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Research Article

Asymmetric Organocatalytic Methylation of Prochiral Phosphinic Acids: Construction of P(V)-Stereogenic Centers

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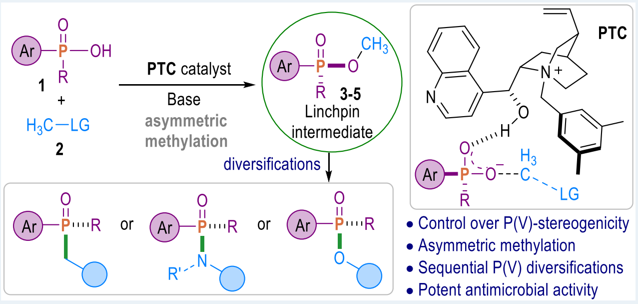

ABSTRACT: Asymmetric alkylation is a fundamental strategy for the stereoselective construction of chiral molecules, traditionally focusing on control over the carbon stereocenters. Recent advances have extended this approach to heteroatom-centered systems, enabling selective C−heteroatom bond formation to generate heteroatom stereogenicity. While sulfur-based alkylations have attracted considerable attention in recent studies, efficient alkylation strategies for the synthesis of P-stereogenic compounds remain limited despite their pivotal significance in catalysis and drug development. Here, we present an organocatalytic enantioselective methylation of prochiral phosphinic acids to access P(V)-stereogenic phosphorus compounds. Employing a cinchonidine-derived phase-transfer catalyst, the formation of a tight ion pair with a prochiral phosphinic acid anion enables highly stereoselective formation of an O−C bond using simple methylating agents under mild conditions. The resulting chiral phosphinates serve as linchpin intermediates that can undergo stereospecific nucleophilic substitution to afford a broad range of P-stereogenic molecules, including tertiary phosphine oxides, phosphinamides, and phosphinates. These chiral phosphorus compounds display promising biological activities, underscoring their potential in the development of agrochemical agents.

KEYWORDS: *asymmetric alkylation, P-stereogenic compounds, organocatalysis, phase-transfer catalyst, heteroatom stereogenicity*

■ INTRODUCTION

The stereocontrolled alkylation is a pivotal method in organic synthesis for the construction of chiral molecules.[1−3] Classical enantioselective alkylations typically involve carbonyl compounds, such as ketones, esters, amides, and malonates, wherein α-hydrogens are deprotonated by a base to form enolates or derived nucleophilic intermediates.[4−6] These intermediates subsequently react with alkyl halides or analogous electrophiles under the stereocontrol of a chiral catalyst or auxiliary, allowing precise face-selective C−C bond formation and furnishing products with high enantioselectivity (Figure 1A, left). Representative strategies include chiral-auxiliary-based methods[7−11] and asymmetric alkylation mediated by metals, small-molecule catalysts or enzymes.[12−18] As a fundamental synthetic strategy, asymmetric alkylation enables the direct installation of chiral carbon centers into molecular frameworks, thereby providing versatile and efficient routes for the synthesis of pharmaceuticals, natural products, and functional materials.[1−3]

Although asymmetric alkylation remains a central tool for installing carbon stereocenters in modern asymmetric synthesis, recent years have witnessed rapid progress beyond carbon-centered systems toward the development of heteroatom-involved stereocontrolled alkylations. In these transformations, catalysts control the formation of C−heteroatom bonds, enabling the efficient synthesis of a variety of chiral compounds featuring heteroatom stereogenicity (Figure 1A, right). A notable advance is the development of asymmetric alkylation strategies for sulfur-stereogenic centers. For instance, Ellman and co-workers very recently reported a Rh-catalyzed synthesis of S(IV)-chiral sulfilimines, in which diazo esters served as precursors to chiral alkyl−metal carbene intermediate, which subsequently engages in stereocontrolled C−S bond formation with nucleophiles (Figure 1B, left).[19,20] Alternatively, both Ellman and Zhang group independently developed ion-pairing catalyst-mediated asymmetric alkylations of sulfenamides with alkyl halide electrophiles to access sulfur-stereogenic sulfilimines (Figure 1B, right).[21,22] On the other hand, phosphorus (P) represents another highly significant heteroatom. Organophosphorus compounds are widely distributed in functional molecules, and P-stereogenic scaffolds, in particular, play crucial roles in drugs, ligands, and chiral catalysts (Figure 1C).[23−32] Consequently, the efficient construction of P-chiral compounds has long attracted considerable attention.[33−46] Asymmetric

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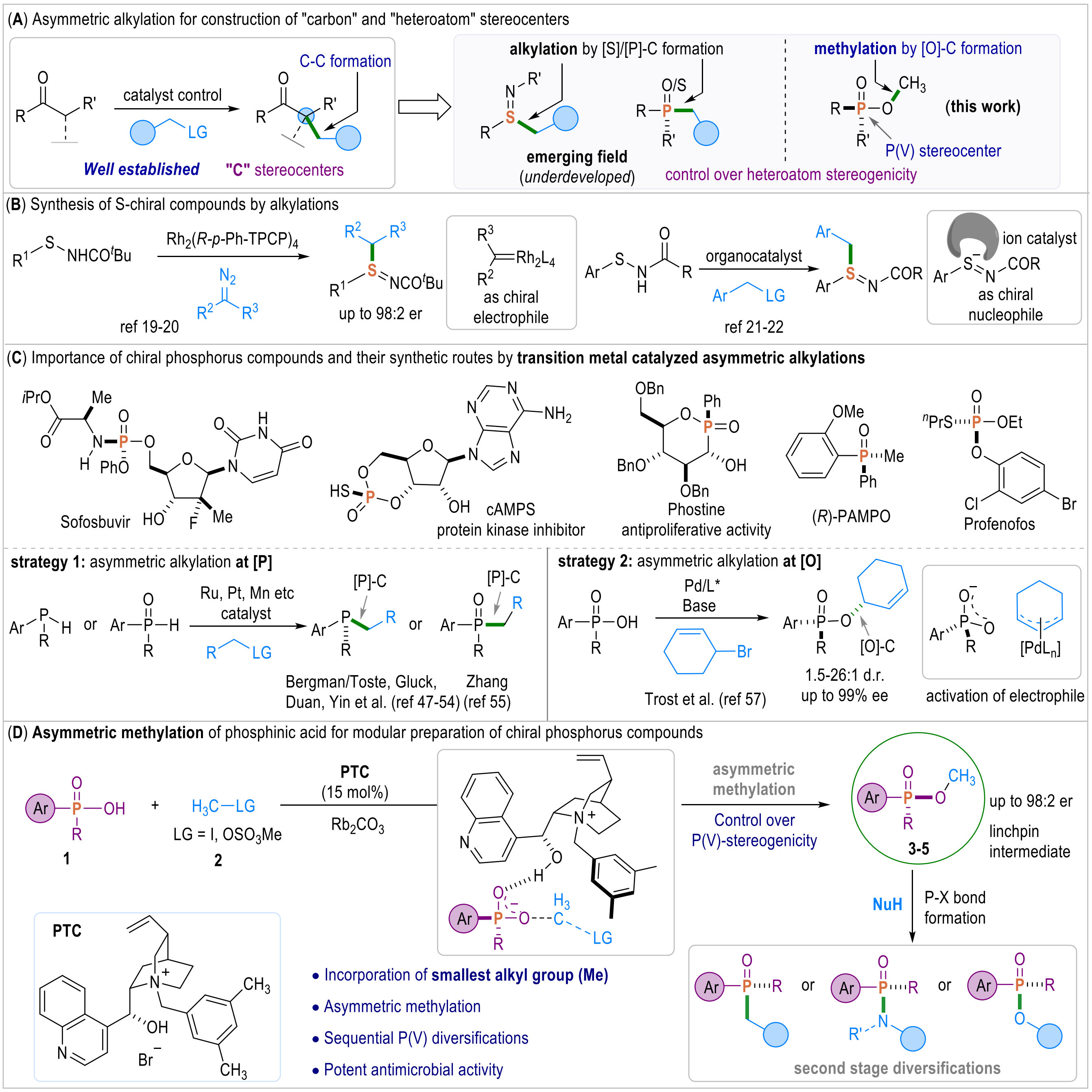
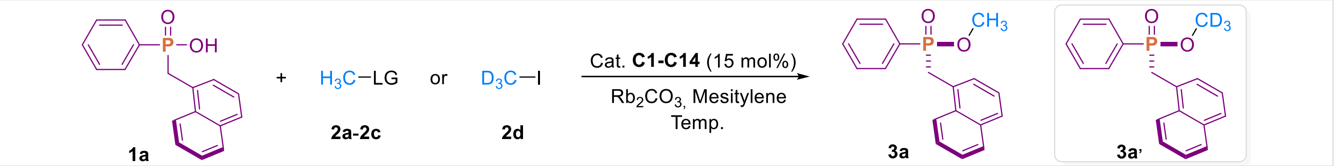


Figure 1. (A) State-of-the-art stereoselective alkylations in the construction of carbon and heteroatom stereogenic compounds. (B) Alkylations for the preparation of sulfur-chiral compounds. (C) Transition metal-catalyzed synthesis of P-chiral molecules by asymmetric alkylations. (D) Our proposed two-stage modular preparation of chiral phosphorus molecules by organocatalytic asymmetric methylation of phosphinic acids.

alkylation has emerged as a powerful strategy in this context, particularly with substrates containing a P−H bond such as secondary phosphines. In these reactions, the P−H bond is activated (acidified) by a suitable metal catalyst as the mediator to generate a phosphorus-centered chiral nucleophile and thus engage in the subsequent stereoselective C−P bond formation. For example, Bergman/Toste, Glueck, Duan, Yin, and others independently developed catalytic enantioselective alkylations of secondary phosphines using chiral metal complexes, delivering P-stereogenic phosphines in high yields and enantioselectivity (Figure 1C, strategy 1).[47−54] Related C−P alkylation methods with secondary phosphine oxide has also been reported by the Zhang group.[55] In addition, phosphinic acids have emerged as stable and readily available prochiral precursors for asymmetric alkylation. Johnston and co-workers reported a Brønsted acid-catalyzed phosphoramidic acid intramolecular addition to alkenes for diastereo- and enantioselective synthesis of chiral phosphoramidates.[56] Trost and co-workers first reported a metal-catalyzed asymmetric alkylation of phosphinic acids via π-allyl−palladium intermediates, wherein chiral metal complexes exerted high stereocontrol over the O−C bond-forming step, enabling efficient preparation of chiral phosphorus compounds with high enantioselectivity but modest diastereoselectivity (Figure 1C, strategy 2).[57] Very recently, the group of Li achieved a similar desymmetrization using copper-catalyzed asymmetric arylation reaction of phosphonic acids.[58]



Entry	Cat.	Temp. (°C)	2	Yield (%)	E.r.
1	**C1**	r.t.	**2a**	45	55:45
2	**C2**	r.t.	**2a**	47	65:35
3	**C3**	r.t.	**2a**	44	48:52
4	**C4**	r.t.	**2a**	42	40:60
5	**C5**	r.t.	**2a**	38	70:30
6	**C6**	r.t.	**2a**	40	72:38
7	**C7**	r.t.	**2a**	40	65:35
8	**C8**	r.t.	**2a**	27	55:45
9	**C9**	r.t.	**2a**	46	67:33
10	**C10**	r.t.	**2a**	36	60:40
11	**C11**	r.t.	**2a**	51	75:25
12	**C12**	r.t.	**2a**	56	78:22
13	**C13**	r.t.	**2a**	59	85:15
14	**C14**	r.t.	**2a**	55	82:18
15	**C13**	r.t.	**2b**	63	92:8
16[b]	**C13**	0	**2b**	76	95:5
17[c]	**C13**	0	**2c**	86	91:9
18[d]	**C13**	-10	**2c**	81	95:5
19[b]	**C13**	0	**2d**	71	96:4

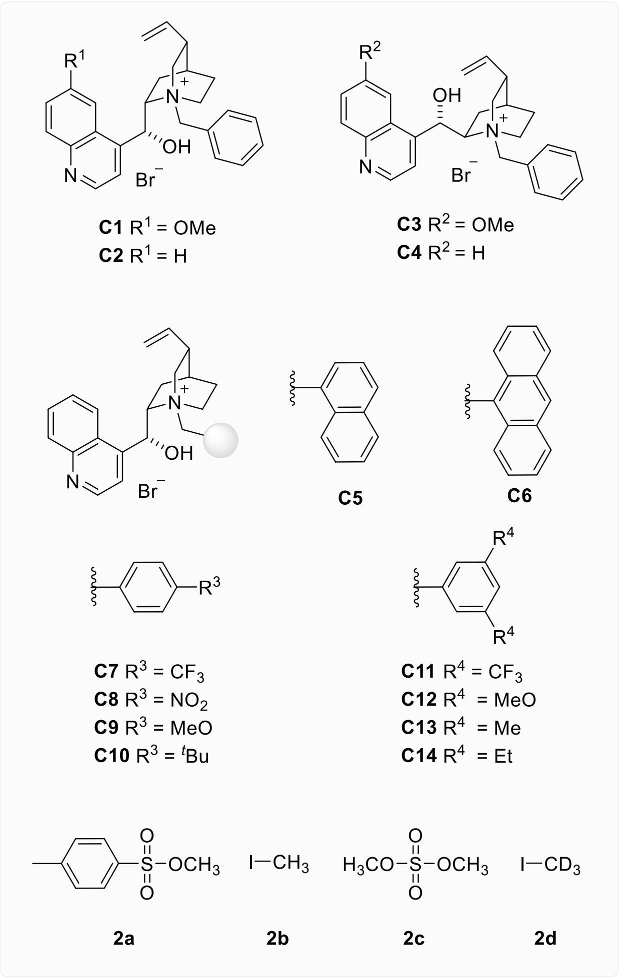


Figure 2. [a]Reactions were performed with **1a** (0.1 mmol, 1.0 equiv), catalyst (15 mol %), Rb_2CO_3 (2.0 equiv), and mesitylene (1.0 mL) at r.t. for 10 d. [b]The reaction was conducted at 0 °C for 10 d then at 30 °C for 3 d. [c]The reaction was conducted at 0 °C for 24 h. [d]The reaction was conducted at −10 °C for 24 h. Isolated yields were reported. E.r. values were determined by chiral HPLC analysis. See Supporting Information for detail.

Notably, despite numerous advances in enantioselective alkylation reactions, the direct and highly stereocontrolled incorporation of a methyl group (as the smallest alkyl moiety) remains elusive and a significantly challenging task in synthetic chemistry.[59−61] This transformation is particularly valuable in drug discovery, as the introduction of a "magic methyl" can profoundly alter the bioactivity of drug candidates.[62−64] Motivated by these precedents and challenges, we envisioned that organocatalytic strategies, such as ion-pair catalysis,[65−70] could be harnessed to generate a tight ion pair between a chiral catalyst and a phosphinic acid anion behaving as a chiral nucleophile, thereby enabling stereoselective O−C bond-forming reaction with simple methylating agents. Such an approach would allow the development of a mild, efficient, and highly stereoselective asymmetric alkylation method, expanding the synthetic toolbox for P(V)-stereogenic functional molecules. Herein, we report a cinchonidine-derived phase-transfer catalyst that forms a chiral cavity around a prochiral phosphinic acid anion, governing high stereocontrol over the formation of the O−C bond to achieve asymmetric methylation (Figure 1D). Under mild conditions, our protocol delivers highly efficient methylation of phosphinic acids to provide an array of chiral phosphorus compounds with high enantioselectivity. The resulting chiral phosphinates can undergo further stereospecific nucleophilic substitutions into a diverse range of P-stereogenic functional molecules, including tertiary phosphine oxides, phosphinamides, and phosphinates. Moreover, these chiral phosphorus compounds exhibit promising potential biological activities, offering new opportunities for the development of new agrochemical agents.

METHODS SECTION

General Procedure for Catalytic Preparation of Chiral Phosphinate Products 3. To a 4.0 mL oven-dried vial equipped with a magnetic stir bar, substrate **1** (0.1 mmol, 1.0 equiv), **2c** (0.2 mmol, 2.0 equiv), Rb_2CO_3 (0.2 mmol, 2.0 equiv), Cat. **C13** (15 mol %), and mesitylene (1.0 mL) were added. The mixture was cooled to −10 °C and kept stirring for

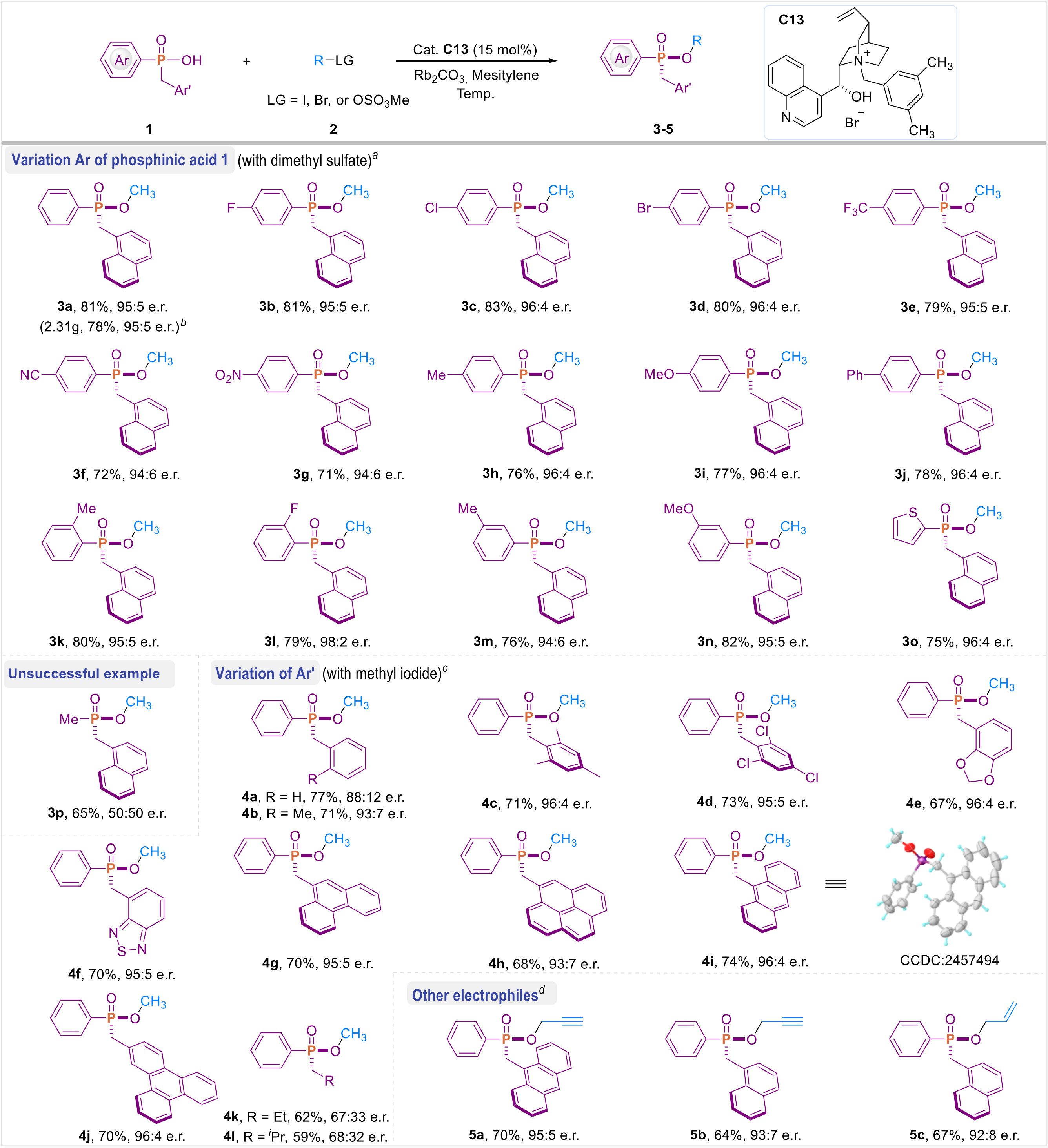


Figure 3. Substrate scope of the enantioselective synthesis of P-chiral phosphinates **3**−**5**. [a]The reactions were conducted with **1** (0.1 mmol, 1.0 equiv), **2c** (0.2 mmol, 2.0 equiv), Cat. **C13** (15 mol %), Rb_2CO_3 (2.0 equiv) in mesitylene (1.0 mL) at −10 °C for 24 h. [b]Reaction on 10.0 mmol scale. [c]Reactions with I-CH_3 (**2b**, 0.2 mmol, 2.0 equiv) at 0 °C for 10 d then at 30 °C for 3d. [d]Reactions with corresponding alkyl bromides. Isolated yields were reported, er values were determined by chiral HPLC analysis. See Supporting Information for details.

24 h at −10 °C. When substrate **1** was consumed completely (monitored by TLC), the resulting residue was purified through silica gel column chromatography to afford the desired product **3**.

General Procedure for Catalytic Preparation of Chiral Phosphinate Products 4. To a 4.0 mL oven-dried vial equipped with a magnetic stir bar, substrate **1** (0.1 mmol, 1.0 equiv), **2b** (0.2 mmol, 2.0 equiv), Rb_2CO_3 (0.2 mmol, 2.0 equiv), Cat. **C13** (15 mol %), and mesitylene (1.0 mL) were added. The mixture was cooled to 0 °C and kept stirring for 10 d at 0 °C, then the reaction was heated to 30 °C and kept stirring for 3 d. Once the starting material was fully consumed, the resulting residue was purified through silica gel column chromatography to afford the desired product **4**.

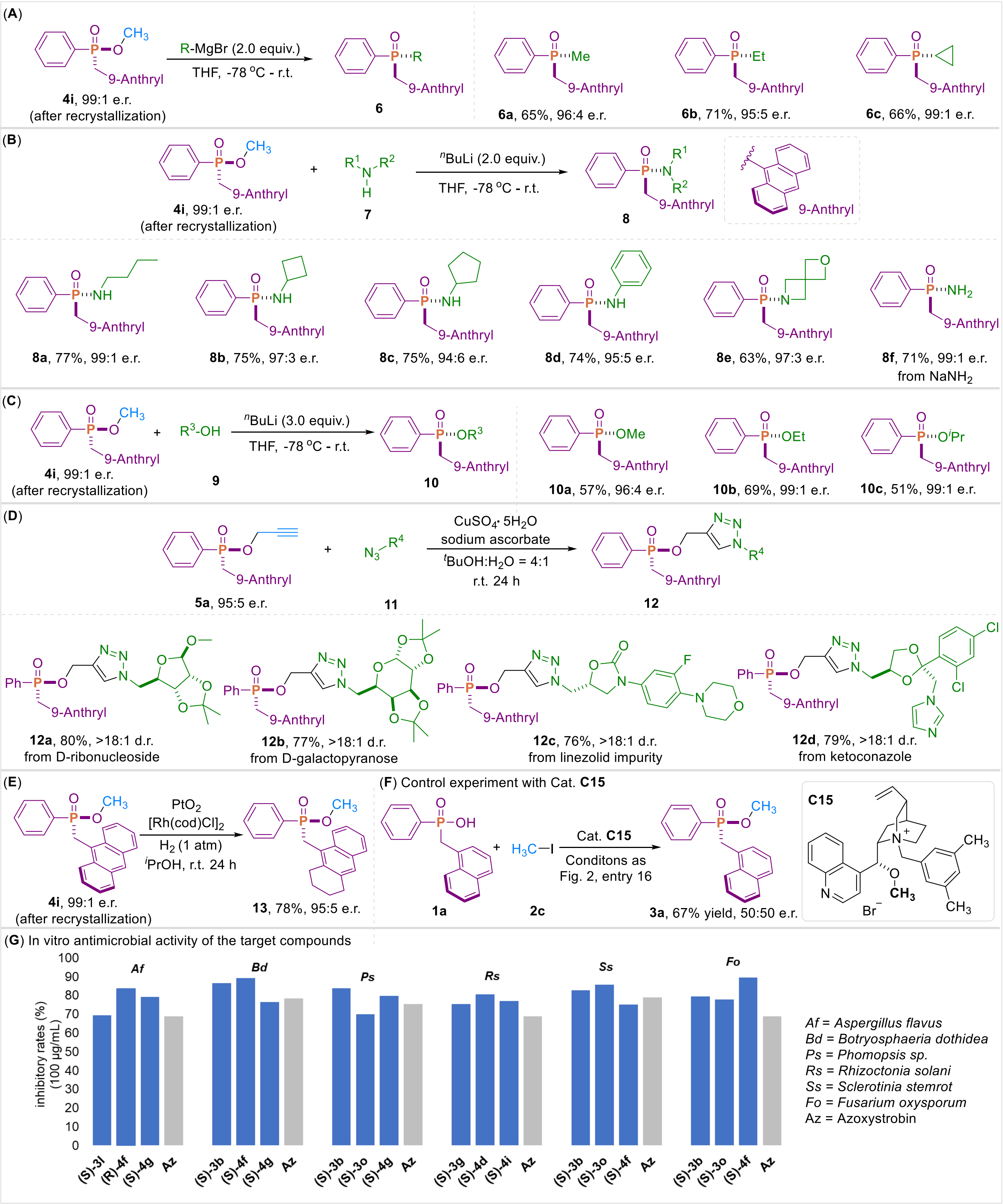


Figure 4. (A) Preparation of P(V)-chiral phosphine oxides. (B) Stereoselective synthesis of chiral phosphinamides **8**. (C) Ester exchange of **4i** with various alcohols. (D) Modification of complex molecules by a click reaction. (E) Hydrogenation reduction of **4i** to the synthesis of **13**. (F) A control experiment. (G) Bioassay studies. See Supporting Information for details.

RESULTS AND DISCUSSION

We initiated our investigation on the stereoselective synthesis of P(V)-chiral phosphinates by choosing readily accessible phosphinic **1a** and methyl *p*-toluenesulfonate (**2a**) as the primary starting materials.[71] A range of chiral phase-transfer catalysts (PTCs) was first evaluated in the presence of Rb_2CO_3 and mesitylene at room temperature (Figure 2). Typical phase-transfer catalysts **C1**−**C4** gave chiral phosphinate **3a** in 42−47% yields with only modest enantioselectivity (52:48−65:35 er) (entries 1−4). Modification of the N-substituents on the quinuclidine of the PTC catalysts showed a significant impact on stereocontrol (entries 5−14). Catalysts **C5** and **C6** afforded the product **3a** in low yields, wherein promising enantioselectivities were observed (entries 5−6). The impact at the *para* position of the benzylating reagents was also examined. Unfortunately, these conditions did not lead to the enhancement of the selectivity of product **3a** (entries 7−10). Encouragingly, catalysts with either electron-withdrawing (**C11**) or electron-donating groups (**C12**) at the 3- and 5-positions showed good enantioselectivity (75:25 and 78:22 er, respectively) (entries 11 and 12). To our delight, we found that the catalyst **C13** was superior to deliver the product **3a** in modest yield (59%) and excellent enantioselectivity (85:15 er) (entry 13). To further improve the efficiency, we optimized the electrophile and reaction temperature with **C13**. The use of methyl iodide (**2b**) at 0 °C gave the chiral product **3a** in an acceptable yield and enantioselectivity (76%, 95:5 er) (entry 16). In addition to methyl iodide (**2b**), we were pleased to find that the reaction with dimethyl sulfate (**2c**) at −10 °C could also deliver the product **3a** in good yield and high enantioselectivity (entry 18). Notably, the deuterated analog **3a’** was obtained as well in 71% yield and 96:4 er employing CD_3I as the alkylation agent under the optimized conditions (entry 19).

With the optimized conditions in hand, we set out to study the scope of the organocatalytic enantioselective synthesis of P(V)-chiral phosphinates (Figure 3). Initially, phosphinic acids **1** with various substitution groups (e.g., F, Cl, Br) at the *para* positions of the aromatic ring were examined with dimethyl sulfate (**2c**) as the methylation agent (conditions in Figure 2, entry 18). These substrates were smoothly converted to the corresponding phosphinate products **3b**−**3d** with 80−83% yields and excellent enantioselectivity. Electron-deficient substituents, such as CF_3, CN, and NO_2, were well tolerated, providing the corresponding products (**3e**−**3g**) in good yields and high stereoselectivity. Substrates with Me, MeO, and Ph also underwent efficient transformation to give rise to the products **3h**−**3j** with 76−78% yields and 96:4 er. Furthermore, substituents featured at the *ortho*- or *meta*-sites of the aromatic units furnished the chiral phosphinates **3k**−**3n** with 76−82% yields and 94:6−98:2 er. Replacing the phenyl unit of **1** with a 2-thienyl substituent afforded product **3o** in 75% yield with 96:4 er. In contrast, an aliphatic substrate gave desired product **3p** in 65% yield but with no enantioinduction. Notably, a gram-scale reaction was performed under the optimized conditions, delivering **3a** in 78% yield with 95:5 er, thereby highlighting the practicality of the method. Subsequently, we evaluated the influence of different aromatic groups replacing the naphthalene unit of phosphinic acid **1**. As a technical note, reaction conditions utilizing methyl iodide (**2b**) as the methylation agent (conditions in Figure 2, entry 16) was employed in these cases due to the enhanced enantioselectivity (see SI for details). We found that the steric hindrance of the Ar moiety is crucial to the stereoselectivity: substrate with simple benzyl gave product **4a** in a diminished 88:12 er, whereas the introduction of methyl at the ortho position delivered product **4b** with an improved 93:7 er. Moreover, the benzyl group with 2-, 4-, and 6-trisubstitution significantly enhanced the selectivity, affording products **4c** and **4d** with 96:4 and 95:5 er, respectively. Substrates containing a benzoheterocycle also proceeded well to furnish products **4e**−**4f** in good yields and excellent enantioselectivity. Additionally, **1** with extended aromatics, such as phenanthrene (**4g**), pyrene (**4h**), anthracene (**4i**), and triphenylene (**4j**), worked smoothly to afford the chiral phosphinates **4g**−**4j** in 68−74% yields and high selectivity. Substrates bearing alkyl-containing arylphosphinic acids delivered products **4k** and **4l** in modest yield and decreased enantioselectivity (67:33 and 68:32, respectively). Having established the enantioselective methylation scope of phosphinic acid **1**, we then explored alternative halide electrophiles. Both propargyl and allyl bromides were compatible with this reaction, delivering the corresponding products **5a**−**5c** in 64−70% yields and high stereoselectivity ranging from 92:8 to 95:5 er. The absolute configuration of **3** was determined as (*S*) by analogy to product **4i**, as determined through X-ray crystallographic analysis.

The optically enriched phosphinate products **3** and **4** served as linchpin P(V)-chiral building blocks, which could be easily transformed to afford a diverse set of P(V)-stereogenic compounds in a stereoselective fashion. For instance, nucleophilic substitution of product **4i** with various Grignard reagents readily delivered the corresponding products **6a**−**6c** in modest yields and high stereospecificity (Figure 4A).[58] Next, N-centered nucleophiles were employed for the synthesis of chiral phosphinamide **8** (Figure 4B). In this context, reactions with aliphatic amines in the presence of *n*-BuLi proceeded smoothly to furnish products **8a**−**8c**. Aromatic amine was also compatible with this transformation, affording product **8d** in 74% yield and 95:5 er. Additionally, N-heterocycles reacted effectively with **4i** to yield the product **8e** with excellent enantioselectivity.[58] The simple N-free chiral phosphinamide **8f** was obtained using $NaNH_2$ as the nucleophile, without erosion of the enantiopurity. In addition, P−O bond formation with ROH/*n*-BuLi enabled the preparation of phosphinates **10a**−**10c** (Figure 4C).[72] Notably, **10a**, as the opposite enantiomer of product **4i**, was readily accessible through this transformation. To further demonstrate synthetic utility, a set of important molecules containing an azide unit, such as D-ribonucleoside (**12a**), D-galactopyranose (**12b**), linezolid impurity (**12c**), ketoconazole (**12d**), were successfully incorporated into the chiral phosphinate scaffold via a Cu-catalyzed click reaction, affording products in 76−80% yields and with high diastereoselectivity (Figure 4D).[73,74] Intriguingly, straightforward hydrogenation of **4i** with $PtO_2/[Rh(cod)Cl]_2$ efficiently provided product **13** with 79% yield and 95:5 er (Figure 4E).[75] A control experiment on the model reaction with hydroxyl-protected catalyst **C15** instead of **C13** was performed to gain insights into the role of the OH group in the catalyst on the catalytic reaction. As shown in Figure 4F, the control reaction afforded the product **3a** in a racemic 50:50 er, which strongly implies the importance of the OH moiety in the catalyst, presumably owing to the resulting hydrogen-bonding interaction in the catalytic intermediates.

Motivated by the broad biological activity of phosphorus compounds,[23−25] we conducted bioassay studies to evaluate the antimicrobial activity of the prepared chiral P(V) compounds, with the aim to identify promising antimicrobial agrochemicals for plant protection.[76] In vitro bioassays were carried out at a concentration of 100 μg/mL to examine their inhibitory effects against a panel of common phytopathogens. As shown in Figure 4G, the phosphinate products exhibited broad-spectrum inhibition activity against various plant fungal pathogens, including *Af*, *Bd*, *Ps*, *Rs*, *Ss*, and others. Notably, (*S*)-**4f** showed excellent inhibition rates of 83.5 and 89.4% against *Af* and *Fo*, respectively, which were slightly superior to those of the

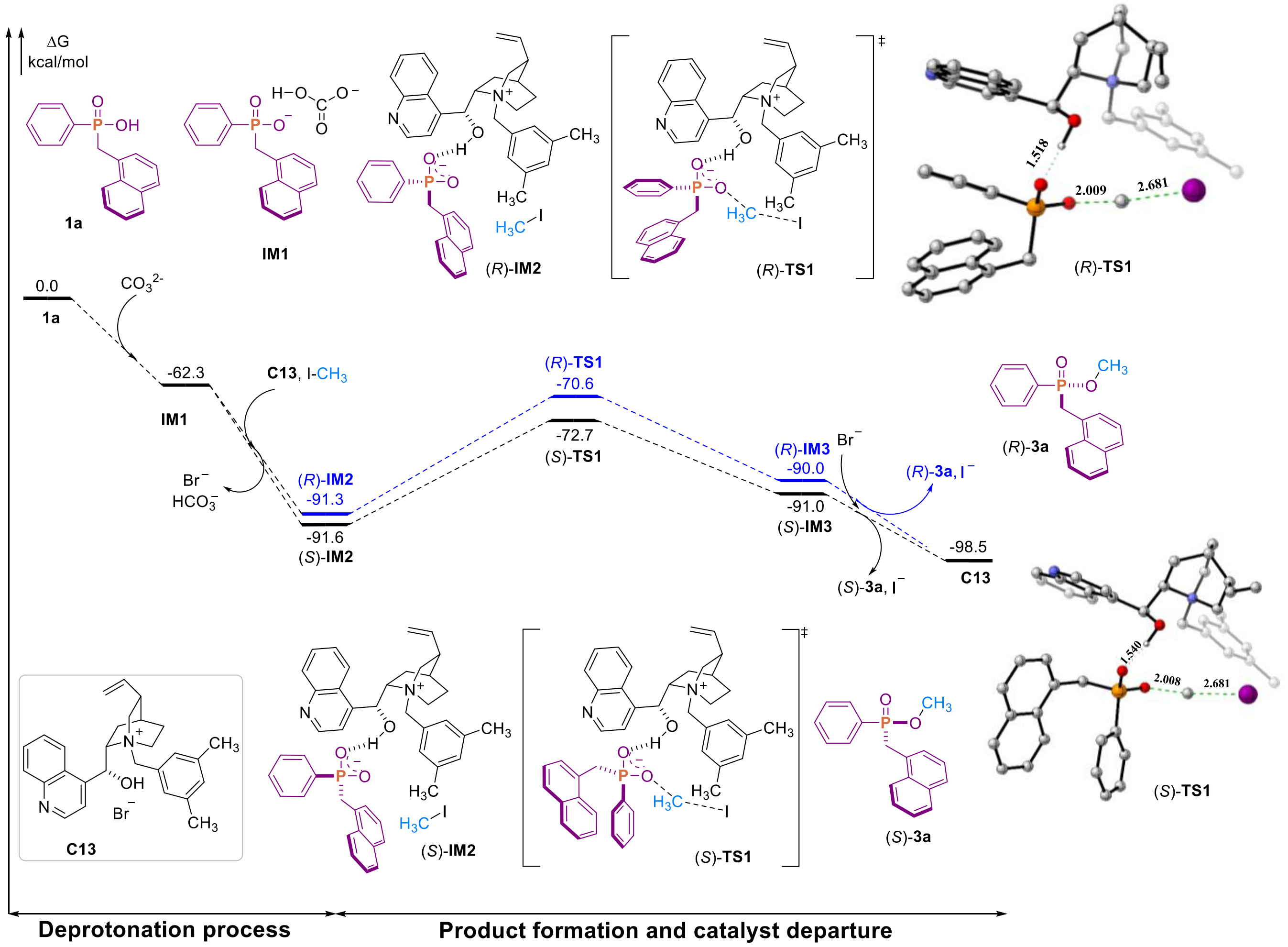


Figure 5. Gibbs free-energy profiles for the enantioselective formation of **3a**. DFT-optimized structures of the enantio-determining transition states are presented, with key bond lengths (in Å) labeled. Nonpolar hydrogen atoms are omitted for clarity.

commercial bactericides. Furthermore, both (*S*)-**3b** and (*S*)-**3o** exhibited significant activity against *Ss*. These findings highlight the potential of our chiral phosphinate products as a valuable scaffold for the development of potent agrochemical agents.

■ MECHANISTIC STUDIES

To investigate the mechanistic origin of the pronounced enantioselectivity in the **C13**-catalyzed enantioselective methylation of **1a** into **3a**, we conducted density functional theory (DFT) calculations on the model reaction with the simple methyl iodide (Figure 2, entry 16) at the PCM/B3LYP-D3(BJ)/def2-TZVP//PCM/B3LYP-D3(BJ)/def2-SVP level. As depicted in Figure 5, the reaction proceeds through the initial deprotonation of **1a** to generate intermediate **IM1**, which engages in simultaneous interactions with catalyst **C13** and methyl iodide (ICH_3), affording the diastereomeric intermediates (*R*)-**IM2** and (*S*)-**IM2**. Stabilized by hydrogen-bonding networks, the nucleophilic O atom of the phosphinic acid anion subsequently attacks the electrophilic methyl iodide through either (*R*)-**TS1** or (*S*)-**TS1**, leading to (*R*)-**IM3** or (*S*)-**IM3**, respectively. Catalyst dissociation then affords the final optically enriched products (*R*)-**3a** and (*S*)-**3a**. Notably, the computed free-energy difference between (*R*)-**TS1** and (*S*)-**TS1** (2.1 kcal/mol) accounts for the observed stereochemical outcome, with a predicted enantiomeric ratio of 97:3 that closely matches the experimental 95:5 er (Figure 2, entry 16). To probe the underlying factors, further reduced density gradient (RDG) analysis was performed for both transition states (*R*)-/(*S*)-**TS1** (Figure S3, Supporting Information). This analysis reveals distinct noncovalent interaction patterns between the two transition states involving the catalyst's aromatic moiety and the substrate. In (*R*)-**TS1**, a strong $\pi-\pi$ stacking interaction is present, whereas (*S*)-**TS1** is stabilized primarily by CH$-\pi$ contacts. This preference correlates with the geometry imposed by the methylene substituent attached to the phosphorus center: in (*S*)-**TS1**, its orientation is more favorable for CH$-\pi$ rather than $\pi-\pi$ stacking, consistent with the experimental observation of (*S*)-**3a** as the predominant enantiomer.

■ CONCLUSIONS

In summary, we have developed an organocatalytic asymmetric alkylation strategy for the synthesis of P(V)-stereogenic phosphorus compounds via stereoselective O−C bond formation. Utilizing a cinchonidine-derived phase-transfer catalyst, an ion pair is formed between the chiral catalyst and a prochiral phosphinic acid anion, generating a chiral environment that enables high stereocontrol over methylation with simple methylating agents. This mild and efficient protocol affords a broad array of chiral phosphorus compounds with high enantioselectivity, thereby expanding the synthetic toolbox for

P(V)-stereogenic functional molecules. Moreover, the resulting chiral phosphinates serve as versatile linchpin intermediates, undergoing stereospecific nucleophilic substitutions to furnish diverse phosphorus-containing scaffolds, including tertiary phosphine oxides, phosphinamides, and phosphinates. This method not only provides new access to structurally diverse P-chiral compounds but also offers promising candidates for applications in the discovery of agrochemical lead compounds and other biologically relevant fields.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.5c07607.

> Experimental details for the preparation of all new compounds, and their spectroscopic and chromatographic data generated in this study (PDF)

Accession Codes

The X-ray crystallographic coordinates for structures of the compounds (*S*)-**4i** reported in this study have been deposited at the Cambridge Crystallographic Data Centre (CCDC), under deposition numbers **CCDC 2457494**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. The full experimental details for the preparation of all new compounds, and their spectroscopic and chromatographic data generated in this study are provided in the Supporting Information.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Principles of Asymmetric Synthesis 2nd ed.; Gawley, R. E.; Aub8, J., Eds.; Elsevier: Amsterdam, 2012. chapter 3.

(2) Farina, V.; Reeves, J. T.; Senanayake, C. H.; Song, J. Asymmetric synthesis of active pharmaceutical ingredients. *Chem. Rev.* **2006**, *106*, 2734−2793.

(3) Zetzsche, L. E.; Narayan, A. R. H. Broadening the scope of biocatalytic C−C bond formation. *Nat. Rev. Chem.* **2020**, *4*, 334−346.

(4) Stoltz, B. M.; Bennett, N. B.; McGeever, Z. M.; Duquette, D. C.; Goldberg, A. F. G.; Liu, Y.; Loewinger, M. B.; Reeves, C. M.; Kerrigan, N. J. Alkylations of enols and enolates. *Comprehens. Organic Synth* **2014**, *3*, 1−70.

(5) Cano, R.; Zakarian, A.; McGlacken, G. P. Direct asymmetric alkylation of ketones: still unconquered. *Angew. Chem., Int. Ed.* **2017**, *56*, 9278−9290.

(6) Modern carbonyl Chemistry; Otera, J., Ed.; Wiley-WCH: Weinheim, 2000.

(7) Enders, D.; Eichenauer, H. Enantioselective alkylation of aldehydes via metalated chiral hydrazones. *Tetrahedron Lett.* **1977**, *18*, 191−194.

(8) Schmierer, R.; Grotemeier, G.; Helmchen, G.; Selim, A. Functional groups at concave sites: asymmetric alkylation of esters with very high stereoselectivity and reversal of configuration by change of solvent. *Angew. Chem., Int. Ed.* **1981**, *20*, 207−208.

(9) Evans, D. A.; Ennis, M. D.; Mathre, D. J. Asymmetric alkylation reactions of chiral imide enolates. A practical approach to the enantioselective synthesis of.alpha.-substituted carboxylic acid derivatives. *J. Am. Chem. Soc.* **1982**, *104*, 1737−1739.

(10) Oppolzer, W.; Moretti, R.; Thomi, S. Asymmetric alkylation of N-acylsultams: A general route to enantiomerically pure, crystalline C(α,α)-disubstituted carboxylic acid derivatives. *Tetrahedron Lett.* **1989**, *30*, 5603−5606.

(11) Kummer, D. A.; Chain, W. J.; Morales, M. R.; Quiroga, O.; Myers, A. G. Stereocontrolled alkylative construction of quaternary carbon centers. *J. Am. Chem. Soc.* **2008**, *130*, 13231−13233.

(12) Doyle, A. G.; Jacobsen, E. N. Enantioselective alkylations of tributyltin enolates catalyzed by Cr(salen)Cl: access to enantiomerically enriched all-carbon quaternary centers. *J. Am. Chem. Soc.* **2005**, *127*, 62−63.

(13) Fischer, C.; Fu, G. C. Asymmetric nickel-catalyzed negishi cross-couplings of secondary α-bromo amides with organozinc reagents. *J. Am. Chem. Soc.* **2005**, *127*, 4594−4595.

(14) Vignola, N.; List, B. Catalytic asymmetric intramolecular α-alkylation of aldehydes. *J. Am. Chem. Soc.* **2004**, *126*, 450−451.

(15) Filippini, G.; Silvi, M.; Melchiorre, P. Enantioselective formal α-methylation and α-benzylation of aldehydes by means of photo-organocatalysis. *Angew. Chem., Int. Ed.* **2017**, *56*, 4447−4451.

(16) Mukherjee, S.; Yang, J.; Hoffmann, S.; List, B. Asymmetric enamine catalysis. *Chem. Rev.* **2007**, *107*, 5471−5569.

(17) Sandoval, B. A.; Hyster, T. K. Emerging strategies for expanding the toolbox of enzymes in biocatalysis. *Curr. Opin. Chem. Biol.* **2020**, *55*, 45−51.

(18) Ju, S.; Kuzelka, K. P.; Guo, R.; Krohn-Hansen, B.; Wu, J.; Nair, S. K.; Yang, Y. A biocatalytic platform for asymmetric alkylation of α-keto acids by mining and engineering of methyltransferases. *Nat. Commun.* **2023**, *14*, No. 5704.

(19) Greenwood, N. S.; Champlin, A. T.; Ellman, J. A. Catalytic enantioselective sulfur alkylation of sulfenamides for the asymmetric synthesis of sulfoximines. *J. Am. Chem. Soc.* **2022**, *144*, 17808−17814.

(20) Boyer, Z. W.; Kwon, N. Y.; Ellman, J. A. Ruthenium-catalyzed enantioselective alkylation of sulfenamides: a general approach for the synthesis of drug relevant *S*-methyl and *S*-cyclopropyl sulfoximines. *J. Am. Chem. Soc.* **2025**, *147*, 14954−14959.

(21) Champlin, A. T.; Kwon, N. Y.; Ellman, J. A. Enantioselective S-alkylation of sulfenamides by phase-transfer catalysis. *Angew. Chem., Int. Ed.* **2024**, *63*, No. e202408820.

(22) Wang, L. J.; Xiang, W.; Xie, Y.; Huai, L.; Zhang, L.; Zhang, X. Synthesis of chiral sulfilimines by organocatalytic enantioselective sulfur alkylation of sulfenamides. *Sci. Adv.* **2024**, *10*, No. eadq2768.

(23) Sørensen, M. D.; Blaehr, L. K. A.; Christensen, M. K.; Høyer, T.; Latini, S.; Hjarnaac, P. J. V.; Björkling, F. Cyclic phosphinamides and phosphonamides. novel series of potent matrix metalloproteinase inhibitors with antitumour activity. *Bioorg. Med. Chem.* **2013**, *11*, 5461−5484.

(24) Horsman, G. P.; Zechel, D. L. Phosphonate biochemistry. *Chem. Rev.* **2017**, *117*, 5704−5783.

(25) Mehellou, Y.; Rattan, H. S.; Balzarini, J. The protide prodrug technology: from the concept to the clinic. *J. Med. Chem.* **2018**, *61*, 2211−2226.

(26) Rodriguez, J. B.; Gallo-Rodriguez, C. The role of the phosphorus atom in drug design. *ChemMedChem* **2019**, *14*, 190−216.

(27) Pradere, U.; Garnier-Amblard, E. C.; Coats, S. J.; Amblard, F.; Schinazi, R. F. Synthesis of nucleoside phosphate and phosphonate prodrugs. *Chem. Rev.* **2014**, *114*, 9154−9218.

(28) Guo, H.; Fan, Y.; Sun, Z.; Wu, Y.; Kwon, O. Phosphine organocatalysis. *Chem. Rev.* **2018**, *118*, 10049−10293.

(29) Ni, H.; Chan, W.-L.; Lu, Y. Phosphine-catalyzed asymmetric organic reactions. *Chem. Rev.* **2018**, *118*, 9344−9411.

(30) Tang, W.; Zhang, X. New chiral phosphorus ligands for enantioselective hydrogenation. *Chem. Rev.* **2003**, *103*, 3029−3070.

(31) Fernández-Pérez, H.; Etayo, P.; Panossian, A.; Vidal-Ferran, A. Phosphine-phosphinite and phosphine-phosphite ligands: preparation and applications in asymmetric catalysis. *Chem. Rev.* **2011**, *111*, 2119−2176.

(32) Imamoto, T. P-stereogenic phosphorus ligands in asymmetric catalysis. *Chem. Rev.* **2024**, *124*, 8657−8739.

(33) Mathew, R.; Maligres, P.; Hyde, A. M.; Limanto, J.; Brunskill, A.; Ruck, R. T.; Campeau, L. C.; Davies, I. W.; et al. A multifunctional catalyst that stereoselectively assembles prodrugs. *Science* **2017**, *356*, 426−430.

(34) Featherston, A. L.; Kwon, Y.; Pompeo, M. M.; Engl, O. D.; Leahy, D. K.; Miller, S. J. Catalytic asymmetric and stereodivergent oligonucleotide synthesis. *Science* **2021**, *371*, 702−707.

(35) Forbes, K. C.; Jacobsen, E. N. Enantioselective hydrogen-bond-donor catalysis to access diverse stereogenic-at-P(V) compounds. *Science* **2022**, *376*, 1230−1236.

(36) Formica, M.; Rogova, T.; Shi, H.; Sahara, N.; Ferko, B.; Farley, A. J. M.; Christensen, K. E.; Duarte, F.; Yamazaki, K.; Dixon, D. J. Catalytic enantioselective nucleophilic desymmetrization of phosphonate esters. *Nat. Chem.* **2023**, *15*, 714−721.

(37) Lovinger, G. J.; Sak, M. J.; Jacobsen, E. N. Catalysis of an S_N2 pathway by geometric preorganization. *Nature* **2024**, *632*, 1052−1059.

(38) Nie, X.-K.; Zhang, S.-Q.; Wang, X.-Y.; Yang, W.-T.; Zhang, X.; Chen, S.-J.; Cui, X.; Tang, Z.; Li, G.-X. Catalytic enantioselective nucleophilic desymmetrization at phosphorus(V): a three-phase strategy for modular preparation of phosphoramidates. *J. Am. Chem. Soc.* **2025**, *147*, 11010−11018.

(39) Zheng, G.-L.; Zhang, Y.; Zhang, J.-M.; Chen, L.; Xue, X.-S.; He, Z.-T. Stereogenic P(V) synthesis via catalytic continuous substitutions. *J. Am. Chem. Soc.* **2025**, *147*, 13566−13576.

(40) Daniels, B. S.; Blackburn, B. G.; Scribner, S. J.; Dong, V. M. Pathway to P(V)-stereogenic phosphoramidates by enantioselective yttrium catalysis. *J. Am. Chem. Soc.* **2025**, *147*, 21339−21346.

(41) Yao, H.-Q.; Cai, Y.-M.; Xie, T.; Lv, J.-Y.; Fang, S.-S.; Li, M.-H.; Shang, M. Modular access to P(V)-stereogenic compounds via Cu-catalyzed desymmetrization of (thio)phosphonic dichlorides. *Angew. Chem., Int. Ed.* **2025**, No. e202509807.

(42) Kang, Y.-L.; Shi, Y.; Huang, G.-P.; Li, X.-W. Rhodium-catalyzed asymmetric access to P-chiral triarylphosphine oxides via insertion of P−H bonds into diazonaphthoquinones. *Angew. Chem., Int. Ed.* **2025**, No. e202500436.

(43) Dai, Q.; Li, W.; Li, Z.; Zhang, J. P-chiral phosphines enabled by palladium/Xiao-phos-catalyzed asymmetric P−C cross-coupling of secondary phosphine oxides and aryl bromides. *J. Am. Chem. Soc.* **2019**, *141*, 20556−20564.

(44) Wang, H.; Qian, H.; Zhang, J.; Ma, S. Catalytic asymmetric axially chiral allenyl C−P bond formation. *J. Am. Chem. Soc.* **2022**, *144*, 12619−12626.

(45) Zhu, R.-Y.; Chen, L.; Hu, X.-S.; Zhou, F.; Zhou, J. Enantioselective synthesis of P-chiral tertiary phosphine oxides with an ethynyl group via Cu(I)-catalyzed azide−alkyne cycloaddition. *Chem. Sci.* **2020**, *11*, 97−106.

(46) Xu, P.; Zhou, F.; Zhu, L.; Zhou, J. Catalytic desymmetrization reactions to synthesize all-carbon quaternary stereocentres. *Nat. Synth.* **2023**, *2*, 1020−1036.

(47) Chan, V. S.; Stewart, I. C.; Bergman, R. G.; Toste, F. D. Asymmetric catalytic synthesis of P-stereogenic phosphines via a nucleophilic ruthenium phosphido complex. *J. Am. Chem. Soc.* **2006**, *128*, 2786−2787.

(48) Chan, V. S.; Chiu, M.; Bergman, R. G.; Toste, F. D. Development of ruthenium catalysts for the enantioselective synthesis of P-stereogenic phosphines via nucleophilic phosphido intermediates. *J. Am. Chem. Soc.* **2009**, *131*, 6021−6032.

(49) Scriban, C.; Glueck, D. S. Platinum-catalyzed asymmetric alkylation of secondary phosphines: enantioselective synthesis of P-stereogenic phosphines. *J. Am. Chem. Soc.* **2006**, *128*, 2788−2789.

(50) Wang, G.; Gibbons, S. K.; Glueck, D. S.; Sibbald, C.; Fleming, J. T.; Higham, L. J.; Rheingold, A. L. Copper-phosphido intermediates in Cu (IPr)-catalyzed synthesis of 1-phosphapyracenes via tandem alkylation/arylation of primary phosphines. *Organometallics.* **2018**, *37*, 1760−1772.

(51) Gallant, S. K.; Tipker, R. M.; Glueck, D. S. Copper-catalyzed asymmetric alkylation of secondary phosphines via rapid pyramidal inversion in P-stereogenic Cu-phosphido intermediates. *Organometallics.* **2022**, *41*, 1721−1730.

(52) Wang, C.; Huang, K.; Ye, J.; Duan, W.-L. Asymmetric synthesis of P-stereogenic secondary phosphine-boranes by an unsymmetric bisphosphine pincer-nickel complex. *J. Am. Chem. Soc.* **2021**, *143*, 5685−5690.

(53) Wang, C.; Dai, Y.-H.; Wang, Z.; Lu, B.; Cao, W.; Zhao, J.; Mei, G.; Yang, Q.; Guo, J.; Duan, W.-L. Nickel-catalyzed enantioselective alkylation of primary phosphines. *J. Am. Chem. Soc.* **2024**, *146*, 27843−27851.

(54) Zhang, S.; Xiao, J.-Z.; Li, Y.-B.; Shi, C.-Y.; Yin, L. Copper (I)-catalyzed asymmetric alkylation of unsymmetrical secondary phosphines. *J. Am. Chem. Soc.* **2021**, *143*, 9912−9921.

(55) Liu, X.-T.; Zhang, Y.-Q.; Han, X.-Y.; Sun, S.-P.; Zhang, Q.-W. Ni-catalyzed asymmetric allylation of secondary phosphine oxides. *J. Am. Chem. Soc.* **2019**, *141*, 16584−16589.

(56) Toda, Y.; Pink, M.; Johnston, J. N. Brønsted acid catalyzed phosphoramidic acid additions to alkenes: diastereo- and enantioselective halogenative cyclizations for the synthesis of C- and P-chiral phosphoramidates. *J. Am. Chem. Soc.* **2014**, *136*, 14734−14737.

(57) Trost, B. M.; Spohr, S. M.; Rolka, A. B.; Kalnmals, C. A. Desymmetrization of phosphinic acids via Pd-catalyzed asymmetric allylic alkylation: rapid access to P-chiral ohosphinates. *J. Am. Chem. Soc.* **2019**, *141*, 14098−14103.

(58) Yan, M.; Zou, J.-W.; Fang, D.-M.; Zhang, S.-Q.; Cui, X.; Tang, Z.; Li, G.-X. Enantioselective desymmetrization of phosphinic acids via Cu-catalyzed O-arylation. *ACS Catal.* **2025**, *15*, 4719−4725.

(59) Stivala, C. E.; Zakarian, A. Highly enantioselective direct alkylation of arylacetic acids with chiral lithium amides as traceless auxiliaries. *J. Am. Chem. Soc.* **2011**, *133*, 11936−11939.

(60) Yu, K.; Lu, P.; Jackson, J. J.; Nguyen, T. D.; Alvarado, J.; Stivala, C. E.; M, Y.; Mack, K. A.; Hayton, T. W.; Collum, D. B.; Zakarian, A. Lithium enolates in the enantioselective construction of tetrasubstituted carbon centers with chiral lithium amides as noncovalent stereodirecting auxiliaries. *J. Am. Chem. Soc.* **2017**, *139*, 527−533.

(61) Nagib, D. A. Catalytic desymmetrization by C-H functionalization as a solution to the chiral methyl problem. *Angew. Chem., Int. Ed.* **2017**, *56*, 7354−7356.

(62) Schönherr, H.; Cernak, T. Profound methyl effects in drug discovery and a call for new C-H methylation reactions. *Angew. Chem., Int. Ed.* **2013**, *52*, 12256−12267.

(63) Barreiro, E. J.; Kümmerle, A. E.; Fraga, C. A. The methylation effect in medicinal chemistry. *Chem. Rev.* **2011**, *111*, 5215−5246.

(64) Leung, C. S.; Leung, S. S. F.; Tirado-Rives, J.; Jorgensen, W. L. Methyl effects on protein−ligand binding. *J. Med. Chem.* **2012**, *55*, 4489−4500.

(65) Lee, H.-J.; Maruoka, K. Asymmetric phase-transfer catalysis. *Nat. Rev. Chem.* **2024**, *8*, 851−859.

(66) Starks, C. M. Phase-transfer catalysis. i. heterogeneous reactions involving anion transfer by quaternary ammonium and phosphonium salts. *J. Am. Chem. Soc.* **1971**, *93*, 195−199.

(67) Makosza, M. Phase-transfer catalysis. a general green methodology in organic synthesis. *Pure Appl. Chem.* **2000**, *72*, 1399−1403.

(68) Shirakawa, S.; Maruoka, K. Recent developments in ssymmetric phase-transfer reactions. *Angew. Chem., Int. Ed.* **2013**, *52*, 4312−4348.

(69) Hashimoto, T.; Maruoka, K. Recent development and application of chiral phase-transfer catalysts. *Chem. Rev.* **2007**, *107*, 5656−5682.

(70) Lee, H.-Y.; Maruoka, K. Recent asymmetric phase-transfer catalysis with chiral binaphthyl-modified and related phase-transfer catalysts over the last 10 years. *Chem. Rec.* **2023**, *23*, No. e202200286.

(71) Notably, during the preparation of this manuscript, a peptide-phosphonium salt-catalyed asymmetric tosylation for desymmetrization of phosphinic acids was reported by Wang Yang, S.; Luo, X.; Liu, Z.; Fang, S.; Wu, J.-H.; Wang, T.; et al. Bioinspired peptide-phosphonium salt catalysis unlocks asymmetric desymmetrization of phosphoryl acids: programmable synthesis of P(V)-stereogenic molecules. *Angew. Chem., Int. Ed.* **2025**, *64*, No. e202510513.

(72) Tripolszky, A.; Németh, K.; Szabó, P. T.; Bálint, E. Synthesis of (1,2,3-triazol-4-yl)methyl phosphinates and (1,2,3-triazol-4-yl)methyl phosphates by copper-catalyzed azide-alkyne cycloaddition. *Molecules* **2019**, *24*, No. 2085.

(73) Worrell, B. T.; Malik, J. A.; Fokin, V. V. Direct evidence of a dinuclear copper intermediate in Cu(I)-catalyzed azide-alkyne cycloadditions. *Science* **2013**, *340*, 457−460.

(74) Li, H.-X.; Yu, Z.-X. Arene reduction by Rh/Pd or Rh/Pt under 1 atm hydrogen gas and room temperature. *Org. Lett.* **2024**, *26*, 3458−3462.

(75) Chen, J.; Zhang, M.; Yuan, C.; Zhang, T.; Wu, Z.; Li, T.; Chi, Y. R. Design, synthesis, and antifungal activity of acrylamide derivatives containing trifluoromethylpyridine and piperazine. *J. Agric. Food Chem.* **2024**, *72*, 11360−11368.

(76) Yang, X.; Jiang, S.; Zhang, M.; Li, T.; Jin, Z.; Wu, X.; Chi, Y. R. Discovery of novel piperidine-containing thymol derivatives as potent antifungal agents for crop protection. *Pest Manage. Sci.* **2024**, *80*, 4906−4914.