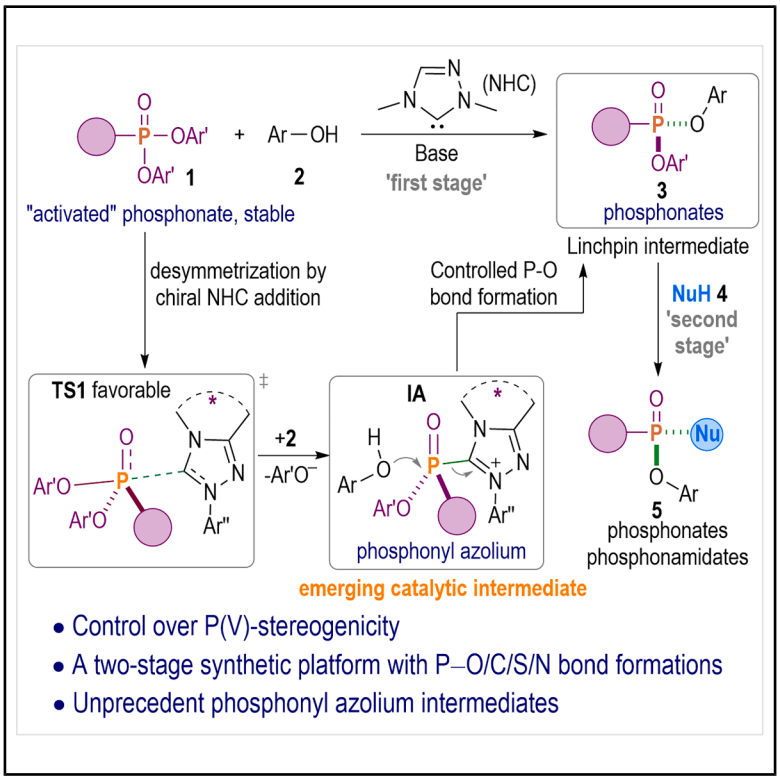
Chem

NHC-catalyzed covalent activation and control of P(V)-stereogenic phosphorus centers via phosphonyl azolium intermediates

Graphical abstract



Highlights

- Covalent organocatalysis for enantioselective construction of phosphorus scaffold
- Formation of phosphonyl azolium intermediates to enable further catalyst control
- Broad scope with P–O/C/S/N bond formations through a two-stage synthetic platform
- Potential application as novel scaffolds for potent bactericidal agrochemicals

Authors

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In brief

A new mode of covalent organocatalysis for enantioselective construction of chiral phosphorus scaffolds via P–O bond formations is disclosed. Key steps in this approach involve the formation of pivotal phosphonyl azolium reactive intermediates that realize an efficient catalyst control over P(V)-stereogenicity, which is distinct from classical NHC organocatalysis focusing on "C"-stereocenters. The resulting phosphonate products bearing a leaving group allow further stereospecific P–O/N coupling, facilitating the phosphonylated functionalization of a broad range of natural products and biologically relevant molecules.

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NHC-catalyzed covalent activation and control of P(V)-stereogenic phosphorus centers via phosphonyl azolium intermediates

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THE BIGGER PICTURE Enantiomerically enriched P-stereogenic compounds are widely present in biomolecules, drugs, and other functional molecules. Consequently, the preparation of chiral P-stereogenic compounds has received increasing attention over the past decades. Although impressive advancements have been achieved, control of P(V)-stereogenicity with covalent nucleophilic catalysts for direct synthesis of a broad range of chiral phosphorus compounds remains relatively underdeveloped. Herein, we disclosed an N-heterocyclic carbene (NHC)-catalyzed covalent activation and control of P(V)-stereogenic phosphorus centers via phosphonyl azolium intermediates, affording a diverse set of P(V) chiral products in high selectivity. Unlike classical NHC organocatalysis that focuses on "C"-stereocenters, this study realizes efficient catalyst control over P(V)-stereogenicity for the first time and shall inspire further exploration of novel covalent bond activation strategies to address the challenges in the preparation of phosphorus stereogenic compounds with nucleophilic catalysts.

SUMMARY

Despite various impressive advancements in the construction of chiral phosphorus centers, enantioselective control of P(V)-stereogenicity with covalent nucleophilic catalysts for direct preparation of chiral phosphorus compounds remains relatively underdeveloped. Here, we disclose a new mode of covalent organocatalysis for enantioselective construction of chiral phosphorus scaffolds via new P–O bond formations. Key steps in our approach involve the addition of an *N*-heterocyclic carbene (NHC) catalyst to a phosphonate, leading to the formation of a pivotal phosphonyl azolium reactive intermediate that effectively forges the asymmetric P–O bond formation in high selectivity. The resulting phosphonate products bearing a leaving group allow further stereospecific P–O/N coupling, facilitating the phosphonylated functionalization of diverse natural products and bioactive molecules. Unlike classical NHC organocatalysis that focuses on "C"-stereocenters, this study realizes efficient catalyst control over P(V)-stereogenicity through phosphorus-based azolium intermediates for the first time, offering a new platform for covalent bond activation in the synthesis of stereogenic phosphorus compounds.

INTRODUCTION

The asymmetric catalytic construction of carbon atom chiral centers has been widely explored with enormous success by using enzymes, transition metal catalysts, and organocatalysts.[1–6] By contrast, controlling the chirality of heteroatoms (such as sulfur and phosphorus atoms) in chemical transformations is much more challenging.[7–11] For instance, P-containing phosphorus compounds represent a unique class of functional molecules featuring pentavalent P(V)-stereogenicity. The chiral P(V) scaffolds are widely present in biomolecules, drugs, and other functional molecules such as catalysts (Figure 1A).[12–15] The enantioselective construction of chiral phosphorus centers therefore receives increasing attention. To date, access to stereogenic

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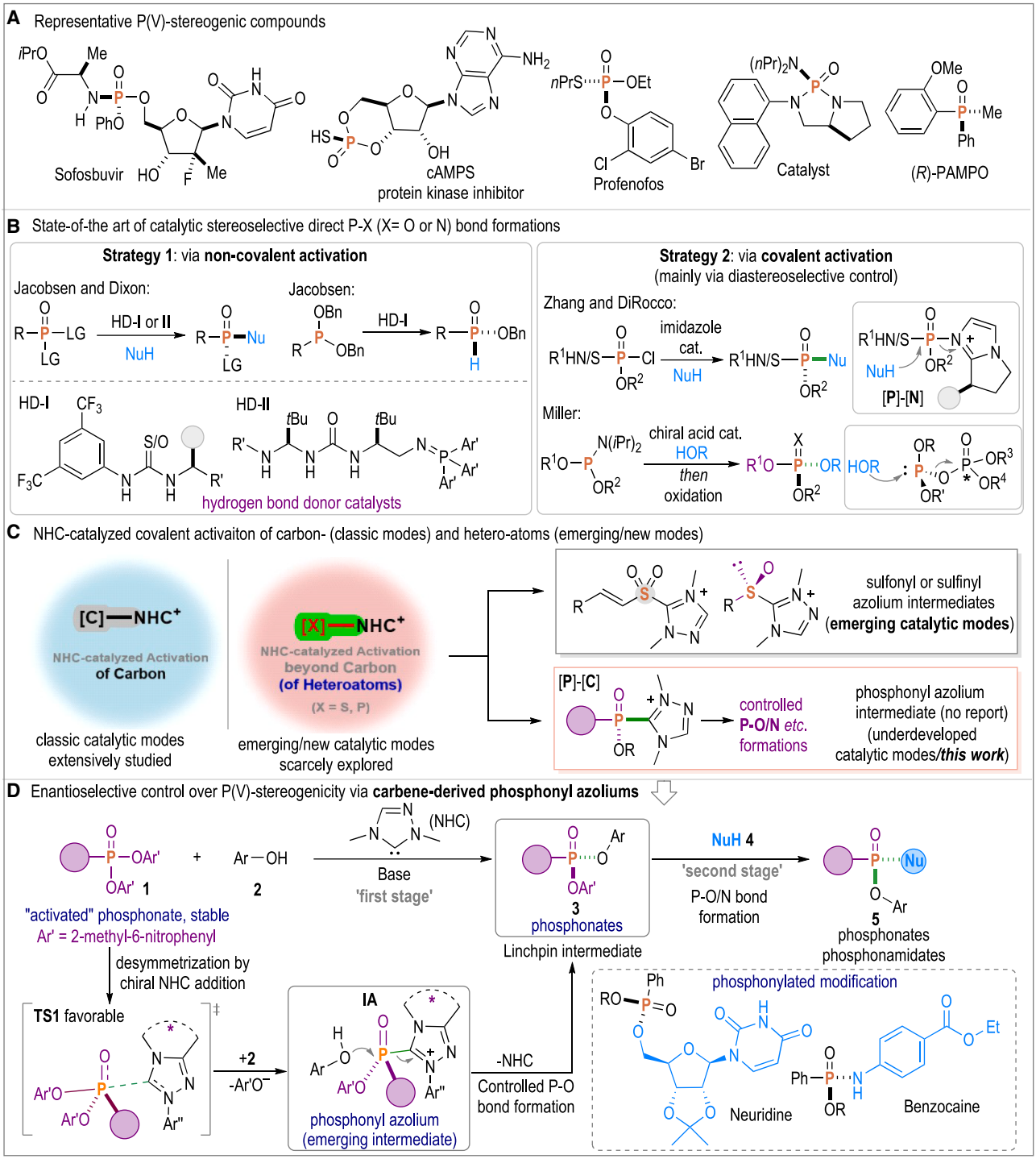

Figure 1. Catalytic enantioselective preparation of P(V)-stereogenic compounds

(A) Representative P(V)-stereogenic compounds.

(B) State-of-the-art catalytic stereoselective direct P-X (X= O or N) bond formations.

(C) NHC-catalyzed covalent activation of carbon- (classic modes) and heteroatoms (new modes).

(D) Enantioselective control over P(V)-stereogenicity via carbene-derived phosphonyl azoliums.

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phosphorus compounds has primarily relied on resolution methods or diastereoselective synthesis by the use of stoichiometric resolving agents or chiral auxiliaries.[16–21] Contemporary enantioselective catalytic methods have also been developed, including asymmetric P–C couplings with secondary phosphine oxides[22–31] and indirect construction of P(V) stereogenic centers through functionalization of prochiral P-bound moieties.[32–40]

Despite these impressive advancements, achieving direct catalyst control at the phosphorus atom through P–O or P–N bond formation remains relatively underdeveloped. In this context, Jacobsen[41,42] and Dixon[43,44] have independently realized the highly enantioselective synthesis of chiral phosphonates, phosphinates, or phosphonamidates utilizing non-covalent catalytic systems such as thiourea-derived hydrogen bond donor catalysts (Figure 1B, strategy 1). Alternatively, covalent bond activation in the presence of nucleophilic catalysts, involving the formation of catalyst-bound phosphorus species that could govern subsequent P–O or P–N bond formations, provides a complementary route to obtaining chiral P(V) compounds (Figure 1B, strategy 2). Pioneering contributions by Zhang and DiRocco revealed that the bicyclic imidazole organocatalysts could mediate the preparation of an array of chiral P(V) stereogenic compounds through a catalyst-bound [**P**]-[**N**] intermediate.[45–47] Intriguingly, Miller et al. realized the asymmetric and stereodivergent oligonucleotide synthesis utilizing a chiral Brønsted acid catalyst as both acid and nucleophilic catalyst.[48] Although these catalytic systems were highly effective for assembling P–O bonds,[46–48] it should be noted that the processes were diastereoselective, with stereocontrol depending on the matched combination of the catalyst and optically enriched materials. Nevertheless, enantioselective control of P(V)-stereogenicity with nucleophilic catalysts for direct preparation of a diverse set of chiral phosphorus compounds remains a significant challenge[45–49] and is highly desirable.

N-Heterocyclic carbene (NHC) is one of the most extensively studied organocatalysts for the synthesis of a wide range of enantioenriched functional molecules, driven by the development of novel activation modes and various NHC-bound reactive intermediates.[50–56] For instance, the carbene-derived acyl azolium and α,β-unsaturated acyl azolium species[57–60] have found particular explorations that enabled numerous (non)enantioselective C–C/heteroatom bond-forming transformations (Figure 1C, left).[60–69] In stark contrast to these well-studied "carbon-centered" NHC intermediates, the development of heteroatom-based azolium intermediates has long been overlooked, but once realized, it would significantly expand their synthetic potential, particularly in the stereoselective carbon-heteroatom bond formations (Figure 1C, right). In 2016, Lupton and coworkers were the first to investigate an "S-centered" α,β-unsaturated sulfonyl azolium intermediate to access a wide array of δ-sultones.[70] Very recently, we developed a catalytic method to generate another "S-centered" azolium (sulfinyl azolium) that enables the highly enantioselective synthesis of chiral sulfinyl compounds.[71] Despite these successful preliminary studies on sulfur-based intermediates, catalytic NHC activation to form other heteroatom-derived azoliums, such as phosphonyl azoliums, remains yet to be achieved. The capture of such intermediates offers vast synthetic potential to forge diverse P–O/N bond constructions, which is particularly valuable in achieving the challenging catalyst-controlled synthesis of phosphorus(V)-stereogenic compounds.

Here, we disclose a new mode of covalent organocatalysis for enantioselective construction of chiral phosphorus scaffolds via new P–O bond formation (Figure 1D). Key steps in our approach involve the addition of an NHC catalyst to a readily stable activated phosphonate ester **1**, leading to the formation of pivotal phosphonyl azolium reactive intermediate **IA**. Unlike the previous covalent catalysis where the nitrogen atom of the catalyst adds to the phosphorus atom,[45–47] our approach involves the chiral "P"-based azolium intermediate that imparts high efficiency for the subsequent P–O bond formation. It is worth noting that although NHCs and chiral bicyclic imidazoles as nucleophilic organocatalysts share certain similarities in catalytic activities, their different properties and performance have been widely observed in numerous reactions.[50–56,72–74] Therefore, our first use of NHC (with the carbene carbon to form a [**P**]-[**C**] bond in the catalytic intermediate) shall provide new insights and development in activating and asymmetric transformation of phosphorus compounds. The catalytically obtained chiral P(V) products feature a nitrophenol leaving group that provides a synthetic platform for further stereospecific transformations, such as the displacement of various nucleophiles to enable P–O/N couplings with a diverse set of natural products, drugs, and biologically relevant molecules. Unlike the extensive studies of NHCs to activate carbon centers for enantioselective reactions,[57–60] our approach achieves efficient catalyst control over the phosphorus stereocenter through the use of a unique P-based azolium reactive intermediate for the first time. This study is expected to inspire further exploration of novel covalent bond activation strategies to address the challenges in the preparation of phosphorus stereogenic compounds with carbene organocatalysts.

RESULTS AND DISCUSSION

Reaction development

We began our investigation of the desymmetrization reaction with phosphonate **1a** and 1-naphthol (**2a**) as the primary model substrates (Table 1). An array of NHC catalysts in the presence of Cs_2CO_3 and toluene at –30°C was first explored to test our hypothesis. We were pleased to find that the reaction enabled by NHC **A** gave rise to the desired product **3a** in 42% yield and 55:45 er, demonstrating the feasibility of NHC-catalyst control over the P(V)-stereocenter (entry 1). Notably, catalyst **C**, which bears a pentafluoro substituent, provided the product with a higher yield (85%) and significantly improved enantioselectivity (76:24 er) (entry 3 vs. entries 1–2). However, other catalysts, including **D** and **E**, failed to give better results on the stereochemical outcome (entries 4–5). To tackle a more effective catalytic system, we turned to investigate the effects of various bases and solvents. Although the employment of K_2CO_3 or Na_2CO_3 led to significantly enhanced selectivity (entries 6–7), the yields of product **3a** were considerably low. Encouragingly, we found that the choice of solvent showed a notable impact on the enantiocontrol, wherein PhF was particularly effective in the desymmetrization reaction to give the desired product **3a** in 85% isolated yield and excellent enantioselectivity (97:3 er) (entry 11). It

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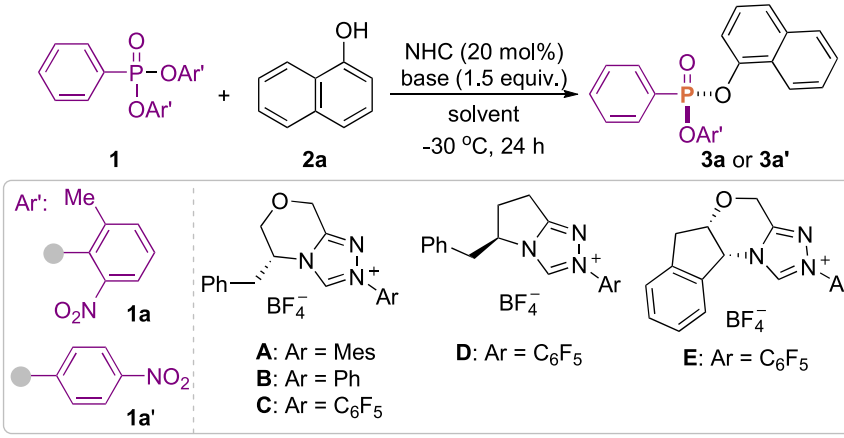
Table 1. Optimization of the carbene-catalyzed enantioselective desymmetrization of phosphonate ester 1



Entry[a]	NHC	Base	Solvent	Yield (%)[b]	E.r[c]
1	**A**	Cs_2CO_3	toluene	42	55:45
2	**B**	Cs_2CO_3	toluene	42	56:44
3	**C**	Cs_2CO_3	toluene	85	76:24
4	**D**	Cs_2CO_3	toluene	49	26:74
5	**E**	Cs_2CO_3	toluene	80	61:39
6	**C**	K_2CO_3	toluene	10	89:11
7	**C**	Na_2CO_3	toluene	11	94:6
8	**C**	Cs_2CO_3	$CHCl_3$	10	96:4
9	**C**	Cs_2CO_3	THF	80	51:49
10	**C**	Cs_2CO_3	PhCl	42	94:6
11	**C**	Cs_2CO_3	PhF	86 (85)	97:3
12	**C**	Cs_2CO_3	PhF	25[d]	57:43

[a]The reactions were performed with phosphonate **1a** (0.05 mmol, 1.0 equiv), 1-naphthol (**2a**, 0.055 mmol, 1.1 equiv), NHC **A–E** (20 mol %), and base (0.075 mmol, 1.5 equiv) in solvent (2.0 mL) at –30°C for 24 h.
[b]Yields of **3a** were determined via ^{1}H NMR analysis with 1,3,5-trimethoxy-benzene as an internal standard. Isolated yield in the parenthesis.
[c]Enantiomeric ratio (E.r.) values were determined by chiral HPLC analysis.
[d]Product **3a'** was obtained from reaction with **1a'** instead of **1a**. See supplemental information for details.

is also noteworthy that the steric hindrance of the leaving group with 2,6-disubstituents in phosphonate **1a** played a crucial role in the stereoselective control. For example, when the leaving group was replaced with a simple 4-nitrophenyl group (**1a′**), the enantioselectivity of **3a′** sharply decreased to 57:43 er (entry 12).

Reaction scope

With the optimal reaction conditions established, we proceeded to examine the scope of the carbene-catalyzed preparation of P(V)-chiral phosphonates **3** (Figure 2). A variety of substituents on the aromatic unit of phenols **2** were initially investigated in the catalytic desymmetrization reaction. Under the optimal conditions, substrates with methyl, chloro, and bromo groups were efficiently transformed into the corresponding products **3b–3d** in 68%–90% yields and high enantioselectivity. 1-Pyrenol with extended conjugated aromaticity reacted smoothly to give rise to the product **3e** with 81% yield and 96:4 er. Phenols bearing 2,4-disubstituents were also feasible to deliver the corresponding products **3f–3h** with good yields and selectivity. It is noteworthy to mention that our catalytic reaction offers a versatile, modular platform for the phosphonylation of various biologically relevant phenol-containing molecules. In these cases, a diverse set of phosphonates derived from methyl vanillate (**3i**), eugenol (**3j**), ethyl ferulate (**3k**), and fenhexamid (**3l**) were readily obtained in 50%–87% yields and high stereoselectivity, which significantly expands the scope and applicability of our developed phosphonate nucleophilic desymmetrization approach. Moreover, the absolute configuration of the catalytically obtained phosphonate products **3** was assigned as (*S*) by analogy to product **3d**, as determined via X-ray crystallographic analysis. It is worth mentioning that various thiols, amines, and aliphatic alcohols failed to give the corresponding P(V)-chiral products with satisfactory results (see supplemental information, Tables S12–S14; Scheme S13 for details).

Next, we turned to identify the generality of phosphonates **1** by using **2a** as the model phenol substrate (Figure 2). The optimal conditions tolerated a wide range of substitutions on the aromatic moiety of phosphonate **1**. For instance, Me, *n*Bu, *i*Pr, and *t*Bu at the para position of the phenyl group of **1** gave the corresponding chiral phosphonates **3m–3p** with excellent enantioselectivity.

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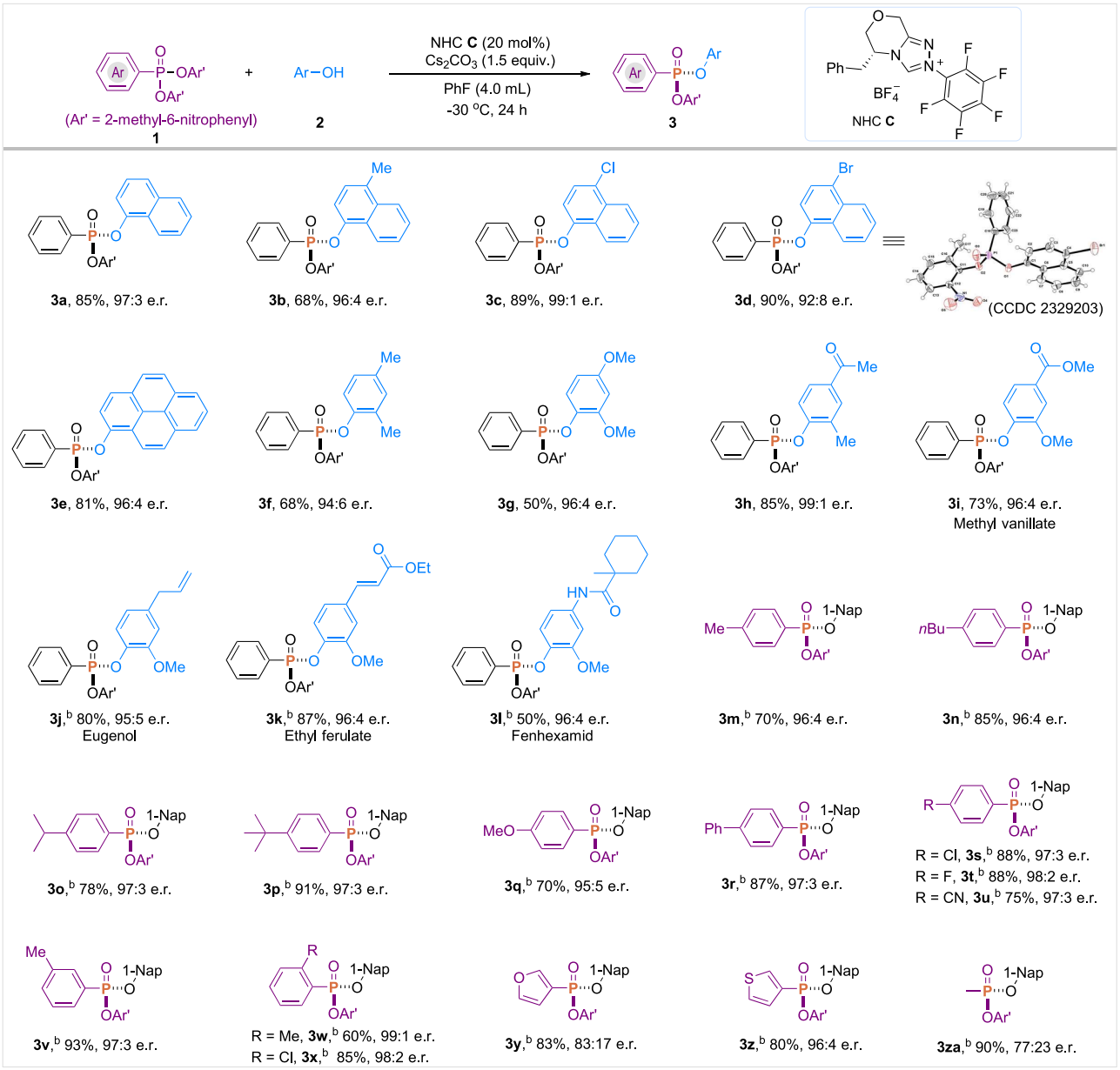

Figure 2. Substrate scope of the enantioselective synthesis of chiral phosphorus products 3

(A) The reactions were performed with **1** (0.1 mmol, 1.0 equiv), NHC **C** (20 mol %), phenol **2** (0.11 mmol, 1.1 equiv), Cs_2CO_3 (0.15 mmol, 1.5 equiv), and PhF (4.0 mL) at –30°C for 24 h.

(B) The reactions were performed with Rb_2CO_3 (0.2 mmol, 2.0 equiv) at –20°C. See supplemental information for details.

Additionally, substrates containing OMe, Ph, and Cl units delivered the corresponding products **3q–3s** in 70%–88% yields and high er values. Reactions with electron-deficient substrates under the optimal conditions afforded the corresponding products **3t–3u** in 88%, 98:2 er, and 75%, 97:3 er, respectively. Phosphonate analogs **1** with meta- or ortho-substitution also smoothly converted into chiral products **3v–3x** with excellent selectivity. The heteroaromatic moiety-derived phosphonates were also compatible with the reaction to give the desired products **3y–3z** in high selectivity. Moreover, the method was compatible with aliphatic phosphonates, as demonstrated by methyl phosphonate that led to the formation of P(V)-chiral product **3za** in 90% yield, though with a modest enantioselectivity of 77:23.

Featuring a nitrophenol as the leaving group, the obtained product **3a** serves as a versatile platform for second derivatization through enantiospecific nucleophilic displacement, enabling the modular synthesis of various P(V)-stereogenic compounds such as chiral phosphonates, phosphonamidates, etc. by P-X (X = O, N, etc.) bond formations (Figure 3). For instance, we were delighted to find that the nucleophilic substitution of chiral

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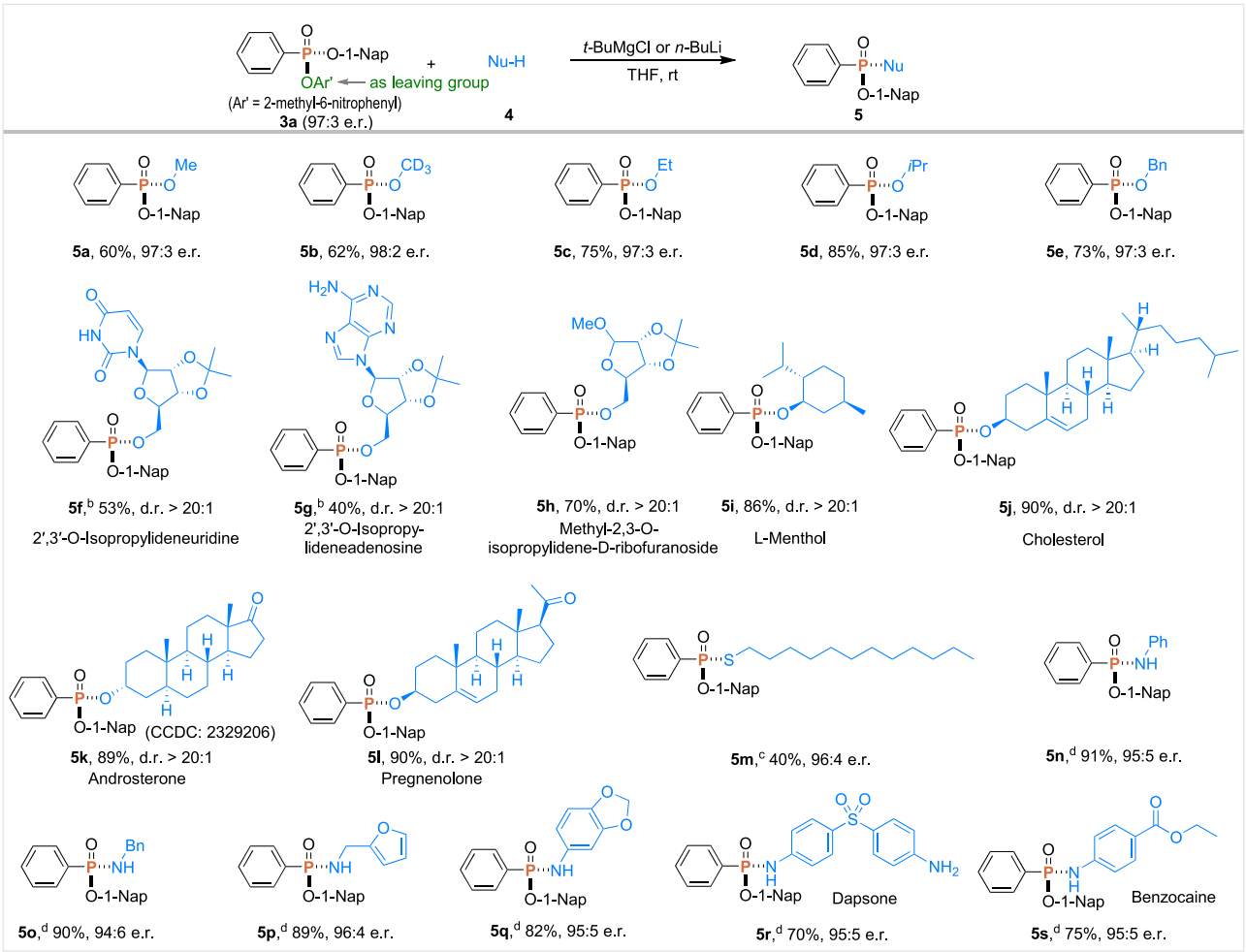

Figure 3. Versatile access to diverse P(V)-stereogenic compounds via second-stage P–O/S/N bond formations

(A) Reaction conditions: alcohol nucleophiles **4** (0.15 mmol, 1.5 equiv), *t*BuMgCl (0.15 mmol, 1.5 equiv), (*S*)-**3a** (0.10 mmol, 1.0 equiv), THF (2.0 mL), d.r., diastereomeric ratio.

(B) *t*BuMgCl (3.0 equiv) was used.

(C) 1-Dodecanethiol nucleophile (0.3 mmol, 3.0 equiv), 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (0.3 mmol, 3.0 equiv), and (*S*)-**3a** (0.10 mmol, 1.0 equiv) in THF at rt for 2 h.

(D) Amine **4** (0.30 mmol, 3.0 equiv), *n*-BuLi (0.30 mmol, 3.0 equiv), (*S*)-**3a** (0.10 mmol, 1.0 equiv), THF (1.0 mL), –78°C to rt. See supplemental information for details.

phosphonate **3a** was effective under the conditions with alcohol and *t*BuMgCl in THF. A range of simple alcohols, including MeOH, CD_3OH, EtOH, *i*PrOH, and BnOH, reacted successfully to deliver the corresponding phosphonates **5a**–**5e** with 60%–85% yields and excellent enantiospecificity. Encouraged by the high efficiency of the second P–O bond formations, we applied the synthetic protocol to the late-stage phosphonylated functionalization of complex alcohols. Nucleosides were readily installed with an optically enriched P(V) moiety, affording products **5f**–**5g** with modest yields and >20:1 d.r. Acetal-protected D-ribofuranoside and L-menthol were also functionalized to give phosphonates **5h**–**5i** with high yields and stereoselectivity. Additionally, the optimal conditions were compatible with P–O bond formation in various terpenes, including cholesterol (**5j**), androsterone (**5k**) (Cambridge Crystallographic Data Centre (CCDC): 2329206), and pregnenolone (**5l**). We further achieved phosphonylation with thiol nucleophiles, as demonstrated with 1-dodecanethiol (**5m**) using a slightly modified condition with DBU as the base. Notably, P–N forming derivatization of the linchpin phosphonate **3a** was also achieved, yielding a variety of phosphonamidates **5n**–**5p** in high enantiopurity. In these transformations, *n*-BuLi was employed to promote the nucleophilic displacement with high efficiency. Of great significance, the two-stage synthetic strategy readily allows for the pro-drug modification of various commercial drugs, such as dapsone (**5r**) and benzocaine (**5s**).

Synthetic applications

The straightforward preparation of P(V)-stereogenic phosphinate esters **6** was achieved upon treatment of phosphonate

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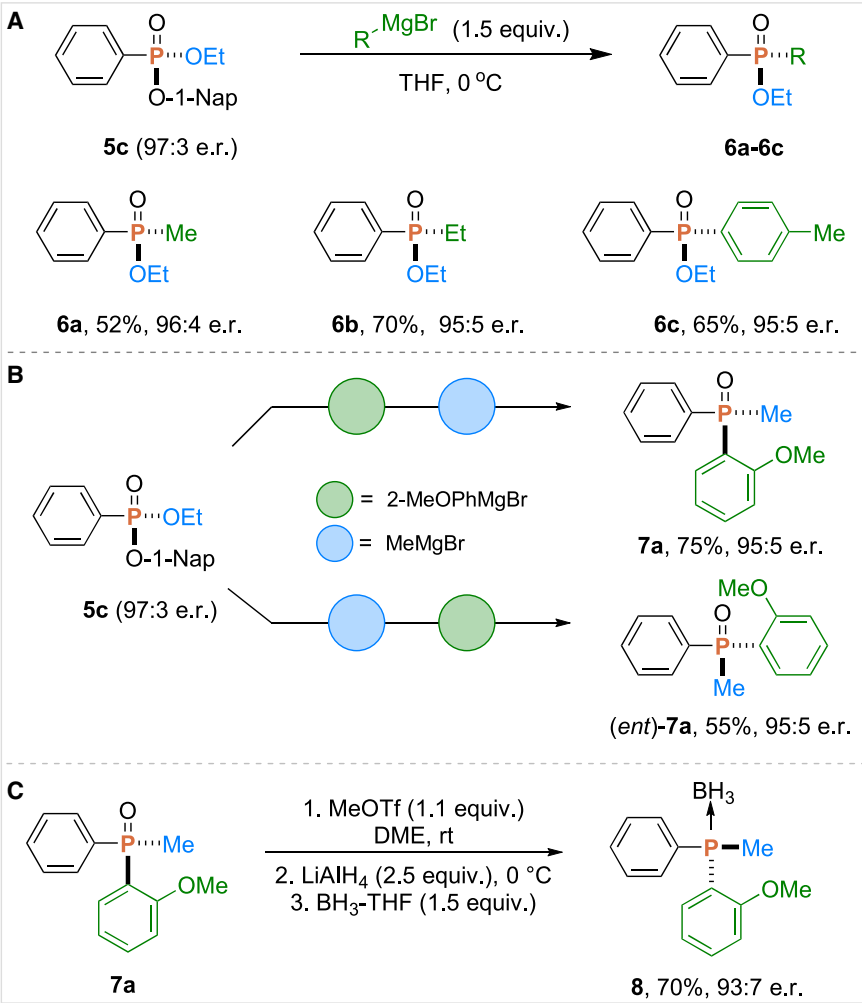

Figure 4. Stereospecific nucleophilic substitutions of P-chiral compounds

(A) Preparation of enantioenriched phosphinate esters.

(B) Preparation of enantioenriched phosphine oxides.

(C) Phosphine oxide reduction.

product **5c** with various Grignard reagents in THF (Figure 4). Both aliphatic and aryl magnesium bromides were highly selective to undergo the nucleophilic addition to produce the corresponding P-stereogenic products **6a–6c** (Figure 4A). It is interesting to note that tertiary phosphine oxides **7** with both configurations could be accessed by altering the sequence of Grignard reagent additions. For instance, the (*R*)-**7a** was generated through the sequential addition of 2-methoxyphenyl and methyl magnesium bromide, while its opposite enantiomer (*ent*)-**7a** was produced by reversing the order of additions (Figure 4B). We have also shown that the resulting phosphine oxide **7a** could be readily reduced to the corresponding phosphine by treatment with MeOTf-$LiAlH_4$ and BH_3.THF, affording the borane complex **8** in 70% overall yield and high optical purity (Figure 4C).

Mechanistic studies

To elucidate the catalytic reaction process, we have studied the non-linear effect of carbene catalyst on the corresponding product **3a**. As illustrated in Scheme S9, a linear correlation between the ee of the carbene catalyst **C** and the product **3a** was observed, suggesting that the carbene species activates only one reactant in the enantioselectivity-determining step. Additionally, we performed experimental kinetic studies with the model reaction under optimal conditions (Figures S1–S4). The reaction exhibited first-order dependence on the concentrations of NHC **C** and **1a** but zero-order kinetics with respect to the concentration of alcohol **2a** (Figure S3). These results indicate that the NHC addition to the phosphonate substrate **1a** is likely involved in the rate-determining step.

To gain a further understanding of the reaction mechanism and determine the origin of enantioselectivity, we have performed density functional theory (DFT) calculations (Figure 5). Initially, the catalyst NHC **C** undergoes a nucleophilic attack on the phosphonate **1a**, forming pentacoordinate P(V) intermediates (*R*)-**M1** and (*S*)-**M1** via transition states (*R*)-**TS1** ($\Delta G‡$ = 10.0 kcal/mol) and (*S*)-**TS1** ($\Delta G‡$ = 8.5 kcal/mol), respectively. Subsequently, assisted by naphthol **2a**, these intermediates cross energy barriers of 11.9 kcal/mol and 11.3 kcal/mol via transition states (*R*)-**TS2** and (*S*)-**TS2**, eliminating the nitrophenolate anion to form the pivotal phosphonyl azolium (*R*)-M2 and (*S*)-**M2** (see Figures S5–S11 for additional evidence from $^{1}H/^{31}P$ NMR and HRMS detection). Following this, the nitrophenolate anion promotes the nucleophilic attack of naphthol **2a** on the phosphorus (V) intermediate, passing through phosphonylation transition states (*R*)-**TS3** ($\Delta G‡$ = 0.8 kcal/mol) and (*S*)-**TS3** ($\Delta G‡$ = –0.1 kcal/mol) to form pentacoordinate intermediates (*R*)-**M3** and (*S*)-**M3** bearing naphthoxy groups. The relatively high energy barriers observed in the naphthol-assisted reaction process prompted us to further investigate other possible reaction pathways. Previous studies showed that both the base and its conjugate acid facilitate proton transfer[75–77]; therefore, we considered the $CsHCO_3$ and its conjugate acid $CsH_2CO_3^+$ assisted proton transfer pathways for the 2 proton transfer processes. The computed results show that the 2 steps including 2,6-dinitrophenolate anion dissociation coupled with a proton transfer and nucleophilic attack of naphthol **2a** coupled with a proton transfer, can occur smoothly via transition states (*R*)/(*S*)-**TS2^{Cs}** and (*R*)/(*S*)-**TS3^{Cs}** with the energy barriers of 0.2/0.6 and 2.5/1.9 kcal/mol, respectively. Obviously, the 2 $CsH_2CO_3^+$-assisted proton transfer pathways have much lower

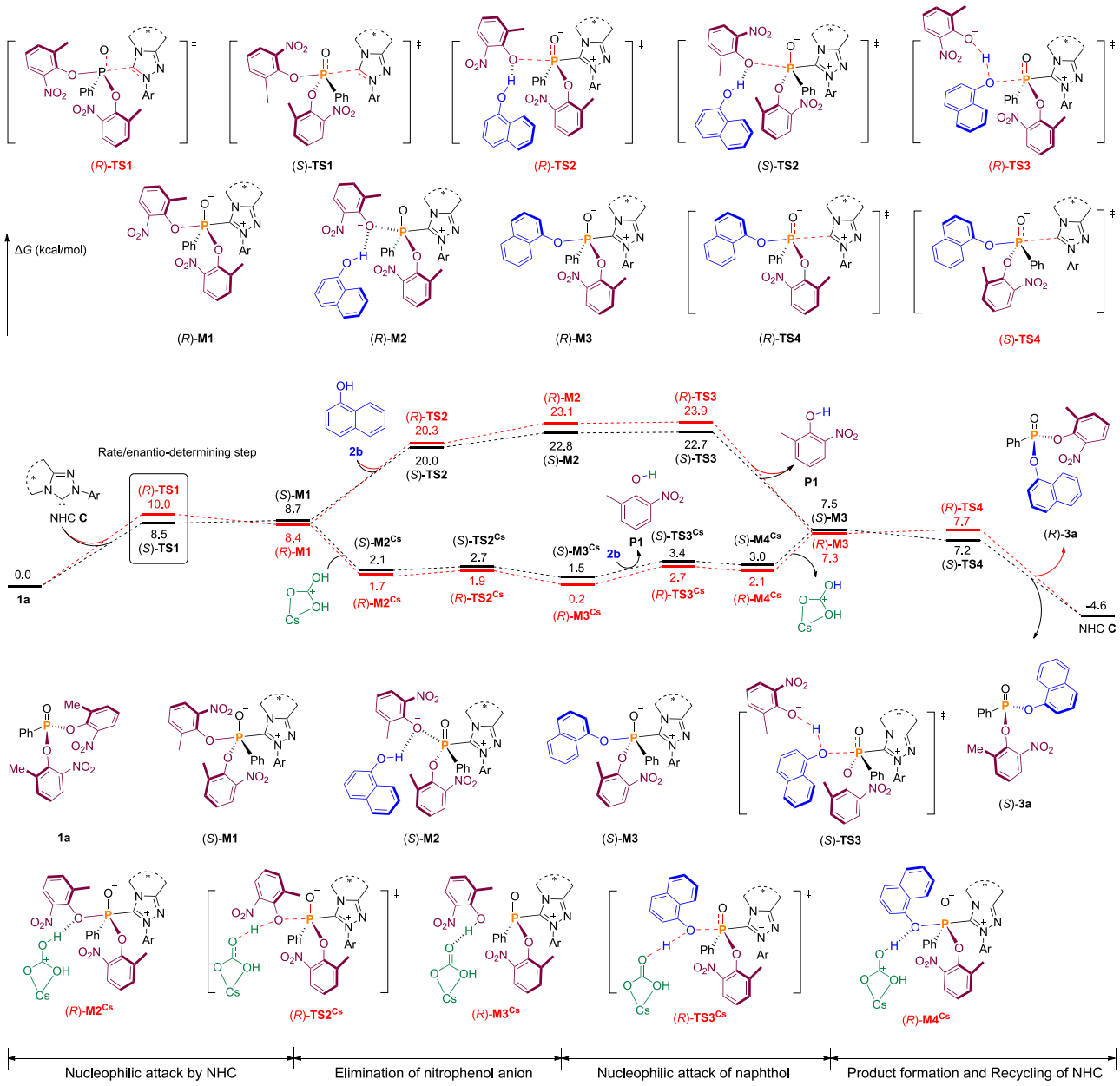

Figure 5. DFT-calculated results

Gibbs energy profiles for the enantioselective nucleophilic desymmetrization reaction catalyzed by NHC **C** of phosphonate substrate **1a** and 1-naphthol (**2a**) computed at the M06-2X/6-311++G(d,p.) (SDD for Cs)/IEFPCM(fluorobenzene)//M06-2X/6-31G(d,p) (SDD for Cs)/Integral equation formalism polarizable continuum model (IEFPCM)(fluorobenzene) level of theory. The Ar group represents pentafluorophenyl.

Gibbs free energy barriers, indicating the base plays an important role in this reaction. Although the $CsH_2CO_3^+$ should exist in only a small amount in the catalytic reaction, its trace presence could readily facilitate efficient proton transfer throughout these steps. More results on other possible pathways can be found in the supplemental information (Figures S15–S18). Finally, the NHC is easily eliminated, yielding enantioenriched product (*R*)/(*S*)-**3a**. The Gibbs energy barrier difference between the transition states (*R*)-**TS1** and (*S*)-**TS1** ($\Delta\Delta G^{\ddagger}$ = 1.5 kcal/mol) indicates that the product (*S*)-**3a** forms more readily than (*R*)-**3a**, with a predicted enantiomeric excess of 98%, which is consistent with the experimentally observed enantiomeric excess of 94%. The computational results show that the nucleophilic attack of the catalyst NHC **C** to substrate **1a** possesses the highest energy barriers, thus determining the overall reaction rate. By contrast, the nucleophilic attack of naphthol and the subsequent elimination of NHC **C** occur more facilely. This aligns with the kinetic analysis experimental observations showing that the reaction

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Table 2. *In vitro* antibacterial activities of the target compounds against *Xoo* and *Xoc* at 100 μg/mL

Compounds	*Xoo* inhibition rate (%)[a]	*Xoc* inhibition rate (%)[a]
(*S*)-**3b**	75.47 ± 2.60	65.03 ± 2.00
(±)-**3b**	74.81 ± 2.24	63.70 ± 1.58
(*R*)-**3g**	49.23 ± 1.21	71.21 ± 1.55
(±)-**3g**	34.49 ± 2.14	64.23 ± 1.27
(*S*)-**3q**	59.72 ± 2.20	87.36 ± 1.94[c]
(±)-**3q**	52.81 ± 1.64	77.77 ± 1.25
(*S*)-**3x**	92.60 ± 2.32[c]	55.58 ± 1.99
(±)-**3x**	86.51 ± 1.69	36.73 ± 1.35
(S)-**5c**	86.56 ± 1.94	56.46 ± 0.87
(±)-**5c**	73.23 ± 1.16	55.63 ± 1.26
BT[b]	57.74 ± 1.28	69.11 ± 0.51
TC[b]	42.23 ± 1.81	60.82 ± 2.75

[a]All data were average data of 3 replicates.
[b]Commercial bactericide was used as the positive control. TC, thiodiazole copper; BT, bismerthiazol.
[c]The notable highest inhibition rate of these compounds.

exhibits first-order dependence on the concentrations of NHC **C** and **1a**, while displaying zero-order kinetics with respect to the concentration of the substrate naphthol **2a** (Figures S1–S3). Additionally, to explore the role of the NHC catalyst in controlling enantioselectivity, we used non-covalent interaction (NCI) analysis and atoms in molecules (AIMs) analysis to examine the transition states (*R*)-**TS1** and (*S*)-**TS1** of the initial nucleophilic attack, finding stronger and more C–H···O and LP-π interactions, as well as a notable C–H···F hydrogen bond formed between the F atom in the C_6F_5 group of the catalyst and the methyl group of reactant **1a**, in the (*S*)-**TS1** leading to the major phosphonate enantiomer (*S*)-**3a** (more details are found in Figure S14).

Bioassay studies

Prompted by the intriguing biological activities of organo-phosphorus compounds,[78–80] we carried out preliminary studies on the antibacterial activity of the catalytically generated chiral phosphonate products to seek new antimicrobial agrochemicals for crop protection. We thereby performed *in vitro* bioassays to evaluate the inhibitory activity against 2 plant pathogens, *Xanthomonas oryzae* pv. *oryzae* (*Xoo*) and *Xanthomonas oryzae* pv. *oryzicola* (*Xoc*), which are responsible for bacterial leaf blight and streak diseases in rice plants, respectively.[81,82] We were pleased to find that most of these compounds exhibited notable inhibition effects against these 2 bacteria (Table 2). Particularly, compound (*S*)-**3x** exhibited superior efficiency (92.60%) against *Xoo* at a concentration of 100 μg/mL compared with the positive control with commercial bactericidal agents, bismerthiazol (BT) and thiodiazole copper (TC). Similarly, phosphonate (*S*)-**3q** showed improved efficacy (87.36%) against *Xoc* compared with BT (69.11%) and TC (60.82%). It is worth mentioning that the racemates of the corresponding phosphorus products generally exhibited slightly reduced inhibition activity, as observed with compounds **3x** and **3q**. These findings highlight the potential of our phosphonate products as novel scaffolds for developing potent bactericidal agrochemicals.

Conclusions

In summary, we have developed an organocatalytic desymmetrization approach for the rapid preparation of chiral phosphorus scaffolds with readily stable activated phosphonate esters by exploring a novel covalent activation mode of carbene organocatalysis. Conferred by the initial stereoselective formation of "non-carbon" centered phosphonyl azolium species, asymmetric P-O bond formation through nucleophilic addition of phenols affords the final optically enriched phosphonate products **3** with high enantioselectivity. The presence of another ester leaving group readily allows a sequential stereospecific displacement manipulation for divergent synthesis of a wide range of P(V)-chiral phosphonates, phosphonamidates, etc. through P–N/O or P–C bond formations. Moreover, the utilization of the developed method was also demonstrated by phosphonyl functionalization of a broad array of natural products, drugs, and biologically interesting molecules. Unlike classical NHC-acyl azoliums that focus on "C" stereocenters, this study explores a unique phosphorus-based azolium reactive intermediate and demonstrates efficient catalyst control over phosphorus stereogenicity for the first time. Ongoing research in our laboratory aims to further explore novel covalent bond activation strategies to address the challenges in preparing phosphorus stereogenic compounds with nucleophilic catalysts.

METHODS

Asymmetric catalytic synthesis of phosphorus products 3a–3za

Under N_2 atmosphere, to an oven-dried 10.0 mL screw-cap vial charged with a magnetic stirring bar was added **1** (0.1 mmol, 1.0 equiv), NHC pre-catalyst **C** (0.02 mmol, 20 mol %), and Cs_2CO_3 (0.15 mmol, 1.5 equiv) in PhF (4.0 mL). After stirring at 0°C for 1 h, the solution was cooled to –30°C, and the nucleophilic reagent **2** (0.11 mmol, 1.1 equiv) was added. When the substrate was consumed completely, hydrogen chloride in 1,4-dioxane solution (4.0 M, 0.2 mL) was slowly added dropwise to quench the reaction. The resulting reaction mixture was then directly purified through column chromatography over silica gel to afford the desired chiral products **3a–3za**. Note: for reactions to prepare chiral products **3j–3za**, Rb_2CO_3 (0.2 mmol, 2.0 equiv) as base at –20°C under the optimal conditions was used.

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Yonggui Robin Chi (robinchi@ntu.edu.sg).

Materials availability

All materials generated in this study are available from the lead contact without restriction.

Data and code availability

All of the data supporting the findings of this study are presented within the article and supplemental information. The X-ray crystallographic coordinates for structures of compounds (*S*)-**3d** and (*S*)-**5k** reported in this article have been deposited at the CCDC under deposition numbers CCDC: 2329203 and 2329206. These data can be obtained free of charge from the CCDC via http://www.ccdc.cam.ac.uk/data_request/cif. See Tables S1–S5 for

supplemental condition optimization; Schemes S1–S8 for procedure to prepare substrates and chiral phosphorus products; Tables S6, Figures S1–S11, and Schemes S9–S12 for preliminary mechanistic studies; Tables S7 and S8 and Figures S12–S18 for computational studies; Tables S9–S11 for antibacterial activity studies *in vitro*; and Tables S12–S14 and Scheme S13 for investigation of other nucleophiles. See Data S1 for copies of NMR spectra and Data S2 for high-performance liquid chromatography (HPLC) traces of the obtained chiral phosphorus products. All other data are available from the authors upon reasonable request.

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AUTHOR CONTRIBUTIONS

Y.W. performed main methodology development, scope evaluation, and synthetic application. K.C. and D.W. carried out detailed DFT calculations and drafted the discussions on the mechanism. F.C., S.Z., P.F., and Q.Z. contributed to earlier studies and scope examination. Y.R.C. and X.W. conceptualized and directed the project and drafted the manuscript with assistance from all co-authors.

DECLARATION OF INTERESTS

The authors declare no competing interests.

SUPPLEMENTAL INFORMATION

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