levels of enantioenrichment following *in situ* elimination. The mildness of this method permits a range of substrates bearing potentially sensitive functionalities, including alkenes, to be competent in this reaction. Given the broad utility of alcohol oxidation, we envisage that our method can serve as a powerful complement to established oxidations capable of being deployed as a strategic transformation in asymmetric synthesis.[28] Additionally, this method demonstrates the potential

https://doi.org/10.1021/jacs.4c13919
J. Am. Chem. Soc. 2024, 146, 33302–33308

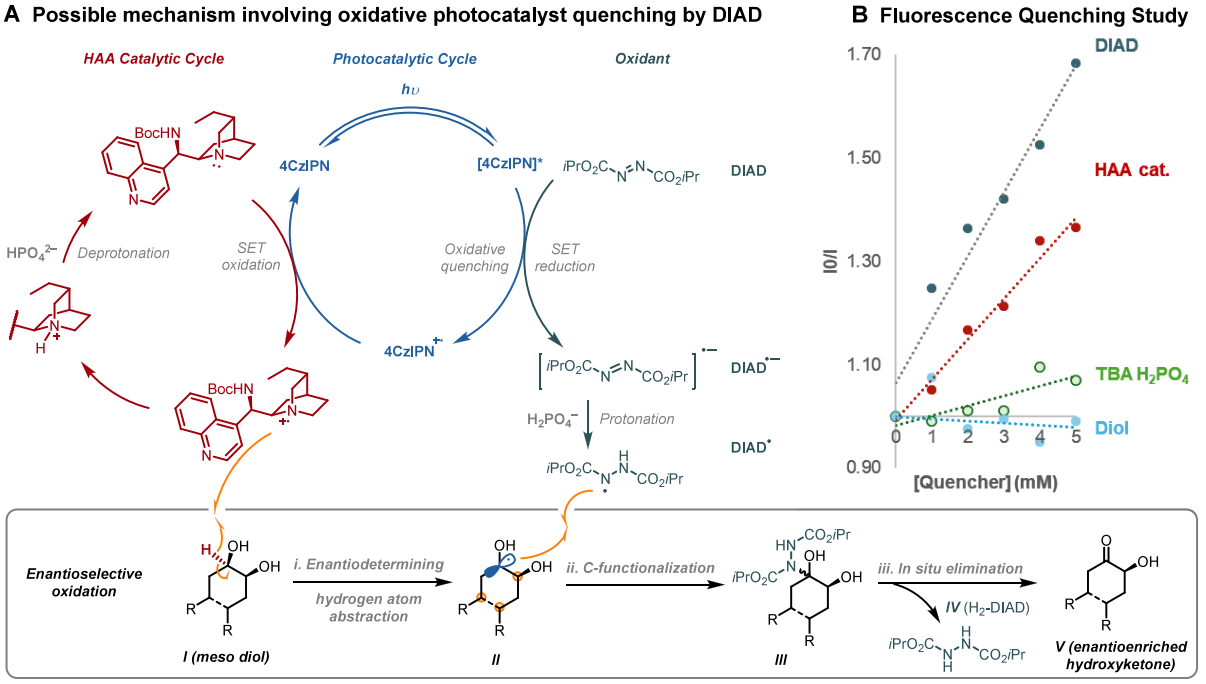


Figure 2. (a) Possible reaction mechanism; (b) Fluorescence quenching study indicates competitive quenching of the excited state photocatalyst by DIAD.

offered by chiral catalysts capable of enantioselective HAA, facilitating new asymmetric approaches to abundant motifs.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.4c13919.

Reaction optimization, procedures, characterization data and mechanistic discussion (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Robert J. Phipps − *Yusuf Hamied Department of Chemistry, Cambridge CB2 1EW, United Kingdom;* orcid.org/0000-0002-7383-5469; Email: rjp71@cam.ac.uk

Authors

Nelson Y. S. Lam − *Yusuf Hamied Department of Chemistry, Cambridge CB2 1EW, United Kingdom;* Present Address: Department of Chemistry, University of Victoria, 3800 Finnerty Road, Victoria, B.C. V8P 5C2, Canada; orcid.org/0000-0002-9307-0619

Jyoti Dhankhar − *Yusuf Hamied Department of Chemistry, Cambridge CB2 1EW, United Kingdom*

Antti S. K. Lahdenperä − *Yusuf Hamied Department of Chemistry, Cambridge CB2 1EW, United Kingdom*

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.4c13919

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to Dr. Rafel Cabot and Dr. Tim Chisholm for assistance in acquiring fluorescence spectroscopy measurements. We are also grateful to Trinity Hall, Cambridge (Research Fellowship to N.Y.S.L.). the Swiss National Science Foundation (Postdoctoral Fellowship to J.D.) and the EPSRC (EP/Y02348X/1) for funding.

■ REFERENCES

(1) Brown, D. G.; Boström, J. Analysis of Past and Present Synthetic Methodologies on Medicinal Chemistry: Where Have All the New Reactions Gone? *J. Med. Chem.* **2016**, *59*, 4443−4458.

(2) (a) Sigman, M. S.; Jensen, D. R. Ligand-Modulated Palladium-Catalyzed Aerobic Alcohol Oxidations. *Acc. Chem. Res.* **2006**, *39*, 221−229. (b) Sheldon, R. A.; Arends, I. W. C. E.; ten Brink, G.-J.; Dijksman, A. Green, Catalytic Oxidations of Alcohols. *Acc. Chem. Res.* **2002**, *35*, 774−781. (c) Campbell, A. N.; Stahl, S. S. Overcoming the "Oxidant Problem": Strategies to Use O2 as the Oxidant in Organometallic C−H Oxidation Reactions Catalyzed by Pd (and Cu). *Acc. Chem. Res.* **2012**, *45*, 851−863. (d) Kopylovich, M. N.; Ribeiro, A. P. C.; Alegria, E. C. B. A.; Martins, N. M. R.; Martins, L. M. D. R. S.; Pombeiro, A. J. L. Chapter Three - Catalytic Oxidation of Alcohols: Recent Advances. In *Adv. Organomet. Chem.*; Pérez, P. J., Ed.; Academic Press: 2015; Vol. *63*, pp 91−174.

(3) (a) Ma, Z.; Huang, Q.; Bobbitt, J. M. Oxoammonium salts. 5. A new synthesis of hindered piperidines leading to unsymmetrical TEMPO-type nitroxides. Synthesis and enantioselective oxidations with chiral nitroxides and chiral oxoammonium salts. *J. Org. Chem.* **1993**, *58*, 4837−4843. (b) D'Accolti, L.; Detomaso, A.; Fusco, C.; Rosa, A.; Curci, R. Selective oxidation of optically active sec,sec-1,2-diols by dioxiranes. A practical method for the synthesis of homochiral. alpha.-hydroxy ketones in high optical purity. *J. Org. Chem.* **1993**, *58*, 3600−3601. (c) Adam, W.; Saha-Möller, C. R.; Zhao, C.-G. Asymmetric C−H Oxidation of vic-Diols to α-Hydroxy Ketones by a Fructose-Derived Dioxirane: Electronic Effects on the Enantioselectivity of Oxygen Transfer. *J. Org. Chem.* **1999**, *64*, 7492−7497.

(4) For reviews, see: (a) Pellissier, H. Recent developments in non-enzymatic catalytic oxidative kinetic resolution of secondary alcohols. *Tetrahedron* **2018**, *74*, 3459−3468. (b) Yang, H.; Zheng, W.-H. Recent advances on nonenzymatic catalytic kinetic resolution of diols. *Tetrahedron Lett.* **2018**, *59*, 583−591.

(5) For selected examples, see: (a) Kuroboshi, M.; Yoshihisa, H.; Cortona, M. N.; Kawakami, Y.; Gao, Z.; Tanaka, H. Electro-oxidative kinetic resolution of sec-alcohols by using an optically active N-oxyl mediator. *Tetrahedron Lett.* **2000**, *41*, 8131−8135. (b) Masutani, K.; Uchida, T.; Irie, R.; Katsuki, T. Catalytic asymmetric and chemoselective aerobic oxidation: kinetic resolution of sec-alcohols. *Tetrahedron Lett.* **2000**, *41*, 5119−5123. (c) Ferreira, E. M.; Stoltz, B. M. The Palladium-Catalyzed Oxidative Kinetic Resolution of Secondary Alcohols with Molecular Oxygen. *J. Am. Chem. Soc.* **2001**, *123*, 7725−7726. (d) Jensen, D. R.; Pugsley, J. S.; Sigman, M. S. Palladium-Catalyzed Enantioselective Oxidations of Alcohols Using Molecular Oxygen. *J. Am. Chem. Soc.* **2001**, *123*, 7475−7476. (e) Bagdanoff, J. T.; Ferreira, E. M.; Stoltz, B. M. Palladium-Catalyzed Enantioselective Oxidation of Alcohols: A Dramatic Rate Acceleration by Cs2CO3/t-BuOH. *Org. Lett.* **2003**, *5*, 835−837. (f) Sun, W.; Wang, H.; Xia, C.; Li, J.; Zhao, P. Chiral-Mn(Salen)-Complex-Catalyzed Kinetic Resolution of Secondary Alcohols in Water. *Angew. Chem., Int. Ed.* **2003**, *42*, 1042−1044. (g) Radosevich, A. T.; Musich, C.; Toste, F. D. Vanadium-Catalyzed Asymmetric Oxidation of α-Hydroxy Esters Using Molecular Oxygen as Stoichiometric Oxidant. *J. Am. Chem. Soc.* **2005**, *127*, 1090−1091. (h) Arita, S.; Koike, T.; Kayaki, Y.; Ikariya, T. Aerobic Oxidative Kinetic Resolution of Racemic Secondary Alcohols with Chiral Bifunctional Amido Complexes. *Angew. Chem., Int. Ed.* **2008**, *47*, 2447−2449. (i) Ebner, D. C.; Trend, R. M.; Genet, C.; McGrath, M. J.; O'Brien, P.; Stoltz, B. M. Palladium-Catalyzed Enantioselective Oxidation of Chiral Secondary Alcohols: Access to Both Enantiomeric Series. *Angew. Chem., Int. Ed.* **2008**, *47*, 6367−6370. (j) Minato, D.; Arimoto, H.; Nagasue, Y.; Demizu, Y.; Onomura, O. Asymmetric electrochemical oxidation of 1,2-diols, aminoalcohols, and amino-aldehydes in the presence of chiral copper catalyst. *Tetrahedron* **2008**, *64*, 6675−6683. (k) Shiigi, H.; Mori, H.; Tanaka, T.; Demizu, Y.; Onomura, O. Chiral azabicyclo-N-oxyls mediated enantioselective electrooxidation of sec-alcohols. *Tetrahedron Lett.* **2008**, *49*, 5247−5251. (l) Brown, M. K.; Blewett, M. M.; Colombe, J. R.; Corey, E. J. Mechanism of the Enantioselective Oxidation of Racemic Secondary Alcohols Catalyzed by Chiral Mn(III)−Salen Complexes. *J. Am. Chem. Soc.* **2010**, *132*, 11165−11170. (m) Kunisu, T.; Oguma, T.; Katsuki, T. Aerobic Oxidative Kinetic Resolution of Secondary Alcohols with Naphthoxide-Bound Iron(salan) Complex. *J. Am. Chem. Soc.* **2011**, *133*, 12937−12939. (n) Mizoguchi, H.; Uchida, T.; Katsuki, T. Ruthenium-Catalyzed Oxidative Kinetic Resolution of Unactivated and Activated Secondary Alcohols with Air as the Hydrogen Acceptor at Room Temperature. *Angew. Chem., Int. Ed.* **2014**, *53*, 3178−3182. (o) Murakami, K.; Sasano, Y.; Tomizawa, M.; Shibuya, M.; Kwon, E.; Iwabuchi, Y. Highly Enantioselective Organocatalytic Oxidative Kinetic Resolution of Secondary Alcohols Using Chiral Alkoxyamines as Precatalysts: Catalyst Structure, Active Species, and Substrate Scope. *J. Am. Chem. Soc.* **2014**, *136*, 17591−17600.

(6) (a) Shimizu, H.; Onitsuka, S.; Egami, H.; Katsuki, T. Ruthenium(salen)-Catalyzed Aerobic Oxidative Desymmetrization of meso-Diols and Its Kinetics. *J. Am. Chem. Soc.* **2005**, *127*, 5396−5413. (b) Brenna, E.; Cannavale, F.; Crotti, M.; De Vitis, V.; Gatti, F. G.; Migliazza, G.; Molinari, F.; Parmeggiani, F.; Romano, D.; Santangelo, S. Synthesis of Enantiomerically Enriched 2-Hydroxymethylalkanoic Acids by Oxidative Desymmetrisation of Achiral 1,3-Diols Mediated by Acetobacter aceti. *ChemCatChem.* **2016**, *8*, 3796−3803. (c) Yamamoto, K.; Ishimaru, S.; Oyama, T.; Tanigawa, S.; Kuriyama, M.; Onomura, O. Enantioselective Synthesis of α-Substituted Serine Derivatives via Cu-Catalyzed Oxidative Desymmetrization of 2-Amino-1,3-diols. *Org. Process Res. Dev.* **2019**, *23*, 660−666. (d) Yamamoto, K.; Suganomata, Y.; Inoue, T.; Kuriyama, M.; Demizu, Y.; Onomura, O. Copper-Catalyzed Asymmetric Oxidative Desymmetrization of 2-Substituted 1,2,3-Triols. *J. Org. Chem.* **2022**, *87*, 6479−6491. (e) Suzuki, T.; Morita, K.; Matsuo, Y.; Hiroi, K. Catalytic asymmetric oxidative lactonizations of meso-diols using a chiral iridium complex. *Tetrahedron Lett.* **2003**, *44*, 2003−2006. (f) Rein, J.; Rozema, S. D.; Langner, O. C.; Zacate, S. B.; Hardy, M. A.; Siu, J. C.; Mercado, B. Q.; Sigman, M. S.; Miller, S. J.; Lin, S. Generality-oriented optimization of enantioselective aminoxyl radical catalysis. *Science* **2023**, *380*, 706−712.

(7) Arterburn, J. B. Selective oxidation of secondary alcohols. *Tetrahedron* **2001**, *57*, 9765−9788.

(8) (a) Jakka, K.; Zhao, C.-G. Highly Enantioselective CH Oxidation of vic-Diols with Shi's Oxazolidinone Dioxiranes. *Org. Lett.* **2006**, *8*, 3013−3015. (b) Nakamura, Y.; Egami, H.; Matsumoto, K.; Uchida, T.; Katsuki, T. Aerobic oxidative kinetic resolution of racemic alcohols with bidentate ligand-binding Ru(salen) complex as catalyst. *Tetrahedron* **2007**, *63*, 6383−6387. (c) Onomura, O.; Arimoto, H.; Matsumura, Y.; Demizu, Y. Asymmetric oxidation of 1,2-diols using N-bromosuccinimide in the presence of chiral copper catalyst. *Tetrahedron Lett.* **2007**, *48*, 8668−8672. (d) Suzuki, T.; Ghozati, K.; Katoh, T.; Sasai, H. Ir-Catalyzed Oxidative Desymmetrization of meso-Diols. *Org. Lett.* **2009**, *11*, 4286−4288. (e) Moritani, J.; Hasegawa, Y.; Kayaki, Y.; Ikariya, T. Aerobic oxidative desymmetrization of meso-diols with bifunctional amidoiridium catalysts bearing chiral N-sulfonyldiamine ligands. *Tetrahedron Lett.* **2014**, *55*, 1188−1191. (f) Rong, Z.-Q.; Pan, H.-J.; Yan, H.-L.; Zhao, Y. Enantioselective Oxidation of 1,2-Diols with Quinine-Derived Urea Organocatalyst. *Org. Lett.* **2014**, *16*, 208−211.

(9) Hao, B.; Gunaratna, M. J.; Zhang, M.; Weerasekara, S.; Seiwald, S. N.; Nguyen, V. T.; Meier, A.; Hua, D. H. Chiral-Substituted Poly-N-vinylpyrrolidinones and Bimetallic Nanoclusters in Catalytic Asymmetric Oxidation Reactions. *J. Am. Chem. Soc.* **2016**, *138*, 16839−16848.

(10) Jeffrey, J. L.; Terrett, J. A.; MacMillan, D. W. C. O-H hydrogen bonding promotes H-atom transfer from α-C-H bonds for C-alkylation of alcohols. *Science* **2015**, *349*, 1532−1536.

(11) Lahdenperä, A. S. K.; Dhankhar, J.; Davies, D. J.; Lam, N. Y. S.; Bacoş, P. D.; de la Vega-Hernández, K.; Phipps, R. J. A Chiral Hydrogen Atom Abstraction Catalyst for the Enantioselective Epimerization of Meso Diols. *Science* **2024**, *386*, 42−49.

(12) For important early studies relating to chiral HAA catalysts, see: (a) Mok, P. L. H.; Roberts, B. P. Enantioselective α-hydrogen-atom abstraction from an ester by an optically active amine-boryl radical. *J. Chem. Soc., Chem. Commun.* **1991**, *0*, 150−152. (b) Mok, P. L. H.; Roberts, B. P. Enantioselective hydrogen-atom abstraction by optically active amine-boryl radicals: An ESR spectroscopic study. *Tetrahedron Lett.* **1992**, *33*, 7249−7252. (c) Mok, P. L. H.; Roberts, B. P.; McKetty, P. T. Homolytic reactions of ligated boranes. Part 16. Enantioselective hydrogen-atom abstraction by chiral amine−boryl radicals: catalytic kinetic resolution of esters and of camphor. *J. Chem. Soc., Perkin Trans. 2* **1993**, 665−674. (d) Dang, H.-S.; Diart, V.; Roberts, B. P. Homolytic reactions of ligated boranes. Part 18. The scope of enantioselective hydrogen-atom abstraction by chiral amine−boryl radicals for kinetic resolution under conditions of polarity reversal catalysis. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1033−1041.

(13) For examples of enantioselective hydrogen atom abstraction applied to deracemization, see: (a) Großkopf, J.; Plaza, M.; Seitz, A.; Breitenlechner, S.; Storch, G.; Bach, T. Photochemical Deracemization at sp3-Hybridized Carbon Centers via a Reversible Hydrogen Atom Transfer. *J. Am. Chem. Soc.* **2021**, *143*, 21241−21245. (b) Großkopf, J.; Plaza, M.; Kutta, R. J.; Nuernberger, P.; Bach, T. Creating a Defined Chirality in Amino Acids and Cyclic Dipeptides by Photochemical Deracemization. *Angew. Chem., Int. Ed.* **2023**, *62*, No. e202313606. (c) Kutta, R. J.; Großkopf, J.; van Staalduinen, N.; Seitz, A.; Pracht, P.; Breitenlechner, S.; Bannwarth, C.; Nuernberger, P.; Bach, T. Multifaceted View on the Mechanism of a Photochemical Deracemization Reaction. *J. Am. Chem. Soc.* **2023**, *145*, 2354−2363. (d) Großkopf, J.; Heidecker, A. A.; Bach, T. Photochemical Deracemization of 3-Substituted Oxindoles. *Angew. Chem., Int. Ed.* **2023**, *62*, No. e202305274.

(14) For selected examples of enantioselective hydrogen atom abstraction in radical rebound-type mechanisms, see: (a) Punniyamurthy, T.; Miyafuji, A.; Katsuki, T. Chiral Mn-salen catalyzed enantiotopic selective C-H oxidation of meso-pyrrolidine derivatives. *Tetrahedron Lett.* **1998**, *39*, 8295−8298. (b) Frost, J. R.; Huber, S. M.;

https://doi.org/10.1021/jacs.4c13919
J. Am. Chem. Soc. 2024, 146, 33302−33308

Breitenlechner, S.; Bannwarth, C.; Bach, T. Enantiotopos-Selective C-H Oxygenation Catalyzed by a Supramolecular Ruthenium Complex. *Angew. Chem., Int. Ed.* **2015**, *54*, 691−695. (c) Milan, M.; Bietti, M.; Costas, M. Highly Enantioselective Oxidation of Nonactivated Aliphatic C−H Bonds with Hydrogen Peroxide Catalyzed by Manganese Complexes. *ACS Cent. Sci.* **2017**, *3*, 196−204. (d) Lang, K.; Torker, S.; Wojtas, L.; Zhang, X. P. Asymmetric Induction and Enantiodivergence in Catalytic Radical C−H Amination via Enantiodifferentiative H-Atom Abstraction and Stereoretentive Radical Substitution. *J. Am. Chem. Soc.* **2019**, *141*, 12388−12396. (e) Nakafuku, K. M.; Zhang, Z.; Wappes, E. A.; Stateman, L. M.; Chen, A. D.; Nagib, D. A. Enantioselective radical C−H amination for the synthesis of β-amino alcohols. *Nat. Chem.* **2020**, *12*, 697−704. (f) Call, A.; Capocasa, G.; Palone, A.; Vicens, L.; Aparicio, E.; Choukairi Afailal, N.; Siakavaras, N.; Lopez Salo, M. E.; Bietti, M.; Costas, M. Highly Enantioselective Catalytic Lactonization at Nonactivated Primary and Secondary gamma-C-H Bonds. *J. Am. Chem. Soc.* **2023**, *145*, 18094−18103.

(15) (a) Wang, Y.; Carder, H. M.; Wendlandt, A. E. Synthesis of rare sugar isomers through site-selective epimerization. *Nature* **2020**, *578*, 403−408. (b) Zhang, Y.-A.; Gu, X.; Wendlandt, A. E. A Change from Kinetic to Thermodynamic Control Enables trans-Selective Stereochemical Editing of Vicinal Diols. *J. Am. Chem. Soc.* **2022**, *144*, 599−605.

(16) (a) Capaldo, L.; Ravelli, D. Hydrogen Atom Transfer (HAT): A Versatile Strategy for Substrate Activation in Photocatalyzed Organic Synthesis. *Eur. J. Org. Chem.* **2017**, 2056−2071. (b) Cao, H.; Tang, X.; Tang, H.; Yuan, Y.; Wu, J. Photoinduced intermolecular hydrogen atom transfer reactions in organic synthesis. *Chem. Catal.* **2021**, *1*, 523−598.

(17) Yang, C.-J.; Liu, L.; Gu, Q.-S.; Liu, X.-Y. Research Progress in Enantioselective Radical Desymmetrization Reactions. *CCS Chemistry* **2024**, *6*, 1612−1627.

(18) Péter, Á.; Agasti, S.; Knowles, O.; Pye, E.; Procter, D. J. Recent advances in the chemistry of ketyl radicals. *Chem. Soc. Rev.* **2021**, *50*, 5349−5365.

(19) (a) Hoyos, P.; Sinisterra, J.-V.; Molinari, F.; Alcántara, A. R.; Domínguez de María, P. Biocatalytic Strategies for the Asymmetric Synthesis of α-Hydroxy Ketones. *Acc. Chem. Res.* **2010**, *43*, 288−299. (b) Palomo, C.; Oiarbide, M.; García, J. M. α-Hydroxy ketones as useful templates in asymmetric reactions. *Chem. Soc. Rev.* **2012**, *41*, 4150−4164.

(20) For examples of manipulations of enantioenriched α-hydroxy ketones, see: (a) Matsumoto, T.; Murayama, T.; Mitsuhashi, S.; Miura, T. Diastereoselective synthesis of a key intermediate for the preparation of tricyclic β-lactam antibiotics. *Tetrahedron Lett.* **1999**, *40*, 5043−5046. (b) Fang, Q. K.; Han, Z.; Grover, P.; Kessler, D.; Senanayake, C. H.; Wald, S. A. Rapid access to enantiopure bupropion and its major metabolite by stereospecific nucleophilic substitution on an α-ketotriflate. *Tetrahedron: Asymmetry* **2000**, *11*, 3659−3663. (c) Lebsack, A. D.; Overman, L. E.; Valentekovich, R. J. Enantioselective Total Synthesis of Shahamin K. *J. Am. Chem. Soc.* **2001**, *123*, 4851−4852. (d) Lebel, H.; Guay, D.; Paquet, V.; Huard, K. Highly Efficient Synthesis of Terminal Alkenes from Ketones. *Org. Lett.* **2004**, *6*, 3047−3050. (e) Krawczyk, E.; Koprowski, M.; Łuczak, J. A stereoselective approach to optically active butenolides by Horner−Wadsworth−Emmons olefination reaction of α-hydroxy ketones. *Tetrahedron: Asymmetry* **2007**, *18*, 1780−1787. (f) Dunet, G.; Mayer, P.; Knochel, P. Highly Diastereoselective Addition of Cinnamylzinc Derivatives to α-Chiral Carbonyl Compounds. *Org. Lett.* **2008**, *10*, 117−120. (g) Barluenga, J.; Escribano, M.; Aznar, F.; Valdés, C. Arylation of α-Chiral Ketones by Palladium-Catalyzed Cross-Coupling Reactions of Tosylhydrazones with Aryl Halides. *Angew. Chem., Int. Ed.* **2010**, *49*, 6856−6859. (h) Mohar, B.; Stephan, M.; Urleb, U. Stereoselective synthesis of fluorine-containing analogues of anti-bacterial sanfetrinem and LK-157. *Tetrahedron* **2010**, *66*, 4144−4149. (i) Cheng, B.; Trauner, D. A Highly Convergent and Biomimetic Total Synthesis of Portentol. *J. Am. Chem. Soc.* **2015**, *137*, 13800−13803. (j) Wu, H.; Su, H.; Schulze, E. J.; Peters, B. B. C.; Nolan, M. D.; Yang, J.; Singh, T.; Ahlquist, M. S. G.; Andersson, P. G. Site- and Enantioselective Iridium-Catalyzed Desymmetric Mono-Hydrogenation of 1,4-Dienes. *Angew. Chem., Int. Ed.* **2021**, *60*, 19428−19434. (k) Jänner, S.; Isak, D.; Li, Y.; Houk, K. N.; Miller, A. K. Bioinspired Asymmetric Total Synthesis of Emeriones A−C. *Angew. Chem., Int. Ed.* **2022**, *61*, No. e202205878.

(21) (a) Suzuki, T. Recent topics in the desymmetrization of meso-diols. *Tetrahedron Lett.* **2017**, *58*, 4731−4739. (b) Nájera, C.; Foubelo, F.; Sansano, J. M.; Yus, M. Enantioselective desymmetrization reactions in asymmetric catalysis. *Tetrahedron* **2022**, *106*−*107*, No. 132629.

(22) Zhou, Q.; Gong, X.; Yan, G. Recent Advances in Radical Reactions of Azo Compounds. *Adv. Synth. Catal.* **2023**, *365*, 1565−1579.

(23) For selected examples of radical trapping with DIAD or related reagents, see: (a) Grochowski, E.; Bolesławska, T.; Jurczak, J. Reaction of Diethyl Azodicarboxylate with Ethers in the Presence of N-Hydroxyimides as Catalysts. *Synthesis* **1977**, 718−720. (b) Waser, J.; Gaspar, B.; Nambu, H.; Carreira, E. M. Hydrazines and Azides via the Metal-Catalyzed Hydrohydrazination and Hydroazidation of Olefins. *J. Am. Chem. Soc.* **2006**, *128*, 11693−11712. (c) Schmidt, V. A.; Alexanian, E. J. Metal-Free Oxyaminations of Alkenes Using Hydroxamic Acids. *J. Am. Chem. Soc.* **2011**, *133*, 11402−11405. (d) Amaoka, Y.; Kamijo, S.; Hoshikawa, T.; Inoue, M. Radical Amination of C(sp3)−H Bonds Using N-Hydroxyphthalimide and Dialkyl Azodicarboxylate. *J. Org. Chem.* **2012**, *77*, 9959−9969. (e) Miyake, Y.; Nakajima, K.; Nishibayashi, Y. Direct sp3 C-H Amination of Nitrogen-Containing Benzoheterocycles Mediated by Visible-Light-Photoredox Catalysts. *Chem. Eur. J.* **2012**, *18*, 16473−16477. (f) Bentley, K. W.; Dummit, K. A.; Van Humbeck, J. F. A highly site-selective radical sp3 C−H amination of azaheterocycles. *Chem. Sci.* **2018**, *9*, 6440−6445. (g) Shamsabadi, A.; Maruani, A.; Ahmed, N.; Chudasama, V. Aerobically-initiated C(sp3)−H bond amination through the use of activated azodicarboxylates. *Org. Biomol. Chem.* **2020**, *18*, 6258−6264. (h) Jia, P.; Li, Q.; Poh, W. C.; Jiang, H.; Liu, H.; Deng, H.; Wu, J. Light-Promoted Bromine-Radical-Mediated Selective Alkylation and Amination of Unactivated C(sp3)-H Bonds. *Chem.* **2020**, *6*, 1766−1776.

(24) Gorelik, D. J.; Dimakos, V.; Adrianov, T.; Taylor, M. S. Photocatalytic, site-selective oxidations of carbohydrates. *Chem. Commun.* **2021**, *57*, 12135−12138.

(25) Hayes, C. J.; Heathcock, C. H. A Method for Constructing the C18−C28 Dispiroacetal Moiety of Altohyrtin A. *J. Org. Chem.* **1997**, *62*, 2678−2679.

(26) Mallia, C. J.; Baxendale, I. R. The Use of Gases in Flow Synthesis. *Org. Process Res. Dev.* **2016**, *20*, 327−360.

(27) The $Bu_4N{\cdot}H_2PO_4$ additive quenches, but to a much lower degree, and does not alter the relative quenching abilities of either the HAA catalyst or DIAD. See SI for full details.

(28) Merad, J.; Candy, M.; Pons, J. M.; Bressy, C. Catalytic Enantioselective Desymmetrization of Meso Compounds in Total Synthesis of Natural Products: Towards an Economy of Chiral Reagents. *Synthesis* **2017**, *49*, 1938−1954.

https://doi.org/10.1021/jacs.4c13919
J. Am. Chem. Soc. 2024, 146, 33302−33308