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Article

Catalytic Asymmetric Access to Structurally Diverse *N*-Alkoxy Amines via a Kinetic Resolution Strategy

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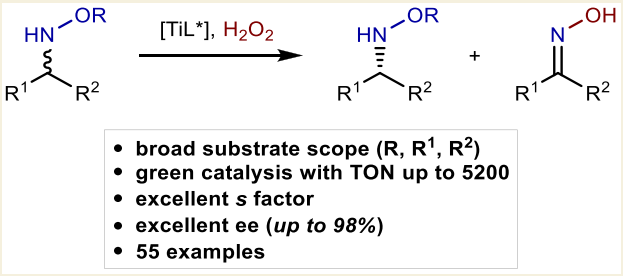
ABSTRACT: Chiral *N*-alkoxy amines are increasingly vital substrates in bioscience. However, asymmetric synthetic strategies for these compounds remain scarce. Catalytic kinetic resolution represents an attractive approach to prepare structurally diverse enantiopure *N*-alkoxy amines, which has remained elusive due to the notably reduced nucleophilicity of the nitrogen atom together with the low bond dissociation energies of labile NO−C and N−O bonds. We here report a general kinetic resolution of *N*-alkoxy amines through chemo- and enantioselective oxygenation. The mild and green titanium-catalyzed approach features broad substrate scope (55 examples), noteworthy functional group compatibility, high catalyst turnover number (up to 5200), excellent selectivity factor (s > 150), and scalability.



KEYWORDS: *N-alkoxy amine, asymmetric catalysis, kinetic resolution, green oxygenation, earth-abundant metal*

INTRODUCTION

N-Alkoxy amines have become increasingly common structural motifs in pharmaceuticals and agrochemicals because the *O*-alkylhydroxylamine unit provides favorable biological and physical properties (Scheme 1A).[1−6] Despite these elegant examples, current studies in drug discovery typically focus on simple *N*-methoxy compounds that either lack chirality or are marketed as racemates. A reliable enantioselective access to structurally diverse *N*-alkoxy amines would facilitate incorporation of chiral three-dimensional scaffolds as design elements in drug discovery.[7,8] In this context, existing methods typically focus on direct enantioselective manipulation of *N*-alkoxy moieties involving hydrogenation of oxime ethers and aza-Michael reaction with methoxylamine, which still suffer from limited generality with respect to *O*- and *N*-linkages (Scheme 1B).[9−14]

Catalytic kinetic resolution of racemates is a powerful and practical approach to the synthesis of enantiomerically pure compounds, especially in cases where other methods are not possible or provide insufficient enantiocontrol.[15−18] In this context, kinetic resolution of amines is a well-established method and is frequently employed industrially.[19−24] In sharp contrast, a related study on *N*-alkoxy amines has proven elusive presumably due to the notably reduced nucleophilicity of the nitrogen atom and the low bond dissociation energies of labile NO−C and N−O bonds.[1,25,26] To the best of our knowledge, only one isolated example of enzymatic kinetic resolution via a polar nucleophilic addition/proton abstraction pathway has been reported (Scheme 1C).[27] Furthermore, this method is merely suitable for a specific α,α-cyclohexyl-methyl *N*-methoxy amine substrate in which the cyclohexyl group is crucial to basic reactivity. Development of a general nonenzymatic kinetic resolution approach would be highly demanded. As part of our ongoing interest in the development of sustainable asymmetric oxidation methods,[28−32] we decided to explore oxidative kinetic resolution of *N*-alkoxy amines. To our knowledge, even a chemocatalytic non-asymmetric oxidation of *N*-alkoxy amines has never been established.[33] Herein, we report the first nonenzymatic kinetic resolution of *N*-alkoxy amines as well as the first example of nonenzymatic catalytic oxidation of these substrates (Scheme 1D). The titanium-catalyzed chemo- and enantioselective oxygenation employs green and economic aqueous H_2O_2 as oxidant and is applicable for a wide variety of *N*-alkoxy amines bearing diverse substituent patters on both *O*- and *N*-linkages with high turnover numbers (TONs) and excellent selectivity factors.

RESULTS AND DISCUSSION

Initially, kinetic resolution of *N*-benzyloxy α-methylbenzylamine rac-**1a** was selected as a reference reaction with H_2O_2 as the oxidant for a search for a suitable chiral earth-abundant metal catalyst (Table 1). Chiral manganese(salen) **C1** and iron(salen) **C2** exhibited no oxidation catalysis reactivity (entries 1 and 2).

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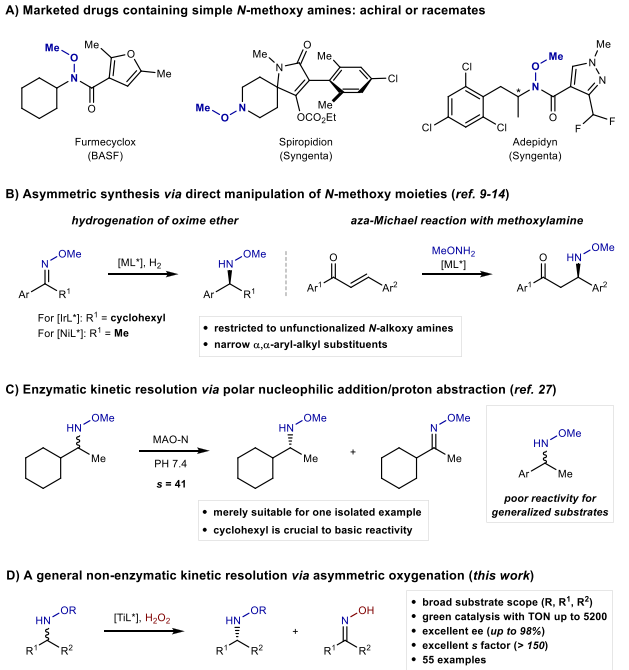
Scheme 1. Overview of Asymmetric Synthesis of Chiral *N*-Alkoxy Amines

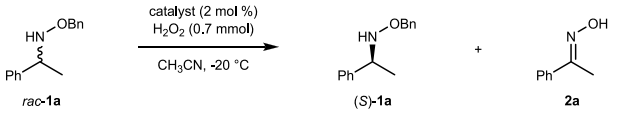


Di-μ-oxo titanium(salen) **C3** proved to be an effective complex to catalyze the oxidation of rac-**1a** to oxime **2a**, though only an extremely low level of chiral recognition was observed (entry 3).[34] Titanium(salalen) **C4** that was prepared by reducing one of the two imines of **C3** provided no obvious improvement with respect to the enantiocontrol (entry 4).[35,36] This chiral recognition ability was completely lost for **C5** with 1,2-diphenylethylenediamine (entry 5). The fully reduced titanium-(salan) **C6** containing two NH moieties exhibited promising ability in differentiating the two enantiomers (entry 6).[37−39] Further fine-tuning salan substituent patterns identified complex **C11** bearing a *para*-methoxyphenyl group at C3(C3′) to be superior, and (*S*)-**1a** was recovered in 49% yield with 92% ee (s = 53, entries 6−11).[40]

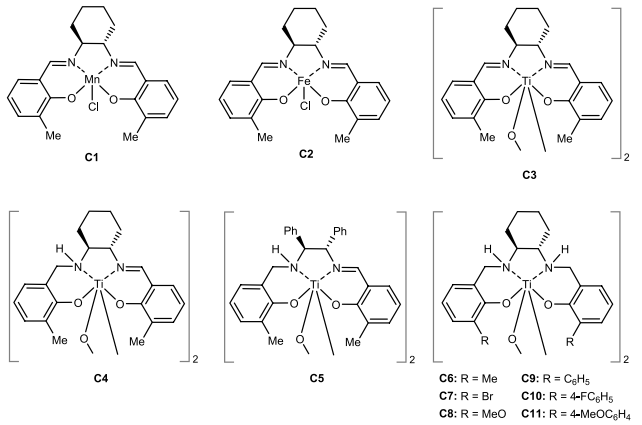
This single-operation kinetic resolution is easy to handle and highly efficient. For example, a catalyst loading at 0.01 mol % (TON up to 5200) proved sufficient for oxidation of rac-**1a** without obvious loss of enantiocontrol, despite a prolonged time period (Scheme 2A). Moreover, the scalability of the approach is demonstrated by conducting rac-**1a** oxidation on a 5 mmol scale. The method is fairly general for *N*-alkoxy amines with an α,α-aryl-alkyl pattern (Scheme 2A). For example, a variety of substrates bearing electronically varied α-aryl groups, including *ortho*- (**1b**−**1e**), *meta*-(**1f**−**1j**), and *para*-substituents (**1k**−**1n**), serve as effective components, and the remaining *N*-alkoxy amines are recovered in good yield and enantioselectivity. 1-Naphthyl **1o** and α-heteroaryl **1p** and **1q** are also suitable partners. Furthermore, substrates **1r**−**1y**, bearing diverse α-alkyl substituents with varied aliphatic chain lengths, are tolerated. The method is compatible with an array of functional groups, such as alkyl chloride and bromide, primary alcohol, methyl ether, and alkene (**1u**−**1y**).

The method is also applicable for *N*-alkoxy amines with an α,α-alkynyl-alkyl pattern (Scheme 2B). Kinetic resolution of racemic **1z**−**1ad** containing electronically varied α-arylacetylenes, heteroarylacetylenes, and aliphatic acetylenes proceeds

Table 1. Reaction Condition Optimization.[a]



Entry	Catalyst	Conv. (%)[b]	ee (%)[c]	s[d]
1	**C1**	< 5	< 5	n.a.
2	**C2**	< 5	< 5	n.a.
3	**C3**	55	19	1.6
4	**C4**	57	25	1.8
5	**C5**	60	< 5	n.a.
6	**C6**	46	56	8.4
7	**C7**	52	76	13
8	**C8**	50	48	4.5
9	**C9**	53	80	14
10	**C10**	52	88	28
11	**C11**	51	92	53



[a]Reaction conditions: rac-**1a** (0.1 mmol), catalyst (2 mol %), and H_2O_2 (0.07 mmol) in CH_3CN (1 mL) at −20 °C for 24 h. [b]Conversion was calculated from the yield of recovered **1a**. [c]Determined by HPLC analysis on a chiral stationary phase. [d]Selectivity (s) values were calculated through the equation $s = \ln[(1 - C)(1 - ee)]/\ln[(1 - C)(1 + ee)]$, where C is the conversion. n.a. = not available.

smoothly. Moreover, α,α-dialkyl-substituted **1ae** with two electronically similar 1° and 2° alkyl groups is well tolerated. Notably, the more challenging dialkyl substrates **1af**−**1ai** bearing two sterically and electronically similar 1° alkyl groups are also compatible.

The scope with respect to the substituent patterns on the *O*-linkage is also broad (Scheme 3). For example, high levels of chiral recognition are observed for *N*-alkoxyamines with diverse *O*-alkyl groups that vary in chain length and steric demand (**3a**−**3f**) and can bear functional groups including an alkyl chloride, fluoride, primary alcohol, acetal, cyano motif, carboxylic ester, alkyne, and alkene (**3g**−**3n**, Scheme 3A). Furthermore, a series of functionalized *N*-alkoxy amines containing marketed drugs on the *O*-linkage like indomethacin **3o**, probenecid **3p**, gemfibrozil **3q**, and oxaprozin **3r** are well tolerated (Scheme 3B).

Chiral *N*-alkoxy amines can be transformed to a range of valuable N−O-containing compounds with high stereochemical fidelity (Scheme 4). For example, the recovered enantiopure **1a** or **3a** undergoes acylation, sulfonylation, and alkylation, furnishing respective *N*-acyl **5a** and **5b**, *N*-sulfonyl **5c**, and *N*-

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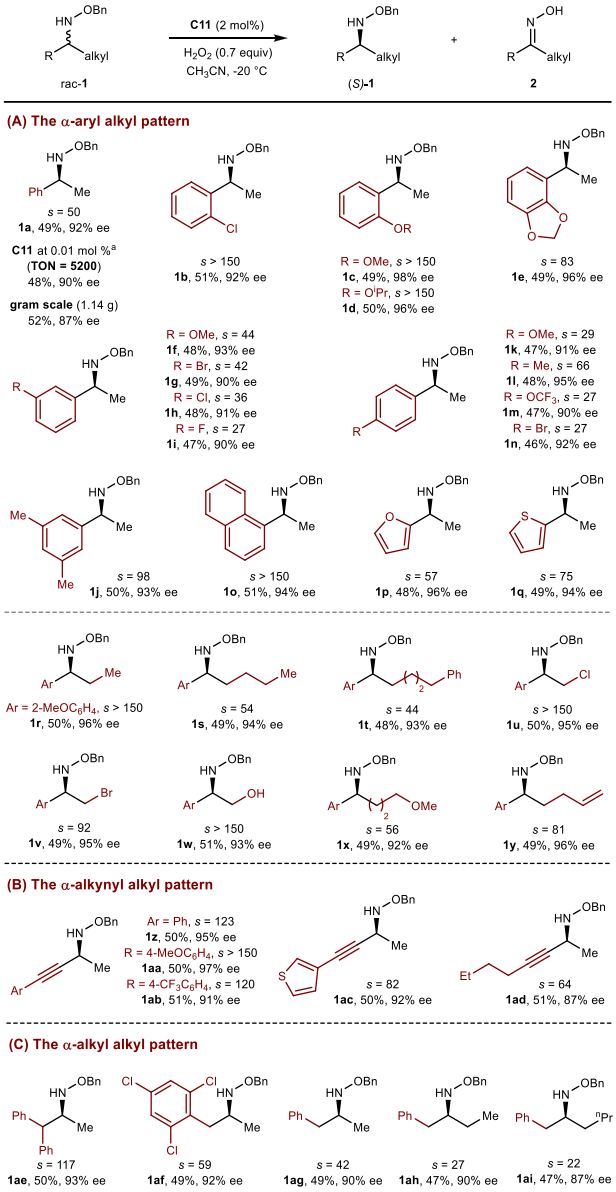
Scheme 2. Substituent Patterns on α-Stereocenter of the *N*-Linkage[b]

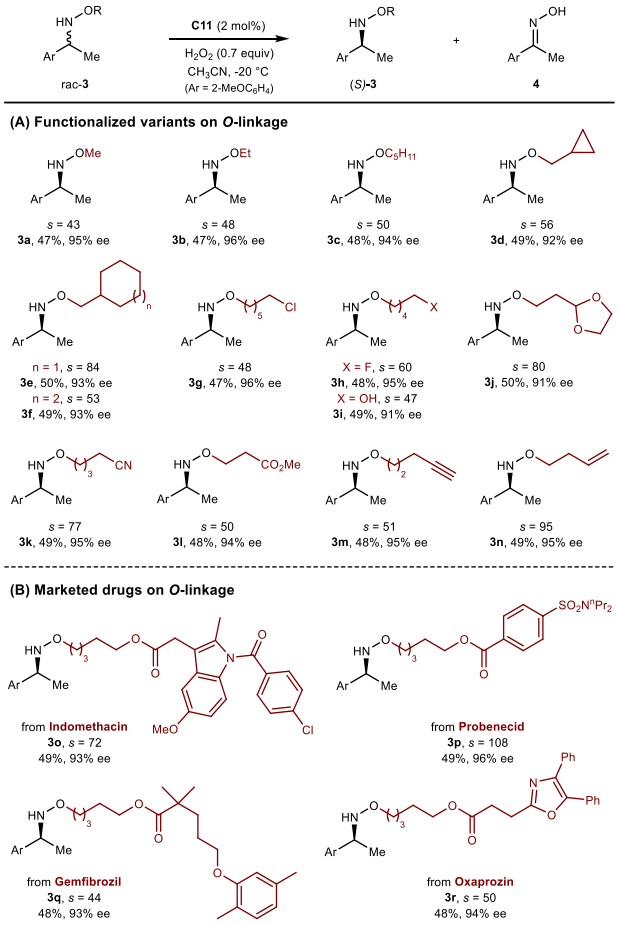


[a]Reaction with **C11** (0.01 mol %) and H_2O_2 (0.2 mmol) for 60 h. [b]Reaction conditions: rac-**1a** (0.1 mmol), **C11** (2 mol %), and H_2O_2 (0.07 mmol) in CH_3CN (1 mL) at −20 °C for 24 h. Isolated yields are given. *s* values were calculated through the equation $s = \ln[(1 - C)(1 - ee)]/\ln[(1 - C)(1 + ee)]$. For reactions with $50 < s < 150$, *s* was determined by linear regression analysis through plotting $\ln[(1 - C)(1 - ee)]$ against $\ln[(1 - C)(1 + ee)]$ for different conversion points.[41]

propargyl **5d** in high efficiency. Notably, chiral *N*-benzyloxy analogue **5g** of Adepidyn that is a broad-spectrum foliar fungicide can be facilely prepared by acylation of α,α-dialkyl **1af**.[5] Moreover, *O*-carboxylic ester-containing **3l** undergoes intramolecular amidation, delivering cyclic *N*,*N*-acyl-alkoxy amine **5e**. α-Alkyl **1w**, bearing a primary alcohol, participates in double phosphorylation on respective *N*- and *O*-moieties, giving cyclophosphamide analogue **5f**.

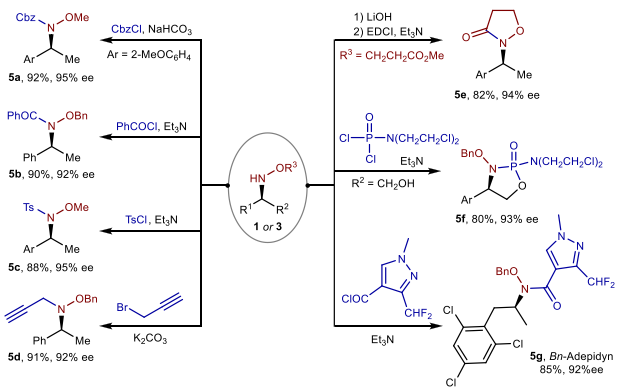
A series of control experiments were performed to obtain a preliminary understanding of the oxidation process of *N*-alkoxy amines (Figure 1A–C). During the oxidation of rac-**1a**, a small

Scheme 3. Substituent Patterns on the *O*-Linkage[a]



[a]Reaction conditions: rac-**1a** (0.1 mmol), **C11** (2 mol %), and H_2O_2 (0.07 mmol) in CH_3CN (1 mL) at −20 °C for 24 h. Isolated yields are given. For reactions with $50 < s < 150$, *s* was determined by linear regression analysis through plotting $\ln[(1 - C)(1 - ee)]$ against $\ln[(1 - C)(1 + ee)]$ for different conversion points.

Scheme 4. Synthetic Applications



amount of azodioxy intermediate **6a** was detected (Figure 1A-1). Under standard conditions, **6a** was efficiently converted to oxime **2a**, while no back reaction for **2a** was detected (Figure 1A-2 and -3). Given the fact that **6a** can be facilely generated through dimerization of a monomeric nitroso precursor, the observations suggest that the latter might be generated as an oxidized intermediate.[42−44] Isotope labeling experiments were then conducted (Figure 1B). Generation of $Bn^{18}OH$ together

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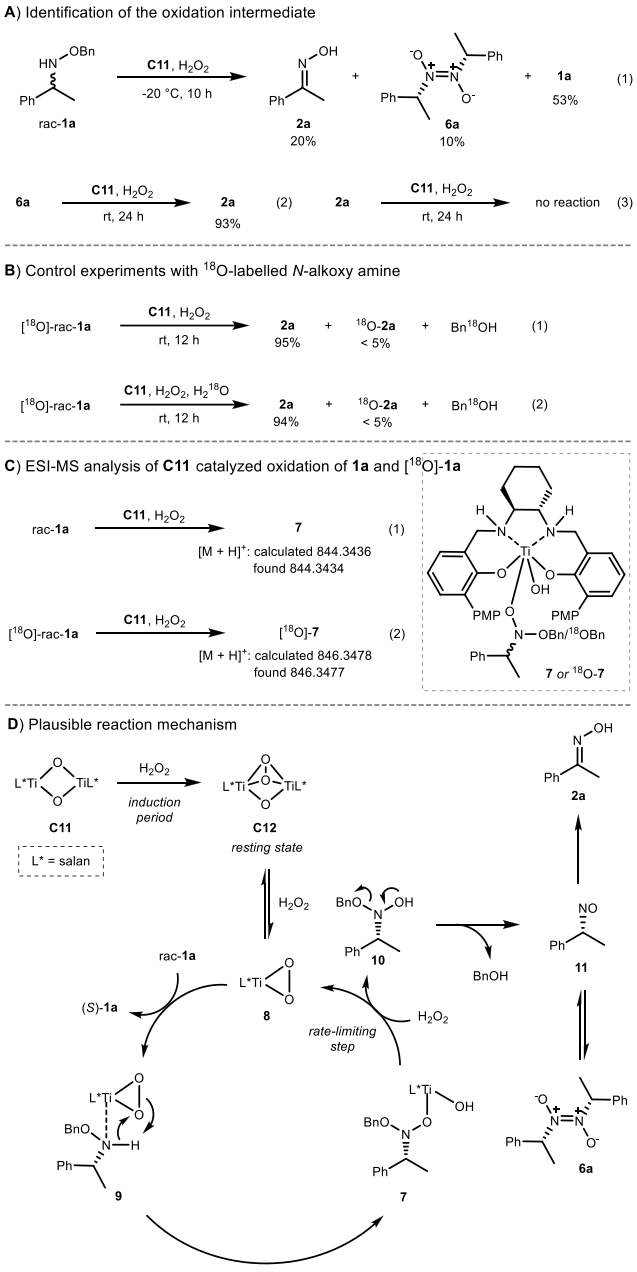

Figure 1. Mechanistic studies.

with no incorporation of ^{18}O in the oxime product was detected for oxidation of ^{18}O-labeled rac-**1a** in the absence or presence of $H_2{}^{18}O$, suggesting that the oxygen in **2a** might originate from H_2O_2. Next, ESI-mass spectrometry (MS) analysis of oxidation of respective rac-**1a** and rac-^{18}O-**1a** revealed the generation of adducts **7** and ^{18}O-**7** (Figure 1C). The results indicate that a direct oxygenation of the nitrogen atom of *N*-alkoxy amine by a monomeric peroxo titanium species might be involved. To shed light on the working details of the enantio-differentiating oxidation, the kinetic profiles of enantiopure *N*-alkoxy amines (*R*)-**1a** and (*S*)-**1a** were respectively explored (Figure S16 in the Supporting Information). The reaction of (*R*)-**1a** is much faster with a measured initial rate of 4.26×10^{-3} mol L^{-1} h^{-1} than that of (*S*)-**1a** with a rate of 0.084×10^{-3} mol L^{-1} h^{-1}.

According to the experiments described above, a plausible reaction mechanism is suggested (Figure 1D). Ti(salan) **C11** reacts slowly with H_2O_2, affording μ-oxo-μ-peroxo **C12**, which is supported by ESI-MS and kinetic profile studies (Figures S8 and S11 in the Supporting Information).[35,36] The combination of **C12** and H_2O_2 promoted the reaction, whereas no reactivity was observed without H_2O_2, suggesting that **C12** might be a thermodynamic reservoir for active species. **C12** further reacts with H_2O_2, giving monomeric peroxo **8** that selectively oxygenates *N*-alkoxy amine (*R*)-**1a**, producing aminooxy titanium **7**. This process is supported by the observation in Figure 1C and a series of nonlinear effect studies (Figure S10 in the Supporting Information).[45−48] Adduct **7** reacts with H_2O_2, giving *N*-alkoxy-*N*-hydroxy amine **10** and peroxo **8** for a new catalytic oxidation cycle. **10** collapses, furnishing nitroso **11**, which tautomerizes to oxime **2a**. Kinetic analysis revealed a first-order dependence of reaction rate on concentrations of respective **C11** and H_2O_2, whereas a zero-order dependence on substrate concentration (Figures S13−S15 in the Supporting Information). The observations implied that the oxidative generation of oxygen-transferring species **8** by H_2O_2 might be the rate-limiting step.

CONCLUSIONS

In conclusion, the first nonenzymatic kinetic resolution of *N*-alkoxy amines as well as the first example of nonenzymatic catalytic oxidation of these substrates have been described. The mild and green titanium-catalyzed chemo- and enantioselective oxygenation can be scaled-up and is applicable for a wide variety of *N*-alkoxy amines bearing diverse substituent patters on both *O*- and *N*-linkages with a TON up to 5200. It also features excellent selectivity factors, noteworthy functional group compatibility, great synthetic utilities, and scalability. This approach would furnish a reliable platform to rapidly access structurally diverse chiral *N*-alkoxy amines for drug discovery.

METHODS

General Procedure for Oxidative Kinetic Resolution of *N*-Alkoxy Amines

To a solution of racemic substrate (0.1 mmol, 1.0 equiv) in CH_3CN (1.0 mL) was added 30% aqueous hydrogen peroxide (0.07 mmol, 0.7 equiv) and **C11** (2 mmol %, 0.02 equiv) at −20 °C. The reaction was stirred for 24 h and monitored by TLC analysis. Then the mixture was diluted with EtOAc (10 mL), washed with water (10 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel chromatography (EtOAc/petroleum ether) to give the desired product.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacsau.4c00174.

Experimental procedures, experimental mechanistic studies, and spectral data (PDF)
X-ray crystallographic data for **2a** (CIF)
X-ray crystallographic data for **6a** (CIF)

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Author Contributions

[#]M.C., Z.W., and F.H. contributed equally to this work. CRediT: **Min Cao** investigation, methodology; **Zehua Wang** investigation, methodology; **Fangao Hou** investigation, methodology; **Xiaoyuan Liu** methodology; **Shutao Sun** funding acquisition, validation; **Xinning Wang** methodology; **Lei Liu** conceptualization, project administration, supervision, writing-original draft, writing-review & editing.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Nesvadba, P. *N*-Alkoxyamines: Synthesis, Properties, and Applications in Polymer Chemistry, Organic Synthesis, and Materials Science. *Chimia* **2006**, *60*, 832−860.

(2) Khlestkin, V. K.; Mazhukin, D. G. Recent Advances in the Application of *N*,*O*-Dialkylhydroxylamines in Organic Chemistry. *Curr. Org. Chem.* **2003**, *7*, 967−993.

(3) Batoo, Z.; Lomakin, I. B.; Polikanov, Y. S.; Bunick, C. G. Sarecycline Interferes with tRNA Accommodation and Tethers mRNA to the 70S Ribosome. *Proc. Natl. Acad. Sci. U.S.A.* **2020**, *117*, 20530−20537.

(4) Muehlebach, M.; Buchholz, A.; Zambach, W.; Schaetzer, J.; Daniels, M.; Hueter, O.; Kloer, D. P.; Lind, R.; Maienfisch, P.; Pierce, A.; Pitterna, T.; Smejkal, T.; Stafford, D.; Wildsmith, L. Spiro *N*-Methoxy Piperidine Ring Containing Aryldiones for the Control of Sucking Insects and Mites: Discovery of Spiropidion. *Pest. Manag. Sci.* **2020**, *76*, 3440−3450.

(5) Stierli, D.; Haas, H. U.; Rajan, R.; Bartlett, D.; Sierotzki, H.; Cederbaum, F.; Walter, H.; Lamberth, C. Chapter 22−ADEPIDYN−the First *N*-methoxy-substituted Carboxamide Among the Succinate Dehydrogenase Inhibitors. In *Recent Highlights in the Discovery and Optimization of Crop Protection Products*; Maienfisch, P.; Mangelinckx, S., Eds.; Academic Press, 2021; pp 357−366.

(6) Lambert, K. M.; Cox, J. B.; Liu, L.; Jackson, A. C.; Yruegas, S.; Wiberg, K. B.; Wood, J. L. Total Synthesis of (±)-Phyllantidine: Development and Mechanistic Evaluation of A Ring Expansion for Installation of Embedded Nitrogen-Oxygen Bonds. *Angew. Chem., Int. Ed.* **2020**, *59*, 9757−9766.

(7) Direct *O*-alkylation of chiral free hydroxylamines with diverse electrophiles is fraught due to competing *N*-alkylation at the more nucleophilic nitrogen atom (see ref 2) as well as lack of efficient methods for chiral free hydroxylamines. For an isolated example of asymmetric synthesis of chiral free hydroxylamines, see: Wang, F.; Chen, Y.; Yu, P.; Chen, G.-Q.; Zhang, X. Asymmetric Hydrogenation of Oximes Synergistically Assisted by Lewis and Brønsted Acids. *J. Am. Chem. Soc.* **2022**, *144*, 17763−17768.

(8) Hill, J.; Beckler, T. D.; Crich, D. Recent Advances in the Synthesis of Di- and Trisubstituted Hydroxylamines. *Molecules.* **2023**, *28*, 2816−2837.

(9) Mas-Roselló, J.; Smejkal, T.; Cramer, N. Iridium-Catalyzed Acid-Assisted Asymmetric Hydrogenation of Oximes to Hydroxylamines. *Science.* **2020**, *368*, 1098−1102.

(10) Li, B.; Chen, J.; Liu, D.; Gridnev, I. D.; Zhang, W. Nickel-Catalysed Asymmetric Hydrogenation of Oximes. *Nat. Chem.* **2022**, *14*, 920−927.

(11) Gao, X.; Turel-Herman, J. R.; Choi, Y. J.; Cohen, R. D.; Hyster, T. K. Photoenzymatic Synthesis of α-Tertiary Amines by Engineered Flavin-Dependent "ene"-Reductases. *J. Am. Chem. Soc.* **2021**, *143*, 19643−19647.

(12) Sibi, M. P.; Shay, J. J.; Liu, M.; Jasperse, C. P. Chiral Lewis Acid Catalysis in Conjugate Additions of *O*-benzylhydroxylamine to Unsaturated Amides. Enantioselective Synthesis of β-Amino Acid Precursors. *J. Am. Chem. Soc.* **1998**, *120*, 6615−6616.

(13) Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. Heterobimetallic Catalysis in Asymmetric 1,4-Addition of *O*-Alkylhydroxylamine to Enones. *J. Am. Chem. Soc.* **2003**, *125*, 16178−16179.

(14) Robinson, J. R.; Fan, X.; Yadav, J.; Carroll, P. J.; Wooten, A. J.; Pericàs, M. A.; Schelter, E. J.; Walsh, P. J. Air- and Water-Tolerant Rare Earth Guanidinium Binolate Complexes as Practical Precatalysts in Multifunctional Asymmetric Catalysis. *J. Am. Chem. Soc.* **2014**, *136*, 8034−8041.

(15) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. Practical Considerations in Kinetic Resolution Reactions. *Adv. Synth. Catal.* **2001**, *343*, 5−26.

(16) Breuer, M.; Ditrich, K.; Habicher, T.; Hauer, B.; Keβeler, M.; Stürmer, R.; Zelinski, T. Industrial Methods for the Production of Optically Active Intermediates. *Angew. Chem., Int. Ed.* **2004**, *43*, 788−824.

(17) Vedejs, E.; Jure, M. Efficiency in Nonenzymatic Kinetic Resolution. *Angew. Chem., Int. Ed.* **2005**, *44*, 3974−4001.

(18) Pellissier, H. Catalytic Non-Enzymatic Kinetic Resolution. *Adv. Synth. Catal.* **2011**, *353*, 1613−1666.

(19) Müller, C. E.; Schreiner, P. R. Organocatalytic Enantioselective Acyl Transfer onto Racemic as well as *meso* Alcohols, Amines, and Thiols. *Angew. Chem., Int. Ed.* **2011**, *50*, 6012−6042.

(20) Kranov, V. P.; Gruzdev, D. A.; Levit, G. L. Nonenzymatic Acylative Kinetic Resolution of Racemic Amines and Related Compounds. *Eur. J. Org. Chem.* **2012**, *2012*, 1471−1493.

(21) Kreituss, I.; Bode, J. W. Catalytic Kinetic Resolution of Saturated *N*-heterocycles by Enantioselective Amidation with Chiral Hydroxamic Acids. *Acc. Chem. Res.* **2016**, *49*, 2807−2821.

(22) Arai, S.; Bellemin-Laponnaz, S.; Fu, G. C. Kinetic Resolution of Amines by A Nonenzymatic Acylation Catalyst. *Angew. Chem., Int. Ed.* **2001**, *40*, 234−236.

(23) De, C. K.; Klauber, E. G.; Seidel, D. Merging Nucleophilic and Hydrogen Bonding Catalysis: An Anion Binding Approach to the Kinetic Resolution of Amines. *J. Am. Chem. Soc.* **2009**, *131*, 17060−17061.

(24) Fowler, B. S.; Mikochik, P. J.; Miller, S. J. Peptide-Catalyzed Kinetic Resolution of Formamides and Thioformamides as An Entry to Nonracemic Amines. *J. Am. Chem. Soc.* **2010**, *132*, 2870−2871.

(25) Marsal, P.; Roche, M.; Tordo, P.; de Sainte Claire, P. Thermal Stability of O−H and *O*−alkyl Bonds in *N*-alkoxyamines. A Density Functional Theory Approach. *J. Phys. Chem. A* **1999**, *103*, 2899−2905.

(26) Bach, R. D.; Schlegel, H. B. The Bond Dissociation Energy of the N−O Bond. *J. Phys. Chem. A* **2021**, *125*, 5014−5021.

(27) Eve, T. S. C.; Wells, A.; Turner, N. J. Enantioselective Oxidation of *O*-methyl-*N*-hydroxylamines Using Monoamine Oxidase N as Catalyst. *Chem. Commun.* **2007**, 1530−1531.
(28) Lu, R.; Cao, L.; Guan, H.; Liu, L. Iron-Catalyzed Aerobic Dehydrogenative Kinetic Resolution of Cyclic Secondary Amines. *J. Am. Chem. Soc.* **2019**, *141*, 6318−6324.
(29) Sun, S.; Yang, Y.; Zhao, R.; Zhang, D.; Liu, L. Site- and Enantiodifferentiating C(sp^3)−H Oxidation Enables Asymmetric Access to Structurally and Stereochemically Diverse Saturated Cyclic Ethers. *J. Am. Chem. Soc.* **2020**, *142*, 19346−19353.
(30) Guan, H.; Tung, C.-H.; Liu, L. Methane Monooxygenase Mimic Asymmetric Oxidation: Self-Assembling μ-Hydroxo, Carboxylate-Bridged Diiron(III)-Catalyzed Enantioselective Dehydrogenation. *J. Am. Chem. Soc.* **2022**, *144*, 5976−5984.
(31) Cao, M.; Wang, H.; Ma, Y.; Tung, C.-H.; Liu, L. Site- and Enantioselective Manganese-Catalyzed Benzylic C−H Azidation of Indolines. *J. Am. Chem. Soc.* **2022**, *144*, 15383−15390.
(32) Wang, G.; Chen, T.; Jia, K.; Ma, W.; Tung, C.-H.; Liu, L. Catalytic Asymmetric Oxidation of Amines to Hydroxylamines. *J. Am. Chem. Soc.* **2023**, *145*, 22276−22283.
(33) Only one isolated example of chemical oxidation of *N*-alkoxy amines with stoichiometric oxidants has been reported; see: Weiss, R. H.; Furfine, E.; Hausleden, E.; Dixon, D. W. Oxidation of *N*, *N*′-Dialkyl-1,2-bis(hydroxylamines). *J. Org. Chem.* **1984**, *49*, 4969−4972.
(34) The absolute configuration of **2a** and **6a** was determined by X-ray diffraction analysis. See the Supporting Information for details.
(35) Matsumoto, K.; Sawada, Y.; Saito, B.; Sakai, K.; Katsuki, T. Construction of Pseudo-Heterochiral and HomoChiral Di-μ-oxotitanium (schiff base) dimers and Enantioselective Epoxidation Using Aqueous Hydrogen Peroxide. *Angew. Chem., Int. Ed.* **2005**, *44*, 4935−4939.
(36) Talsi, E. P.; Rybalova, T. V.; Bryliakov, K. P. Isoinversion Behavior in the Enantioselective Oxidations of Pyridylmethylthiobenzimidazoles to Chiral Proton Pump Inhibitors on Titanium Salalen Complexes. *ACS Catal.* **2015**, *5*, 4673−4679.
(37) Kondo, S.; Saruhashi, K.; Seki, K.; Matsubara, K.; Miyaji, K.; Kubo, T.; Matsumoto, K.; Katsuki, T. A. μ-oxo-μ-η^2:η^2-Peroxo Titanium Complex as A Reservoir of Active Species in Asymmetric Epoxidation Using Hydrogen Peroxide. *Angew. Chem., Int. Ed.* **2008**, *47*, 10195−10198.
(38) Talsi, E. P.; Samsonenko, D. G.; Bryliakov, K. P. Titanium Salan Catalysts for the Asymmetric Epoxidation of Alkenes: Steric and Electronic Factors Governing the Activity and Enantioselectivity. *Chem.—Eur. J.* **2014**, *20*, 14329−14335.
(39) Talsi, E. P.; Bryliakova, A. A.; Bryliakov, K. P. Titanium Salan/Salalen Complexes: The Twofaced Janus of Asymmetric Oxidation Catalysis. *Chem. Rec.* **2016**, *16*, 924−939.
(40) Kagan, H. B.; Fiaud, J. C. In *Topics in Stereochemistry*, Vol. *18*; Eliel, E. L.; Wilen, S. H., Eds.; Wiley: New York, 1988; pp 249−330.
(41) Greenhalgh, M. D.; Taylor, J. E.; Smith, A. D. Best Practice Considerations for Using the Selectivity Factor, *s*, As A Metric for the Efficiency of Kinetic Resolutions. *Tetrahedron* **2018**, *74*, 5554−5560.
(42) Beaudoin, D.; Wuest, J. D. Dimerization of Aromatic *C*-Nitroso Compounds. *Chem. Rev.* **2016**, *116*, 258−286.
(43) Greer, M. L.; Sarker, H.; Mendicino, M. E.; Blackstock, S. C. Azodioxide Radical Cations. *J. Am. Chem. Soc.* **1995**, *117*, 10460−10467.
(44) Shaabani, A.; Bijanzadeh, H. R.; Karimi, A. R.; Teimouri, M. B.; Soleimani, K. Synthesis and Tautomerization Study of Pseudonitrosites to 1,2-Nitroximes. *Can. J. Chem.* **2008**, *86*, 248−252.
(45) Blackmond, D. G. Kinetic Aspects of Nonlinear Effects in Asymmetric Catalysis. *Acc. Chem. Res.* **2000**, *33*, 402−411.
(46) Noyori, R.; Kitamura, M. Enantioselective Addition of Organometallic Reagents to Carbonyl Compounds. *Angew. Chem., Int. Ed.* **1991**, *30*, 49−69.
(47) Alassad, Z.; Nandi, A.; Kozuch, S.; Milo, A. Reactivity and Enantioselectivity in NHC Organocatalysis Provide Evidence for the Complex Role of Modifications at the Secondary Sphere. *J. Am. Chem. Soc.* **2023**, *145*, 89−98.
(48) Sekiguchi, Y.; Yoshikai, N. Enantioselective Conjugate Addition of Catalytically Generated Zinc Homoenolate. *J. Am. Chem. Soc.* **2021**, *143*, 4775−4781.

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