

Pathway to P(V)-Stereogenic Phosphoramidates by Enantioselective Yttrium Catalysis

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ABSTRACT: P-stereogenic phosphoramidates prove essential in agrochemicals and medicines, but their construction remains a challenge for enantioselective catalysis. We describe a Yttrium-catalyzed desymmetrization supported by Feng-ligands. An achiral oxazolidinyl phosphorodichloridate undergoes enantioselective nucleophilic substitution with phenols at ambient temperatures, followed by a stereospecific addition with amines in one pot. The resulting P-stereogenic phosphoramidate serves as a trifunctional building block to access diverse P(V) motifs, enabling the stereodivergent synthesis of protected ProTides and the first stereoselective total synthesis of phosmidosine.

Once an academic curiosity,¹ the creation of chiral-at-phosphorus molecules transformed organic synthesis and human health. A P(III)-stereogenic phosphine sparked the explosion of enantioselective catalysis, the modern paradigm for chiral building blocks.² Conversely, a P(V)-chiral center underpins McGuigan's ProTide approach, resulting in the life-changing antivirals sofosbuvir and remdesivir.³ Outside synthetic motifs, P-stereogenic phosphoramidates occur in nature, exemplified by natural antibiotics microcin C and phosmidosine.^{4–7} The configuration at phosphorus influences its biological function.^{8–19} Given their growing significance, a pathway to these P(V)-stereogenic scaffolds, bearing four distinct heteroatom groups, warrants development by enantioselective catalysis (Figure 1A).

Considering this P(V) challenge, we imagined a Lewis-acid-catalyzed desymmetrization of an achiral phosphorodichloridate reagent bearing an oxazolidinone.^{20–22} The oxazolidinone serves dual roles: (1) favors bidentate coordination of substrate to a chiral catalyst and (2) acts as a leaving group to be displaced downstream without loss of stereochemistry. For the two nucleophilic partners, we chose phenols for the enantioselective desymmetrization, followed by amines for stereospecific substitution in one pot. The resulting P-stereogenic phosphoramidate represents a modular scaffold for late-stage diversification under orthogonal conditions: the oxazolidinone can be displaced under Lewis-acidic conditions, the phenol under Brønsted acidic conditions, and the amine under Brønsted acidic conditions, all with stereospecificity. This trifunctional building block provides an entry to P(V)-stereogenic chemical space, including prodrugs and natural products (Figure 1B).

Our proposed desymmetrization at phosphorus builds on contributions from both academic and industrial laboratories (Figure 1C). Industrial synthesis of ProTide drugs requires separation of a diastereomeric mixture by recrystallization, followed by stereospecific substitution at phosphorus—a scalable but wasteful strategy with limited generality.^{23–25} A more mechanistically guided approach uses chiral auxiliaries to

differentiate diastereotopic leaving groups at phosphorus.^{26–28} Alternatively, DyKAT features a single leaving group on a phosphorus center appended to a chiral amine; inherent selectivity can be enhanced or reversed via catalytic additives, including achiral Lewis-acids,²⁹ chiral Lewis-acids,³⁰ achiral Lewis-bases,³¹ or chiral Lewis-bases^{32,33} (Figure 1C).

Desymmetrization represents a challenging advance, where two enantiotopic leaving groups must be differentiated by a chiral catalyst. Jacobsen and Dixon demonstrated this concept to prepare phosphonates and phosphoramidates (containing P–C bonds) through H-bond donor³⁴ and bisiminophosphorane^{35,36} catalysis, respectively. In the Jacobsen design, orthogonal reactivity is confined to two substituents, defining a 2D space for downstream diversification. By mapping this concept onto a reagent featuring a displaceable (achiral) auxiliary in place of a static P–C bond, we introduce a third axis of reactivity. During the preparation of this manuscript, two independent manuscripts reported desymmetrization of aryloxy-phosphorodichloridates using chiral phosphoric acid (CPA) and Lewis-base catalysts, respectively.^{37,38} Both feature aliphatic alcohols and require cryogenic conditions (–70 °C for >24 h or –80 °C for >48 h). In contrast, we report a yttrium-catalyzed desymmetrization featuring aromatic alcohols at ambient temperatures in under 1 h. While industrial routes require balancing numerous factors, the academic studies by Li, He, and our team provide a conceptual path to P-stereogenic phosphoramidates with complementary scope and modes of catalysis.

Results and Discussion. To illustrate our concept, we identified the appropriate reagent, catalyst, and base combina-

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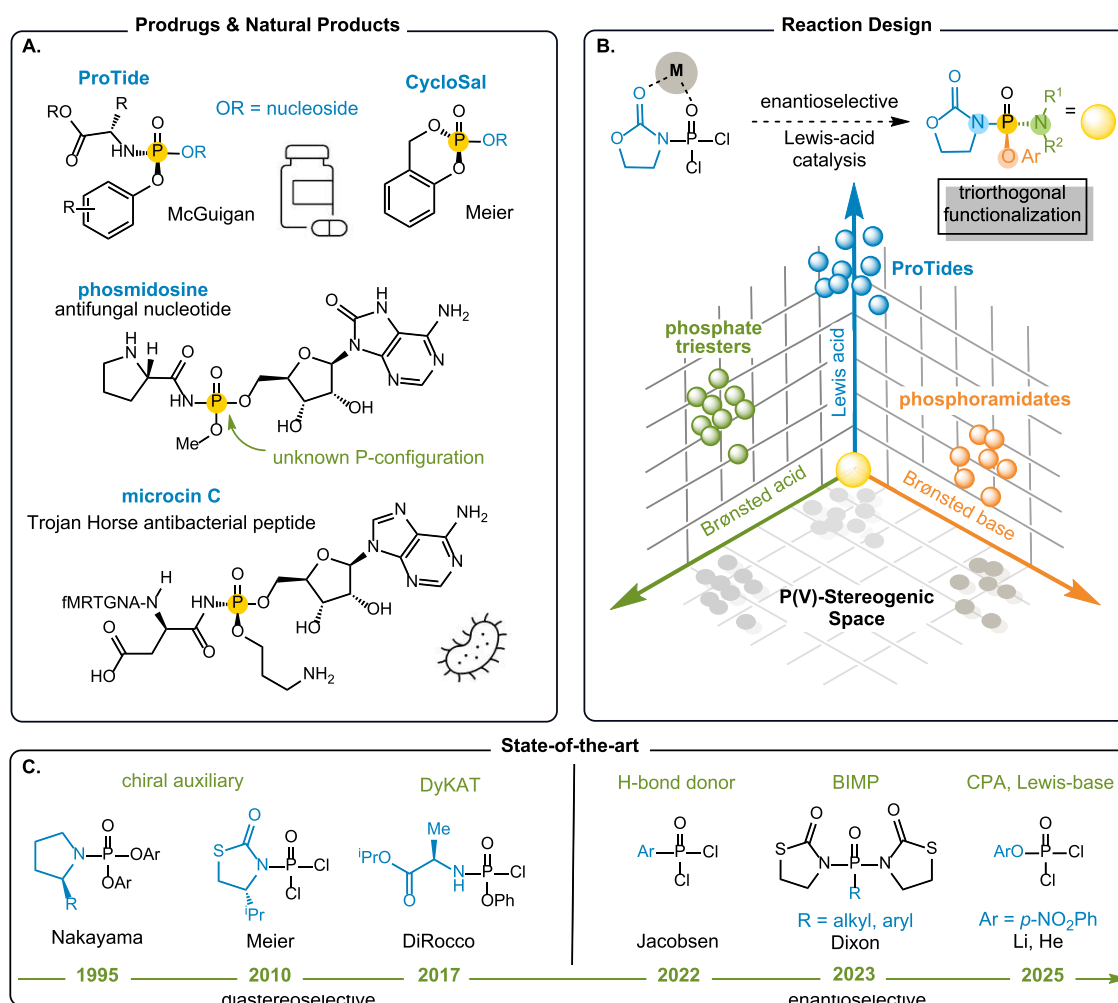


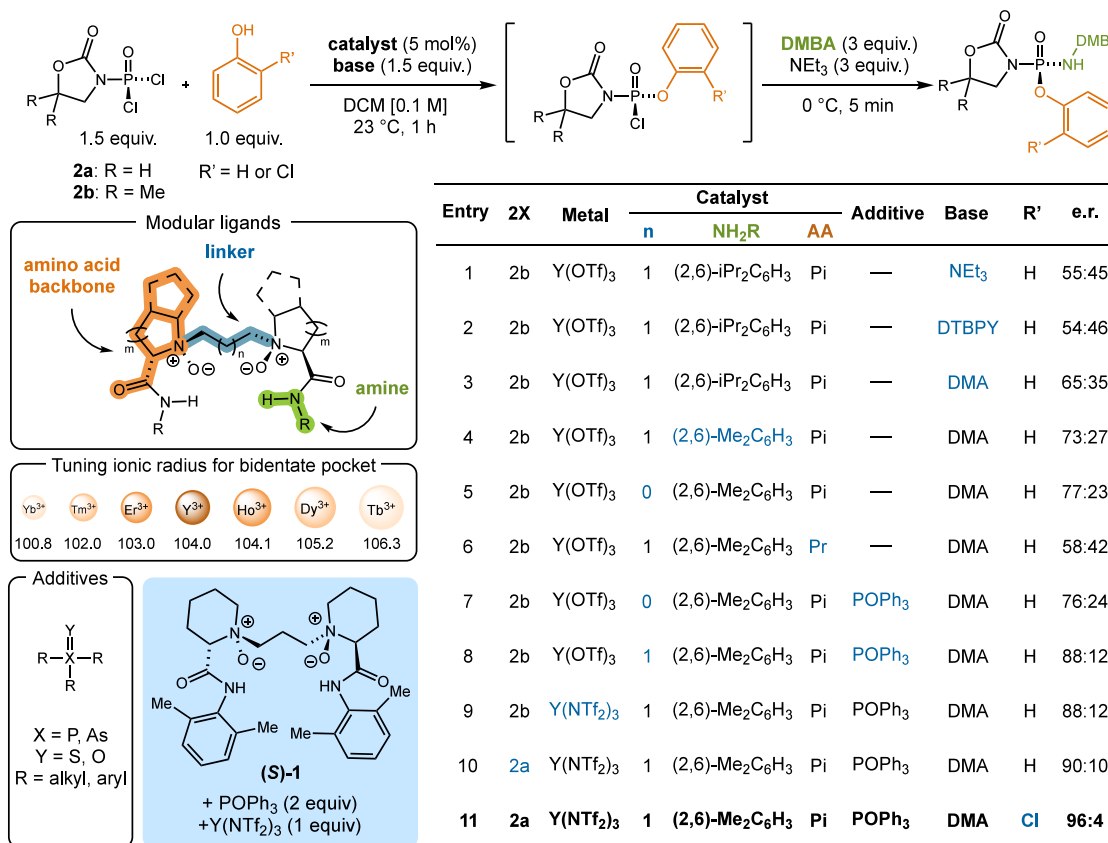
Figure 1. A. P(V)-stereogenic prodrugs and natural products. B. Proposed Lewis-acid catalysis to access P-stereogenic phosphoramidates for triorthogonal functionalization. C. From chiral auxiliaries to enantioselective catalysis.

tion. From a study of phosphorodichloridates incorporating achiral auxiliaries, oxazolidinone emerged. It engages in bidentate coordination with the Lewis-acid catalyst, tempers reactivity to suppress background, and undergoes displacement under mild conditions (*vide infra*). We developed a multigram synthesis of oxazolidinyl-phosphorodichloridates **2a** and **2b** from POCl_3 . Among Lewis-acid salts, we found lanthanide triflates uniquely effective. Yttrium triflate delivered optimal enantioselectivity, while lanthanides with larger or smaller ionic radii gave diminished selectivity, suggesting a strong size-match for catalyst-substrate fit. Tridentate ligands such as PyBox gave inconsistent results, while tetradentate scaffolds like BiPyBox and Feng ligands^{39,40} showed more uniform behavior. Tetradentate ligands provide greater control over the primary coordination sphere, helping to suppress catalyst speciation (Scheme 1).

Using this reagent/catalyst platform, we found that the base plays a role in enantiocontrol. With phenol as a relatively acidic nucleophile, strong bases like Et_3N ($\text{p}K_{\text{a}} \approx 10.7$) accelerate background, diminishing enantioselectivity (entry 1). Weaker bases, such as 2,6-di-*tert*-butylpyridine (DTBPY) and *N,N*-dimethyl aniline (DMA), precluded background reactivity at room temperature. DTBPY has a similar basicity ($\text{p}K_{\text{aH}} = 4.95$)⁴¹ to DMA ($\text{p}K_{\text{aH}} = 5.07$),⁴² but DTBPY gave intermediate enantioselectivity, suggesting basicity alone does

not account for the observed trend (entry 2). We suspect that DMA's electronic and structural features can influence the chiral environment by coordination to yttrium (entry 3).

Inspired by the modular design of Feng ligands, we prepared and investigated over 30 variants. Ligands derived from pipercolic acid, 2- and 3-carbon linkers, and 2,6-disubstituted anilines gave the most promising results (entries 4–6). Adding triphenylphosphine oxide (Ph_3PO) improved enantioselectivity, with optimal results obtained using two equivalents relative to the metal salt.⁴³ The effect was strongly ligand-dependent: while L3-Pi-Me₂ showed substantial improvement (entry 4 vs entry 8), the corresponding two-carbon linker ligand, L2-Pi-Me₂, saw no benefit (entry 5 vs entry 7). Also, L3-Pi-Et₂ gave higher selectivity than L3-Pi-Me₂ without an additive, but this trend reversed upon additive inclusion. Switching the triflate counterion to bistriflimide accelerated the transformation (completion within 30 min compared to 2 h) but had no appreciable effect on enantioselectivity (entry 9). The catalyst may be generated *in situ* by combining $\text{Y}(\text{NTf}_2)_3$, L3-Pi-Me₂, and Ph_3PO in a 1:1:2 molar ratio or preformed by mixing the components in THF followed by solvent removal under reduced pressure. Our current protocol features phosphorodichloridate **2a** (1.5 equiv), 2-chlorophenol (1.0 equiv), and DMA (1.5 equiv) in DCM (0.1 M), at 5 mol % catalyst loading. Within 1 h at ambient temperature, the reaction

Scheme 1. Reagent, Catalyst, and Reaction Development^a

^aIonic radii listed in picometers (see the SI for full details). DMBA, 2,4-dimethoxybenzylamine; DMA, *N,N*-dimethylaniline; L2, 2-methylene linker; L3, 3-methylene linker; Pi, derived from pipecolic acid; Pr, derived from proline; NH₂R, specifies amine used to synthesize ligand; AA, specifies amino acid used to synthesize ligand.

mixture is cooled to 0 °C and treated with a solution of 2,4-dimethoxybenzylamine (3 equiv) and Et₃N (3 equiv). This mild one-pot sequence provided P-stereogenic phosphoramidate in 87% yield with 96:4 er, using preformed catalyst (S)-1 (entry 11).

Amines and Phenols. With this protocol, we examined the scope of both amine and phenol nucleophiles (Scheme 2). A broad range of amines proved to be compatible when 2-chlorophenol was used in the desymmetrization step. This scope included primary (3a), secondary (3b–3e), *N*-aryl (3f), and heterocyclic (3) amines. Notably, solid amine hydrochloride salts could be added directly to the reaction mixture and treated with NEt₃ to furnish products 3b and 3c. The similar er values observed across these amines indicate that enantioinduction arises during phenol substitution, with subsequent chloride displacement occurring stereospecifically.

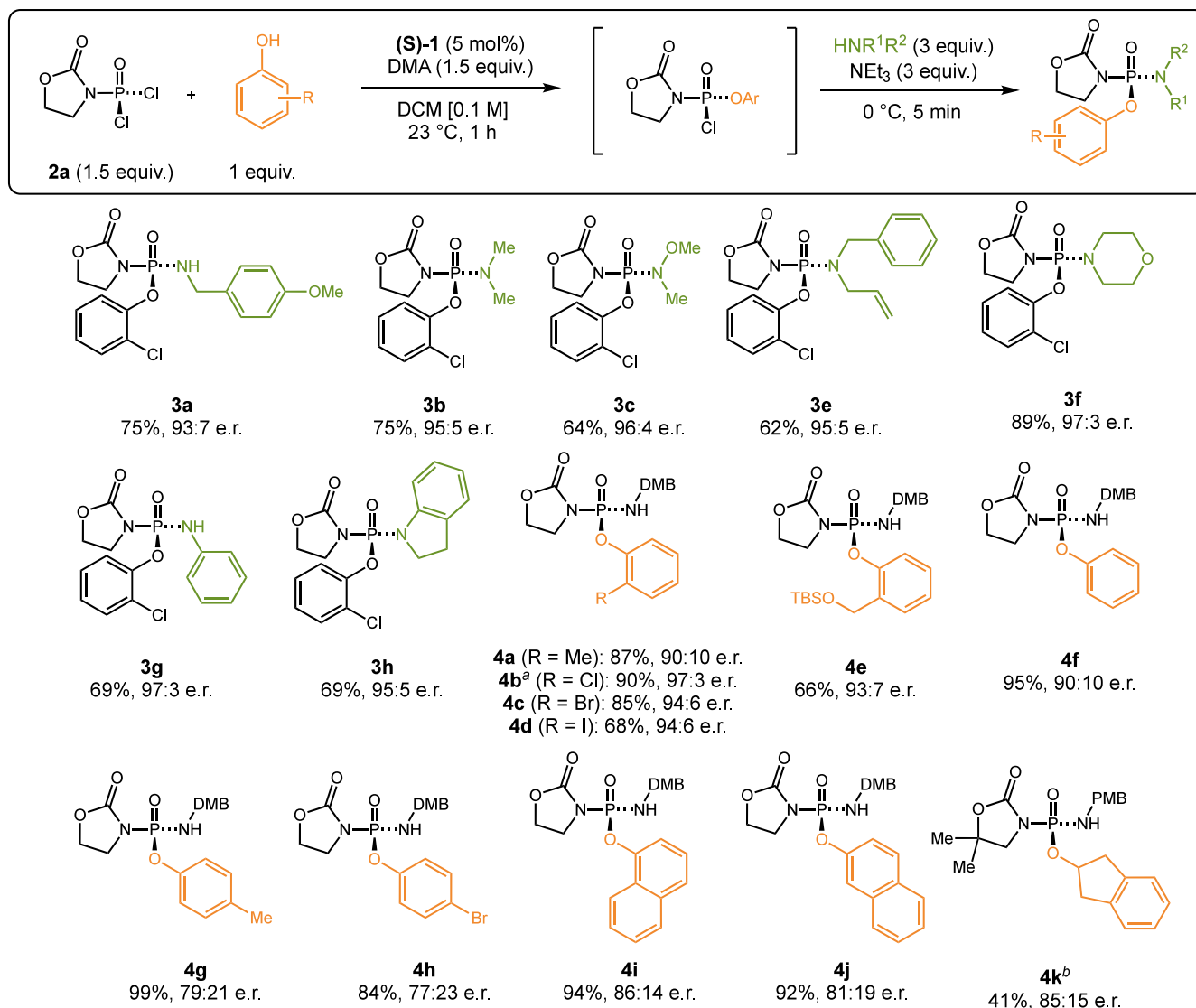
Phenol substitution was also broadly tolerated. Ortho-substituted phenols (4a–e) consistently gave high yields and enantioselectivity, including the CycloSal precursor 4e (66% yield, 93:7 e.r.). Unsubstituted phenol 4f afforded product in 95% yield and 90:10 e.r. Para-substituted phenols (4g,h), 1-naphthol (4i), and 2-naphthol (4j)—all relevant in ProTide design—provided high yields (84–92%) but more modest enantioselectivity (77:23–86:14). Under modified conditions involving NEt₃ and a reoptimized ligand (see the SI), indanol (4k) gave 85:15 e.r., whereas it was otherwise unreactive under standard conditions. These findings suggest that further tuning of the catalyst environment would encompass alkyl alcohol

nucleophiles. Our initial studies focused on phenols because of their relevance to prodrugs.

Prodrugs. Chiral-at-phosphorus prodrugs such as remdesivir and sofosbuvir exemplify the ProTide strategy, which transformed development of nucleoside drugs.³ While highly effective, this technology comes at the cost of increased synthetic complexity, namely, controlling the configuration at phosphorus. The amino acid moiety introduces an additional stereogenic element, and catalytic DyKAT approaches can exploit this preset center to access the (*R*, *R*_p),³² (*S*, *S*_p),³³ or mismatched (*R*, *S*_p)/(*S*, *R*_p)³⁰ diastereomers by distinct optimizations. In contrast, our enantioselective strategy represents a unified and stereodivergent approach, where the configuration of the phosphorus center can be independently selected without relying on substrate chirality. By simply choosing the enantiomer of the catalyst for desymmetrization, followed by stereospecific substitution with either D- or L-alanine, we can prepare precursors to all four possible ProTide diastereomers (5a–5d) in 69–80%. Each was obtained with a 9:1 dr (by ³¹P NMR), matching the enantiomeric ratio observed for 4f, and isolated as single stereoisomers after chromatography (Scheme 3A). The absolute configuration of 5a was determined by X-ray analysis.

Using MgCl₂ and NEt₃, we achieved high yields and diastereoselectivity for oxazolidinone substitution in the (*S*, *R*_p) and (*R*, *S*_p) diastereomers, delivering BOM-protected stavudine conjugates 6a (77% yield, >20:1 d.r.) and 6d (71% yield, 14:1 d.r.). In contrast, the (*S*, *S*_p) and (*R*, *R*_p) diastereomers

Scheme 2. Scope of Alcohols and Amines for Enantioselective Synthesis of Phosphoramidates



^aPerformed on 1.5 g scale in 90% yield and 95:5 e.r. ^bSeparate conditions; see the SI for details.

gave lower selectivity (3.6:1 and 5.8:1 dr) under these conditions. ³¹P NMR studies revealed that d.r. erosion arose from epimerization of the starting material: (*S*, *S_p*) and (*R*, *R_p*) gradually isomerized to their respective (*S*, *R_p*) and (*R*, *S_p*) counterparts, which then underwent substitution to form the undesired diastereomers. This issue was compounded by the slower substitution rates of the (*S*, *S_p*) and (*R*, *R_p*) starting materials relative to their epimerized forms.

To address this, we identified alternative conditions using Me_2AlCl and 2,6-lutidine, which suppressed epimerization while maintaining the reactivity. These conditions, originally developed by Silverman and co-workers at Merck & Co. for industrial ProTide synthesis, proved effective here.^{23,24} Substitution of the (*R*, *R_p*) and (*S*, *S_p*) diastereomers with BOM-protected stavudine now proceeded stereospecifically, providing the desired **6b** and **6c** in 56% and 62% yield, respectively, each with >20:1 d.r. In addition, we coupled the (*S*, *R_p*) intermediate with protected derivatives of additional nucleosides under the $\text{MgCl}_2/\text{NEt}_3$ conditions. Nucleosides derived from sofosbuvir (**7**), zidovudine (**8**), and remdesivir (**9**) furnished the corresponding ProTide conjugates in 78%,

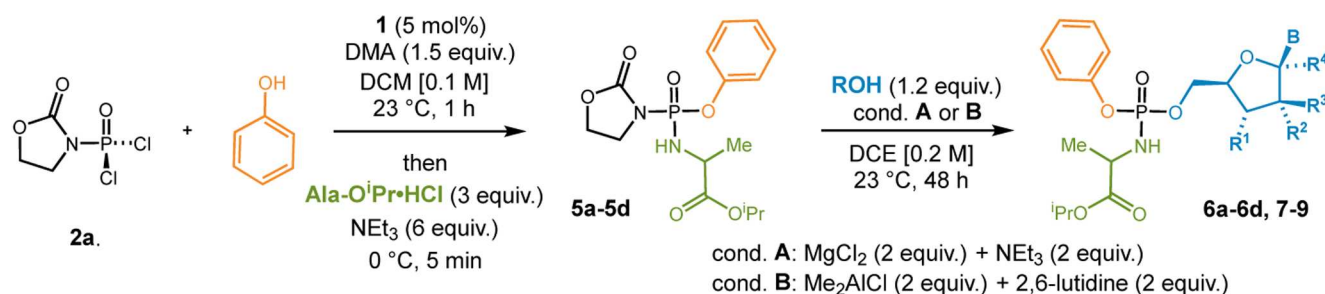
75%, and 73% yield, all with >20:1 d.r. While the He strategy³⁸ features simplified nucleosides, we focused on the medically relevant ones; we found that protection of the nucleobase nitrogen gave superior yields to the unprotected nucleosides.

The Meier's CycloSal prodrug offers a promising route for nucleoside delivery.^{28,44} Treating **4e** with para-toluene sulfonic acid (p-TsOH) results in deprotection of the TBS group and concomitant cyclization to afford CycloSal oxazolidone **10** in 80% yield with excellent stereospecificity. This transformation highlights how the orthogonal reactivity of the amine provided the *S_p* diastereomer of CycloSal (**11**), derived from BOM-protected stavudine with complete stereospecificity, albeit in a low yield under standard conditions optimized for ProTides (Scheme 3B).

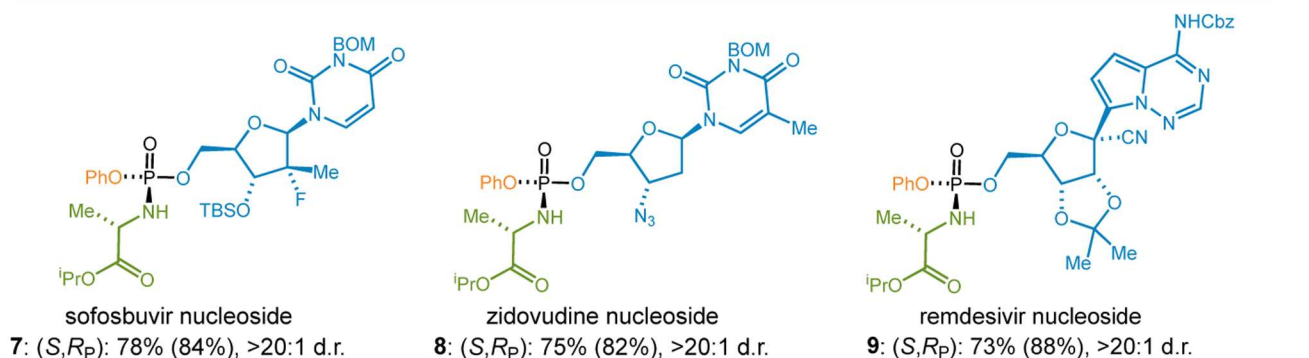
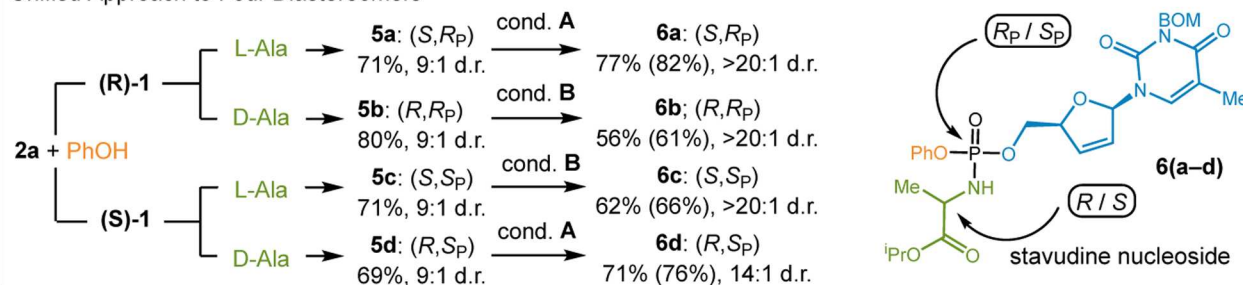
Natural Products. The ability to sequentially and stereospecifically substitute the oxazolidinone and phenol groups under orthogonal conditions can provide access to P-chiral natural products. Phosmidosine acts as a natural antibiotic and shows anticancer activity.^{6,7} It has been prepared as a mixture of diastereomers requiring preparative HPLC for separation, but the absolute configuration at the phosphorus atom has

Scheme 3. Stereodivergent Strategy for Preparing Prodrugs^a

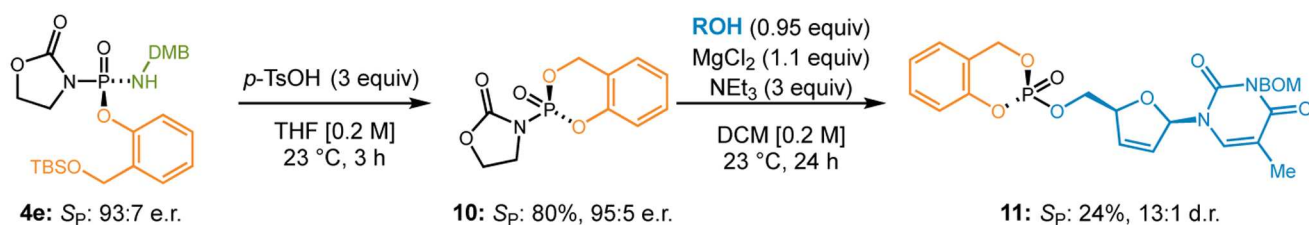
A. ProTide Synthesis: Displacement of oxazolidinone under Lewis-acid conditions



Unified Approach to Four Diastereomers



B. CycloSal synthesis: Displacement of the amine under Brønsted-acid conditions

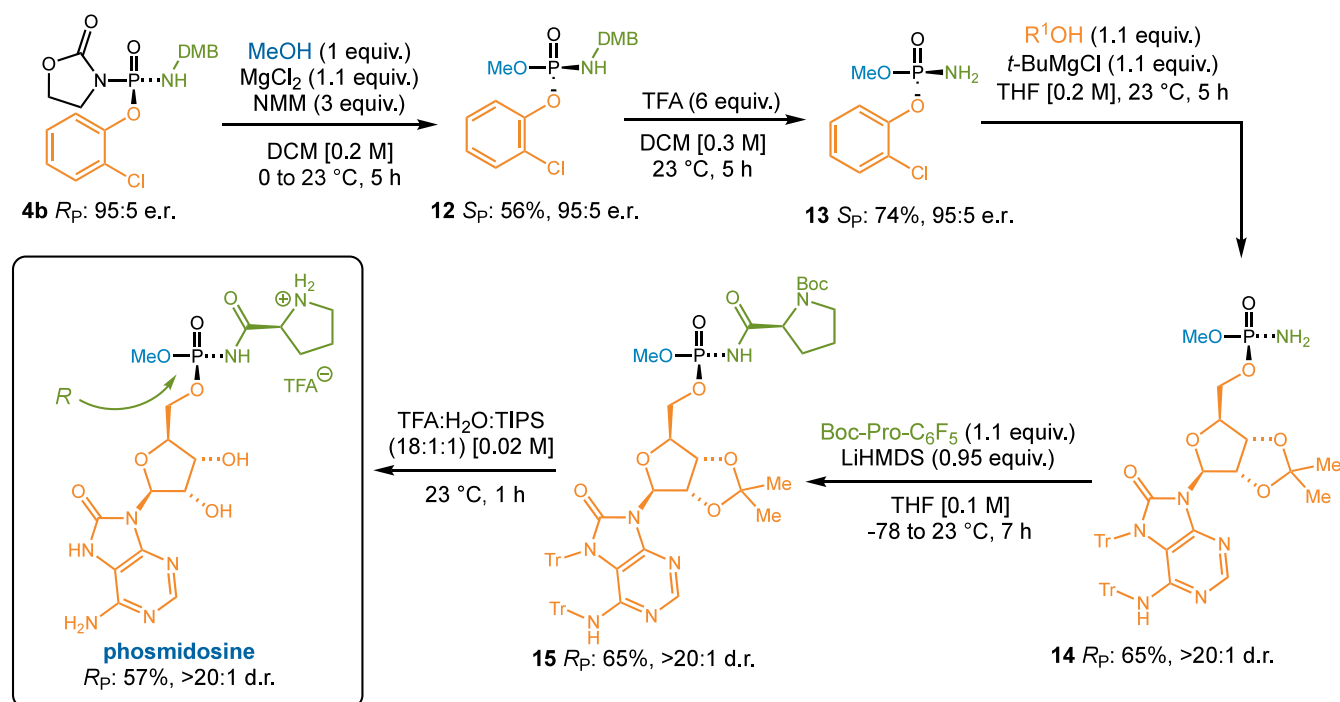


^aThe isolated yields are reported, along with NMR yields (in parentheses) and d.r. values determined from the reaction mixture by quantitative ³¹P NMR, using triphenylphosphine sulfide as the internal standard.

remained unassigned. To achieve a stereoselective total synthesis, we began with enantioenriched (R)-4b, prepared on a 1.5 g scale in 90% yield and 95:5 e.r. (Scheme 4). Substitution of the oxazolidinone with methanol under Lewis-acidic conditions provided intermediate 12 in 56% yield and 95:5 e.r. Subsequent cleavage of the dimethoxybenzylamine group with TFA in DCM afforded 13 in 74% yield and preserved the enantiopurity. The 2-chlorophenol was then displaced using a protected nucleoside under Brønsted-basic conditions (*t*-BuMgCl), affording 14 in 65% yield and >20:1 d.r. (determined by ³¹P NMR and assigned as R_p assuming S_N2 at P from (R)-4b).⁴⁵ Acylation of the free phosphoramidate

with Boc-proline pentafluorophenyl ester yielded fully protected R_p-phosmidosine 15, which was converted to R_p-phosmidosine 16 upon global deprotection. This R_p isomer of phosmidosine exhibited both the downfield ³¹P NMR chemical shift and a slower elution time in reverse-phase analytical HPLC, consistent with the natural product profile proposed by Sekine and co-workers.⁷

Conclusion. Translating Evans' chiral auxiliary to enantioselective Lewis-acid catalysis represents a powerful strategy for creating chiral carbon centers⁴⁶—yet its potential for chiral phosphorus centers remained unrealized. By this strategy, we provide P-stereogenic trifunctional building blocks: ProTide

Scheme 4. Stereoselective Total Synthesis of Phosmidosine^a^aIsolated yields reported.

analogs retain the phenol and amine, requiring only substitution of the oxazolidinone; CycloSal prodrugs incorporate phenol while the amine and oxazolidinone are displaced; and phosmidosine retains the amine while the phenol and oxazolidinone are replaced. Mechanistic studies are underway along with applications to other P-stereogenic prodrugs and natural products.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.5c06639>.

Experimental procedures and spectral data for new compounds (PDF)

Accession Codes

Deposition Number 2446250 contains 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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