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Article

Asymmetric Synthesis of Diverse P(V) Compounds Bearing a C−P Bond via Desymmetrization of Phosphonic Dichlorides Catalyzed by a Chiral Bicyclic Imidazole

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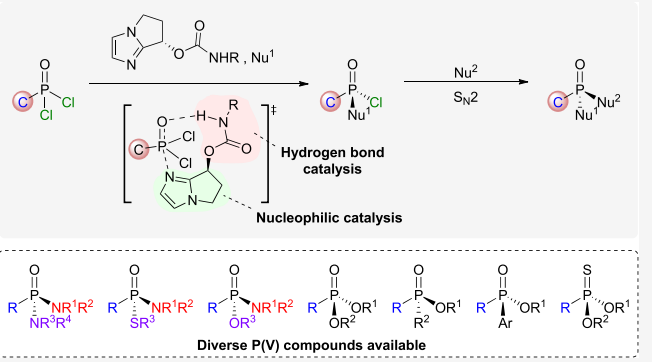
ABSTRACT: Chiral phosphorus(V) compounds bearing one or two C−P bonds exhibit significant utility in pharmacy and catalysis. Although several established methods enable stereoselective access to these P-stereogenic compounds, achieving direct enantiocontrol at phosphorus via catalytic P(V)−heteroatom bond formation remains challenging. Herein, we present a highly efficient strategy to synthesize such chiral P(V) compounds through the asymmetric desymmetrization of phosphonic dichlorides catalyzed by a readily accessible bifunctional chiral bicyclic imidazole. The synergistic combination of Lewis base catalysis and hydrogen bond catalysis is responsible for the high reactivity and stereoselectivity. The one-pot sequential process combining the catalytic desymmetrization and the enantiospecific S_N2 displacement delivers a large number of chiral P(V) compounds with excellent yields and enantioselectivities. This protocol establishes a versatile platform for the concise synthesis of structurally diverse P-chirogenic motifs relevant to high-value bioactive molecules.



INTRODUCTION

P-Stereogenic organophosphorus(V) compounds bearing one or two C−P bonds constitute a class of highly valued structures with broad applications in medicinal chemistry[1−3] and organic synthesis.[4−6] These chiral P(V) compounds are widely found in numerous natural products, drugs, and bioactive molecules. Among these compounds featuring one C−P bond, tenofovir alafenamide serves as a first-line therapeutic agent for chronic hepatitis B,[7] a carbonic anhydrase inhibitor shows potential for treating neuropathic pain,[8] and several other derivatives exhibit antitumor activity.[9,10] Compounds containing two C−P bonds, which can be derived from their single C−P bond counterparts, exhibit diverse biological activities. For instance, phostine[11] demonstrates potent antiproliferative properties, and (−)-SMT022332[12] is a promising therapeutic candidate for Duchenne muscular dystrophy. Additionally, fosinopril[3,13] remains the only approved phosphinate-based drug for high blood pressure (Figure 1).

The development of efficient and highly selective methods for synthesizing P(V)-stereogenic compounds with novel structures and diverse functional groups undoubtedly holds significant research importance and application value for drug discovery and synthetic chemistry. Traditionally, methods for the preparation of P(V)-stereogenic compounds mainly focus on strategies such as chiral resolution of racemic P(V) compounds[14,15] and chiral auxiliary-induced synthesis.[16−18] These methods generally require the use of equivalent or even excessive amounts of chiral reagents, resulting in higher economic costs. Notably, the resolution method suffers from an intrinsic 50% maximum theoretical yield ceiling for the target stereoisomer. Furthermore, the chiral auxiliary-induced method entails installation and subsequent removal of directing groups, resulting in increased reaction steps and low atom economy. In comparison, asymmetric catalysis is currently the most direct and efficient synthetic method for constructing P(V)-stereocenters.

Due to the considerable value of P(V)-stereogenic compounds containing C−P bonds, the asymmetric synthesis of these compounds holds significant research importance. Recent years have witnessed some breakthroughs in the construction of a stereogenic P(V) center with C−P bonds by catalytic asymmetric desymmetrization (Scheme 1A). Notably, Jacobsen's pioneering work developed the first desymmetrization reaction of aryl phosphonic dichlorides catalyzed by a hydrogen-bond-donor catalyst, enabling efficient construction

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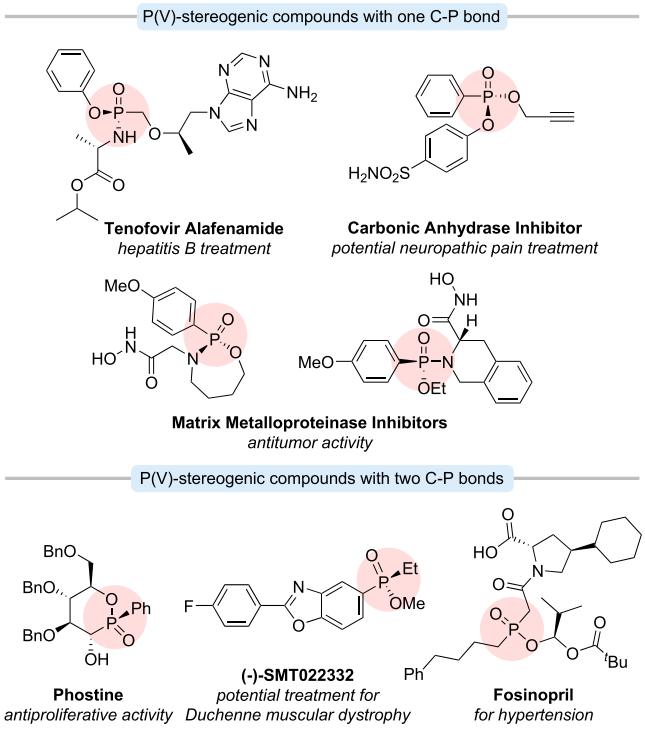

Figure 1. Selected examples of P(V)-stereogenic compounds bearing one or two C−P bonds.

of P(V) stereocenters containing a C−P bond.[19] Almost simultaneously, the groups of Dixon and Yamazaki achieved the intelligent synthesis of such compounds through an asymmetric phosphorylative desymmetrization using phosphodiester and phosphodiacylamide substrates, promoted by a superbasic bifunctional iminophosphorane catalyst.[20,21] Recently, Chi and colleagues introduced an elegant, NHC-catalyzed approach to P(V)-stereogenic compounds containing a C−P bond from phosphodiester substrates.[22] These works synergistically establish a new platform for the catalytic construction of P-stereogenic compounds bearing a C−P bond. Furthermore, utilizing this desymmetrization strategy, research groups of Li,[23] He,[24] Zhang,[25] Dong,[26] and Shang[27] developed several efficient asymmetric syntheses of P(V)-stereogenic compounds devoid of C−P bonds. Despite these advancements, the development of new catalytic systems remains necessary to address the shortcomings of the aforementioned reactions, particularly in achieving high enantioselectivity with readily accessible catalysts.

The catalytic asymmetric phosphorylation reaction is an efficient strategy for the direct construction of P-stereocenters (Scheme 1B). In 2012, our research group achieved the first catalytic asymmetric phosphorylation to access enantioenriched phosphoramidates[28] through the kinetic resolution of racemic phosphoryl chloride catalyzed by a novel chiral bicyclic imidazole.[29] This achievement established the first catalytic system for the asymmetric synthesis of P-stereogenic phosphoric acid derivatives, addressing a significant challenge in stereoselective phosphorus chemistry. The pivotal study by Merck & Co. researchers offered crucial validation for the bicyclic imidazole-catalyzed asymmetric phosphorylation reaction in the synthesis of nucleoside phosphoramidate prodrugs.[30] Then, the Tang group at the University of Wisconsin reported the site- and stereoselective synthesis of P(V)-stereogenic glycosyl phosphoramidates catalyzed by a chiral bicyclic imidazole.[31] Our group accomplished the first highly efficient synthesis of the first P(V)-stereogenic anti-COVID-19 agent remdesivir through asymmetric phosphorylation catalyzed by a chiral bicyclic imidazole in 2020, and the kilogram-scale production via this catalytic process was realized in collaboration with Shanghai NO.1 Biochemical & Pharmaceutical Co., Ltd.[32] Subsequently, a one-pot asymmetric phosphoramidation catalyzed by the new designed chiral bicyclic imidazole for the synthesis of remdesivir was reported by Wong and Hung.[33]

Although the efficacy of chiral bicyclic imidazole catalysts has been established for the asymmetric synthesis of phosphoramidates, which lack C−P bonds, their potential for the catalytic synthesis of P(V)-stereogenic compounds with C−P bonds remains unexplored. The development of such methods is highly desirable, given the readily available access of bicyclic imidazole catalysts and the broad utility of these target molecules. Building on previous research, we hypothesized that a bifunctional bicyclic imidazole catalyst, bearing a N−H motif, could nucleophilically activate the phosphonic dichloride with a C−P bond while simultaneously interacting with the P═O motif via hydrogen bond, thereby enhancing both reactivity and stereodiscrimination (Scheme 1C). This catalysis enables the asymmetric desymmetrization of the phosphonic dichlorides, generating configurationally stable P-chirogenic chlorophosphonamidate intermediates. These intermediates could subsequently participate in the enantiospecific S_N2 displacement, providing desired P(V)-stereogenic compounds with a C−P bond.

Herein, we present a versatile one-pot sequential strategy for the direct construction of P-stereogenic centers featuring a C−P bond. This methodology combines a bifunctional chiral bicyclic imidazole-catalyzed desymmetrization of phosphonic dichlorides with an enantiospecific displacement. This reaction affords structurally diverse P-stereogenic products in satisfactory yields (up to 99%) with excellent enantioselectivities (up to 98% ee). Uniting facile catalyst synthesis with exceptional catalytic efficiency, it offers a general platform for the synthesis of chiral P(V) compounds bearing variable *O*-, *N*-, *S*-, and *C*-substituents (Scheme 1C).

RESULTS AND DISCUSSION

At the outset of our study, we employed the commercially available phenylphosphonic dichloride **1a** as the model substrate, secondary amine **2a**, and sodium methoxide as sequential nucleophiles to systematically evaluate diverse bicyclic imidazole catalysts on reaction performance (Tables 1 and S1). Reaction under catalyst-free conditions failed to produce the target product (Table 1, entry 1). As the well-established catalysts in the *C*-acylation reaction,[34−39] chiral bicyclic imidazoles **C1** and **C2** were employed in this reaction to assess their catalytic competence. However, both catalysts exhibited limited stereoinduction in this transformation (entries 2 and 3). Chiral bicyclic imidazole **C3** has demonstrated superior catalytic efficacy in the asymmetric synthesis of the anti-COVID-19 drug remdesivir.[32] Based on this result, we employed **C3** in this reaction, affording the desired product in 74% conversion with 68% ee (entry 4). Then, the structure of **C3** was modified to investigate its catalytic performance. By comparing **C3** and **C4**, it is shown that replacing the carbamate moiety with a urea structure within the catalyst scaffold substantially increases catalyst

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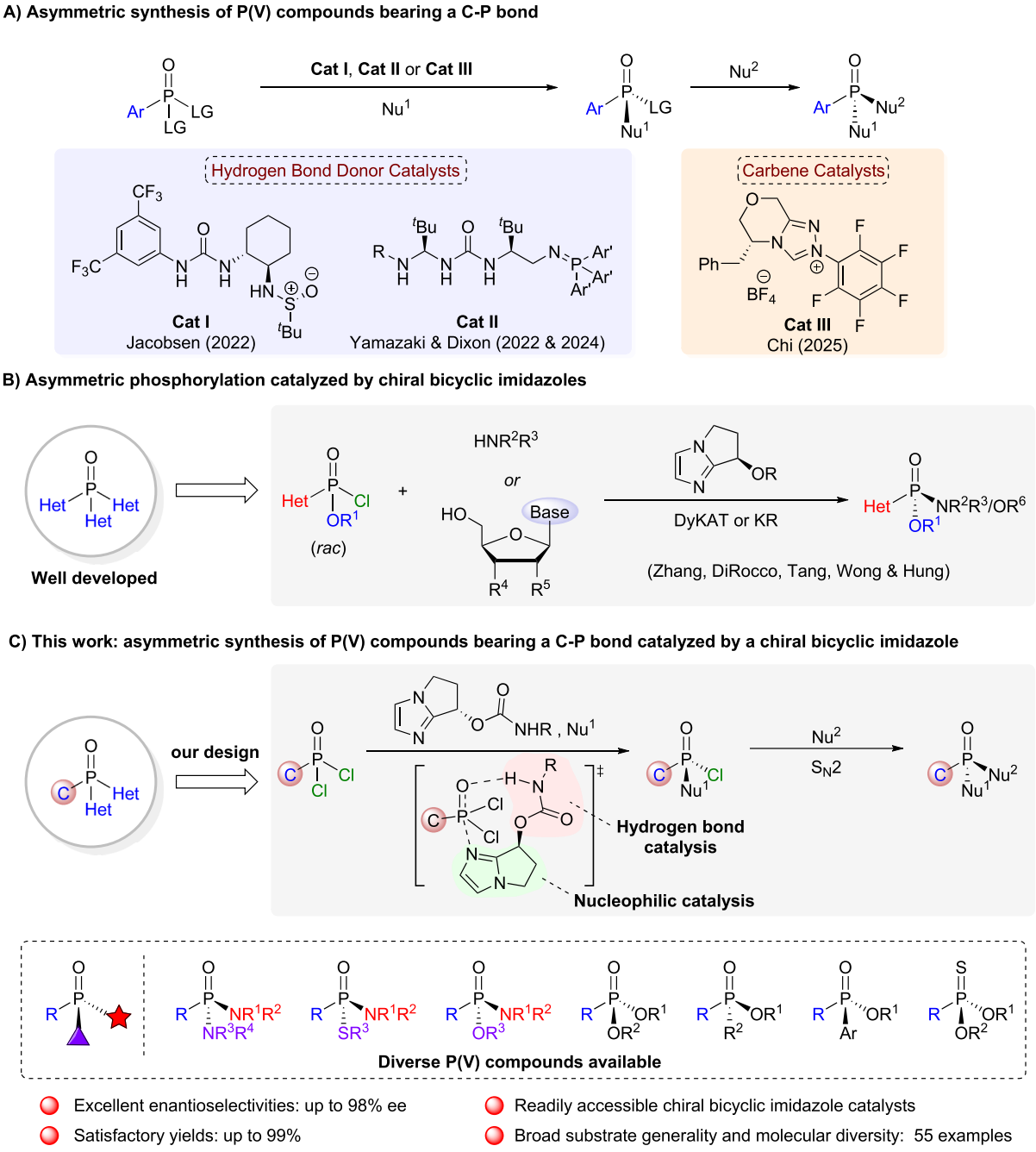
Scheme 1. Asymmetric Catalytic Phosphorylation



activity while sharply decreasing enantioselectivity (entry 5). The *N*-methyl-substituted catalyst **C6** exhibited significantly reduced activity and enantioselectivity compared with catalyst **C5** bearing an N−H bond (entries 6 and 7). The above results underscore the importance of the carbamate moiety (−OCONH−) in the catalyst structure for this reaction. This also reveals a critical hydrogen-bonding interaction between the N−H motif in the catalyst and the phosphonic dichloride substrate, which was further verified through an IGMH analysis in the mechanistic studies. Subsequently, maintaining the carbamate moiety in the catalyst, the substituent at the *N*-position was changed to structurally diverse groups to enhance catalytic efficacy. The chiral dimeric bicyclic imidazole **C7**, whose (*R*)-enantiomer was well-established for the synthesis of MK-3682,[30] was investigated in this reaction and showed unsatisfactory performance (entry 8). After screening a number of bicyclic imidazole catalysts bearing various *N*-substituents, catalyst **C9** featuring the (*R*)-1-phenylethyl substituent demonstrated superior catalytic activity and enantioselectivity. By contrast, catalyst **C8** bearing an (*S*)-1-phenylethyl substituent exhibited notably reduced enantioselectivity (entries 9 and 10). Catalyst **C10** (the absolute configuration is determined based on X-ray crystallography analysis), featuring the replacement of the phenyl group in the structure of **C9** with a naphthyl group, exhibited the highest stereoselectivity (82% ee) among all screened catalysts (entry 11).

Through rational design, catalyst **C10** was identified as the optimal catalyst. Thereafter, a comprehensive solvent screening was conducted to optimize the reaction conditions (see SI,

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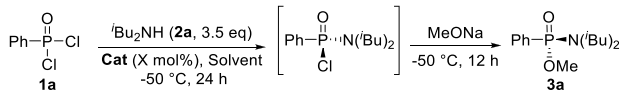
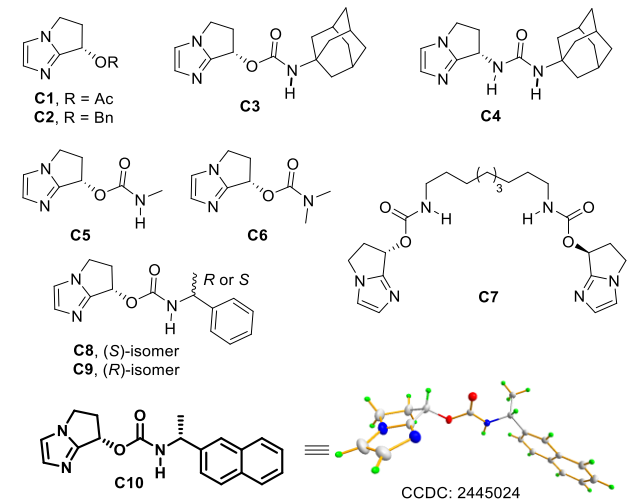
Table 1. Optimization of the Reaction Conditions[a]





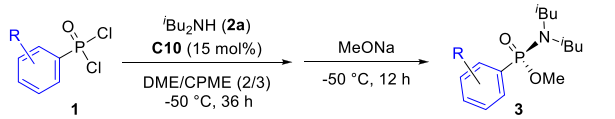
entry	Cat	solvent A	solvent B	V_A (mL):V_B (mL)	conv(%)[b]	ee(%)[c]
1	none	THF	toluene	2:0.5	N.R	–
2	**C1**	THF	toluene	2:0.5	46	40
3	**C2**	THF	toluene	2:0.5	83	28
4	**C3**	THF	toluene	2:0.5	74	68
5	**C4**	THF	toluene	2:0.5	99	6
6	**C5**	THF	toluene	2:0.5	98	74
7	**C6**	THF	toluene	2:0.5	25	5
8	**C7**	THF	toluene	2:0.5	48	33
9	**C8**	THF	toluene	2:0.5	87	71
10	**C9**	THF	toluene	2:0.5	88	78
11	**C10**	THF	toluene	2:0.5	80	82
12	**C10**	DME	toluene	2:0.5	99	83
13	**C10**	DME	CPME	2:0.5	99	84
14[d]	**C10**	DME	CPME	2:0.5	85	84
15[d,e]	**C10**	DME	CPME	2:0.5	99	84
16[d,e]	**C10**	DME	CPME	1:1.5	99	93

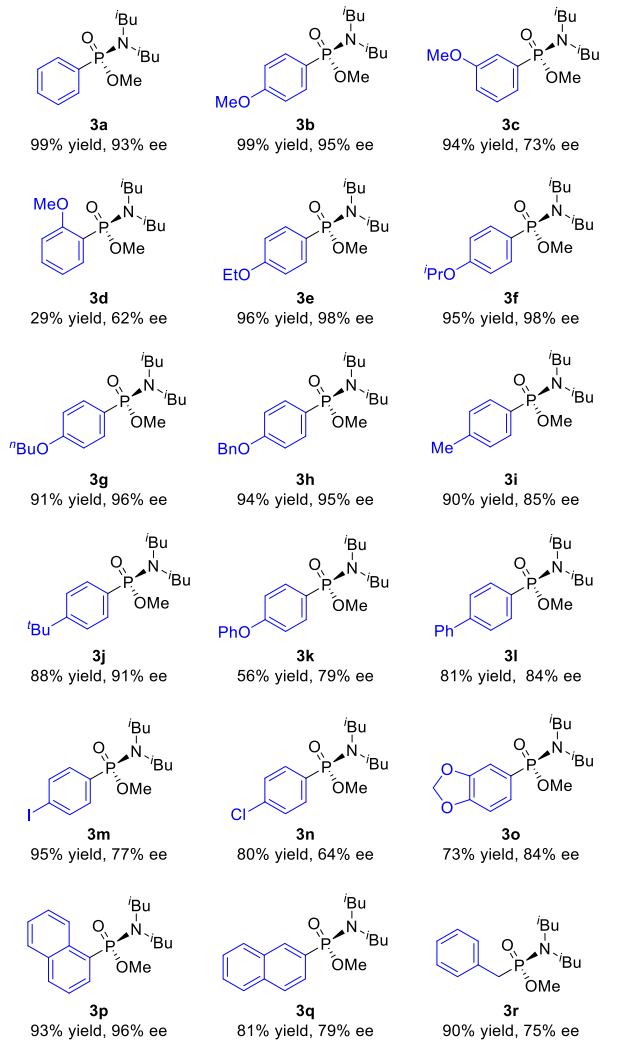
[a]Reaction conditions: A solution of **1a** (0.20 mmol, 1.0 equiv) in solvent B was added to a mixture of **2a** (0.70 mmol, 3.5 equiv), **Cat** (20 mol %), and 4Å MS (70 mg) in solvent A at −50 °C under Ar. After stirring for 24 h at −50 °C, MeONa (2 mmol, 5.4 mol/L in methanol, 30 wt %) was added, and stirring was continued at −50 °C for 12 h. [b]Determined by ^{31}P NMR analysis using P(O)(OMe)$_3$ as the internal standard. [c]Determined by HPLC using Daicel Chiralpak columns. [d]**Cat** (15 mol %). [e]The first step was conducted for 36 h. DME: 1,2-dimethoxyethane. CPME: Cyclopentyl methyl ether.

Tables S3 and S4). Ethereal solvents presumably enhance the catalytic efficacy through the stabilization of *n*−cation interactions between the lone pairs of the ether oxygen and the electropositive imidazolium ring in the catalytic intermediates,[40] accounting for their exceptional performance as reaction solvent. After screening, 1,2-dimethoxyethane (DME) was selected as the optimal reaction solvent instead of THF, and cyclopentyl methyl ether (CPME) was selected as the optimal solvent for dissolving phenylphosphonyl dichloride (entries 12 and 13). Notably, decreasing the catalyst loading to 15 mol % and extending the first step reaction time to 36 h maintained high enantioselectivity and quantitative conversion of the product (entries 14 and 15). Remarkably, employing a 2:3 volume ratio of DME and CPME achieved excellent enantioselectivity (93% ee, entry 16).

With the optimal reaction conditions established, the versatility of phosphonic dichloride substrates was evaluated using diisobutylamine as the nucleophile (Scheme 2). Initially, substrates bearing a methoxy group at the *para*-, *meta*-, and *ortho*-positions of the phenyl ring were tested in the reaction (**3b**−**3d**). The *para*-methoxy-substituted substrate afforded the corresponding product **3b** in near-quantitative yield (99%) with excellent enantioselectivity (95% ee). The stereoselectivity of the corresponding product **3c** decreased when

Scheme 2. Scope of Phosphonic Dichlorides[a]





[a]Reaction conditions: A solution of **1** (0.20 mmol, 1.0 equiv) in 1.5 mL anhydrous CPME was added to a mixture of **2a** (0.70 mmol, 3.5 equiv), **C10** (0.03 mmol, 15 mol %), and 4 Å MS (70 mg) in 1 mL anhydrous DME at −50 °C under Ar. After stirring for 36 h at −50 °C, MeONa (2 mmol, 5.4 mol/L in methanol, 30 wt %) was added, and stirring was continued at −50 °C for 12 h. Isolated yields. The ee values were determined by chiral HPLC. Compounds **3c**, **3d**, **3m**-**3o**: 48 h in the first step.

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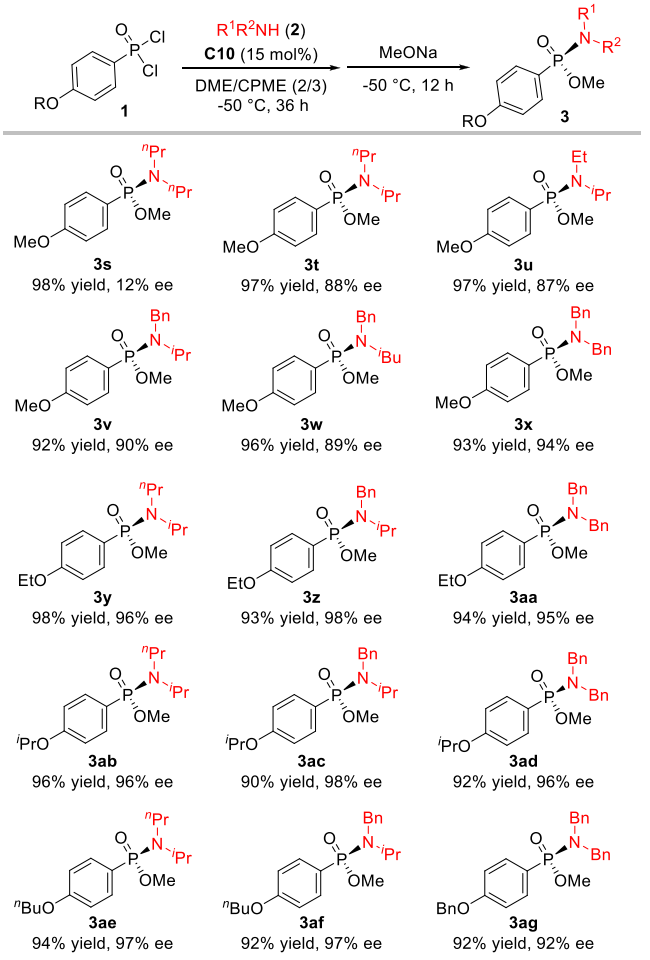
using its *meta*-substituted analogue as a substrate. Additionally, the *ortho*-methoxy-substituted substrate exhibited poorer reactivity, which is likely due to increased steric hindrance near the phosphorus center (**3d**). Following this, the effect of different substituents at the *para*-position of the benzene ring was studied (**3e**−**3n**). Other *para*-alkoxy substituents on the benzene ring afforded the products (**3e**−**3h**) in excellent yields (91−96%) with enantioselectivities (95−98% ee). Substrates bearing a methyl or *tert*-butyl group at the *para*-position of the benzene ring afforded products (**3i** and **3j**) in satisfactory yields and enantioselectivities. When the 4-position of the benzene ring was substituted with a phenoxy group, product **3k** was obtained in 56% yield with 79% ee. Substrates bearing electron-withdrawing substituents exhibited reduced enantioselectivities (**3n**), whereas those with less electron-withdrawing substituents (**3l**−**3m**) afforded corresponding products in good yields (56−95%) and enantioselectivities (77−84% ee). Generally, substrates bearing *para*-electron-donating groups on the phenyl ring showed enhanced reactivity. This improvement is likely ascribed to the increased electron density at the phosphorus center contributed by these substituents, thereby stabilizing the intermediate formed between the substrate and the imidazolium cation (as discussed in the DFT study), ultimately leading to an improved catalytic performance in terms of both activity and stereoselectivity. Following this, we extended our studies to disubstituted benzene substrates (**3o**−**3q**). The results indicated that product **3p** showed the highest activity among them, affording the desired product in 93% yield with 96% ee. Product **3o**, featuring a rigid cyclic framework, exhibited an intermediate catalytic performance. This result is consistent with its steric environment around the phosphorus center, which is less hindered than that in **3p** but more constrained than that in **3q**. Notably, alkyl phosphonic dichloride substrates also demonstrated favorable compatibility in this reaction. The benzylphosphonic dichloride provided product **3r** in 90% yield with 75% ee. Significantly, the enantioselectivity of the P-chirogenic chlorophosphonamidate intermediate generated en route to **3b** was determined to be 96% ee (see SI, Section 5), matching that of product **3b**. This conclusively demonstrates that the chirality of the product in this one-pot reaction is determined by the first step, while the catalyst in this reaction system induces no racemization of the P-chirogenic intermediate.

The secondary amine serves a dual function in the catalytic desymmetrization step of this one-pot reaction: as a nucleophile attacking the phosphonic dichloride and as a Brønsted base neutralizing the HCl byproduct generated during catalysis (Scheme 3). We commenced our investigation by using a *p*-anisyl-substituted substrate to assess the influence of various secondary amines on reactivity (**3b, 3s**−**3x**). Results showed that the enantioselectivity of the product is related to the steric hindrance of the amine nucleophile. Employing an amine nucleophile with proper steric bulk afforded products in excellent yields (92−98%) with high enantioselectivities (87−95% ee). When dipropylamine with low steric hindrance was used as a nucleophile, the corresponding product was obtained with low enantioselectivity (**3s**). However, the reaction failed to proceed when diisopropylamine was employed as the nucleophile owing to its excessive steric bulk (see SI, Section 5). When employing phosphonic dichlorides exhibiting superior stereoselectivities in Scheme 2 as substrates, we observed reduced sensitivity to the steric bulk of amines compared to *p*-anisyl-substituted substrate, with all cases

Scheme 3. Scope of Amine Nucleophiles[a]



[a]Reaction conditions: A solution of **1** (0.20 mmol, 1.0 equiv) in 1.5 mL anhydrous CPME was added to a mixture of **2** (0.70 mmol, 3.5 equiv), **C10** (0.03 mmol, 15 mol %), and 4Å MS (70 mg) in 1 mL anhydrous DME at −50 °C under Ar. After stirring for 36 h at −50 °C, MeONa (2 mmol, 5.4 mol/L in methanol, 30 wt %) was added, and stirring was continued at −50 °C for 12 h. Isolated yields. The ee values were determined by chiral HPLC. Compounds **3v**, **3z**, **3ac**, and **3af**: 48 h in the first step.

delivering products (**3y**−**3ag**) in excellent enantioselectivities (92−98% ee).

The methoxy group, being ubiquitous in natural products, consequently features extensively in natural product-derived drugs.[41] Accordingly, we selected compound **1b**, featuring a 4-methoxyphenyl substituent, as the substrate with diisobutylamine as the nucleophile in the catalytic desymmetrization step to evaluate the effects of diverse nucleophiles in the enantiospecific S_N2 displacement step (Scheme 4). Sodium salts of primary and secondary alcohols proved to be effective nucleophiles in the second step, delivering products **3ah**−**3ao** with consistently excellent enantioselectivities (95−97% ee). When employing certain nucleophiles, we observed diminished enantioselectivities in the final products. This stereochemical erosion can be attributed to the Berry pseudorotation[42,43] in the pentacoordinate P(V) intermediate formed between chlorophosphonamidate and certain nucleophiles. To eliminate the detrimental impact on stereoselectivity, we introduced a silver ion in the reaction system to reduce the concentration

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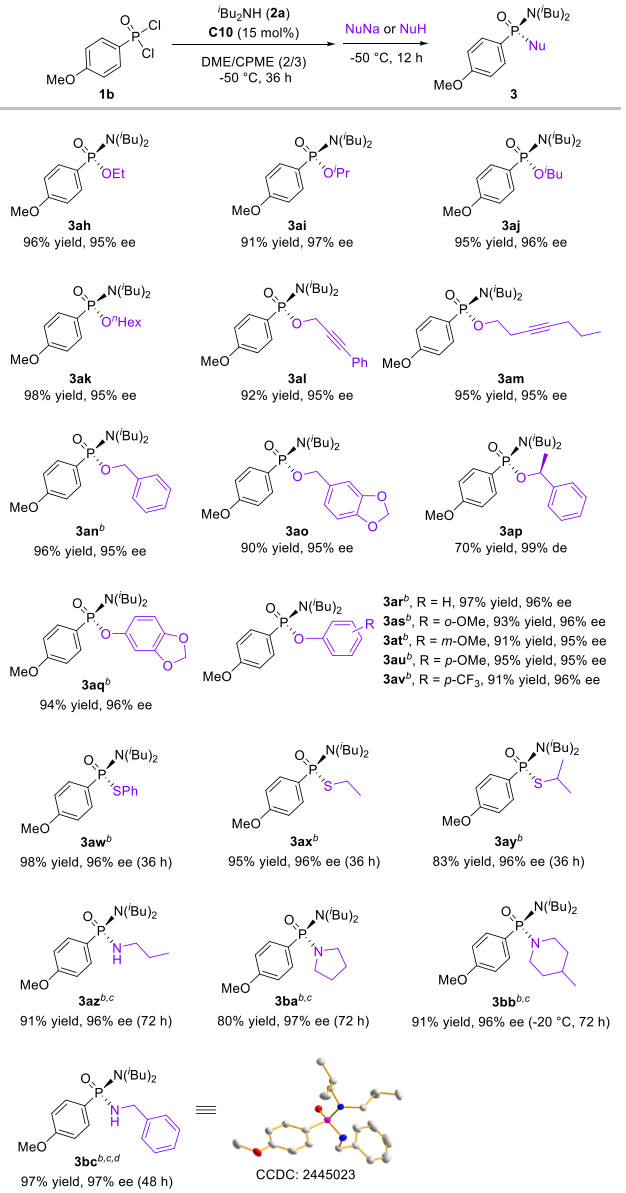
Scheme 4. Scope of Nucleophiles in Enantiospecific S_N2 Displacement of Chiral Chlorides[a]

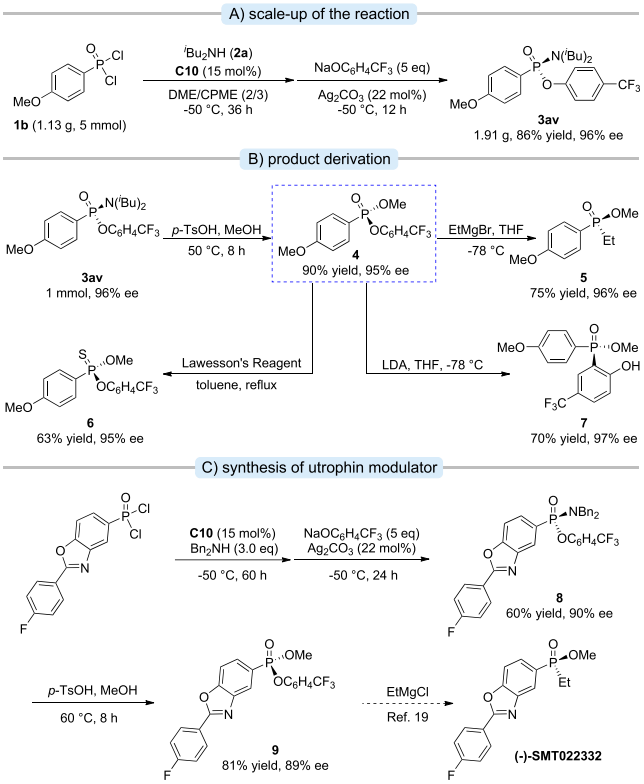


[a]Reaction conditions: A solution of **1b** (0.20 mmol, 1.0 equiv) in 1.5 mL anhydrous CPME was added to a mixture of **2a** (0.70 mmol, 3.5 equiv), **C10** (0.03 mmol, 15 mol %), and 4Å MS (70 mg) in 1 mL anhydrous DME at −50 °C under Ar. After stirring for 36 h at −50 °C, NuNa (2 mmol, 2 mol/L in THF) was added, and stirring was continued at −50 °C for 12 h. Isolated yields. The ee values were determined by chiral HPLC. [b]Synthesis of **3an**, **3aq**−**3bc**: After the reaction mixture was stirred for 36 h in the catalytic step, a suspension of Ag_2CO_3 (20 mol %) in THF (0.5 mL) was added. Then the nucleophile was introduced. [c]The nucleophile is corresponding amine (2 mmol, 10 equiv) instead of NuNa. [d]All H atoms omitted in the X-ray crystallography analysis for clarity. Compounds **3aw**, **3ax**, **3ay**: 36 h in the second step; Compounds **3az** and **3ba**: 72 h in the second step; **3bb**: 72 h under −20 °C in the second step; **3bc**: 48 h in the second step.

of the chloride ion, which would shorten the lifetime of the pentacoordinate P(V) intermediate and accelerate the formation of the product. Ag_2CO_3 was selected as the additive for the S_N2 displacement step when using certain nucleophiles (**3an**, **3aq**−**3bc**). Notably, employing the enantiomerically pure sodium (*S*)-1-phenylethan-1-olate bearing a chiral carbon as the nucleophile furnished product **3ap** with 99% de. Subsequently, employing sodium phenoxide and its analogues bearing diverse substituents on the benzene ring as nucleophiles universally provided the desired products (**3aq**−**3av**) in excellent yields (91−97%) with excellent enantioselectivities (95−96% ee). Highly enantioselective phosphonamidothioates (**3aw**−**3ay**) were accessible in good to excellent yields through nucleophilic substitution with sodium thiophenolates and sodium thiolates. Primary and secondary amines also served as efficient nucleophiles, delivering enantioenriched phosphonic diamides (**3az**−**3bc**) with exceptional stereocontrol (96−97% ee). Through the enantiospecific S_N2 displacement in the second step of this one-pot protocol, various P(V)-stereogenic compounds were efficiently obtained with excellent stereoselectivities (95−97% ee, 99% de). The versatile stereocontrolled formations of P−heteroatom (O/S/N) bonds provide a powerful platform for constructing diverse stereochemically pure P(V) compounds.

Under standard conditions at 5.0 mmol scale using 15 mol % catalyst loading, the synthesis afforded 1.91 g of **3av** in 86% yield with 96% ee, without loss of enantioselectivity (Scheme 5A). We also investigated the recycling performance of the

Scheme 5. Scalability, Functionalization, and Application



catalyst. After four catalytic cycles, the catalyst maintained catalytic efficiency (see SI, Table S7). The P-chirogenic phosphonate **4** could be obtained by alcoholysis under acidic conditions without a loss of enantioselectivity (Scheme 5B). **4** with reduced steric hindrance compared with **3av** can be converted into the following derivatives via distinct reaction pathways, respectively: (i) Phosphonate **4** was reacted with Grignard reagents to deliver the phosphinate ester **5** in 75%

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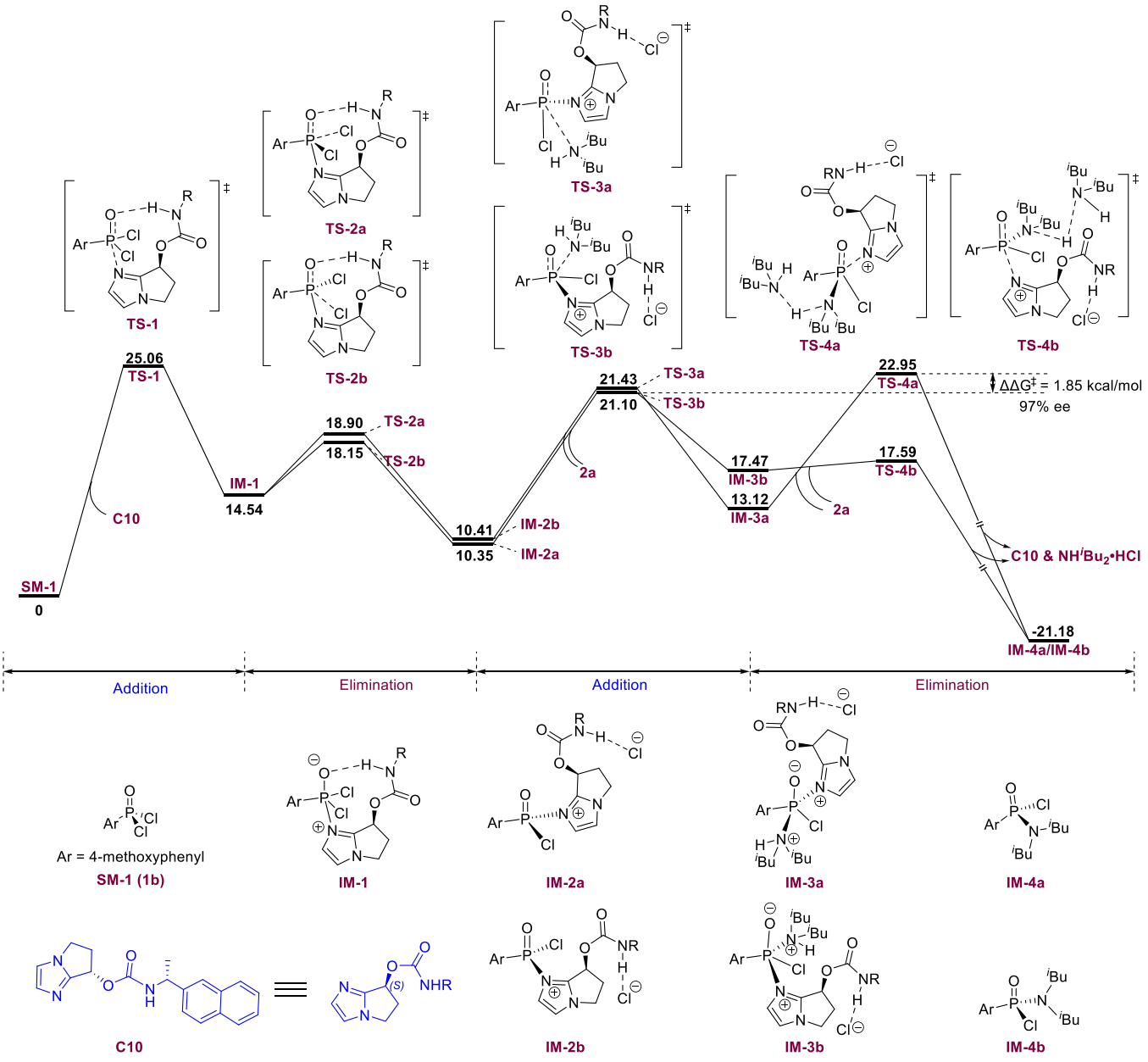

Figure 2. Gibbs energy profile of the overall reactions; the DFT computation is under the PBE0-D3BJ/CBS/PCM$_{DME/CPME=2/3}$ level of theory.

yield with 96% ee; (ii) treatment of **4** with Lawesson's reagent afforded **6** in good yield (63%) with the retention of configuration at the phosphorus center (95% ee); (iii) the lithium-induced intramolecular rearrangement of phosphonates **4** via phosphorus migration from oxygen to carbon atom afforded **7** in good yield (70%) with retained enantioselectivity (97% ee). Moreover, this methodology was applied to the asymmetric synthesis of (−)-SMT022332, a second-generation utrophin modulator preclinical candidate.[5] The optimized protocol afforded the desired product **8** with 90% ee and moderate yield (Scheme 5C). Then, a simple methanolysis of **8** delivered compound **9** in 81% yield, while maintaining high enantioselectivity. Subsequently, compound **9** could be converted to (−)-SMT022332 by substitution with a Grignard reagent.[19]

To further investigate the reaction mechanism and the origins of enantioselectivity, a computational study based on density functional theory (DFT) was performed (Figure 2). The catalytic reaction between 4-methoxyphenylphosphonic dichloride and diisobutylamine, mediated by catalyst **C10**, was computationally modeled to elucidate the reaction pathway and stereoselectivity. Initially, the catalyst **C10** undergoes a nucleophilic addition reaction with substrate **SM-1** (**1b**), forming the penta-coordinated phosphorus intermediate **IM-1** via **TS-1**. Tetra-coordinate phosphonium intermediates **IM-2a** and **IM-2b** are then afforded, followed by elimination of a chloride ion via **TS-2**. Due to the low polarity of the solvent, the chloride ion remains incompletely solvated, forming an ion pair with the imidazolium cation in **IM-2**. Subsequent nucleophilic attack by **2a** on **IM-2** generates the penta-coordinated phosphorus intermediate **IM-3** via **TS-3**. Final products **IM-4a** and **IM-4b** are formed by the elimination of catalyst **C10**, coupled with an acid−base reaction with another molecule of **2a**, via **TS-4**. This step is highly exergonic and irreversible. Based on the energy profile, the enantioselectivity stems from the energy difference between **TS-3b** and **TS-4a**

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($\Delta\Delta G^{\ddagger}$ = 1.85 kcal/mol), indicating 97% calculated ee at −50 °C, matching the experimental data (96% ee). Furthermore, the IGMH analysis of **TS-1** indicates a strong hydrogen bond (approximately −3.9 kcal/mol) between the oxygen atom of the P(V) species and the amide group of the catalyst (Figure 3). This hydrogen bond plays a critical role in enhancing the electrophilicity of the P(V) center by effectively stabilizing the negative charge on the oxygen. Consistent with this, experimental results indicate that substitution of the amide hydrogen with other groups led to a significant drop in reaction yield (Table 1, entries 6 and 7). Thus, this specific hydrogen-bonding interaction enables the nucleophilic catalyst to achieve a high catalytic efficiency even at such low temperatures.

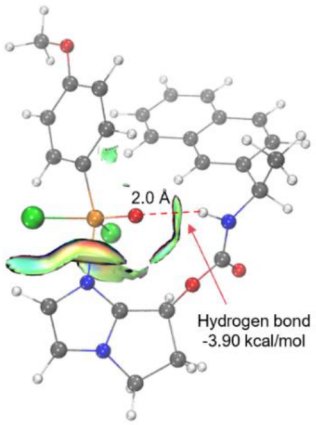

Figure 3. IGMH analysis between the catalyst and substrate in TS-1. The colors of these atoms are black (carbon), white (hydrogen), blue (nitrogen), green (chloride), red (oxygen), and orange (phosphorus).

CONCLUSIONS

In conclusion, we have successfully developed a one-pot sequential strategy integrating bifunctional chiral bicyclic imidazole-catalyzed desymmetrization of phosphonic dichlorides with enantiospecific S_N2 displacement for the direct construction of P-stereogenic centers with a C−P bond. This methodology combines facile catalyst synthesis with exceptional catalytic efficiency, establishing a versatile platform for the synthesis of chiral P(V) compounds featuring flexible combinations of variable O-, N-, S-, and C-substituents. Employing this catalytic system, diverse P-stereogenic products (55 representative products) were obtained in satisfactory yields (up to 99%) with excellent enantioselectivities (up to 98% ee). Crucially, gram-scale reactions maintained activity and stereoselectivity, while the catalyst exhibited excellent recyclability and retained performance through four catalytic cycles. This methodology holds significant promise for broad applications in medicinal chemistry, particularly in the synthesis of P-stereogenic drugs.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.5c17437.

Experimental procedures, computational details, and characterization data for all reactions and products, including ^{1}H, ^{13}C, ^{31}P, and ^{19}F NMR spectra, HPLC data, HRMS, and crystallographic data for **C10**, **3bc**(PDF)

Accession Codes

Deposition numbers 2445023 and 2445024 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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