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Enantioselective Synthesis of Axially Chiral Diaryl Ethers through Chiral Phosphoric Acid-Catalyzed Desymmetric Acylation with Azlactones

Jiawei Xu, Wei Lin, Hanliang Zheng,* and Xin Li*

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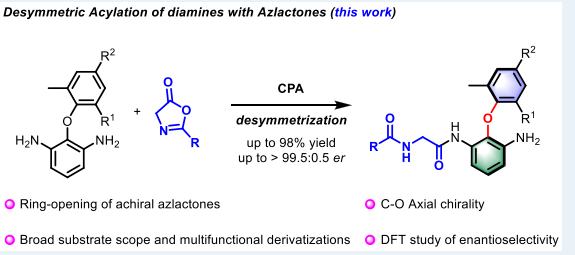
ABSTRACT: C−O axially chiral diaryl ethers play important roles in natural products and bioactive molecules, but because of the low rotational barrier and strict steric hindrance requirements, the catalytic asymmetric construction of axially chiral diaryl ethers still remains a challenge. Herein, we devised a strategy employing achiral azlactone for the desymmetrization of prochiral diamines under the catalysis of chiral phosphoric acid. The targeted C−O axially chiral diaryl ethers were obtained in very good yields (up to 98%) and high enantioselectivities (up to >99.5:0.5 er). The synthetic utility was demonstrated through large-scale reaction and transformations of the products. Moreover, DFT calculations were conducted to probe the origins of enantioselectivity.



KEYWORDS: *C−O axis, axially chiral diaryl ethers, enantioselective desymmetrization, CPA catalysis, achiral azlactone*

INTRODUCTION

Axially chiral compounds are integral to bioactive molecules and natural products, and they serve crucial roles in asymmetric catalysis as ligands and catalysts.[1] Consequently, the synthesis of axially chiral entities has emerged as a focal point in the field of asymmetric synthesis. Extensive research has been conducted on axially chiral molecules with C−C axial frameworks.[2] Very recently, the *C*-heteroatom axially chiral compounds, such as C−N,[3] C−O,[4] C−B,[5] and N−N[6] axially chiral compounds, have attracted particular interest because of their unique biological properties. Among these, C−O axially chiral compounds, typically diaryl ethers, are prevalent in both natural products and pharmaceuticals (Figure 1a). The synthesis of such compounds, however, is challenging because of their complex biaxial structures, low rotational barriers, and the precise steric interactions required. Since Fuji et al.'s initial study on C−O axial diaryl ethers,[7] there have been several examples of their construction via asymmetric catalysis.[8−13] Zhong and Zeng et al. recently described a chiral phosphoric acid (CPA)-catalyzed dynamic kinetic resolution of dicarbaldehydes with anilines to afford C−O axially chiral diaryl ethers through asymmetric hydrogen transfer.[9] Subsequently, Yang et al. demonstrated CPA-catalyzed electrophilic aromatic aminations of 2-aryloxy-1,3-benzenediamines with azodicarboxylates.[10] Moreover, the Biju group, the Ye group, the Zhang group, and the Gao group have independently reported *N*-heterocyclic carbene (NHC)-catalyzed atroposelective esterification of dialdehyde-containing diaryl ethers.[11] The Gao and Yao group and the Lu group represented a copper-catalyzed enantioselective click reaction between bisalkynes and azides to construct axially chiral diaryl ethers.[12] During the submission of the manuscript, the Yu and Li group developed a cobalt-catalyzed photoreductive coupling of dialdehyde and alkyne, which afforded diaryl ethers containing axial and central chirality.[13] Despite these significant contributions, the asymmetric synthesis of C−O axially chiral diaryl ethers remains a nascent area of study.

Azlactone is a potent synthon for the synthesis of chiral amino acids and their derivatives[14] because of its high reactivity toward nucleophilic attack by amines, alcohols, and other nucleophiles. While the construction of centrally chiral compounds from azlactones, which inherently contain chiral centers, has seen substantial progress, the induction of axial chirality using achiral azlactones remains underexplored. In our ongoing research to develop methods for the synthesis of axially chiral compounds using achiral precursor,[15] we proposed that the atroposelective acylation of diamines with a prochiral C−O axis using azlactone could enable the synthesis of axially chiral diaryl ethers. This approach necessitates overcoming significant obstacles: (i) the modulation of sterically hindered nucleophilic addition of aniline to azlactones, which is a process complicated by the requisite bulky substituents essential for stereoinduction and the stabilization of C−O axial chirality, and (ii) the prevention of

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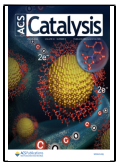

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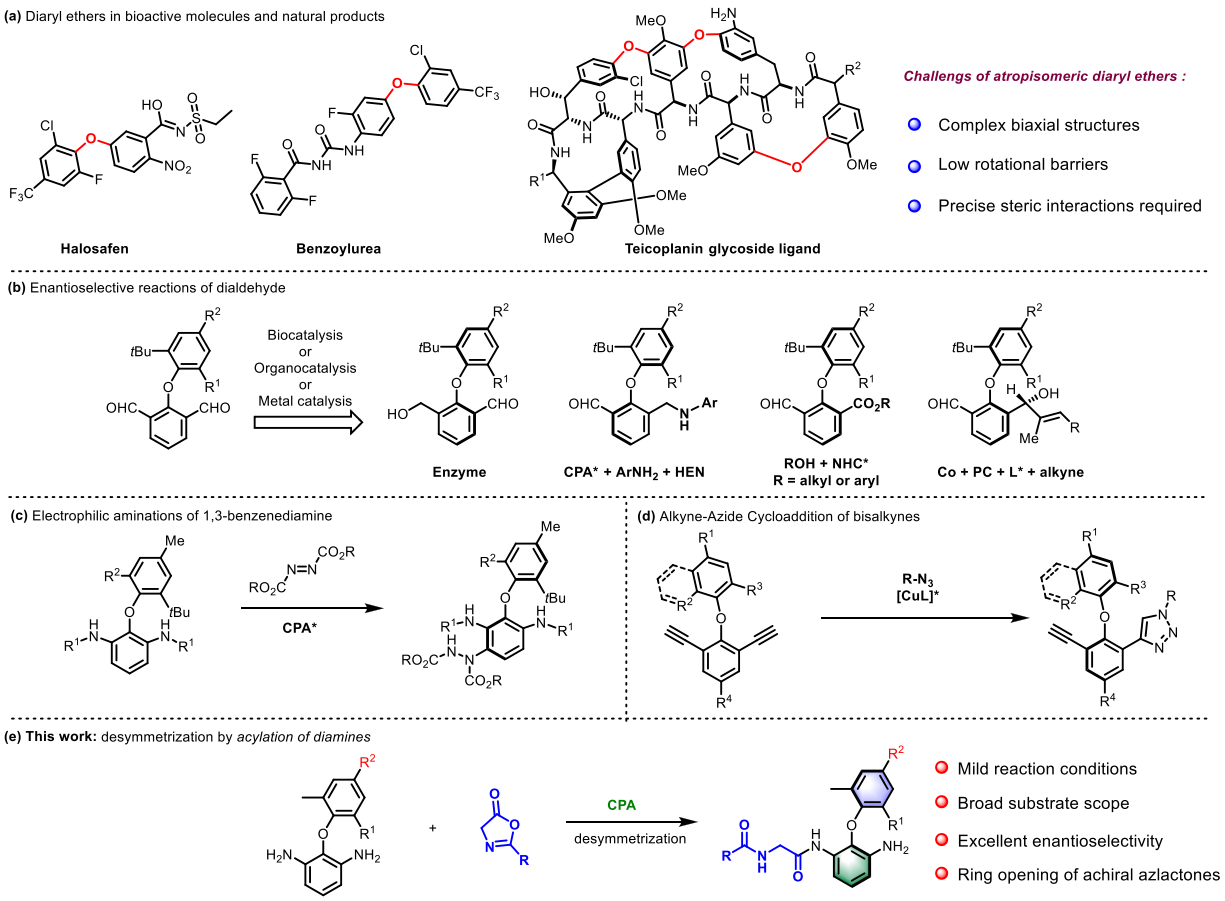
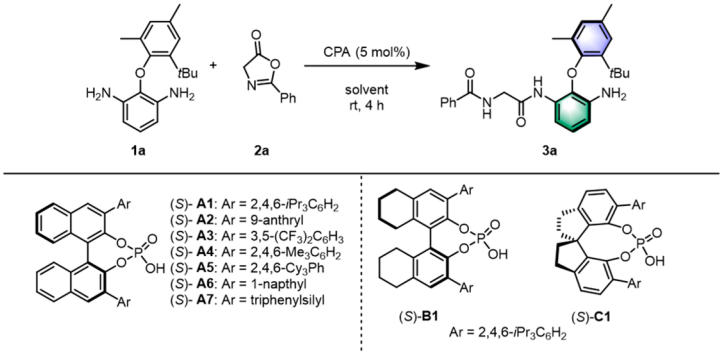


Figure 1. Representive atropisomeric diaryl ethers and asymmetric construction of C−O axially chiral diaryl ethers.

Table 1. Optimization of Reaction Conditions[a]



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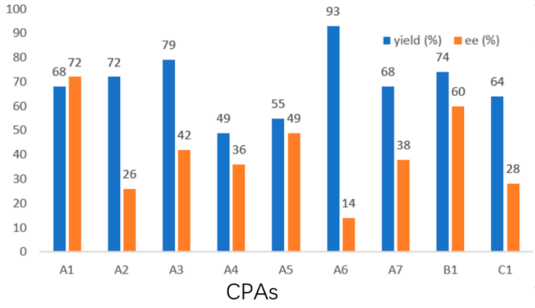

B:

entry	cat.	solvent	yield (%)[b]	er[c]
1	(*S*)-**A1**	$CHCl_3$	60	80:20
2	(*S*)-**A1**	CCl_4	65	91:9
3	(*S*)-**A1**	MeCN	56	90:10
4	(*S*)-**A1**	toluene	58	59:41
5	(*S*)-**A1**	THF	96	68.5:31.5
6[d]	(*S*)-**A1**	CCl_4	76	97:3

[a]General reaction conditions: **1a** (0.1 mmol), **2a** (0.11 mmol), and CPA (5 mol %) in solvent (1.0 mL) at room temperature for 4 h. [b]Yields of isolated products. [c]The enantiomeric ratio (er) values were determined by HPLC analysis. [d]Reacted with 4 Å molecular sieve (MS) (50.0 mg) added.

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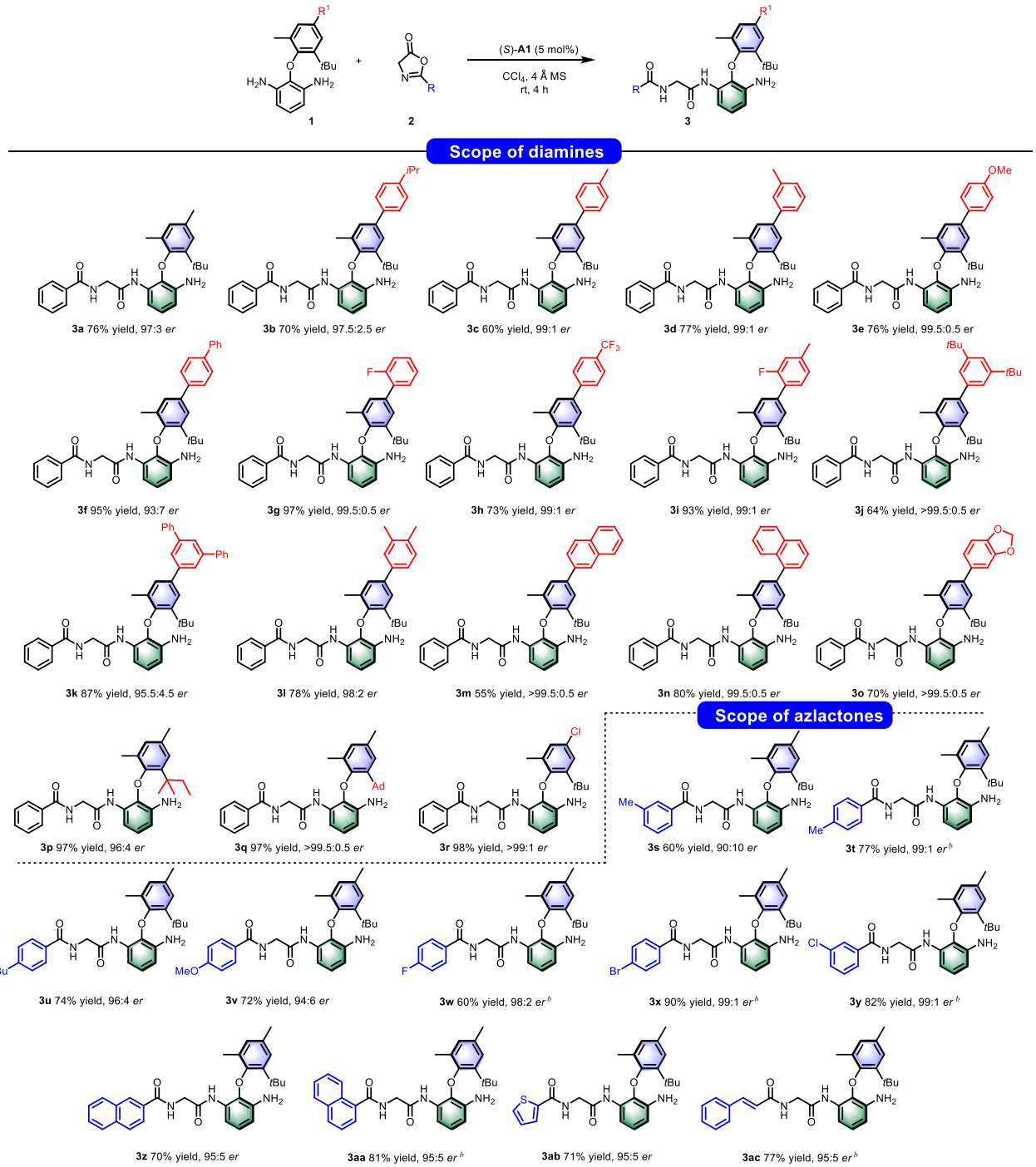
Table 2. Substrate Scope[a]



[a]Reaction conditions: The reactions were conducted with **1** (0.1 mmol), **2** (0.11 mmol), (*S*)-**A1** (5 mol %), and 4 Å MS (50.0 mg) in CCl_4 (1.0 mL) at room temperature for 4 h; er values of isolated yields were determined by chiral HPLC analysis. [b]Compounds **1a** (0.1 mmol), **2** (0.12 mmol, 1.2 equiv), and (*S*)-**A1** (5 mol %) with 50.0 mg 4 Å MS in MeCN/CCl_4 = 4:1 (1.0 mL) at −30 °C for 8 h.

bis-acylation. Herein, we disclose the first CPA-catalyzed enantioselective synthesis of axially chiral diaryl ethers via atroposelective acylation of diamines bearing a prochiral C−O axis via the desymmetrization strategy (Figure 1e).

RESULTS AND DISCUSSION

Conditions Optimizations. Our study was initiated with the model reaction of diamine **1a** and achiral azlactone **2a** catalyzed by CPA (*S*)-**A1** in dichloromethane (CH_2Cl_2) at 25 °C. Gratifyingly, the desired benzamide **3a** was produced in 68% yield and 86:14 er (Table 1A, column 1), thus validating the feasibility of our vision. A series of BINOL-derived CPAs were then assessed (Table 1A, columns 2−7), among which the catalyst (*S*)-**A1**, featuring 2,4,6-triisopropylphenyl substituents at the 3,3′-positions, proved to be the optimal catalyst. Solvents screening revealed that chlorinated solvents, especially carbon tetrachloride (CCl_4), enhanced enantioselectivity, elevating the er of **3a** to 91:9 (Table 1B, entry 2). The addition of 4 Å

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molecular sieves further increased the enantioselectivity to 97:3 er (Table 1B, entry 6).

Substrate Scope. With the optimal conditions in hand (Table 1B, entry 6), we first examined the scope of diamines. As outlined in Table 2, diamines **1b**−**1o** with various *para*- and *meta*-substituted phenyl rings at 4′-position of diaryl ethers were well tolerated, which delivered the corresponding benzamides **3b**−**3o** in excellent enantioselectivities. Both electron-donating groups, such as alkyl substituents (**3b**−**3d**) and methoxy group (**3e**), and electron-withdrawing groups, exemplified by halogen substituent (**3g**), were well tolerated. Furthermore, with strong electron-withdrawing group $-CF_3$, the corresponding benzamide **3h** could also be obtained in 73% yield with 99:1 er. Substrates with two substituents connected to the 4-phenyl group (**1i**−**1l**) were also well compatible and delivered the corresponding axially chiral diaryl ethers **3i**−**3l** in 64−93% yields and 95.5:4.5−99.5:0.5 er. Moreover, substrates with polycyclic (**1m** and **1n**) and heterocyclic (**1o**) substituents smoothly reacted with **2a** under the standard conditions to yield **3m**−**3o** with good yields (55−80%) and up to >99.5:0.5 er. We also expanded the *ortho*-position of diaryl ethers. As indicated in Table 2, substitution of the *tert*-butyl with larger moieties, such as 2-methyl-2-butyl and adamantyl, yielded excellent results in which **3p** and **3q** were obtained with 96:4 and >99.5:0.5 er, respectively.[16]

Besides the excellent performance of diamines, we shifted our focus to investigate achiral azlactones (Table 2). By exploring various substituents on the phenyl ring, we observed that substrates bearing electron-donating groups at the *meta*- or *para*-positions exhibited favorable reactivity (**3s**−**3v**). Notably, a substrate containing bulky *tert*-butyl group was well suited and afforded the target product **3u** in 74% yield with 96:4 er. In addition, electron-withdrawing groups, particularly halogens, also proved effective and yielded the desired **3w**−**3y** in 60−90% yield with 98:2 to >99:1 er. Furthermore, reaction of heterocyclic azlactone, such as 2-thienyl azlactone, could also successfully provide the desired product **3ab** in 71% yield and 95:5 er. Alkenyl azlactone was also proved compatible within the reaction and delivered the product **3ac** in 77% yield and 95:5 er

Large-Scale Reaction. To assess the practical utility of this methodology, a large-scale reaction involving **1a** and **2a** was conducted under the standard conditions. As illustrated in Figure 2a, desired product **3a** was obtained in a yield of 72% with almost retained enantioselectivity (97:3 er) at a 1.0 mmol scale. This depicted the method's potential for large-scale production.

Transformations. The versatility of **3a** was demonstrated by its successful engagement in transformation reactions (Figure 2b). When reacted with benzaldehyde and Hantzsch ester, the corresponding benzylamine **4** was obtained in 85% yield and 96:4 er. By using *tert*-butyl nitrite and azidotrimethylsilane to conduct the diazotization reaction, the azide **5** was obtained in 95% yield and 96:4 er. Furthermore, **3a** can be converted to corresponding urea **6** and thiourea **7** in excellent yields and almost retained er values. Sandmeyer reaction of **3a** occurred smoothly in the presence of $NaNO_2$ and KI to yield **8** in 70% yield and 96:4 er. Notably, the absolute configuration of **6** was determined via X-ray crystallography, and the configurations of other products and derivatives were assigned analogously.[17] Furthermore, after the protection of free-amine moiety, the introduced amide moiety can be removed in the presence of base to obtain another modified free amino group.[18]

Control Experiment. The monoacylation product **3a** could undergo further acylation to form the diacylation adduct, which

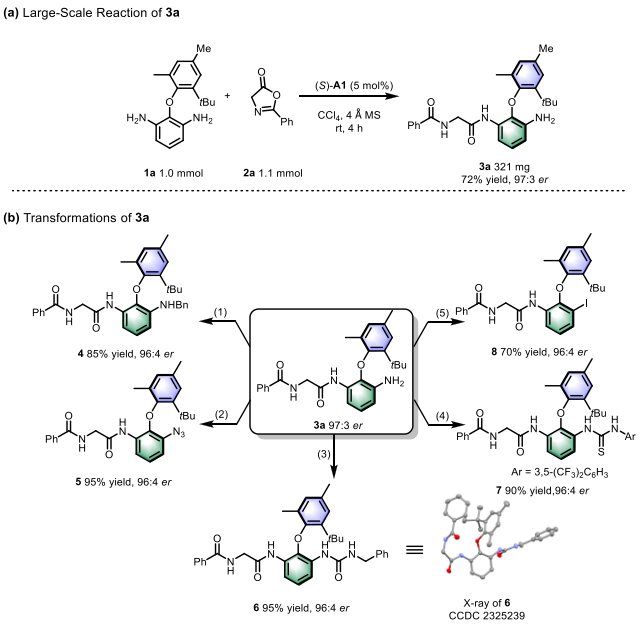

Figure 2. (a) Large-scale reaction; (b) transformations, reaction conditions: (1) (i) PhCHO, Hantzsch ester, $MgSO_4$, CF_3COOH, DCM, 42 °C; (ii) $NaBH_4$, MeOH; (2) *t*$BuNO_2$, $TMSN_3$, MeCN, rt; (3) isocyanate, *rac*-PA, DCM, rt; (4) isothiocyanate, THF, rt; (5) $NaNO_2$, KI, HCl/H_2O/THF, 0 °C to rt.

possibly served as a kinetic resolution process to improve the enantioselectivity of initial monoacylation process. To investigate this hypothesis, a racemic sample of **3a** was subjected to the catalytic conditions (**3a** and **2a** in a 2:1 molar ratio) as shown in Figure 3a. Upon complete consumption of **2a**, the

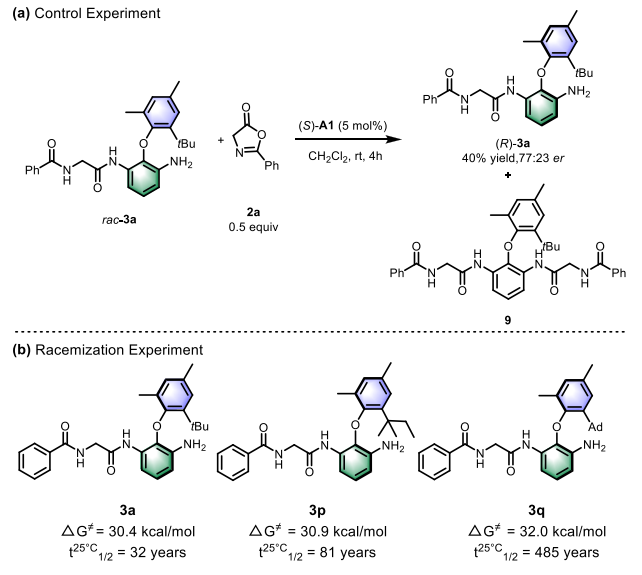

Figure 3. (a) Control experiment; (b) racemization experiment.

monoacylation product **3a** was recovered in 40% yield with 77:23 er. These results provided evidence supporting the proposition that the second acylation step operates as a kinetic resolution process, thereby contributing positively to the overall enantioselectivity of the reaction.[19]

Racemization Experiment. For the purpose of investigating the stability of axial chirality of our products, the

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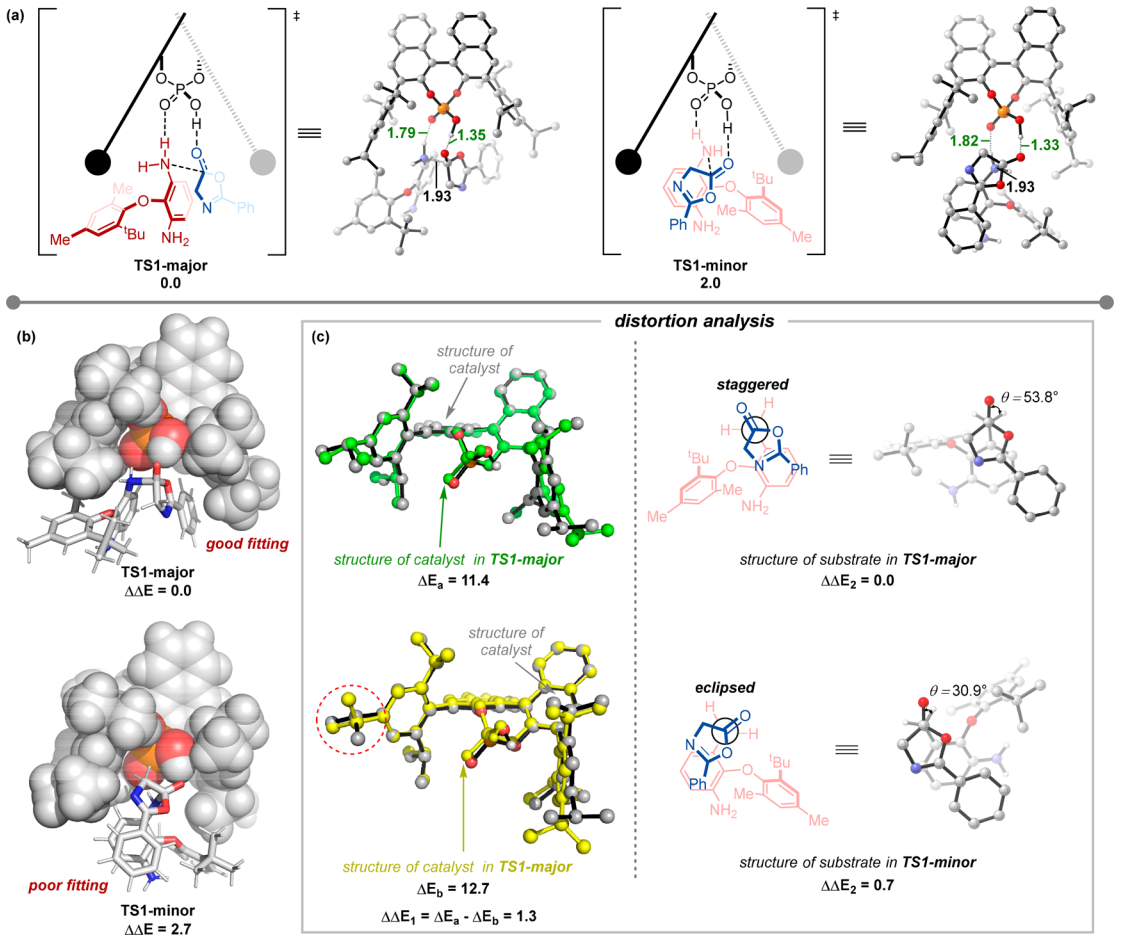

Figure 4. Density functional theory (DFT) calculations. (a) Computationally determined structures of lowest-energy transition states leading to the major and minor atropisomers and their Gibbs free energies in kcal/mol; (b) van der Waals surface representations of **TS1-major** and **TS1 minor**; (c) distortion analysis of the substrate and catalyst in the corresponding transition states. Superimposed representations of the catalyst's initial structure and its configurations in the transition states were provided to demonstrate the geometries' changes. The structure of catalyst in its original state, **TS1-major**, and **TS1 minor** are depicted in gray, green, and yellow, respectively. Reported energies within this analysis refer to the electronic energies in kcal/mol.

racemization experiment of compound **3a** in isopropyl alcohol at 80 °C was carried out. To our delight, the er value of **3a** remained unchanged in 2 h, which revealed it has a high stability. A rotation barrier (ΔG‡) of 30.4 kcal/mol was successfully measured in toluene at 100 °C, thereby indicating the half-life at room temperature ($t_{1/2}^{25\ °C}$) could be as high as 32 years (Figure 3b). Variations of *tert*-butyl substituent to bulkier 2-methyl-2-butyl and adamantyl on the diaryl ethers further enhanced the satiability of axial chirality, as evidenced by the increased rotation barrier of **3p** and **3q** to 30.9 and 32.0 kcal/mol, respectively.

DFT Calculations. Density functional theory (DFT) calculations were conducted to probe the origins of enantioselectivity in the reaction.[20] The results indicated that, for the reaction of **1a** and **2a**, the lowest-lying transition state leading to the major atropisomer (**TS1-major**) has a lower Gibbs free energy than that of **TS1 minor** by 2.0 kcal/mol (Figure 4a). Accordingly, an er value of 98:2 was computed, which was in excellent accordance with the experimental result. The van der Waals surface representations of **TS1-major** and **TS1 minor** suggested that the stereoinduction may stem from the less favorable spatial arrangement of substrates within the chiral phosphoric acid's binding pocket in **TS1 minor**, which would lead to increased structural distortion as consequence (Figure 4b). Our distortion analysis further corroborates this point, thereby indicating that the chiral phosphoric acid and the substrate that was organized in an eclipsed conformation were more distorted in **TS1 minor** by 1.3 and 0.7 kcal/mol in electronic energy, respectively (Figure 4c)

CONCLUSIONS

We have developed a highly efficient protocol for synthesizing C−O axially chiral diaryl ethers through atroposelective desymmetric acylation of prochiral diamines with achiral azlactones as acylation reagents catalyzed by chiral phosphoric acid. The desired atroposelective benzamides were obtained in moderate to excellent yields and high enantioselectivities. This methodology demonstrates broad functional group tolerance under mild reaction conditions. The scalability of this protocol was confirmed through successful large-scale reactions, and the versatility of the products was demonstrated in subsequent transformations. Additionally, density functional theory calculations provided insights into the theoretical basis for the observed enantioselectivities in this reaction.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.4c01489.

Detailed experimental procedures, characterization data, and NMR spectra of new compounds (PDF)

X-ray crystallographic data for **6** (CIF)

Accession Codes

CCDC 2325239 (product **6**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: + 44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Authors

Hanliang Zheng − *Key Laboratory of the Ministry of Education for Advanced Catalysis Materials, College of Chemistry and Materials Science, Zhejiang Normal University, Jinhua 321004, China*; Email: hanliang@zjnu.edu.cn

Xin Li − *State Key Laboratory of Elemento-Organic Chemistry, College of Chemistry, Nankai University, Tianjin 300071, China; Haihe Laboratory of Sustainable Chemical Transformations, Tianjin 300192, China*; orcid.org/0000-0001-6020-9170; Email: xin_li@nankai.edu.cn

Authors

Jiawei Xu − *State Key Laboratory of Elemento-Organic Chemistry, College of Chemistry, Nankai University, Tianjin 300071, China*

Wei Lin − *State Key Laboratory of Elemento-Organic Chemistry, College of Chemistry, Nankai University, Tianjin 300071, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acscatal.4c01489

Author Contributions

X.L. conceived and directed the project. J.X. designed and performed the experiments. W.L. synthesized the substrates. H.Z. conducted the DFT calculations and provided mechanism analysis. X.L., J.X., and H.Z. wrote the paper with inputs from all other authors. All authors discussed the results and commented on the manuscript.

Notes

The authors declare no competing financial interest.

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(17) CCDC 2325239 (**6**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

(18) Using **4**, of which the free-amine moiety was protected by benzyl group for amide removal reaction, in sodium hydroxide/ethanol system, the amide can be removed to obtain the corresponding aniline in 80% yield, 97:3 er. For more details, please see the Supporting Information.

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