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## Enantioselective hydrogen-bond-donor catalysis to access diverse stereogenic-at-P(V) compounds

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### Abstract

The stereoselective synthesis of molecules bearing stereogenic phosphorus(V) centers represents an enduring challenge in organic chemistry. Although stereospecific nucleophilic substitution at P(V) provides a general strategy for elaborating optically active P(V) compounds, existing methods for accessing the requisite chiral building blocks rely almost entirely on diastereocontrol using chiral auxiliaries. Catalytic, enantioselective methods for the synthesis of synthetically versatile stereogenic P(V) building blocks offer an alternative approach to stereogenic-at-P(V) targets without requiring stoichiometric quantities of chiral controlling elements. Herein, we report an enantioselective hydrogen-bond-donor-catalyzed synthesis of aryl chlorophosphonamidates, and the development of these products as versatile chiral P(V) building blocks. We demonstrate that the chlorophosphonamidates possess two leaving groups that can be displaced sequentially and stereospecifically to access a wide variety of stereogenic-at-P(V) compounds featuring diverse substitution patterns.

### One Sentence Summary:

An enantioselective sulfinamidourea-catalyzed synthesis of chlorophosphonamidates underlies a general approach to chiral P(V) compounds

### Introduction

Phosphorus(V) stereocenters are present in a wide assortment of important molecules, including several recently developed pharmaceuticals (Figure 1A). The absolute stereochemistry at phosphorus is often directly associated with the biological activity of those molecules (1–7). Stereogenic-at-phosphorus compounds also serve as broadly useful ligands and catalysts in asymmetric organic synthesis (8, 9). Though a variety of natural

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Supplementary Materials

Materials and Methods

Supplementary Text

Figs. S1 and S2

Tables S1 to S7

References (39–56)

products bearing *P*-stereogenic centers have been identified (10), these molecules are not practical synthetic building blocks due to their sparsity. Thus, whereas the synthesis of compounds bearing *C*-stereogenic centers has historically drawn heavily on nature's chiral pool (11), access to *P*-stereogenic molecules relies entirely on *de novo* synthesis. Nucleophilic substitution at stereogenic P(V) centers can occur stereospecifically, thereby providing a powerful strategy for the synthesis of complex, optically active compounds from simple P(V) building blocks bearing one or more leaving groups attached to phosphorus (9, 11–13).

Effective methods for accessing stereogenic-at-phosphorus targets have relied primarily on the use of covalently attached chiral auxiliaries to achieve diastereocontrol, and a variety of chelating auxiliaries have been developed successfully for this purpose (Fig. 1B) (14–22). Their applicability depends on stereospecific displacement of the auxiliary to forge P(V) stereocenters with absolute stereocontrol. Among noteworthy recent advances using the chiral auxiliary approach, Baran and co-workers reported the development of highly reactive oxathiaphospholane-sulfide building blocks (19, 20). The propensity of the P–S bonds in these building blocks to undergo substitution by both alcohols and organometallic reagents was demonstrated and enables the synthesis of a variety of stereogenic-at-P(V) compounds, ranging from oligonucleotides to chiral phosphine oxides.

Despite important advances in the stereoselective synthesis of chiral P(V) compounds by the chiral auxiliary approach, there is both practical and fundamental motivation for developing asymmetric catalytic strategies toward these targets. In that vein, there have been several recent breakthroughs (Fig. 1B). Dirocco and coworkers developed a chiral bisimidazole catalyzed synthesis of phosphoramidate prodrugs through the diastereoselective addition of nucleosides to chlorophosphoramidates, proceeding via a cooperative mechanism of covalent activation of P(V) and general-base activation of the alcohol nucleophile (23). An alternative approach was demonstrated by Miller and co-workers in the catalytic, stereodivergent synthesis of *P*-stereogenic oligonucleotides from phosphoramidites via chiral phosphoric acid catalysis (24). Finally, in work that appeared as this study was being completed, Dixon and co-workers reported a catalytic, enantioselective desymmetrization of diaryl phosphonate esters by substitution with *ortho*-substituted phenols (25). Although high levels of stereoselectivity were achieved in these catalytic, nucleophilic substitution reactions, each is limited to a narrow class of nucleophiles that are not further displaced. We conceived that the catalytic, enantioselective installation of a nucleophile that could further serve as a leaving group for stereospecific substitution at P(V) could provide a generalizable strategy for the synthesis of chiral P(V) targets with the broad synthetic scope of state-of-the-art auxiliary approaches while avoiding the need for the stoichiometric use of chiral control elements.

We selected chlorophosphoramidates as potential targets of an enantioselective catalytic approach (Fig. 1C). The chloride and amino groups on P(V) possess orthogonal reactivity that might permit sequential and stereospecific displacement *en route* to chiral P(V) targets bearing a broad range of substitution patterns. Given that P–Cl bonds in particular are susceptible to substitution by a wide variety of nucleophiles (26–28), chlorophosphoramidates would be highly versatile precursors to a multitude of P(V)

frameworks. We report here the development of an enantioselective method for the synthesis of chlorophosphoramidate intermediates using a commercially available hydrogen-bond-donor catalyst, and the application of these P(V) building blocks to the synthesis of P(V) compounds featuring diverse substitution patterns.

We recognized that a most concise enantioselective synthesis of chlorophosphoramidates would be realized via a catalytic desymmetrization reaction of phosphonic dichlorides with amines. Dual-hydrogen-bond-donor catalysts have been applied broadly and successfully to promote stereoselective nucleophilic substitution reactions via chloride-abstraction pathways (29–32), and we hypothesized that this reactivity principle could serve to activate one of the two enantiotopic chlorides of a phosphonic dichloride electrophile toward displacement by an amine. Phenyl phosphonic dichloride **2a** was selected as a model substrate in reactions with various amine nucleophiles and potential chiral catalysts (Fig. 2). The chlorophosphoramidate products were found to be too reactive to isolate in pure form, but solutions of **3** were stable and could be separated from other reaction components by filtration through silica. Epimerization of chlorophosphoramidate **3** was not observed under the catalytic conditions, even in the presence of added tetrabutylammonium chloride. However, concentrated solutions of **3** underwent racemization slowly at room temperature over multiple hours (Table S10). For purposes of isolation and analysis, the chlorophosphoramidates were quenched with sodium methoxide at low temperature to produce the corresponding phosphoramidates (e.g. **4a**). After systematic evaluation of a series of chiral dual H-bond-donor catalysts and amine nucleophiles, the sulfinamido urea **1a** (33, 34) was found to promote the nucleophilic substitution by diisoamylamine in 95% enantiomeric excess (ee) and quantitative yield (Fig. 2A, see supplementary materials for optimization studies). Multiple equivalents of amine were required to attain full conversion of **2a**, as the amine functions both as a nucleophile and as a stoichiometric Brønsted base to trap the HCl byproduct produced in the reaction. Examination of the role of catalyst structure revealed the importance of both the H-bond donor and the sulfinamide group in promoting high enantioselectivity. Whereas sulfinamido urea **1a** and its thiourea analog **1b** proved similarly effective as catalysts, the sulfinamide **1d** lacking the H-bond-donor motif induced little acceleration above the uncatalyzed rate (83% vs. 64% yield after 24 h) and afforded only racemic product. The sulfinamido urea **1c** epimeric to **1a** also induced severely diminished enantioselectivity, a stereochemical “mismatch” effect that has also been observed in other applications of this catalyst (33, 34) and one that is strongly suggestive of cooperative participation of the H-bond donor and the sulfinamide in the enantiodetermining step. Arylpyrrolidino (thio)ureas such as **1e–g**, which have proven useful in a wide range of asymmetric anion-binding pathways (35) but lack the sulfinamide moiety, were catalytically active but generally poorly effective with respect to enantiocontrol. The enantioselectivity of the substitution was also closely tied to the identity of the amine, with diisoamylamine undergoing reaction with distinctly superior results relative to any of the other nucleophiles examined (Fig. 2B). Beyond a beneficial effect of distal alkyl branching, it is difficult to discern any straightforward correlation between the steric or electronic properties of the amine and enantioselectivity in the substitution reaction. Control studies suggest that the properties of the dialkylammonium chloride byproducts likely play a critical and complex role in influencing the observed enantioselectivity, either as inhibitors of the

anion-binding H-bond-donor catalyst or by promoting a racemic pathway between **2a** and the dialkylamine (Tables S8–S9).

High levels of enantioselectivity were achieved in the reaction of a variety of aryl phosphonic dichlorides with diisoamylamine (Fig 3A). Substrates bearing arenes with either electron-withdrawing or electron-donating substituents underwent substitution with consistently high levels of enantioselectivity (**4b–g**). In contrast, alkyl phosphonic dichlorides are ineffective substrates for the enantioselective reaction. For example, hexylphosphonic dichloride was converted to the corresponding phosphoramidate in only 26% ee and 50% yield under the catalytic conditions.

The products of the enantioselective reactions feature two chemically distinct leaving groups on phosphorus that could be selectively and stereospecifically displaced to afford access to multiple classes of chiral P(V) compounds. We first explored the scope of nucleophiles capable of enantiospecific displacement of the remaining chloride (Fig. 3B). Reaction of **3** with alkoxides, phenoxides, thiolates, carbamides, and Grignard reagents afforded the desired products with high levels of enantiospecificity (es) in all cases (**5a–h**). The substitution reactions could be performed after the enantioselective catalytic step with or without purification of **3** in solution (see supplementary materials for details). We found that the reactions could be scaled up without loss of enantioselectivity or yield; thus, the synthesis of **5d** was performed by the one-pot procedure on 3 mmol scale with 5 mol% catalyst, affording 1.11 grams of product in 95% yield and 92% ee (Fig. 3D).

The products of the chloride-displacement reactions could be further elaborated to afford alkoxy-substituted P(V) compounds via an acid-mediated stereoinvertive displacement of the diisoamylamino group (Fig. 3C). Substitution of **5a–h** with methanol yielded a variety of enantioenriched phosphonates, phosphinates, and phosphoramidates (**6a–h**) with nearly complete enantiospecificity observed in every case. The slightly diminished stereospecificity observed with **5g** and **5h** is consistent with prior observations (14, 16). Substitution with other primary alcohols proceeded with varied but generally high levels of enantiospecificity (**6i–k**).

The phosphonate ester and thioester products **6b** and **6d** possess further readily displaceable substituents that render them useful synthetic building blocks for further elaboration to chiral P(V) compounds. For example, phosphonate thioester **6d** underwent reaction with functionally complex alcohols to furnish the corresponding phosphorylated biomolecules with high levels of stereospecificity (**7a–c**, Fig. 4A). These substitutions are performed under Brønsted-acid-free conditions using little-or-no excess of the alcohol reagent, highlighting the utility of **6d** for the phosphorylation of precious or acid-sensitive alcohols. Phosphonate **6b** underwent efficient substitution with Grignard reagents with displacement of the electron-deficient aryloxide to yield highly enantioenriched phosphinate esters, known precursors to chiral phosphine oxides (Fig. 4B) (20). This three-step route to phosphinate esters was applied to the synthesis of (+)-SMT022332, a utrophin modulator developed as a potential treatment for Duchenne Muscular Dystrophy (36–38). An analogue of (+)-SMT022332 was previously accessed in 83% ee and 5% overall yield using a chiral auxiliary-based approach (4). Subjection of phosphonic dichloride **9** to

the optimized conditions for the enantioselective substitution yielded phosphoramidate **10**, which was characterized crystallographically (Fig. 4C). Subsequent methanolysis and phenol displacement furnished (+)-SMT022332 (**12**) in 94% ee and 43% overall yield over 3 steps.

In addition to serving as versatile synthetic building blocks, phosphoramidates are often synthetic targets themselves (2, 3, 5, 6, 39–43), and general access to these compounds by the catalytic procedure would be desirable. However, the structural requirements on the amine for achieving high enantioselectivity in catalytic reaction impose restrictions to the *N*-substituents that can be introduced directly (Fig. 2B). We therefore sought to identify amine derivatives that participate successfully in the enantioselective reaction while bearing orthogonally cleavable *N*-protecting groups that might provide centralized access to a variety of substituted phosphoramidates (Fig. 4D). High enantioselectivity was obtained using *N*-allyl benzylamine in the substitution reaction under modified conditions. The benzyl group and the allyl group on the chlorophosphoramidate products can each be cleaved successively, enabling their sequential replacement (see supplementary materials) (44–48). This strategy was exploited in the synthesis of phosphoramidate **17**, a matrix metalloproteinase (MMP) inhibitor with demonstrated anticancer activity (Fig. 4E) (2). Phosphonic dichloride **2h** effectively underwent the catalytic reaction with *N*-allylbenzylamine to produce, after quenching with allyl alkoxide, phosphoramidate **13** in 89% ee and 88% yield. Phosphoramidate **13** was elaborated over three steps to afford cyclic phosphoramidate **16** in 90% ee, completing the enantioselective formal synthesis of MMP inhibitor **17**. We anticipate that *N*-allyl benzylamine's versatility as a masked “–NH<sub>2</sub>” equivalent may enable access to a wide variety of phosphoramidate targets.

We expect the versatile enantioenriched chlorophosphoramidate intermediates accessed via synthetic strategies outlined herein to enable the facile synthesis of both known and new stereogenic-at-P(V) compounds of interest.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Data and materials availability:

Crystallographic data for compound **10** are available free of charge from the Cambridge Crystallographic Data Centre under reference CCDC 2155524. All other data are available in the main text or the supplementary materials.

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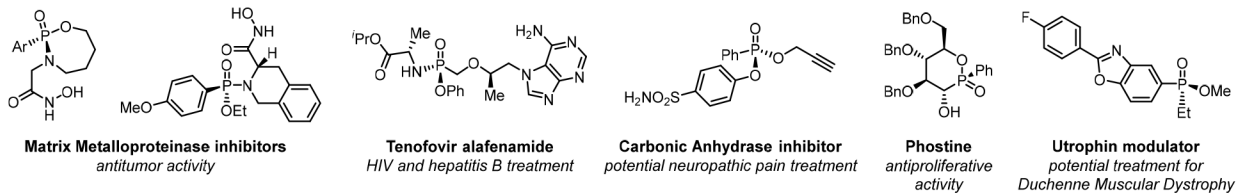
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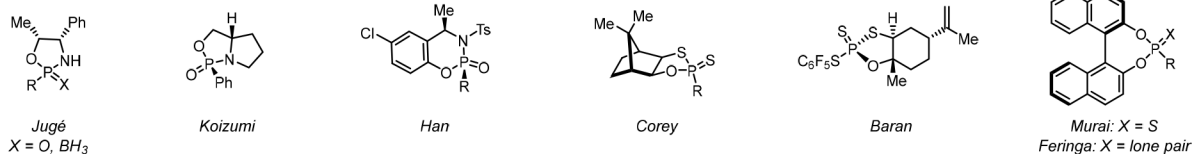
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**A. Examples of phosphoramidates, phosphonates, and phosphinates bearing *P*-stereogenic centers**



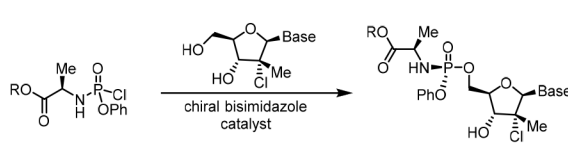
**B. Nucleophilic substitution methods for constructing stereogenic-at-P(V) targets**

*Chiral-Auxiliary-Based Strategies*

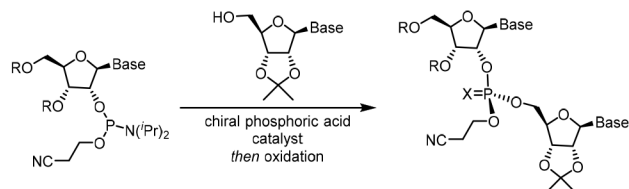


*Catalytic Strategies*

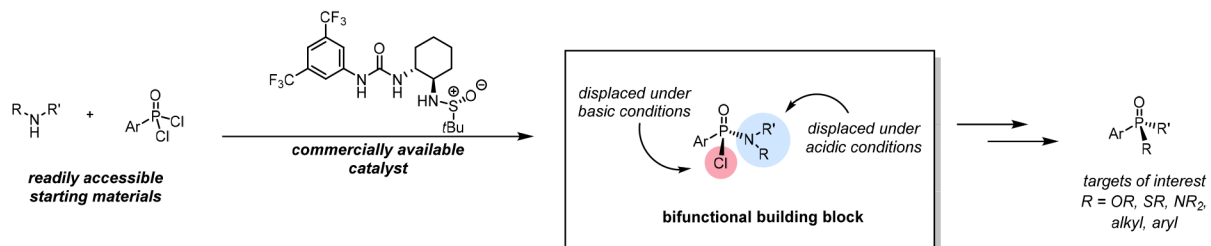
*DiRocco (2017): Dynamic kinetic resolution of chlorophosphoramidates*



*Miller (2021): Dynamic kinetic resolution of phosphoramidites*



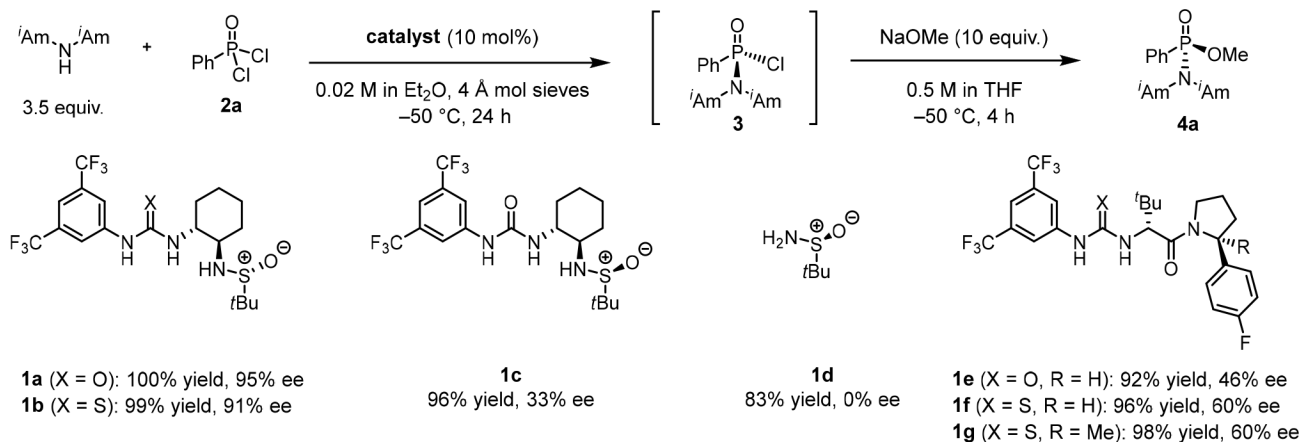
**C. This work:** catalytic synthesis of chiral P(V) building blocks via hydrogen-bond-donor catalysis



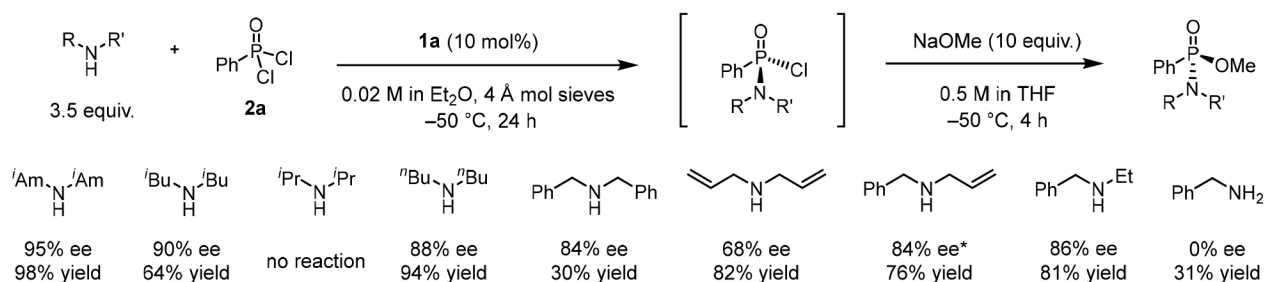
**Fig. 1. Methods for accessing stereogenic P(V) targets.**

(A) Representative bioactive compounds bearing *P*-stereogenic centers. (B) Synthetic approaches to stereogenic-at-P(V) targets using chiral auxiliaries (14–22) and stereoselective catalysis (23, 24). (C) A general approach to chiral P(V) building blocks via enantioselective catalysis/stereospecific substitution.

## A. Catalyst optimization



## B. Effect of Amine Structure



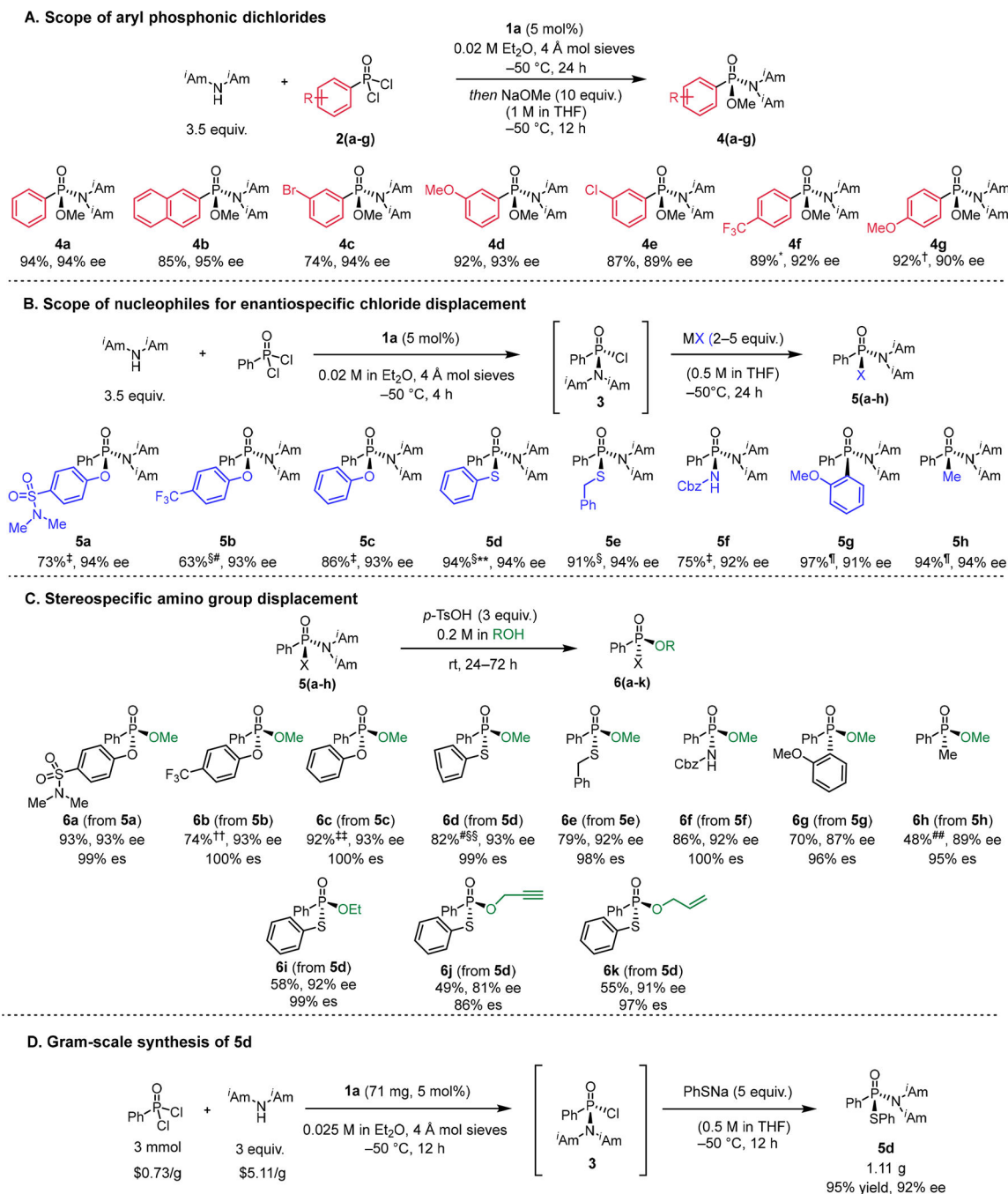
## Figure 2. Optimization studies.

Yield values reflect product quantification by  $^{31}P$  NMR relative to an internal standard.

Reactions were carried out using a one-pot procedure without purification of **3**.

Concentration values correspond to the initial concentration of the limiting stoichiometric reagent. (A) Catalyst optimization for enantioselective reaction of diisoamylamine with phenyl phosphonic dichloride. Reactions were carried out on a 0.06 mmol scale. (B)

Optimization of amine structure for enantioselective substitution reaction with phenyl phosphonic dichloride. Reactions were carried out on a 0.06 mmol scale. \*Reaction performed at  $-40$  °C for 48 h.



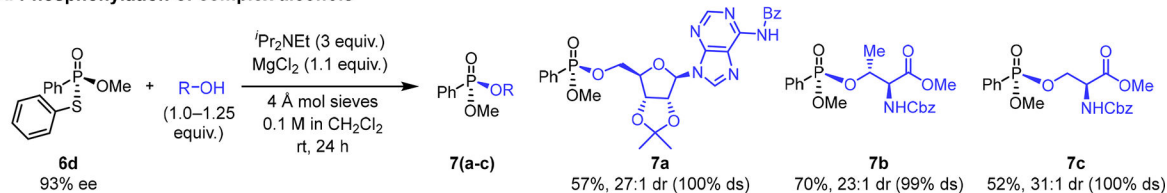
**Fig. 3. Scope of enantioselective addition of diisoamylamine to aryl phosphonic dichlorides and stereospecific elaborations.**

All yield values correspond to chromatographically purified, isolated products.

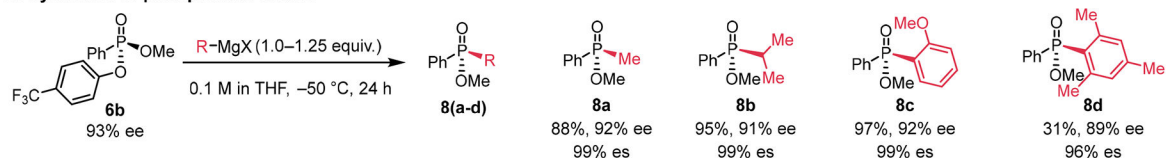
Concentration values correspond to the initial concentration of the limiting stoichiometric reagent. (A) Substrate scope of addition of diisoamylamine to aryl phosphonic dichlorides catalyzed by **1a**. Reactions were carried out on 0.2 mmol scale. The absolute stereochemistry of the products was assigned based on the x-ray crystal structure of **10** and the known optical rotation of **8a** (Fig. 4, see supplementary materials). (B) Scope of

nucleophiles for enantiospecific substitution with **3**. (C) Enantiospecific displacement of the diisoamylamino group with alcohols. See supplementary materials for reaction conditions. (D) Gram-scale synthesis of **5d**. Prices from Thermo Fisher Scientific (February, 2022). \*Reaction was carried out at  $-78\text{ }^{\circ}\text{C}$  with 20 mol% catalyst loading. †Reaction was carried out at  $-40\text{ }^{\circ}\text{C}$  with 4.5 equivalents of diisoamylamine. ‡ Reaction was carried out in a two-pot procedure involving generation of **3** in solution and purification by filtration through silica and subsequent reaction with 2 equivalents of nucleophile. § Reaction was carried out using one-pot procedure without purification of **3** with 5 equivalents of nucleophile. ¶ Reaction was carried out in a two-pot procedure involving generation of **3** in solution and purification by filtration through silica and subsequent reaction with 5 equivalents of nucleophile. #Reaction was carried out on 0.9 mmol scale. \*\*Reaction was carried out on 1.0 mmol scale. ††Reaction was carried out on 0.57 mmol scale. ‡‡Reaction was carried out on 0.24 mmol scale. §§ Reaction was run at 0.3 M concentration instead of 0.2 M. ## $\text{H}_3\text{PO}_3$  was used instead of *para*-tolylsulfonic acid.

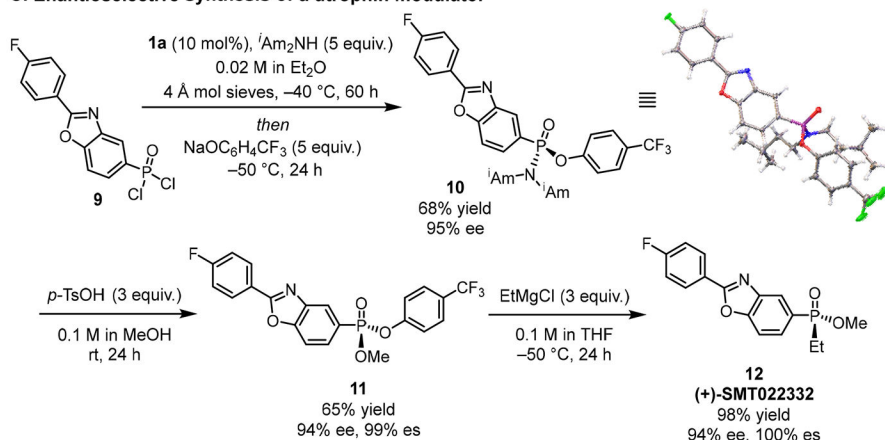
## A. Phosphonylation of complex alcohols



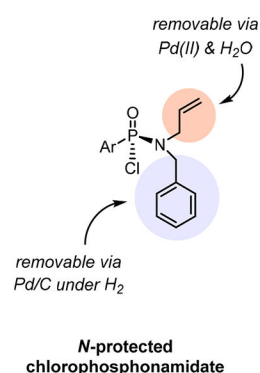
## B. Synthesis of phosphinate esters



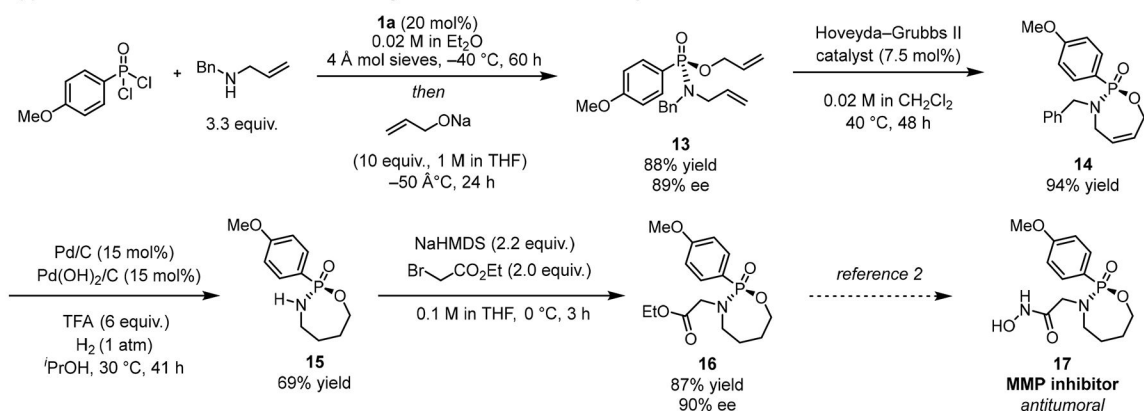
## C. Enantioselective synthesis of a utrophin modulator



## D. Synthetic precursor to N-substituted P(V) targets



## E. Application to the enantioselective formal synthesis of a matrix metalloproteinase inhibitor



## Fig. 4. Application to the synthesis of chiral P(V) targets.

All yield values refer to chromatographically purified, isolated products. Concentration values correspond to the initial concentration of the limiting stoichiometric reagent. (A) Stereospecific phosphonylation of precious alcohols with **6d**. Reactions were carried out on 0.1 mmol scale. (B) Stereospecific addition of Grignard reagents to **6b** for the synthesis of enantioenriched phosphinate esters. Absolute stereochemistry of **8a** was determined by comparison of optical rotation to literature value; others assigned by analogy. Reactions run on 0.05–0.1 mmol scale. \*Prepared from **6b** that was in 92% ee. (C) Application of method

to the enantioselective synthesis of (+)-SMT022332. Yield values refer to isolated yields. Absolute stereochemistry of **10** assigned by the depicted X-ray crystal structure, and of **12** by comparison of the optical rotation to the literature value. **(D)** Orthogonally *N*-protected chlorophosphonamidate. **(E)** Formal synthesis of a matrix metalloproteinase inhibitor. TFA = trifluoroacetic acid.

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