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Synthesis of P(V)-Stereogenic Phosphorus Compounds via Organocatalytic Asymmetric Condensation

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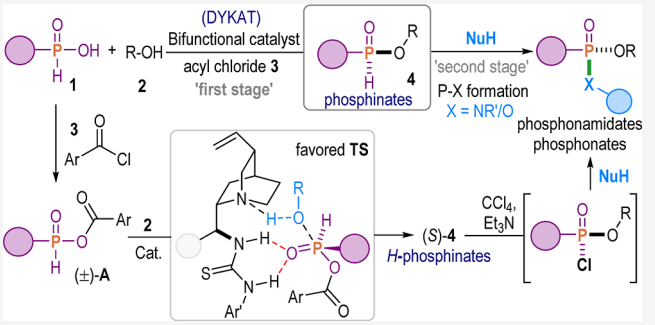
ABSTRACT: Enantioenriched phosphorus(V)-stereogenic compounds, featuring a pentavalent phosphorus atom as the stereogenic center, are crucial in various natural products, drugs, bioactive molecules, and catalysts/ligands. While a handful of stereoselective synthetic approaches have been developed, achieving direct stereocontrol at the phosphorus atom through catalytic generation of phosphorus(V)-heteroatom bonds continues to be a formidable challenge. Here, we disclose an organocatalytic asymmetric condensation strategy that employs a novel activation mode of stable feedstock phosphinic acids by the formation of mixed phosphinic anhydride as the reactive species to facilitate further catalyst-controlled asymmetric P−O bond formations, involving a dynamic kinetic asymmetric transformation (DYKAT) process with alcohol nucleophiles via a cinchonidine-derived bifunctional catalyst. The resulting H-phosphinate intermediates allow further stereospecific derivatizations, affording modular access to a diverse library of chiral phosphonates and phosphonamidates with notable antibacterial activity. Furthermore, this synthetic platform facilitates P−O/N coupling with various natural products and drugs, presenting a valuable tool for medicine and agrochemical discovery.



INTRODUCTION

Enantioenriched phosphorus(V)-stereogenic compounds are a fascinating class of chiral molecules characterized by a pentavalent phosphorus atom as the stereogenic center.[1−4] These compounds have garnered considerable attention due to their unique structural properties and presence in an array of natural products, pharmaceuticals, agrochemicals, and bioactive molecules (Figure 1A).[5−11] For instance, the cyclic *P*-chiral salinipostin A is a natural product with antimalarial activity[8] and sofosbuvir, an effective drug for treating chronic hepatitis C, also contains this structural unit.[9] The stereochemistry of the P(V) stereocenter is essential in the development of chiral drugs as their single enantiomers often have enhanced binding affinity, improved pharmacokinetics, and reduced side effects compared to their racemates.[6] Compounds containing P(V)-stereogenic structures are also important precursors used in the development of chiral catalysts or ligands.[3,4,12,13] As a consequence, developing efficient and highly selective methods for synthesizing novel, multifunctional, high-value-added *P*-chiral phosphorus compounds is of enormous interest in pharmaceutical development and synthetic chemistry. Effective methods to date primarily rely on stoichiometric amounts of chiral reagents, such as approaches including resolution and auxiliary-based diastereoselective synthesis.[14−23] Stereoselective synthesis by means of catalyst control has also been developed, such as the desymmetrization approach with prochiral P(V) scaffolds involving transition metals or small-molecule catalysts.[24−33] There are also a handful of P−C couplings with secondary phosphine oxides wherein fully carbon-substituted phosphine oxides were obtained.[34−42]

Despite impressive advancements, there has been limited success in achieving direct stereocontrol at the phosphorus atom through catalytic generation of phosphorus(V)-heteroatom bonds (Figure 1B). The group of Zhang in 2012 demonstrated the catalytic construction of *P*-chiral phosphoramides for the first time by a nucleophilic activation of racemic thiophosphoryl chlorides with a chiral bicyclic imidazole catalyst, obtaining an enantiomeric excess (ee) of up to 40%.[43,44] Recently, Dirocco and colleagues achieved a breakthrough in the highly diastereoselective preparation of phosphoramidate prodrugs enabled by a multifunctional chiral bisimidazole-catalyzed P−O coupling between chlorophos-

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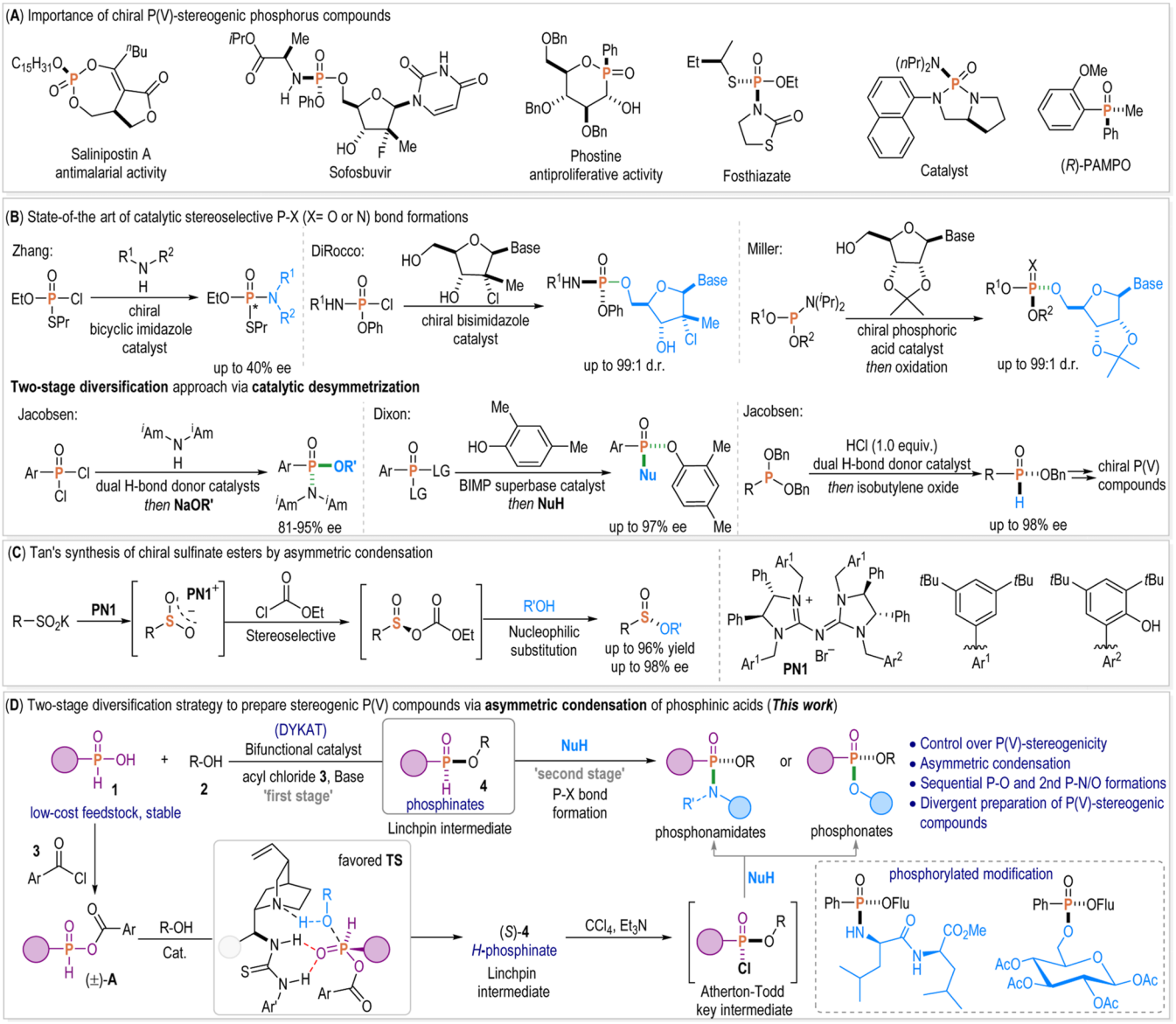

Figure 1. (A) Representative molecules containing P(V)-stereogenic centers; (B) catalytic enantioselective nucleophilic P−X (X = O/N) bond formations; (C) synthesis of chiral sulfinate esters by asymmetric condensation; (D) our proposed two-stage synthetic strategy to access diverse P(V)-stereogenic compounds via an asymmetric condensation approach. DYKAT = dynamic kinetic asymmetric transformation.

phoramidate with various nucleosides.[45] Miller's group realized the stereoselective synthesis of chiral phosphorus(V) oligonucleotides using a chiral phosphoric acid-catalyzed phosphoramidite coupling followed by an oxidation sequence.[46] More recently, Forbes and Jacobsen used a hydrogen-bond-donor catalyst to enable the synthesis of chlorophosphonamidates from desymmetrization of aryl phosphonic dichlorides.[47] Meanwhile, Dixon's group reported the nucleophilic desymmetrization of phosphonate esters by a superbasic bifunctional iminophosphorane catalyst.[48,49] Both methods offer distinct practical two-stage synthetic platforms involving initial desymmetrization and a second derivatization sequence, allowing stereoselective access to a wide range of chiral phosphorus(V) compounds. Noteworthy is that while this paper was under preparation, an elegant catalytic approach involving an S_N2 desymmetrization pathway via geometric preorganization was published by Jacobsen's group to afford an array of chiral H-phosphinites as versatile P(V) building blocks for derivatizations.[50] Nonetheless, the development of catalyst-controlled enantioselective P-heteroatom bond-forming strategies for preparing P(V) stereogenic compounds, particularly with stable, easily available P-precursors/catalysts suitable for late-stage modification of biologically interesting molecules, is still highly demanding.

The utilization of stable carboxylic acids through an in situ anhydride-forming activation approach has enabled versatile enantioselective transformations by means of various small-molecule catalysts.[51−54] Very recently, the group of Tan has demonstrated an intriguing enantioselective condensation approach to access S-chiral sulfinate esters with readily accessible potassium sulfinates through catalytically generated enantioenriched mixed anhydride intermediates (Figure 1C).[55] Prompted by these remarkable successes and our broad interest in the catalytic construction of unique heteroatom-stereogenic compounds,[56,57] we envisioned the activation of feedstock phosphinic acids through the formation of mixed

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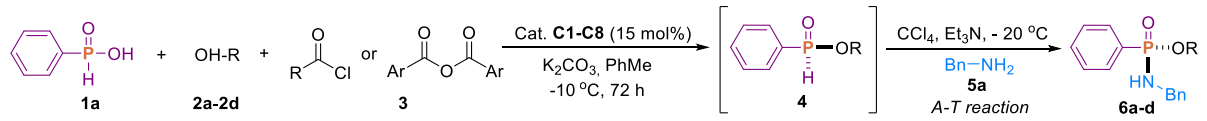

Entry	Cat.	R-OH (2)	3	Yield (%)	E.r.
1	**C1**	Bn-OH (**2a**)	**3a**	**6a**, 46	50:50
2	**C2**	Bn-OH	**3a**	**6a**, 32	45:55
3	**C3**	Bn-OH	**3a**	**6a**, 30	54:46
4	**C4**	Bn-OH	**3a**	**6a**, 37	41:59
5	**C5**	Bn-OH	**3a**	**6a**, 29	58:42
6	**C6**	Bn-OH	**3a**	**6a**, 51	65:35
7	**C7**	Bn-OH	**3a**	**6a**, 65	78:22
8	**C7**	Bn-OH	**3b**	**6a**, 56	75:25
9	**C7**	Bn-OH	**3c**	**6a**, 47	75:25
10	**C7**	EtOH (**2b**)	**3a**	**6b**, 41	61:39
11	**C7**	*i*PrOH (**2c**)	**3a**	**6c**, 43	62:38
12	**C7**	9-Fluorenol (**2d**)	**3a**	**6d**, 87	98:2
13	**C6**	9-Fluorenol	**3a**	**6d**, 73	95:5
14	**C8**	9-Fluorenol	**3a**	**6d**, 75	7:93

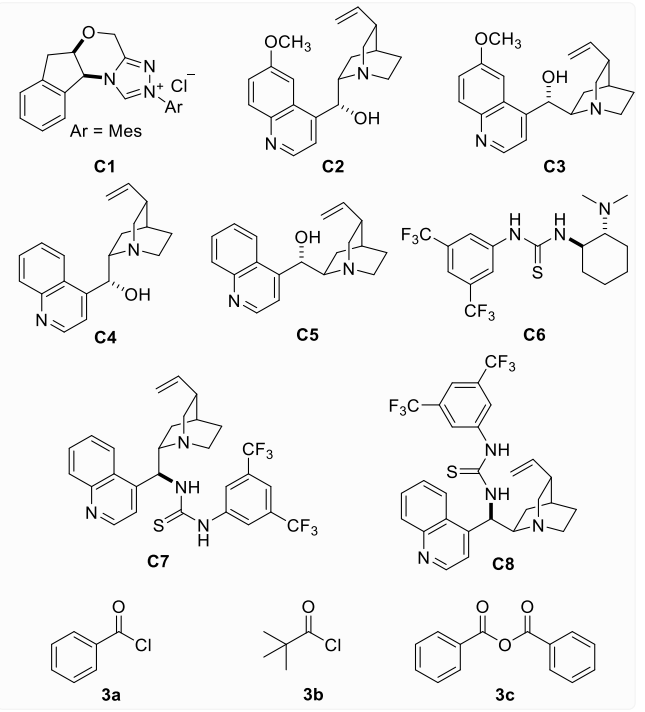

Figure 2. Optimization of the organocatalytic asymmetric condensation of phosphinic acid **1a** and alcohol **2**. [a]The reactions were performed with **1a** (0.1 mmol, 1.0 equiv), catalyst (15 mol %), alcohol **2** (1.2 equiv), **3** (2.0 equiv), K_2CO_3 (2.0 equiv), and $PhCH_3$ (1.5 mL) at −10 °C for 72 h. The semistable phosphinate intermediate **4** was directly subjected to the Atherton−Todd (A−T) reaction, which was conducted with amine **5a** (2.0 equiv) and Et_3N (2.0 equiv) in CCl_4 (1.0 mL) at −20 °C for 72 h. Isolated yields were reported. E.r. values were determined by chiral HPLC analysis. See the Supporting Information for details.

phosphinic anhydrides as reactive species to facilitate further catalyst-controlled asymmetric P−O bond formations with alcohol nucleophiles.[58] Herein, we disclose an organocatalytic enantioselective condensation strategy for rapid access to a broad set of phosphorus(V) stereogenic scaffolds with readily available and stable phosphinic acids (Figure 1D). Specifically, our approach involves the initial formation of phosphinic mixed anhydride **A** as the pivotal species. A dynamic kinetic asymmetric transformation (DYKAT) process imparts high stereocontrol over the subsequent P−O bond-forming reaction with alcohol nucleophiles, facilitated by a cinchonidine-derived bifunctional catalyst. Notably, the catalytically obtained H-phosphinates **4** offer a unique opportunity for further stereospecific derivatization through sequential nucleophilic substitution by in situ generation of its chloride derivative to afford modular access to a diverse library of chiral phosphonates and phosphonamidates, which are highly appealing scaffolds with significant antibacterial activities against typical rice plant pathogens for the development of novel agrochemicals.[59,60] Moreover, our asymmetric condensation approach with inexpensive and stable phosphinic acids enables the P−O/N coupling with a wide array of natural products, drugs, and biologically interesting molecules in excellent stereoselectivity, which could provide a practical synthetic platform for late-stage phosphonylated functionalization of these intriguing compounds and serve as an attractive pro-drug modification strategy for medicine and agrochemical discovery.[7,45]

RESULTS AND DISCUSSION

Initially, we investigated the asymmetric condensation reaction of phosphinic acid **1a** with benzyl alcohol (**2a**) as the primary starting material. Benzoyl chloride (**3a**) was utilized to activate readily available phosphinic acid by forming the pivotal phosphinic mixed anhydride intermediate. Through control of the nucleophilic addition to P-containing anhydride species with small-molecule catalysts, we anticipated realizing an unprecedented asymmetric condensation of phosphinic acid to afford the P−O coupling product **4** in an enantioselective manner. The resulting H-phosphinate **4** is an important structural motif for the rapid construction of versatile P(V)-stereogenic compounds. A combined sequence involving an Atherton−Todd (A−T) reaction was subsequently conducted, allowing for the stereoselective synthesis of phosphonamidate **6a** as the P(V)-chiral product.[59,60] With this in mind, we first exploited an array of typical organocatalysts, such as N-heterocyclic carbenes (NHCs) and cinchona alkaloids to promote the catalytic asymmetric P−O-forming condensation reaction (Figure 2, entries 1−5). Wherein the NHC **C1** catalyst failed to deliver the desired product **6a** with enantiocontrol, utilizing cinchonidine (**C4**) and cinchonine (**C5**) gave the phosphonamidate **6a** in modest yield and promising enantioselectivity (41:59 and 58:42, respectively) (entries 4−5). Encouragingly, when we examined bifunctional catalysts **C6**−**C7**, we were pleased to find that the cinchonidine-derived thiourea catalyst **C7** was particularly

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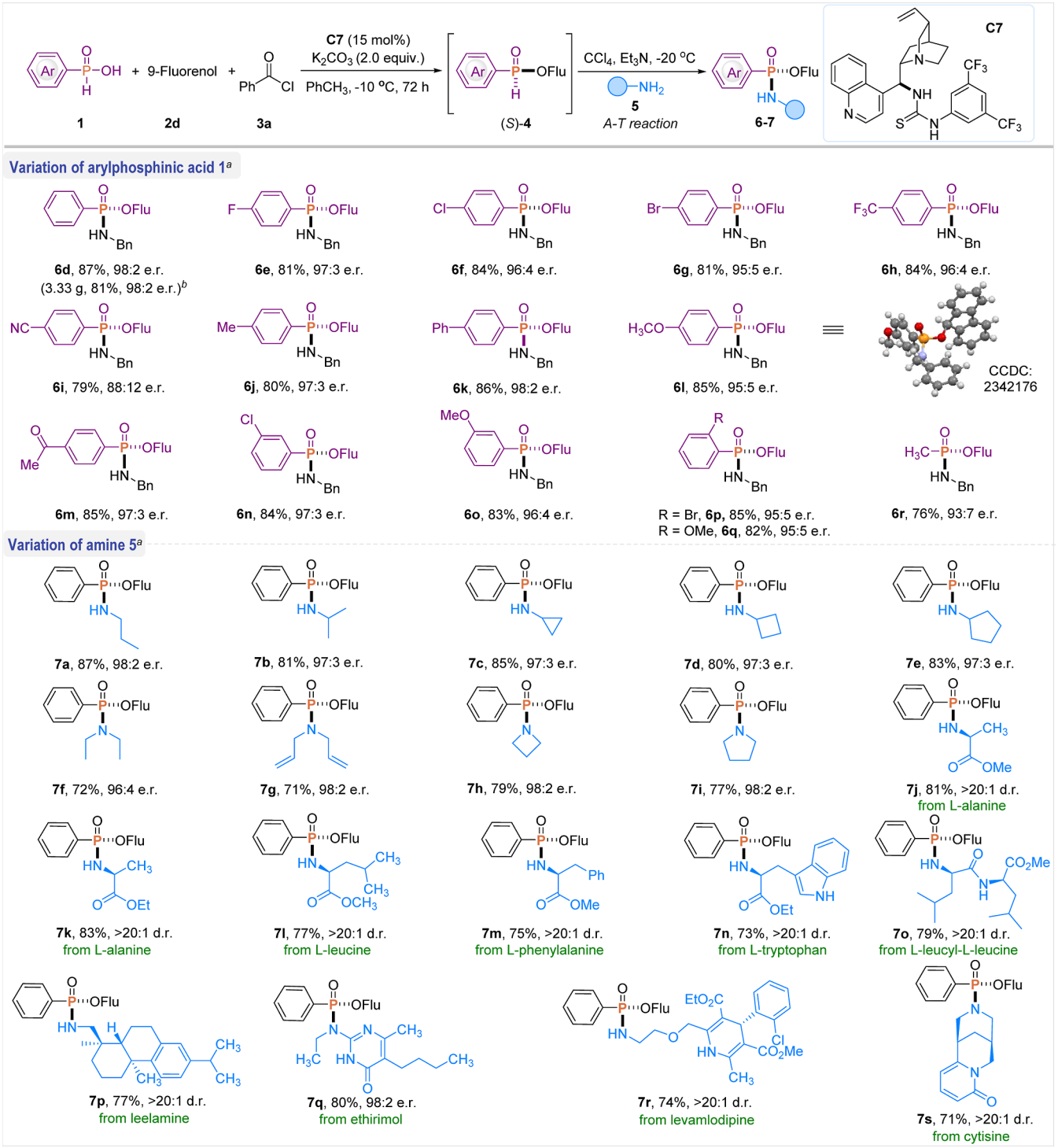

Figure 3. Substrate scope of the enantioselective synthesis of *P*-chiral phosphonamidates **6**–**7**. [a]The reactions were conducted with phosphinic acid **1** (0.1 mmol, 1.0 equiv), cat. **C7** (15 mol %), K_2CO_3 (2.0 equiv), and alcohol **2d** (1.2 equiv) in $PhCH_3$ (1.5 mL), −10 °C, 72 h. Transformation with the Atherton−Todd reaction of the phosphinate intermediate **4** was performed with amine **5** (2.0 equiv), Et_3N (2.0 equiv) in CCl_4 (1.0 mL) at −20 °C for 72 h. Isolated yields were reported, e.r. values were determined by chiral HPLC analysis, and d.r. values were determined by ^1H NMR analysis. [b]Reaction on a 10.0 mmol scale. See the Supporting Information for details.

effective in this unique condensation,[61−71] giving rise to the product **6a** in a 65% yield and significantly increased 78:22 er (entries 6−7). Considering the tunable structure of the formed mixed phosphinic anhydrides, we also tested an array of acyl chlorides or anhydrides **3b**−**3c** as activating reagents (see Table S3 for more details), while these attempts did not provide better enantioselectivity (entries 8−9). Further, we examined alcohols **2b**−**2d** under catalytic conditions in the presence of catalyst **C7** (entries 10−12). Reactions with EtOH or *i*PrOH afforded the corresponding products **6b**−**6c** with moderate enantioselectivity (entries 10−11). Remarkably, the use of 9-fluorenol (**2d**) led to the desired product **6d** in a high yield (87%) and an excellent optical purity of 98:2 er, presumably owing to its notable steric hindrance to diminish

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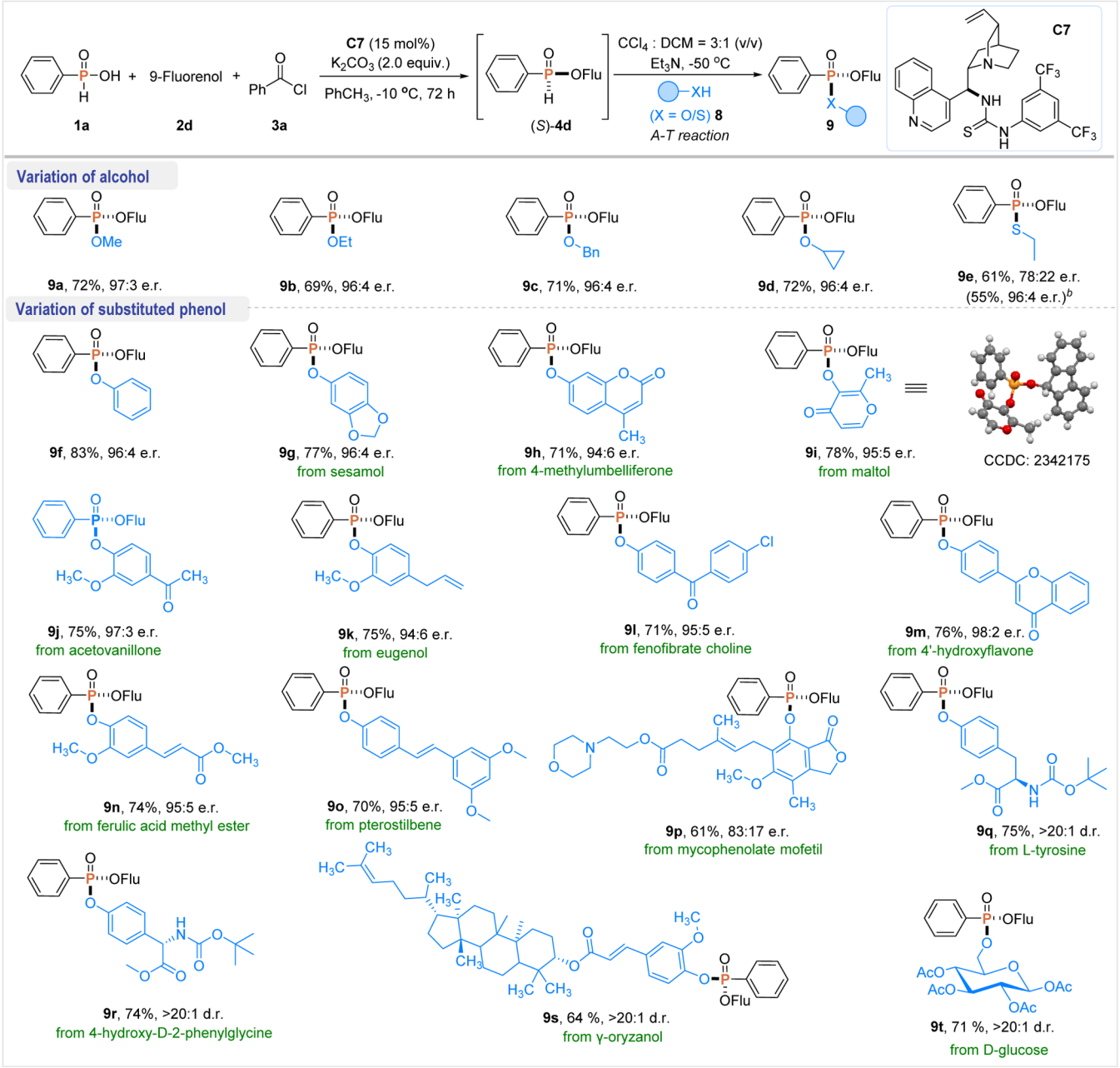

Figure 4. Substrate scope of the enantioselective synthesis of *P*-chiral phosphonates **9**. [a]The reactions were conducted with phenylphosphinic acid **1a** (0.1 mmol, 1.0 equiv), cat. **C7** (15 mol %), K_2CO_3 (2.0 equiv), and alcohol **2d** (1.2 equiv) in $PhCH_3$ (1.5 mL), −10 °C, 72 h. The Atherton−Todd reaction of the phosphinate intermediate **4d** was performed with nucleophile **8** (2.0 equiv) and Et_3N (2.0 equiv) in CCl_4/DCM = 3:1 (v/v) at −50 °C for 72 h. Isolated yields were reported, e.r. values were determined by chiral HPLC analysis, and d.r. values were determined by ^1H NMR analysis. [b]The Atherton−Todd reaction was performed at −70 °C. See the Supporting Information for details.

the background reaction and assist the enantiocontrol in the transition state (entry 12, also see Figure S8 of the Supporting Information for more details). As a technical note, the generated H-phosphinate intermediate **4d** (98:2 er) was prone to degrade slowly when isolated at room temperature. The crude residue from the asymmetric condensation was thereby directly used in the second Atherton−Todd reaction. Moreover, a low temperature (−20 °C) was necessary to ensure the A−T transformation in a highly stereospecific manner (see Table S5 of the Supporting Information for more details). Other catalysts such as **C6** were also highly effective in delivering the corresponding product **6d** in high enantioselectivity (entry 13). Furthermore, the opposite enantiomer of product **6d** was readily accessible using bifunctional catalyst **C8**, which was derived from cinchonine (**C5**) as a pseudoenantiomer of catalyst **C7** (entry 14).

With the optimal reaction procedure established, we set out to study the generality of the organocatalytic stereoselective synthesis of *P*-chiral phosphonamidates **6**−**7** via the asymmetric condensation of phosphonic acid **1** and alcohol **2d** (Figure 3). With benzyl amine as the nucleophile for the Atherton−Todd (A−T) transformation in the sequence, we initially explored phosphinic acid substrates **1** possessing various halide groups (e.g., F, Cl, Br) at the para positions of phenyl unit, yielding the corresponding P(V)-stereogenic products **6e**−**6g** in high yields (81−84%) and excellent

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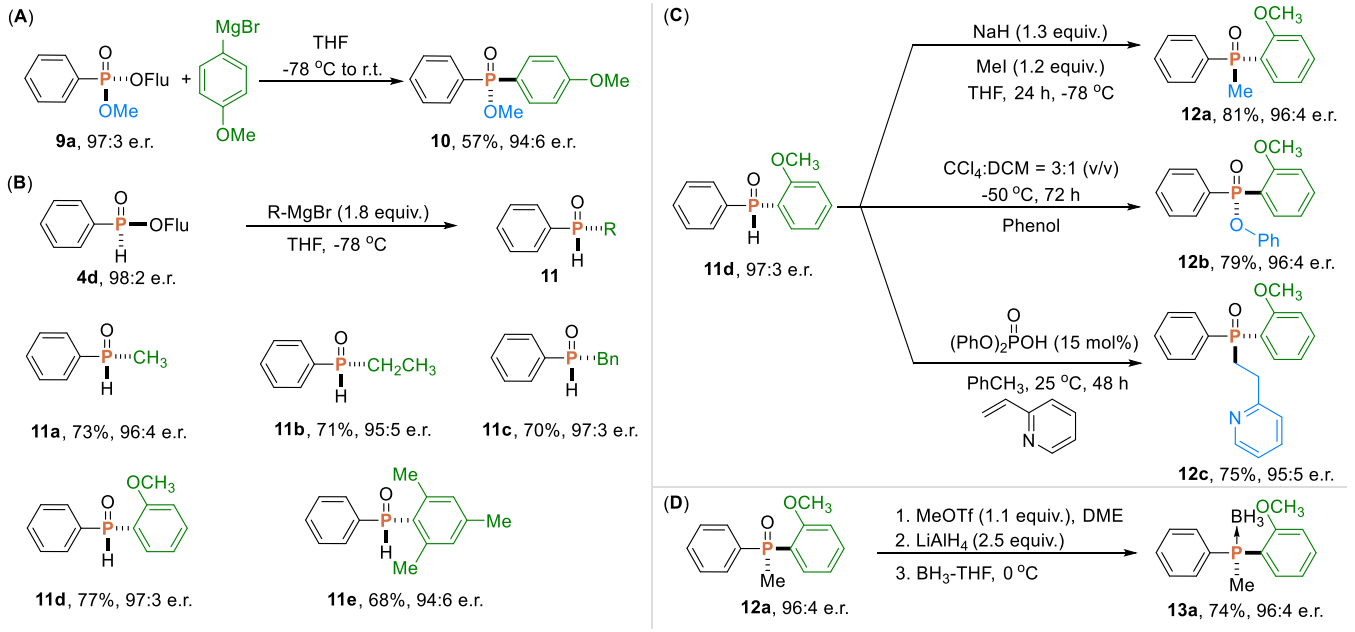

Figure 5. Stereoselective synthesis of diverse P(V)-stereogenic compounds from the catalytically obtained product **9a** and phosphinate **4d**.

enantioselectivity. Substrates with electron-deficient moieties, such as CF_3 and CN, were also readily converted under the optimal conditions, leading to the desired products **6h**−**6i** in good yields, albeit modest enantioselectivity for product **6i** was observed probably due to the presence of the electron-deficient CN group that resulted in slightly dropped enantioselectivity of the initially formed H-phosphinate intermediate **4i** (92:8 er) and the second Atherton−Todd transformation. Additionally, substrates with Me, Ph, OMe, and acetyl moieties were all compatible with the developed reaction sequence, yielding products **6j**−**6m** with good results. We next examined variations at the meta- and ortho-sites of the aromatic units for their impact on the enantioselective preparation of the *P*-chiral products. The optimal conditions were applicable to these substrates, resulting in products **6n**−**6q** with 82−85% yields and 95:5 to 97:3 er values. Alkyl (e.g., methyl)-substituted phosphonic acid also worked well to give the corresponding *P*-chiral product **6r** in good results. Notably, with the mild conditions developed in our method, we were able to achieve a gram-scale synthesis to afford product **6d** in an 81% yield (3.33 g) and 98:2 er. Moreover, the absolute configuration of the obtained *P*-chiral phosphonamidate products **6** was established as (*S*) by analogy to product **6l**, as determined through X-ray crystallographic analysis.

Having established the scope of the enantioselective synthesis of phosphonamidates with respect to phosphinic acid **1**, we turned to assess the second stage of the sequential synthetic strategy: the enantiospecific Atherton−Todd reaction to access versatile P(V)-stereogenic compounds through P−N bond formations with various N-nucleophiles (Figure 3). Under optimal conditions, a diverse set of primary and secondary amines featuring linear or cyclic structures successfully delivered the corresponding phosphonamidates **7a**−**7i** with 71−87% yields and excellent selectivities ranging from 96:4 to 98:2 er. Encouraged by this success, we set out to achieve the synthesis of multiple classes of chiral phosphonamidates by employment of complex or biologically intriguing amines as nucleophiles. In this context, amino acid esters were successfully installed with the chiral P(V) moiety, affording a wide range of phosphonylated amino acid derivatives **7j**−**7n**. The catalytic sequence was also feasible for peptide modification, as demonstrated by the phosphonylation of the dipeptide (**7o**). Furthermore, our method provides a synthetic platform for the rapid coupling of the P(V) stereogenic element to various important molecules, such as the natural product leelamine (**7p**), the pesticide ethirimol (**7q**), and drugs including levamlodipine (**7r**) and cytisine (**7s**).

Considering the broad scope of the reaction sequence, we investigated the stereoselective preparation of *P*-chiral phosphonates **9** through enantiospecific P−O/S bond formations with O/S-centered nucleophiles (Figure 4). Common alcohols such as MeOH, EtOH, BnOH, cyclopropyl alcohol, and thiols were readily coupled with the phosphinate intermediate **4d**, delivering the chiral products **9a**−**9e** in excellent stereoselectivities, except for thiol as the nucleophile, which resulted in modest selectivity likely due to the facile racemization of the in situ-formed chiral phosphonic chloride intermediate. Satisfyingly, when the Atherton−Todd reaction was carried out at a low temperature (−70 °C), the product **9e** could be obtained with an excellent er value of 96:4. Moreover, phenol was also suitable for the P−O couplings, affording chiral phosphonate **9f** in an 83% yield with 96:4 er. As mentioned, the developed method is an ideal synthetic tool for the late-stage modification of naturally occurring molecules into a plethora of P(V) stereogenic centers. Therefore, a broad set of biologically intriguing phenol-containing natural products were applied as nucleophiles in the reaction sequence. Sesamol (**9g**), 4-methylumbelliferone (**9h**), maltol (**9i**), acetovanillone (**9j**), eugenol (**9k**), fenofibrate choline (**9l**), 4′-hydroxyflavone (**9m**), ferulic acid methyl ester (**9n**), and pterostilbene (**9o**) were smoothly converted under the mild conditions, providing the phosphonylation-functionalized analogues with high enantioselectivity. Additionally, a complex molecule, such as mycophenolate mofetil, was also compatible with the reaction to install the chiral P(V) moiety, affording the product **9p** in a 61% yield and modest selectivity. Furthermore, optically enriched molecules such as L-tyrosine derivatives (**9q**), 4-hydroxy-D-2-phenylglycine (**9r**), γ-oryzanol

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(**9s**), and D-glucose (**9t**) delivered their phosphonylated conjugates with high diastereomeric ratios. The absolute configuration of the *P*-chiral stereocenters was determined by an analogy to (*S*) via the X-ray crystallography of product **9i**.

The enantioenriched *P*-chiral product **9** and phosphinate intermediate **4** obtained from asymmetric condensation could be further elaborated to afford versatile P(V)-stereogenic compounds through stereoinvertive substitution with various Grignard reagents as nucleophiles (Figure 5). To this end, conversion of **9a** through nucleophilic substitution with (4-methoxyphenyl)magnesium bromide readily afforded phosphinate product **10** with a 57% yield and 94:6 er (Figure 5A). Furthermore, displacement of the fluorenol group of **4** provided an array of alkyl or aryl-substituted H-phosphinates **11a**−**11e** with high enantiospecificity (Figure 5B). The obtained secondary phosphine oxide product **11d** is an ideal linchpin building block for further synthetic transformations into various chiral P(V)-stereogenic compounds (Figure 5C). For instance, H-phosphinate **11d** underwent a methylation reaction with MeI under basic conditions to furnish the (*S*)-PAMPO ligand **12a** without erosion of optical purity. The Atherton−Todd reaction with phenol at −50 °C readily afforded phosphonate **12b** in a 79% yield and 96:4 er. Upon acid-catalyzed conditions, addition of **11d** to vinylpyridine proceeded smoothly, giving rise to product **12c** with a 75% yield and high stereospecificity. Notably, we have also demonstrated the preparation of the corresponding phosphine through a sequence involving methyl triflate and $LiAlH_4$, which was isolated as borane complex **13a** in a 74% yield and 96:4 er (Figure 5D).

Control experiments were performed to gain insight into the asymmetric condensation process. As illustrated in Figure 6A, under the catalytic conditions, the reaction by utilization of the readily prepared phosphinic mixed anhydride **A1** resulted in the formation of the desired product **6d** in an 85% yield and 98:2 er. The result was comparable to that obtained under the optimal conditions (87%, 98:2 er; Figure 2), suggesting that the catalytic reaction most probably involved a racemic phosphinic anhydride intermediate **A**. Furthermore, the reaction with a monomethylated catalyst **C9** instead of **C7** under the optimal conditions gave rise to the desired product **6d** in a significantly decreased yield and enantioselectivity (45% yield, 70:30 er vs 87% yield, 98:2 er in Figure 2, entry 12), which strongly supports the crucial role of hydrogen bonding in the catalytic process. We also performed an enantiomerization study of the anhydride species, wherein the (*R*)/(*S*)-enantiomer of **A1** was not capable of interconverting in the absence of catalyst **C7** (Table S7, Supporting Information), implying that the thiourea-bifunctional catalyst likely participated in the enantiomerization of anhydride (±)-**A**. Built upon these reaction studies and previous reports,[46,72−74] a plausible mechanism for the asymmetric condensation reaction is proposed in Figure 6C. First, nucleophilic addition of phosphinic acid **1** to benzoyl chloride **3a** would lead to the formation of mixed anhydride (±)-**A** as the pivotal reactive species. Hydrogen bonding interaction between species **A** and the thiourea moiety of Cat. **C7** could activate the P═O bond of anhydride to facilitate the tautomerization of the P(V) to P(III) process. Then, the nucleophilic displacement by benzoate anion might occur to promote the inversion of the generated P(III) intermediate,[46] which could finally result in a facile epimerization of the mixed-valence P(III)−P(V) intermediates in the catalytic reaction

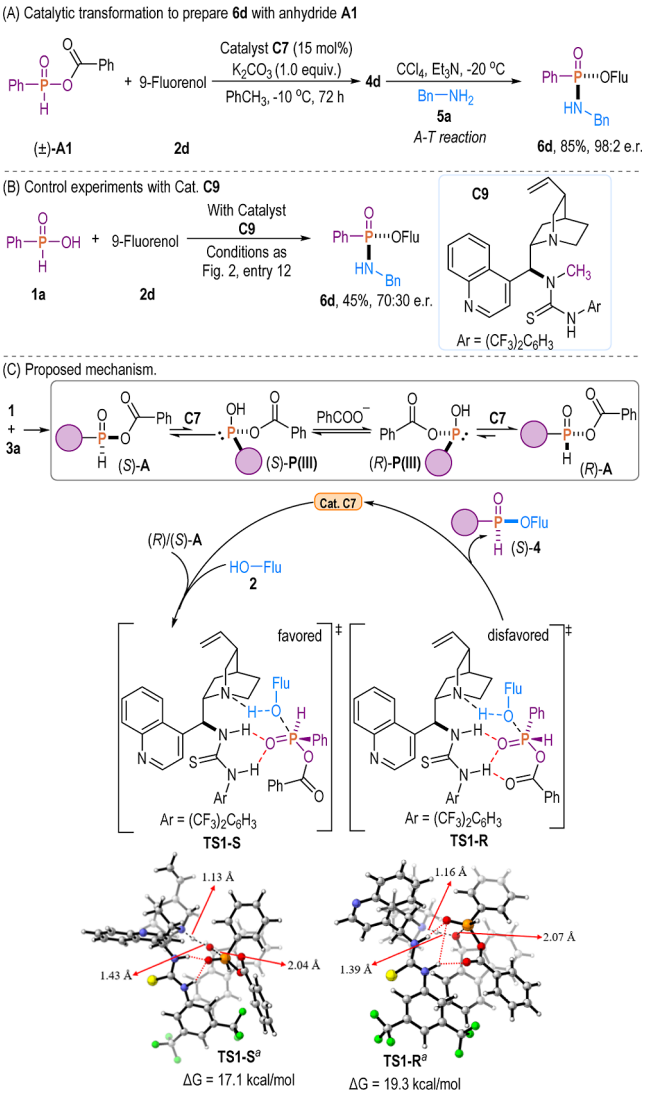

Figure 6. Control experiments (A,B) and proposed mechanism (C). [a]Calculated energy profile of the nucleophilic attack. In the figure, red dashed lines indicate hydrogen bonds, while dashed lines in black represent bonds that are being formed or broken in the transition state.

(see sections 2.3 and 2.4 of the Supporting Information for more details and other plausible pathways).[39,41,72−76] Subsequently, P−O bond formation involving the approach of alcohol nucleophiles from the less hindered P−H bond of **TS1-S** was assumed to afford the desired phosphinates **4** with a high enantioselectivity.

To explore the energy difference between the two transition states (**TS1-S** and **TS1-R**), a density functional theory calculation was conducted. The reaction pathway encompasses two critical transition states: an initial nucleophilic attack of fluorenol (via **TS1-R** and **TS1-S**), followed by product formation through cleavage of the P-benzoate bond (via **TS2-R** and **TS2-S**) (see Supporting Information, Figure S5). As illustrated in Figure 6C, the pathway involving **TS1-S** has a lower reaction energy barrier, which is 2.2 kcal/mol lower than that of **TS1-R**. This predicts an enantiomeric ratio (er) of 97.5:2.5, which is in good agreement with the observed experimental er value of 98:2.

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Fascinated by the diverse biological activities of phosphorus(V) compounds,[5−11] we performed preliminary antibacterial activity studies with the obtained chiral phosphonamidates **6**−**7** and phosphonate products **9** to identify potent antibacterial agrochemicals for crop protection. In vitro assays were carried out to evaluate the biological activity of these products. Intriguingly, most products exhibited significant inhibitory activity against *Xanthomonas oryzae* pv *oryzae* (*Xoo*)[77] and *X. oryzae* pv *oryzicola* (*Xoc*),[78] which are two typical pathogens that could lead to bacterial leaf blight and bacterial leaf streak diseases in rice plants, respectively (Table 1). Notably, (*S*)-**6d**, (*S*)-**6f**, and (*S*)-**7q** showed excellent inhibition rates (95.82%, 95.59%, and 93.19%, respectively) against *Xoo* at a concentration of 50 μg/mL, which was superior to the positive control with commercial bactericides. In comparison, the racemates of compounds **6d** and **6f** exhibited significantly diminished inhibitory activity. Meanwhile, (*R*)-**9a** also showed notable efficiency against *Xoc* with an inhibition rate of 97.83%, notably surpassing that of its racemate (±)-**9a** (62.07%). These findings expand the potential of our products as novel scaffolds for the development of antibacterial agents.

Table 1. In Vitro Antibacterial Activity of the Target Compounds against *Xoo* and *Xoc* at 50 μg/mL[a]

compound	*Xoo* inhibition rate [%]	*Xoc* inhibition rate [%]
(*S*)-**6d**	**95.82±2.64**	27.23±2.91
(±)-**6d**	20.81±3.73	40.41±3.51
(*S*)-**6f**	**95.59±2.61**	54.90±2.17
(±)-**6f**	58.61±4.35	58.35±1.19
(*S*)-**7q**	**93.19±3.74**	79.83±2.98
(±)-**7q**	91.38±2.24	58.67±2.11
(*R*)-**9a**	88.67±1.08	**97.83±2.47**
(±)-**9a**	64.16±4.25	62.07±4.04
(*S*)-**9j**	80.45±2.24	76.25±2.05
(±)-**9j**	60.29±0.33	57.14±1.21
BT[b]	30.79±2.64	45.97±3.97
TC[c]	33.13±2.23	29.09±2.58

[a]All data were average data of three replicates. [b]Commercial bactericide, BT = bismerthiazol was used as the positive control. [c]Commercial bactericide, TC = thiodiazole copper was used as the positive control.

CONCLUSIONS

In summary, we have developed an organocatalytic asymmetric condensation approach with readily stable phosphinic acids and alcohols. By introduction of a novel activation mode for P(V)-based phosphinic acids through forming mixed phosphinic anhydride as the pivotal intermediate, a DYKAT process efficiently facilitates asymmetric P−O bond formations with alcohol nucleophiles under the control of a cinchonidine-derived bifunctional catalyst. A modular divergent synthetic approach allowed for the creation of a library of diverse biologically intriguing P(V) chiral scaffolds, including phosphonates and phosphonamidates, through further enantiospecific P−N, P−O, and P−C bond formations with various nucleophilic components. Our two-stage condensation−substitution sequence provides a synthetic phosphonylated coupling platform for postmodification of natural products, drugs, and other important molecules. The explored asymmetric P−O forming condensation strategy opens new avenues for the preparation of chiral phosphorus-stereogenic scaffolds, and the application of these *P*-chiral compounds in designing new chiral catalysts and discovery of potent agrochemicals could be anticipated.

ASSOCIATED CONTENT

Data Availability Statement

All data are available from the authors upon request.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.4c11956.

Full experimental details for the preparation of all new compounds and their spectroscopic and chromatographic data (PDF)

Accession Codes

Deposition numbers 2342175−2342176 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via the joint Cambridge Crystallographic Data Centre (CCDC) and Fachinformationszentrum Karlsruhe Access Structures service.

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Notes

The authors declare no competing financial interest.

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