

# Enantiodivergent Formation of C–P Bonds: Synthesis of P-Chiral Phosphines and Methylphosphonate Oligonucleotides

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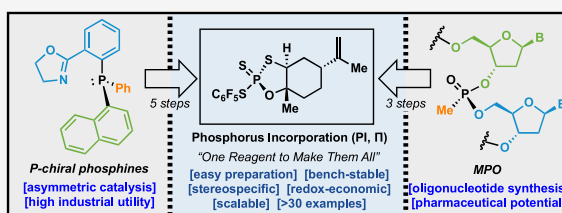
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**ABSTRACT:** Phosphorus Incorporation (PI, abbreviated  $\Pi$ ) reagents for the modular, scalable, and stereospecific synthesis of chiral phosphines and methylphosphonate nucleotides are reported. Synthesized from *trans*-limonene oxide, this reagent class displays an unexpected reactivity profile and enables access to chemical space distinct from that of the Phosphorus–Sulfur Incorporation reagents previously disclosed. Here, the adaptable phosphorus(V) scaffold enables sequential addition of carbon nucleophiles to produce a variety of enantiopure C–P building blocks. Addition of three carbon nucleophiles to  $\Pi$ , followed by stereospecific reduction, affords useful P-chiral phosphines; introduction instead of a single methyl group reveals the first stereospecific synthesis of methylphosphonate oligonucleotide precursors. While both  $\Pi$  enantiomers are available, only one isomer is required—the order of nucleophile addition controls the absolute stereochemistry of the final product through a unique enantiodivergent design.



## INTRODUCTION

Though identified nearly a century after the discovery of plane polarized light rotation,<sup>1</sup> phosphorus asymmetry is now rivaled only by carbon in terms of research interest. One important example is found in the emergence of anti-sense oligonucleotide (ASO) therapeutics, wherein the stereogenic identity of phosphorothioate linkages can influence physical properties.<sup>2</sup> In continuation of our collaborative work, we recently reported a method for the precise stereochemical control of phosphorothioate oligonucleotides using P(V)-based Phosphorus–Sulfur Incorporation (PSI, abbreviated  $\Psi$ ) reagents.<sup>3</sup> In contrast to standard P(III) phosphoramidite reagents,  $\Psi$ -enabled ASO synthesis is redox-economic and relies on air- and moisture-tolerant building blocks.

Methylphosphonate oligonucleotides (MPOs, Scheme 1A), a related class of compounds, comprise a chiral phosphorus backbone that serves to achieve unique pharmacological effects, including superior resistance to phosphodiesterase degradation.<sup>4,5</sup> The absence of non-bridging oxygen atoms lends to a charge-neutral spine, thereby minimizing hydrogen bonding and preventing potentially destabilizing (or unwanted stabilizing) effects on formation of DNA–RNA duplexes.<sup>4a–c</sup> Indeed, one of the first ASO analogs featured an MPO linkage.<sup>6</sup> As with phosphorothioate ASOs, MPOs introduce phosphorus asymmetry, with  $S_p$  and  $R_p$  isomers that may differ in binding affinities and biological activities.<sup>5b</sup> To our knowledge, there exist no methods to access MPOs with complete stereocontrol, and all known approaches are curiously underdeveloped.<sup>5,7,8</sup> Moreover, the typical prepara-

tion of MPO-based building blocks is wedded to a P(III) strategy that requires tedious separation of diastereomers.<sup>7</sup>

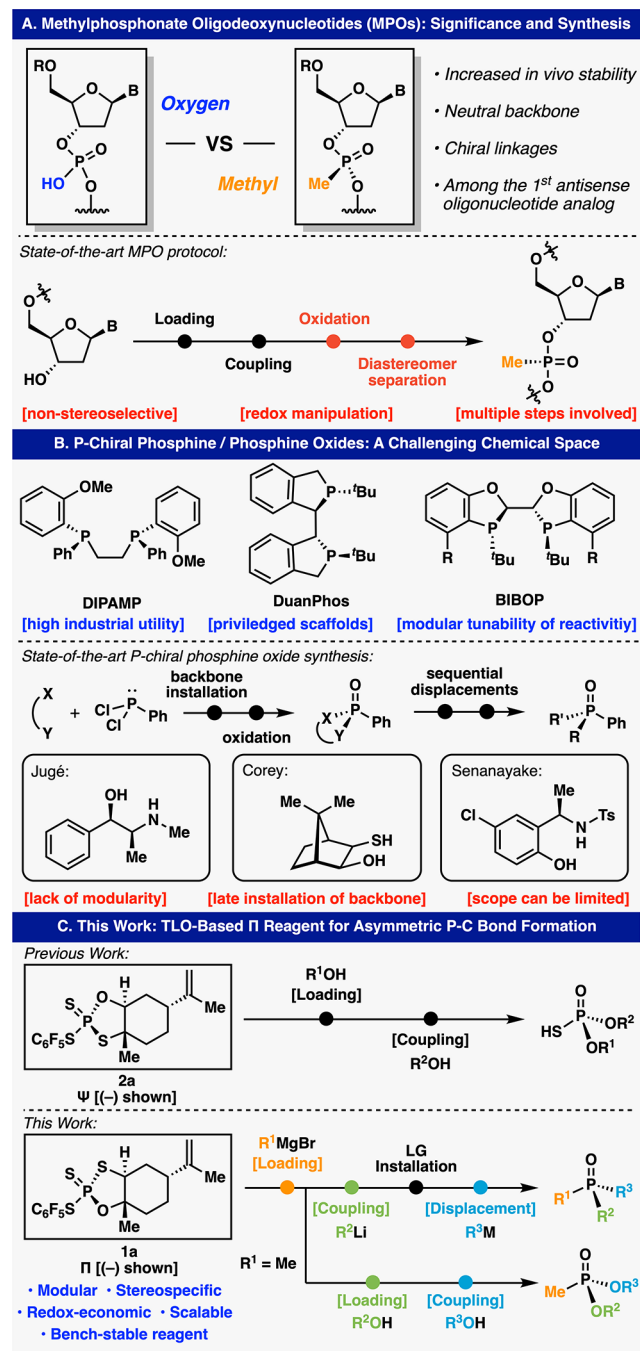
Separately, another class of seemingly unrelated compounds drew our attention—namely, the chiral phosphines that form the basis of some of the most important ligands known (Scheme 1B).<sup>9–11</sup> DIPAMP, for example, was among the first chiral phosphines used for asymmetric hydrogenation and made possible the renowned L-DOPA process, work that eventually led to a Nobel Prize in Chemistry.<sup>9</sup> Numbers of useful ligand scaffolds have since emerged, including DuanPhos<sup>10</sup> and BIBOP,<sup>11</sup> both of which allow installation of new stereogenic carbon centers with near perfect control. Despite this impressive scope of reactivity, a simple and modular approach for the synthesis of P-chiral phosphines remains elusive.

Typical preparative routes are often lengthy, are non-redox-economic [P(III)  $\rightarrow$  P(V)  $\rightarrow$  P(III)], require separation of diastereomers, and/or are case-specific.<sup>9–11</sup> The most practical of these, introduced by Jugé (Scheme 1B), relies on the chiral auxiliary ephedrine.<sup>12</sup> Though a classic approach, the scope is limited, the e.r. inconsistent, and the redox economy poor. Shortly thereafter, Corey reported a camphor-based chiral auxiliary that provides extremely high e.r., but is again limited

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**Scheme 1. (A) Utility of MPO and Limitations of Its Current Synthetic Protocols; (B) Precedents, Synthetic Challenges, and Current State-of-the-Art Syntheses of P-Chiral Phosphines; and (C) A Divergent,  $\Pi$  Reagent-Based Approach to Address Both Challenges**



pair that enables modular and enantiodivergent access to these markedly different classes of molecules (Scheme 1C).

## ■ STEREOSPECIFIC P–C BOND SYNTHESIS: REAGENT DEVELOPMENT

Exploration of carbon nucleophile addition into a P(V) reagent platform commenced with  $\Psi$  (2), a compound class originally developed for stereospecific phosphorothioate synthesis (Scheme 2A). As previously reported,  $\Psi$  derives from *cis*-limonene oxide, and initial success was realized using oxygen nucleophiles (specifically, a nucleoside hydroxyl group) in both the “loading” and “coupling” steps. Synthesis of the coupled product was found to be remarkably efficient and afforded a variety of phosphorothioate dinucleotides with perfect stereocontrol.<sup>3</sup> Early attempts to load carbon nucleophiles onto (–)- $\Psi$  (2a) using Grignard reagents (e.g., PhMgBr) furnished adduct 3 in 50% yield after only 15 min. In contrast to the coupling of oxygen nucleophiles, addition of a second carbon nucleophile (*t*BuLi) to 3 resulted in a counterproductive P–O cleavage (compound 4, 76% yield). Indeed, the subsequent thiirane-limonene immolation event—which renders the sequence traceless—was effectively terminated. Similarly, 2a was treated with MeMgBr to afford 5 (45% yield), a potential MPO precursor. Efforts to then couple 1-adamantylmethanol (a nucleoside alcohol model) proved futile, providing only hydrolysis product 7.

Our limited success with  $\Psi$  compelled investigation of the regioisomeric *trans*-limonene oxide-based analogue. This new compound, Phosphorus Incorporation (PI, abbreviated  $\Pi$ ) reagent (1), was hypothesized to have a starkly different reactivity profile than the *cis*-limonene oxide counterpart (Scheme 2B). As with 2a, the loading of (–)- $\Pi$  (1a) with PhMgBr rapidly delivered adduct 8a in 64% yield. To our delight, coupling with both *t*BuLi and *o*-anisyllithium saw successful thiirane–limonene excision to deliver 9a and 10a (80% and 82%, respectively). Anisyl-derived thiophosphinic acid 10a was also readily methylated to give 11a, the absolute configuration of which was verified by X-ray crystallography. The same promising reactivity was observed in methylated 12a, with the addition of 1-adamantylmethanol delivering (*R<sub>p</sub>*)-6 (68% yield after *S*-benzylation with BnBr, see SI). These investigations laid the necessary groundwork for chiral phosphine and MPO synthesis, as described below.

## ■ MODULAR ASSEMBLY OF CHIRAL PHOSPHINES

With enantiopure thiophosphinic acids [*R*<sub>1</sub>*R*<sub>2</sub>P(O)SH] in hand, our search for the optimal leaving group to allow the final displacement reaction commenced (Table 1). Notably, chlorophosphine sulfide (entry 1) was unresponsive to nucleophilic attack, while chlorophosphine oxide (entry 2) reacted readily but saw diminished e.r. Moreover, the presence of electron-rich aromatic rings proved problematic (entry 3) and resulted in arene chlorination. In a move away from chlorinated species, we predicted that thiophosphinic acid esters (–SH alkylation products) would function as competent leaving groups. Indeed, while the reactions were moderately successful (entries 4–6), erosion of e.r. was again observed (see SI for details). However, a simple leaving group exchange from thioalkoxy to methoxy (stereochemical information preserved) boosted the e.r. of the subsequent displacement to 98:2 while maintaining high reactivity (entry 7). In a final attempt, the more activated leaving group phenoxy (entry 8)

by scope (2 examples) and redox economy.<sup>13</sup> Senanayake then improved on the Jugé approach, using both a P(V) starting material (for phenyl-substituted phosphines) and a more reactive auxiliary.<sup>14</sup> While high yields and e.r. are observed across a range of substrates, the auxiliary requires a six-step preparation sequence.

We therefore sought to design a simple method to control phosphorus stereochemistry, foreseeing potential applications in two distinct fields: oligonucleotide chemistry and asymmetric synthesis. Herein, we trace the realization of a reagent

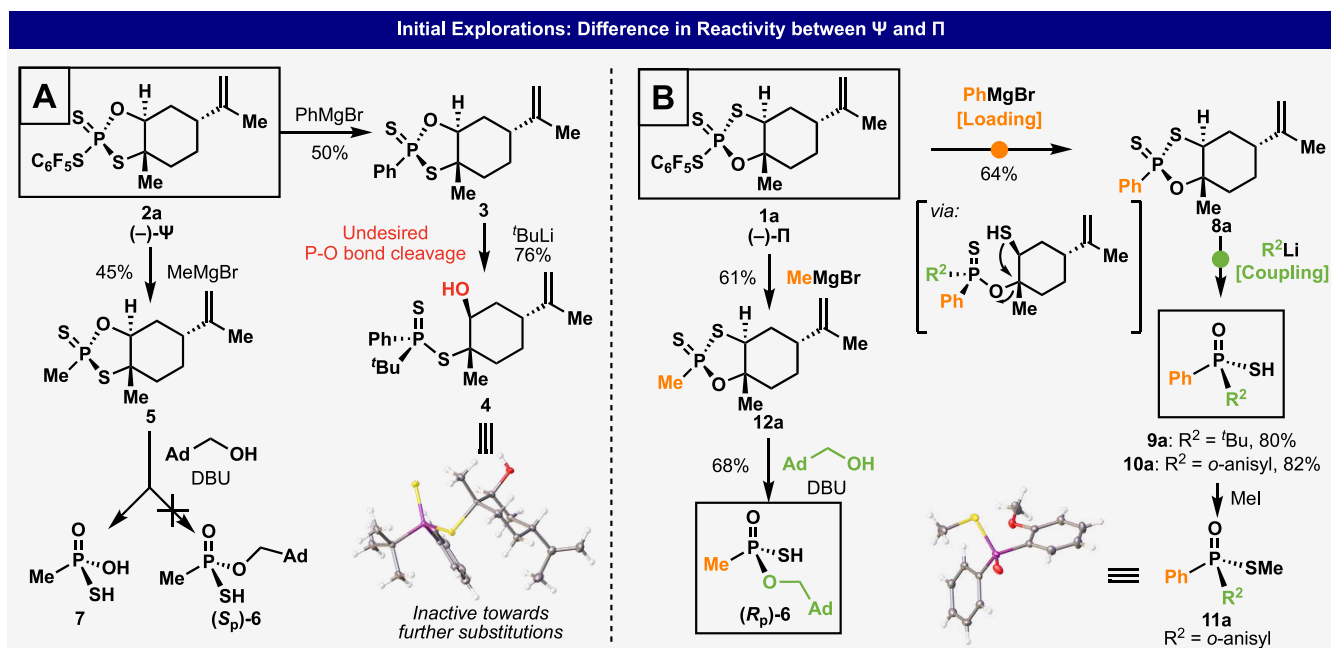
Scheme 2. (A) Initial Exploration with  $\Psi$  Ended in Undesired P–O Bond Cleavage; (B)  $\Pi$  Gave Desired P–S Bond Cleavage and Subsequent Limonene Backbone Immolation<sup>a</sup>

Table 1. Leaving Group Optimization for Final Displacement

Leaving Group Optimization for the Final Displacement					
Entry	X	R <sup>2</sup>	Leaving group (conditions)	Yield	e.r.
1	S	<sup>t</sup> Bu	Cl (SOCl <sub>2</sub> )	no rxn	/
2	O	<sup>t</sup> Bu	Cl (MeI, then SO <sub>2</sub> Cl <sub>2</sub> )	65%	67:33
3	O	<i>o</i> -anisyl	Cl (MeI, then SO <sub>2</sub> Cl <sub>2</sub> )	mixture	/
4	O	<i>o</i> -anisyl	SMe (MeI)	88%	94:6
5	O	<i>o</i> -anisyl	SEt (EtI)	43%	94:6
6	O	<i>o</i> -anisyl	SBn (BnBr)	43%	94:6
7	O	<i>o</i> -anisyl	OMe (MeI, then NaOMe)	77%	98:2
8	O	<i>o</i> -anisyl	OPh (MeI, then NaOPh)	80%	50:50

led to phosphorus racemization. With the most promising results, methoxy was deemed the optimal candidate.

Table 2 illustrates the scope and sequence of  $\Pi$ -enabled phosphine synthesis; net stereoretention for each step was unequivocally confirmed by X-ray crystallography (see SI). As shown in Table 2A, a variety of groups can be installed during loading, including methyl (12), aryl (8, 13, 14, 16, and 17), biaryl (15), vinyl (18), and alkynyl (19) moieties. The coupling step is similarly versatile, enabling the addition of 3° alkyl (22), aryl (11, 20, 21, and 25), heteroaryl (23), and alkynyl (24) groups. In the final displacement, addition of alkyl (26–30), aryl (31–34), and ferrocenyl (35) groups was successful. Compounds originating from either (–)- or (+)- $\Pi$  are denoted by suffixes a and b, respectively. Importantly, the absolute configuration of the final product is determined by order of addition (*vide infra*).

Among the notable substrates accessed through this route is 26 (PAMPO), a precursor to important ligand scaffolds DiPAMP<sup>9a</sup> and JoshPhos.<sup>15</sup> Likewise, compounds 27 and 29, previously prepared through diastereomeric separation, are used in the enantioselective synthesis of allylic alcohols and phenyl sulfides.<sup>16</sup> Racemic versions of ligands similar to 36 (Buchwald-type) have been prepared previously,<sup>17</sup> and the enantioselective variants hold promise for asymmetric synthesis. PHOX-type ligands such as 37 have been widely used in palladium catalysis, including asymmetric allylic substitution.<sup>18</sup> Traditionally, preparation of these ligands relies on racemic phosphorus reagents and existing oxazoline stereocenters to achieve diastereomeric induction, thereby restricting access to select isomers. Ferrocenyl-containing ligand scaffolds such as 38 have been used in alkyne–aldehyde reductive couplings<sup>19</sup> and are typically prepared using Jugé's method (91:9 e.r. prior to recrystallization, compared to 98:2 using the current approach).

To be sure, there exist many literature methods for the stereospecific reduction of chiral phosphine oxides to phosphines. Examples include the use of HSiCl<sub>3</sub> (Et<sub>3</sub>N is optional),<sup>20</sup> HSiCl<sub>3</sub> with sacrificial PPh<sub>3</sub>,<sup>21</sup> polymethylhydrosiloxane (PMHS) and Ti(O*i*Pr)<sub>4</sub>,<sup>14</sup> and MeOTf/Meerwein's salt and NaBH<sub>4</sub>.<sup>22</sup> As an example, NaBH<sub>4</sub> and Meerwein's salt were enlisted to reduce PAMPO 26a to PAMP 39a (eq 1). Indeed, the reaction proceeded smoothly in 60% yield and 96:4 e.r.

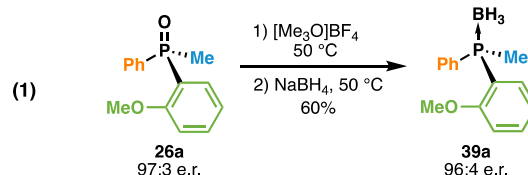
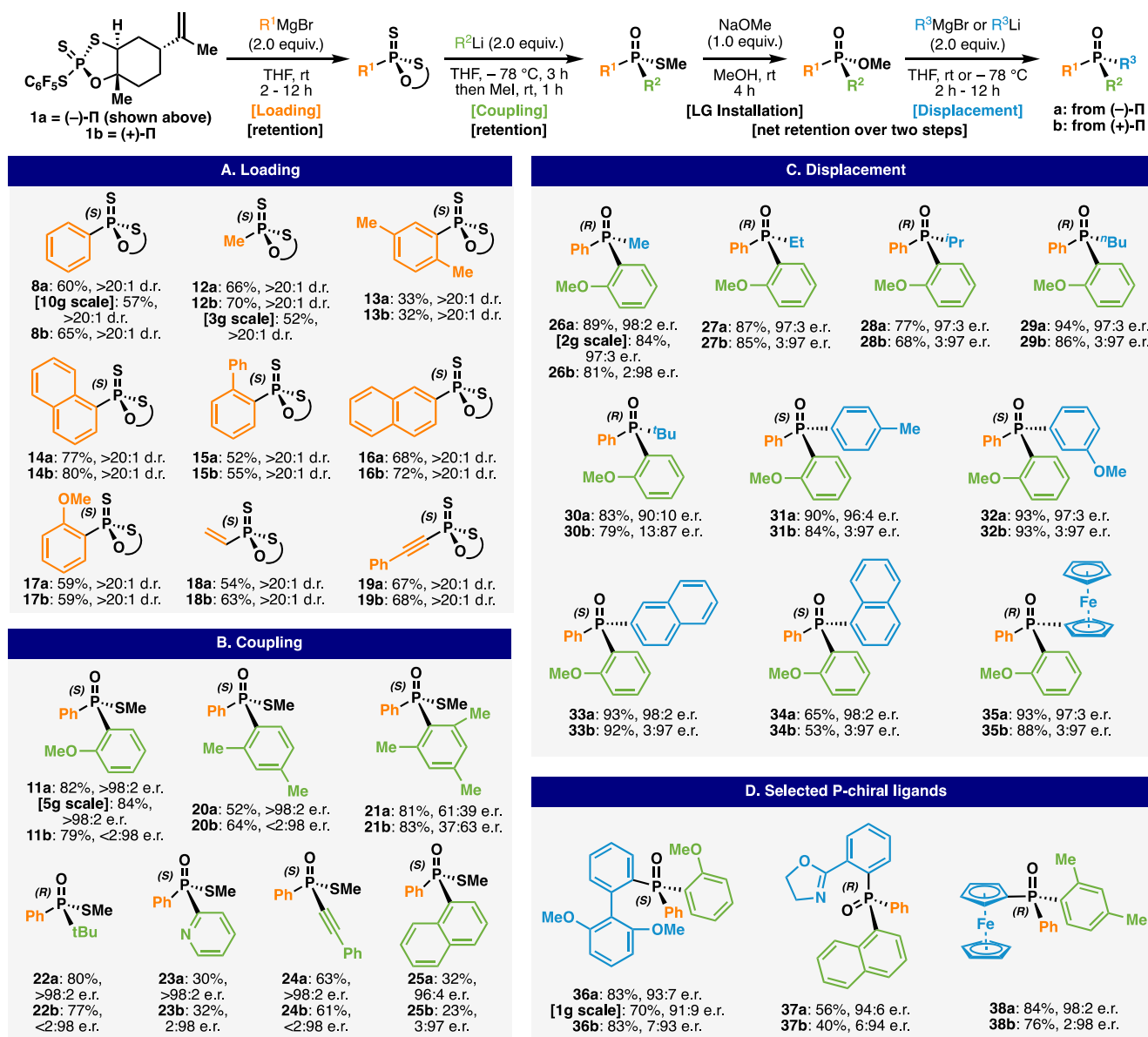


Table 2. Scope of  $\Pi$ -Based Chiral Phosphine/Phosphine Oxide Synthesis<sup>a</sup>

<sup>a</sup>All structures and stereochemistry shown in the scope refer to the corresponding compounds derived from (-)- $\Pi$  (i.e. with suffix a). See SI for detailed stereochemical analysis and reaction parameters.

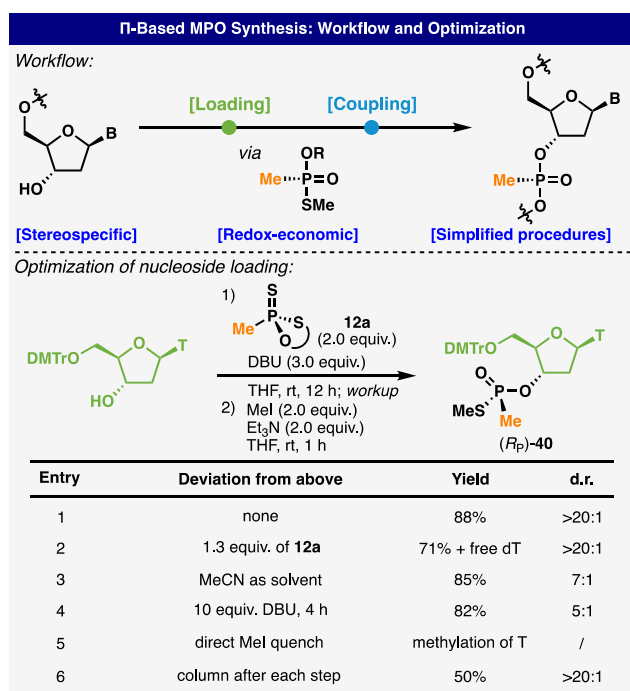
## ■ A SOLUTION TO STEREOSPECIFIC MPO SYNTHESIS

We then looked to the development of the first stereocontrolled synthesis of MPO building blocks. A simple workflow (Scheme 3) wherein a nucleoside is loaded onto reagent **12**, followed by coupling with a second nucleoside, was proposed. Success here hinged on high stereospecificity in both reactions; fortunately, literature review suggested that methylphosphonothioates, previously prepared through tedious separation of diastereomers, could be cleanly coupled with high stereocontrol.<sup>23</sup>

Optimization of the loading step commenced using 5'-DMTr-dT as a model substrate. When a direct MeI quench was performed (i.e., without workup of step 1), methylation of the thymine nucleobase was observed (entry 5). The use of 1.3 equiv of **12** (entry 2) resulted in lower yields, incomplete conversion, and a challenging purification process. Alter-

natively, when MeCN was used as solvent (entry 3), similar yields, but diminished d.r. (7:1), were returned. A large excess of DBU (10 equiv, entry 4) accelerated the reaction (full conversion of dT in 4 h), but likewise led to erosion of d.r. (5:1). The two-step telescoped process proved advantageous over a stepwise approach (entry 6), as the highly polar thiophosphonic acid contributes to significant product loss on purification. In the optimal iteration, the nucleoside was first mixed with 2 equiv of **12** and 3 equiv of DBU in THF for 12 h. Following workup with a PBS buffer solution (see SI for details), residuals were re-dissolved in THF and treated with MeI and Et<sub>3</sub>N to afford (*R<sub>p</sub>*)-**40** in 88% yield and >20:1 d.r. (Scheme 3).

A full exploration of the reaction scope was then carried out. Table 3A outlines the stereochemical path of MPO synthesis, with phosphorus stereoretention in the loading step and inversion in the coupling step (see SI). The four canonical

Scheme 3. Typical Workflow for  $\Pi$ -Based MPO Synthesis and Reaction Optimization<sup>a</sup><sup>a</sup>DMTr = dimethoxytrityl.

DNA bases were readily loaded (Table 3B); dA, dT, and dC proceed in 72–90% yield and  $\geq 20:1$  d.r., while dG sees diminished yields (46–59%) and  $\geq 20:1$  d.r. In accord with Stec's observations,<sup>23</sup> all coupling reactions proceeded smoothly to afford the corresponding dinucleotides in 39–91% yields and excellent d.r. ( $>20:1$ , Table 3C). Notably, no significant difference in the reactivity of *S<sub>p</sub>* and *R<sub>p</sub>* isomers was recorded.

Finally, a chimeric sequence bearing both MPO and chiral phosphorothioates was also prepared. As proof of concept,  $\Psi$  activation of a dT-dT dimer was demonstrated (Table 3C). Following TBS deprotection of (*R<sub>p</sub>*)-44, the 3'-OH of the dT-dT dimer was successfully loaded onto (+)- $\Psi$  to afford activated dimer 60. Controlled alternation of phosphorothioate and methylphosphonate linkages is now within reach, opening the door for unexplored oligonucleotide architectures.

## CONCLUSION AND OUTLOOK

A summary of our growing library of limonene-based P(V) reagents is outlined in Scheme 4A. As with  $\Psi$ , the  $\Pi$  reagents are inexpensive and trivial to prepare, while boasting the same benefits of redox economy and benchtop practicality. A salient feature of this class is true enantiodivergence: choreography of nucleophile addition precisely controls stereochemical outcome (Scheme 4B). In a powerful example, either enantiomer of thiophosphinic acid ester 11 can be procured by simply changing the order of nucleophile addition to (–)- $\Pi$ . Similarly, prudent ordering of the loading/coupling partners with MPO

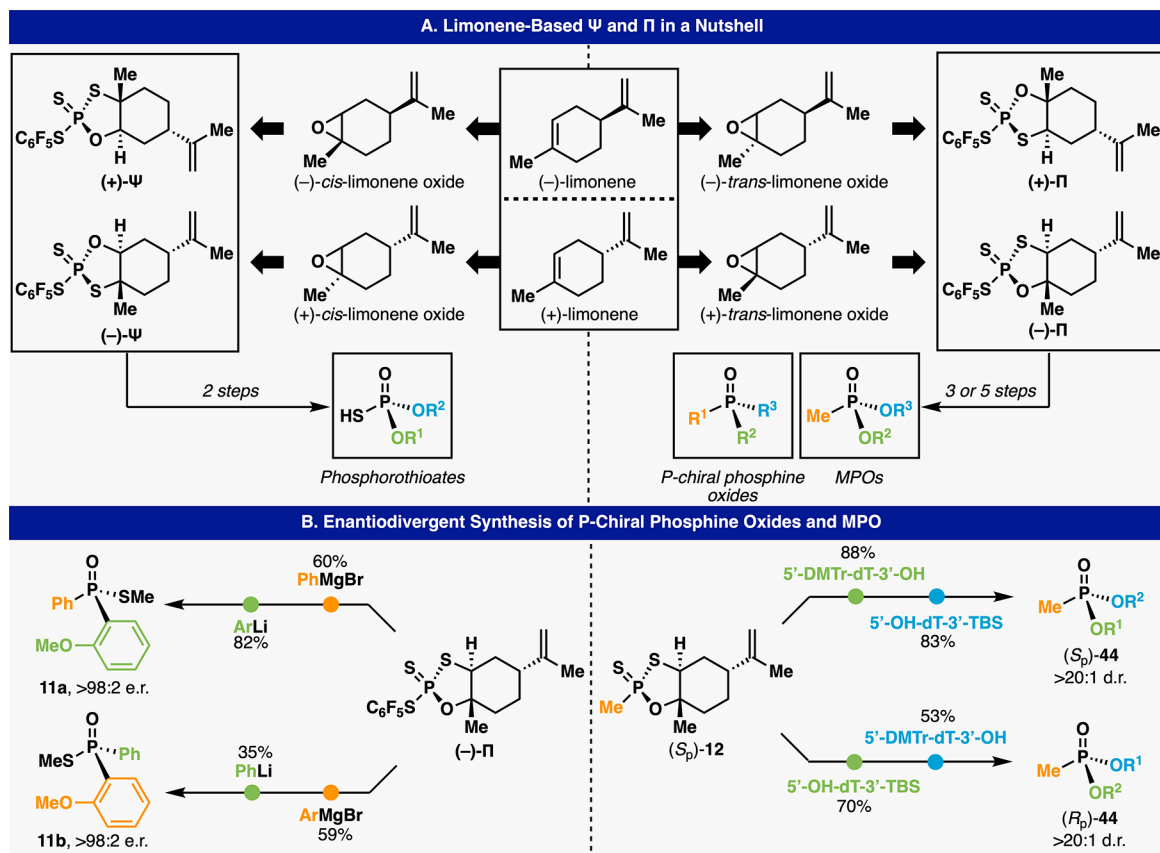
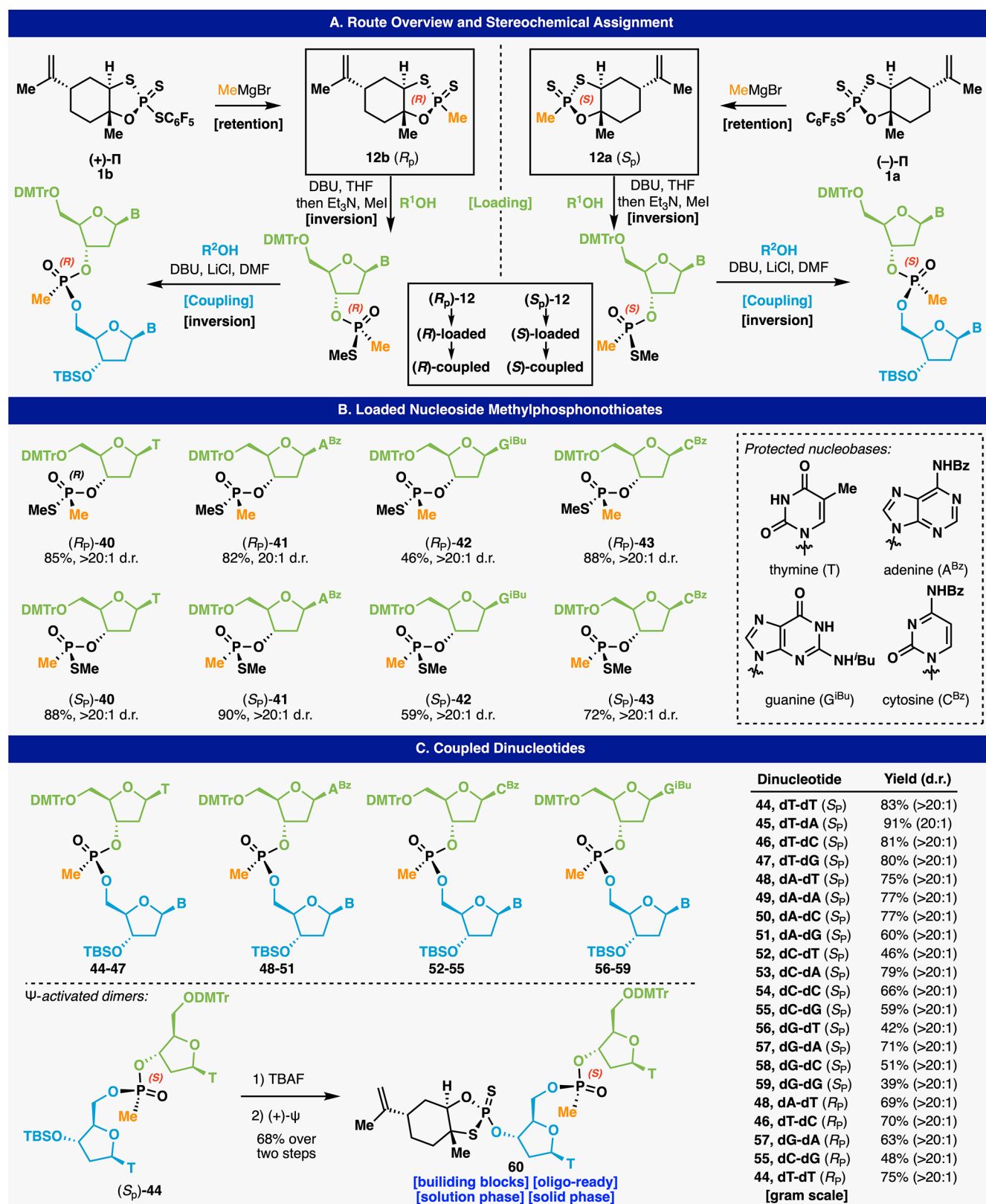
Scheme 4. (A) Painting the Full Picture for Limonene-Based  $\Psi$  and  $\Pi$  Reagents; (B) Enantiodivergent Nature of the  $\Pi$ -Based Chiral Phosphine and MPO Syntheses<sup>a</sup><sup>a</sup>Ar = *o*-anisyl. OR<sup>1</sup> = 5'-DMTr-dT-3'-OH. OR<sup>2</sup> = 5'-OH-dT-3'-TBS.

Table 3. (A) Stereochemical Map of  $\Pi$ -Based MPO Synthesis; (B) Scope of Loaded Nucleoside Methylphosphonothioates; and (C) Scope of Coupled Dinucleotides and Further Applications<sup>a</sup>

<sup>a</sup>DMF = dimethylformamide. Bz = benzoyl. <sup>i</sup>Bu = isobutryl. TBS = *tert*-butyldimethylsilyl. Loading: nucleoside (1 equiv),  $\Pi$  (2 equiv), DBU (3 equiv), THF, 25 °C, 12 h. Coupling: nucleoside (1 equiv), methylphosphonothioate (2 equiv), DBU (20 equiv), LiCl (10 equiv), DMF, 25 °C, 16 h. DMTr = dimethoxytrityl.

precursor **12** provides either ( $R_p$ )-**44** or ( $S_p$ )-**44** with equally minimal effort.

The product MPOs can be further activated for incorporation into oligonucleotides, a process facilitated by the inherent stability of P(V) reagents. By effectively serving as a formal surrogate for “chiral  $POCl_3$ ” through a tunable sequence, the  $\Pi$ -reagent platform provides broad admission to otherwise challenging sectors of chemical space. The full capability of  $\Pi$ -reagents is yet to be revealed, as we are still far from exhausting all the possible permutations of products that can be synthesized, a goal we deemed to be beyond the scope of this Article.

## ■ ASSOCIATED CONTENT

### SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.9b13898>.

Detailed experimental procedures and analytical data (PDF)

X-ray crystallographic data for **1b** (CIF)

X-ray crystallographic data for **4** (CIF)

X-ray crystallographic data for **8a** (CIF)

X-ray crystallographic data for **11a** (CIF)

X-ray crystallographic data for **34a** (CIF)

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### Notes

The authors declare no competing financial interest.

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