Enantiodivergent Formation of C–P Bonds: Synthesis of P-Chiral Phosphines and Methyl-phosphonate Oligonucleotides

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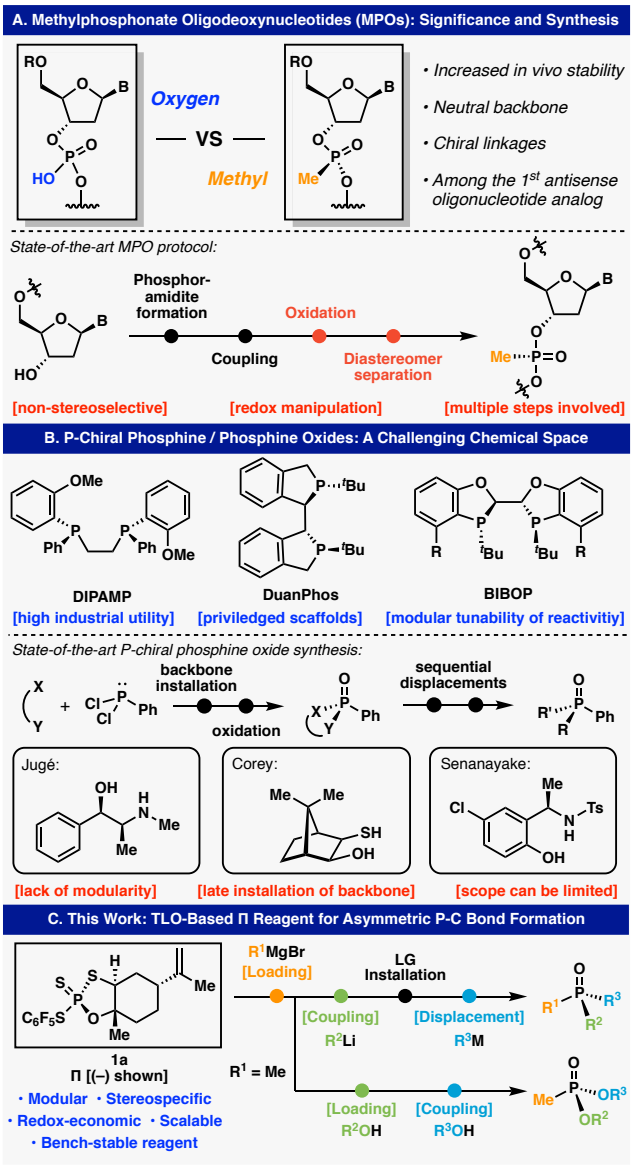
ABSTRACT: A simple limonene-derived P(V)-based reagent for the modular, scalable, and stereospecific synthesis of chiral phosphines and methyl-phosphonate oligonucleotide (MPO) building blocks is presented. Built on a *trans*-limonene oxide (TLO) core, this formally triply electrophilic reagent class displays starkly differing reactivity from the *cis*-limonene oxide derived reagents reported previously [dubbed phosphorus-sulfur incorporation reagents or Ψ (PSI) for short]. These new phosphorus-incorporation reagents (PI, abbreviated as Π) access distinctly different chemical space than Ψ. The P(V)-manifold disclosed herein permits the stereochemically controlled sequential addition of carbon-based nucleophiles (from one to three) to produce a variety of enantiopure C–P bearing building blocks. When three carbon nucleophiles are added, useful P-chiral phosphines can be accessed after stereospecific reduction. When a single methyl group is added, the remaining nucleophiles can be nucleosides thus opening the door to the first stereospecific access to MPO-based oligonucleotide building blocks. Although both enantiomers of Π are available, only one isomer is required as the order of nucleophile addition controls the absolute stereochemistry of the final product through a unique enantiodivergent design.

Introduction

The control of P-centered stereochemistry is an often encountered challenge that presents itself in a variety of areas.[1] One important example stems from the emergence of anti-sense oligonucleotide (ASO) therapeutics, wherein precise control of P-stereogenic centers in a phosphorothioate linkage can impact efficacy and physical properties.[2] Our laboratories recently described a method to precisely control the stereochemical outcome of such systems using a P(V)-based reagent built upon the natural product limonene (phosphorus-sulfur incorporation or Ψ for short).[3] The advantage of such an approach is that, unlike classical phosphoramidite P(III)-based reagents, Ψ-enabled ASO synthesis is redox-economic and involves air and moisture tolerant building blocks.

Another P-based chiral linkage, which is receiving increasing attention due to their potential in therapeutics, are found in methyl-phosphonate oligonucleotides, or MPOs (Figure 1A).[4] Such structures are touted as having superior stability as they are highly resistant to phosphodiesterase degradation.[5] The absence of the non-bridging oxygen atom makes the backbone charge-neutral and unable to H-bond. This can lead to either stabilizing or destabilizing effects when forming DNA-RNA duplexes.[4a-c] As with phosphorothioate-based ASOs, MPOs introduce chirality at phosphorus and as such, S_p and R_p isomers may have different binding affinities and biological activities.[5b] Indeed, one of the first ASO analogs employed an MPO linkage.[6] To our knowledge, there are currently no methods to access MPOs with full stereocontrol and all known access points are severely underdeveloped.[5, 7-8] Additionally, the preparation of MPO-based building blocks are wedded to a P(III)-based strategy that requires tedious separation of diastereomers.[7] These limitations have surely hampered the wide exploration of such interesting linkages for modern therapeutic applications.

Within the seemingly unrelated realm of asymmetric synthesis, another class of P-chiral molecules attracted our attention. Specifically, phosphines that are have stereochemical information at phosphorus represent some of the most important ligands known (Figure 1B).[9-11] For example, DIPAMP was among the first chiral phosphines to be employed in asymmetric hydrogenation, serving as a reaction-critical ligand in the legendary L-DOPA process and leading to a Nobel Prize.[9] Since then, scores of useful ligand scaffolds have emerged such as DuanPhos[10] and BIBOP[11] to install new stereogenic carbon centers with near perfect control. Despite their great utility, a simple modular approach for the synthesis of P-chiral phosphines



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. (C) A divergent, Π reagent-based approach to address both challenges.

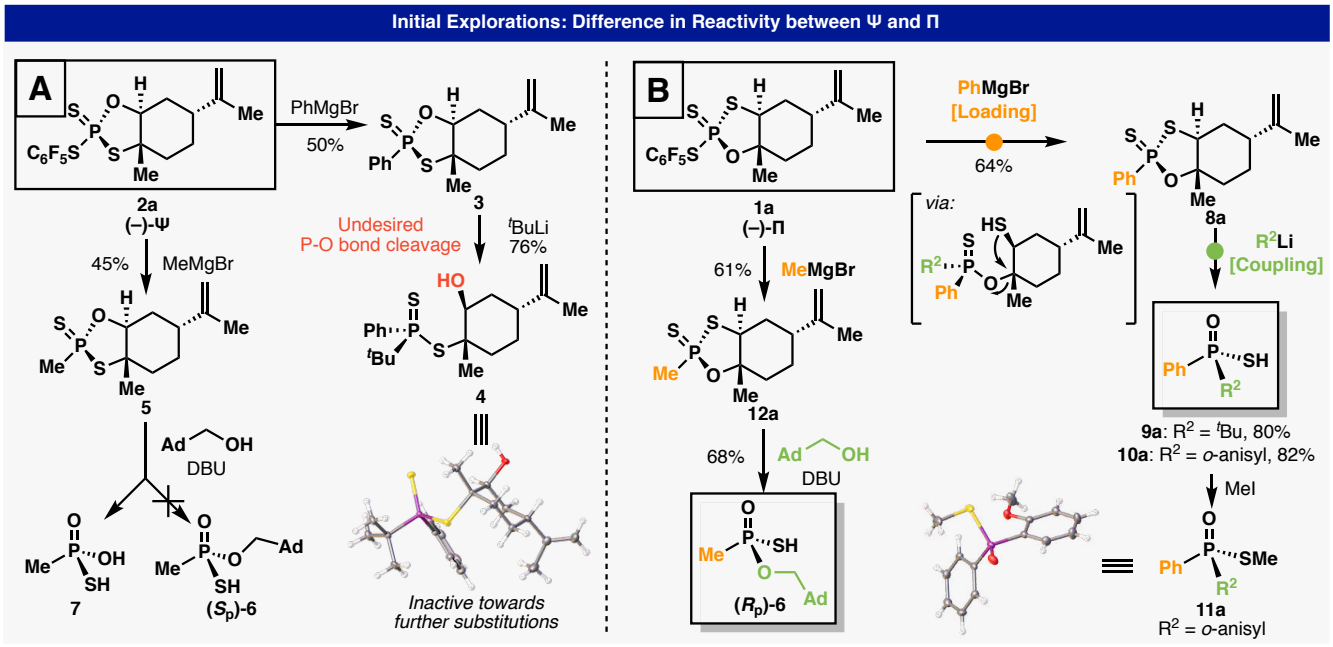
remains an unmet challenge. The known routes to these molecules are often lengthy, non-redox economic [going from P(III) to P(V) and back to P(III)], require resolution or tedious separation of diastereomers, or are case-specific in the approach lacking generality.[9-11] The most practical routes currently known to such structures involve chiral auxiliaries and are outlined in Figure 1B. Jugé was the first to demonstrate that a chiral auxiliary approach was feasible using ephedrine.[12] The scope of this approach is unfortunately limited, the e.r. is often inconsistent, and a P(III)/P(V)/P(III) redox cycle was employed. Corey developed a camphor-based chiral auxiliary which exhibited extremely high e.r. but with limited substrate scope (2 examples) and again, a P(III)/P(V)/P(III) redox cycle was employed.[13] Senanayake improved upon the Jugé approach by commencing with a P(V)-starting material (for phenyl-substituted phosphines) and using a more reactive auxiliary.[14] High yields and e.r. are observed across a range of substrates. However, the auxiliary requires a six-step preparation.

The mission of this venture was therefore to design a simple approach to control P-based stereochemistry with application to these two completely different areas: oligonucleotide chemistry and asymmetric synthesis. This article traces the realization of this vision with the development, optimization, and application of an easily prepared reagent to enable modular and enantiodivergent access to the targets of these seemingly unrelated worlds with exquisite stereocontrol, MPO building blocks and phosphines (Scheme 1C).

Stereospecific P–C Bond Synthesis: Reagent Development

Exploration of carbon nucleophiles addition into a P(V) reagent platform commenced with (–)-Ψ (**2**), that was used successfully for stereospecific phosphorothioate synthesis (Scheme 2A). In our prior work, the first nucleophile is oxygen-based (a nucleoside alcohol) and that "loading" step takes place rapidly and in high yield. The ensuing "coupling" step with a second nucleoside also proceeds with ease to afford a dinucleotide phosphorothioate with perfect stereocontrol. The analogous loading of carbon nucleophiles onto **2a** using Grignard reagents such as PhMgBr proceeded within 15 minutes to furnish adduct **3** in 50% yield (unoptimized). In contrast to the "coupling" step using O-based nucleophiles, the sequential addition of a second carbon-based nucleophile to **3** resulted in an undesired P–O cleavage (using *t*BuLi as nucleophile delivers **4** in 76% yield). Such a result prevents further reactions from taking place and the desired immolation event (which cleaves the limonene derived backbone *via* a thiirane-limonene adduct) cannot take place. The structure of dead-end adduct **4** was verified by X-ray crystallography. In an analogous fashion, **2** reacted readily with MeMgBr to afford potential MPO-precursor **5** in 45% yield. Subsequent attempts to react this adduct with 1-adamantylmethanol (as a model for a nucleoside alcohol) were fruitless, providing only hydrolysis product **7**.

It was reasoned that the regioisomeric Π reagent (phosphorus-incorporation, pi) based on *trans*-limonene oxide (TLO) might afford a different reactivity profile resulting in successful excision of the limonene auxiliary (Scheme 2B). As with **2a**, the loading step of **1a** with PhMgBr rapidly delivered adduct **8a** in 64% yield. To our delight, coupling with either *t*BuLi or *o*-anisyllithium resulted in successful backbone immolation to deliver **9a** in 80% yields and **10a** in 82% yields, respectively. Presumably, the coupling reaction using TLO-derived Π proceeds via the desired P-S bond cleavage to permit



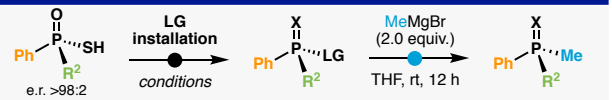
Scheme 2. A) Initial exploration with Ψ ended in undesired P-O bond cleavage. (B) Π gave desired P-S bond cleavage and subsequent limonene backbone immolation. Ad = 1-adamantyl. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

backbone expulsion. Anisyl-derived thiophosphinic acid **10a** could be methylated and its absolute structure **11a** verified by X-ray crystallography. The same promising reactivity could be translated to the TLO-Me derivative **12a** with the addition of 1-adamantylmethanol delivering (R_p)-**6** in 68% yield (after *S*-benzylation with BnBr, see SI). The explorations above laid the groundwork for application to both chiral phosphine and MPO synthesis as described in the sections below.

Modular Assembly of Chiral Phosphines

With enantiomerically-pure thiophosphinic acids [$R_1R_2P(O)SH$] in hand, a search for the optimum leaving group to effect the final displacement reaction commenced (Table 1). Thus, the chlorophosphine sulfide (entry 1) was not active towards nucleophilic attack whereas chlorophosphine oxide (entry 2) reacted readily

Leaving Group Optimization for the Final Displacement



Entry	X	R^2	Leaving group (conditions)	Yield	e.r.
1	S	*t*Bu	Cl ($SOCl_2$)	no rxn	/
2	O	*t*Bu	Cl (MeI, then SO_2Cl_2)	65%	67:33
3	O	*o*-anisyl	Cl (MeI, then SO_2Cl_2)	mixture	/
4	O	*o*-anisyl	SMe (MeI)	88%	94:6
5	O	*o*-anisyl	SEt (EtI)	43%	94:6
6	O	*o*-anisyl	SBn (BnBr)	43%	94:6
7	O	*o*-anisyl	OMe (MeI, then NaOMe)	77%	98:2
8	O	*o*-anisyl	OPh (MeI, then NaOPh)	80%	50:50

Table 1. Leaving group optimization for final displacement.

but gave diminished e.r. Also, the preparation of such species in the presence of electron-rich aromatic rings is problematic (entry 3) due to chlorination of the arenes. In principle, thiophosphinic acid esters (the products of alkylation of the free SH) should function as competent leaving groups.

This prediction proved true (entries 4-6) though diminished e.r. values were observed (see SI for details). However, a simple leaving group exchange from thioalkoxy to methoxy (which preserved the stereochemical information) boosted the e.r. of the subsequent displacement to 98:2 while maintaining high reactivity (entry 7). Finally, attempts to install a more activated leaving group such as phenoxy (entry 8) resulted in racemization at the phosphorus center and thus the –OMe group was chosen for all subsequent studies.

Table 2 illustrates the scope of modular phosphine synthesis enabled by the Π reagent (**1**) which takes place in an assembly line fashion: Loading (to install R^1), coupling (to install R^2), and displacement (leaving group installation followed by R^3 installation). As confirmed by X-Ray crystallography, net stereoretention at P is observed during all of the steps in this sequence. For the loading step (Table 2A), a variety of groups are accessible such as those bearing methyl (**12**), aryl (**8**, **13**, **14**, **16**, and **17**), biaryl (**15**), vinyl (**18**) and alkynyl (**19**) moieties. The coupling step is similarly versatile with the inclusion of 3° alkyl (**22**), aryl (**11**, **20**, **21**, and **25**), heteroaryl (**23**) and alkynyl (**24**) groups. In the final displacement, methyl to 3° alkyl (**26-30**), aryl (**31-34**), and ferrocenyl (**35**) could be installed. Since both (+)- and (–)-Π reagents are readily available all of these substrates could be prepared with any desired absolute configuration. For clarity, compounds originating from either (–)- or (+)-Π are denoted by suffixes **a** and **b** [**a** for (–) and **b** for (+)].

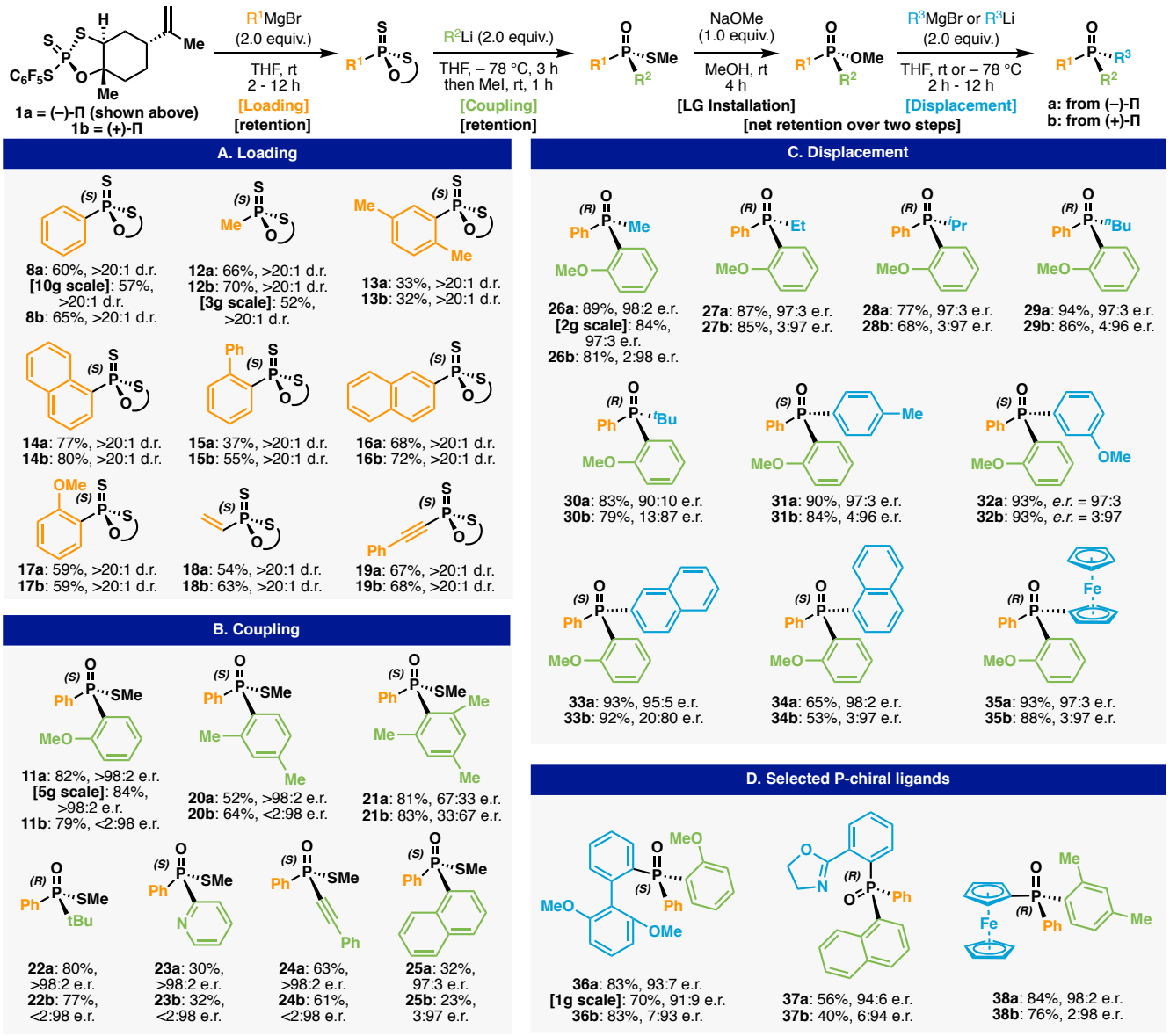


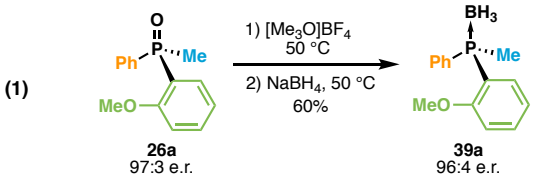
Table 2. Scope of Π-based chiral phosphine / phosphine oxide synthesis. All structures and stereochemistry shown in the scope refer to the corresponding compounds derived from (–)-Π (i.e. with suffix **a**). See SI for detailed stereochemical analysis and reaction parameters.

If, however, only one reagent was in hand, simply changing the order of addition in this modular strategy could lead to either enantiomer of coupling or displacement products (*vide infra*).

Some notable substrates emerging from this route include **26**, aka PAMPO, which is a precursor to important ligand scaffolds such as DiPAMP[9a] and JoshPhos[15]. Compounds **27** and **29**, previously prepared through diastereomeric separation, are used in the enantioselective synthesis of allylic alcohols and phenyl sulfides.[16] Racemic versions of ligands such as **36** (Buchwald-type)[17] have been prepared and the enantioselective variants hold promise as ligands in asymmetric synthesis. PHOX-type ligands[18] such as **37** have been widely used in palladium catalysis such as asymmetric allylic substitution. Previous preparations of such ligands used racemic phosphorus reagents and relied on existing stereocenters on the oxazoline backbone to achieve diastereo-induction thereby limiting access to all possible isomers. Ferrocenyl-containing ligand scaffolds such as **38** have been used in alkyne-aldehyde reductive couplings[19] and have previously been prepared using Jugé's method in 91:9 er prior to recrystallization (compared to 98:2 using current approach).

It is worth noting that there are many existing literature methods for the reduction of chiral phosphine oxides to phosphines in a stereospecific manner. Examples include the use of $HSiCl_3$ (with or without Et_3N),[20] $HSiCl_3$ with sacrificial PPh_3,[21] polymethylhydrosiloxane (PMHS) and $Ti(OiPr)_4$,[14] and MeOTf/Meerwein's salt and $NaBH_4$.[22] To demonstrate this point, the combination of $NaBH_4$ and Meerwein's salt was enlisted to reduce PAMPO **26a** to

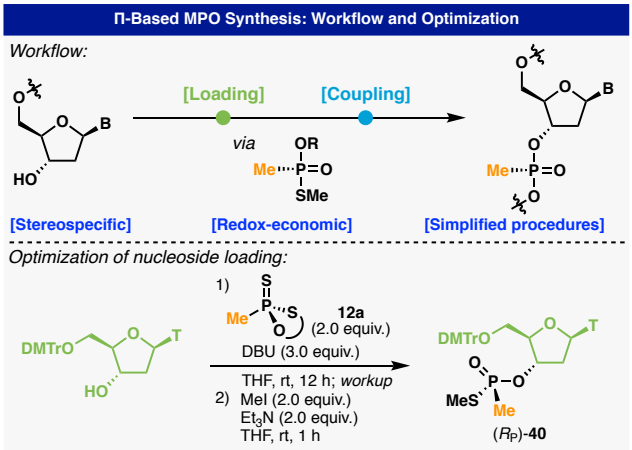
PAMP **39a** (equation 1). Indeed, the reaction proceeded smoothly in 60% yield and 96:4 e.r.



A Solution to Stereospecific MPO Synthesis

The lessons learned during reagent development and phosphine synthesis were then applied to the development of the first stereocontrolled synthesis of MPO building blocks. As depicted in Scheme 3, a simple workflow was envisaged wherein a nucleoside could be loaded onto reagent **12** followed by coupling to another nucleoside. The success of this plan requires that both of these steps take place with high stereospecificity. It was already precedented that methylphosphonothioates, previously prepared through tedious separation of diastereomers, can be cleanly coupled with high stereocontrol to yield MPOs.[22]

Optimization of the loading step commenced using 5'-DMTr-dT as a model substrate. In its fully optimized form, the loading step affords the product (R_P)-**40** in 88% yield and >20:1 d.r. (Scheme 3). In this two-step process the nucleoside is first mixed with 2 equiv. of **12** and 3 equiv. of DBU in THF for 12 h. After workup with a PBS buffer solution (see SI for details), residuals were re-dissolved in THF and treated with MeI and Et_3N. When a direct MeI



Entry	Deviation from above	Yield	d.r.
1	none	88%	>20:1
2	1.3 equiv. of **12a**	71% + free dT	>20:1
3	MeCN as solvent	85%	7:1
4	10 equiv. DBU, 4 h	82%	5:1
5	direct MeI quench	methylation of T	/
6	column after each step	50%	>20:1

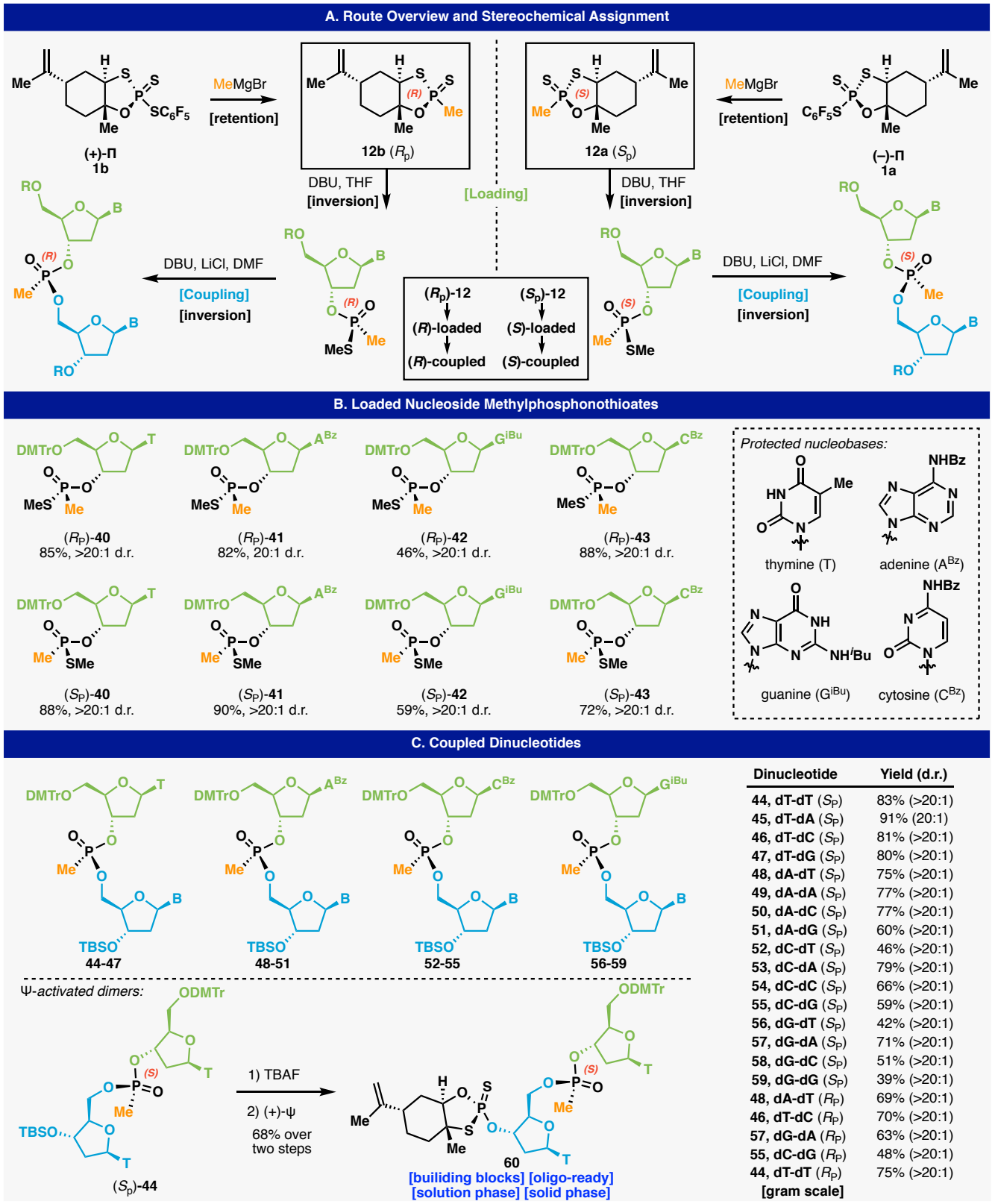
Scheme 3. Typical workflow for Π-based MPO synthesis and reaction optimization. DMTr = dimethoxytrityl.

quench is performed (i.e. without workup of the 1st step), methylation of the thymine nucleobase was observed (entry 5). The use of 1.3 equiv. of **12** instead of 2 equiv. (entry 2) resulted in lower yields, incomplete conversion, and difficult purification as free dT tends to co-elute with product. When MeCN is employed as solvent (entry 3) similar yields are observed but with diminished d.r. (7:1). A large excess of DBU (10 equiv., entry 4) accelerates reaction (full conversion of dT in 4 h) but leads to diminished d.r. (5:1). The two-step telescoped process is desirable over one involving intermediate purification (column after each step, entry 6) as losses during purification are observed due to the highly polar thiophosphonic acid.

With optimal conditions in hand, a full exploration of the reaction scope was carried out. Table 3A provides a map for understanding the stereochemical outcome of this MPO synthesis, with stereoretention at phosphorus occurring for the loading step and inversion for the coupling step (see SI). All four canonical DNA base pairs can be smoothly loaded as shown in Table 3B with dA, dT and dC proceeding in 72-90% yield and ≥ 20:1 dr and dG giving slightly diminished yields (46-59%) with ≥ 20:1 dr. In accord with Stec's procedure,[23] all coupling reactions proceed smoothly to afford the corresponding dinucleotides in 39-91% yields and excellent d.r. (all >20:1, Table 3C). No significant difference was observed between the reactivity of S_p and R_p isomers. Chimeric sequences bearing MPO and chiral phosphorothioates can also be prepared. As an example, Ψ activation of the dT-dT dimer was performed. Thus, after TBS deprotection of (R_p)-**44**, the 3'-OH of the dT-dT dimer was successfully loaded onto (+)-Ψ to afford activated dimer **60**. With such dimers in hand, one can easily follow the published procedures of Ψ coupling to introduce methylphosphonate linkages, *via* solution phase or solid phase, into oligonucleotide sequences. This work therefore bridges an important gap in oligonucleotide synthesis as previous approaches are wedded to laborious diastereomer separation and handling of sensitive P(III)-reagents.[7-8]

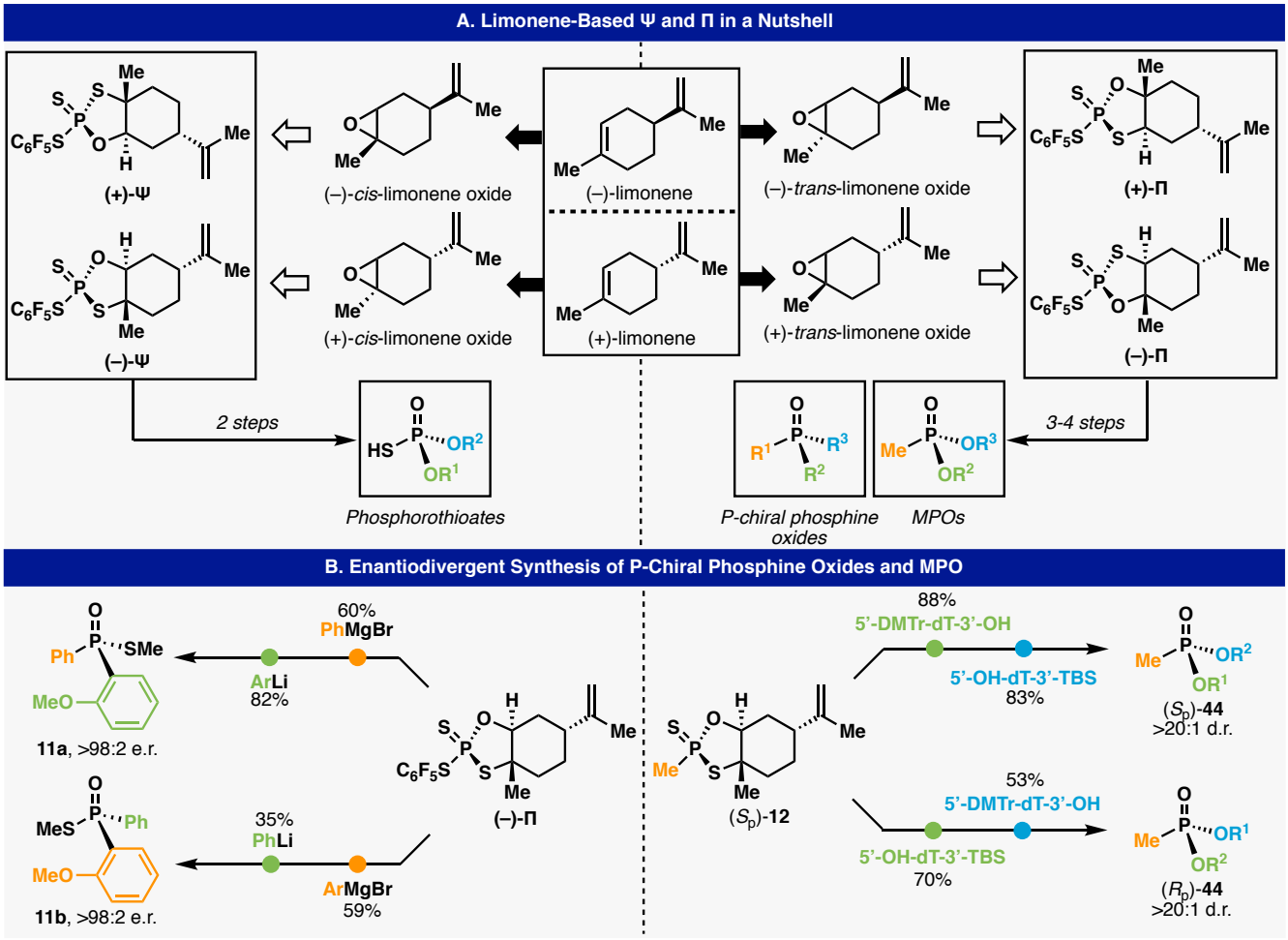
Conclusion and Outlook

This study has resulted in the development of several important methods for the modular preparation of valuable chiral phosphines and building blocks for MPO synthesis. Building off of our initial disclosure in this area that used a *cis*-limonene oxide-derived reagent (Ψ) to access chiral phosphorothioate linkages, the critical observation was that the TLO-derived Π reagent enables reactivity not previously accessible. As with Ψ, the Π reagents are extremely inexpensive and trivial to prepare and carry the same benefit of redox economy and practicality in manipulating P(V) intermediates. The overall utility of limonene-based Ψ and Π reagents disclosed thus far is outlined in Scheme 4A. One salient feature of the disclosed protocol is that the choreography of nucleophile addition can control the enantiomer produced. This interesting example of enantiodivergent synthesis is shown in Scheme 4B. For example, using (–)-Π, either enantiomer of thiophosphinic acid ester **11** can be procured simply by changing the order of nucleophile addition. Similarly, using MPO-precursor Π-reagent **12**,



Dinucleotide	Yield (d.r.)
44, dT-dT (S_P)	83% (>20:1)
45, dT-dA (S_P)	91% (20:1)
46, dT-dC (S_P)	81% (>20:1)
47, dT-dG (S_P)	80% (>20:1)
48, dA-dT (S_P)	75% (>20:1)
49, dA-dA (S_P)	77% (>20:1)
50, dA-dC (S_P)	77% (>20:1)
51, dA-dG (S_P)	60% (>20:1)
52, dC-dT (S_P)	46% (>20:1)
53, dC-dA (S_P)	79% (>20:1)
54, dC-dC (S_P)	66% (>20:1)
55, dC-dG (S_P)	59% (>20:1)
56, dG-dT (S_P)	42% (>20:1)
57, dG-dA (S_P)	71% (>20:1)
58, dG-dC (S_P)	51% (>20:1)
59, dG-dG (S_P)	39% (>20:1)
48, dA-dT (R_P)	69% (>20:1)
46, dT-dC (R_P)	70% (>20:1)
57, dG-dA (R_P)	63% (>20:1)
55, dC-dG (R_P)	48% (>20:1)
44, dT-dT (R_P)	75% (>20:1)
[gram scale]	

Table 3. A) Stereochemical map of Π-based MPO synthesis. B) Scope of loaded nucleoside methylphosphonothioates. C) Scope of coupled dinucleotides and further applications. DMF = dimethylformamide. Bz = benzoyl. ^{i}Bu = isobutyryl. TBS = *tert*-butyldimethylsilyl. Loading: nucleoside (1 equiv.), Π (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.



Scheme 4. (A) Painting the full picture for limonene-based Ψ and Π reagents. (B) Enantiodivergent nature of the Π-based chiral phosphine and MPO syntheses. Ar = *o*-anisyl. OR^1 = 5'-DMTr-dT-3'-OH. OR^2 = 5'-OH-dT-3'-TBS.

modifying the order of nucleoside addition gives precisely the opposite outcome. The product MPOs can be further activated for incorporation into oligonucleotides, a process facilitated by the stability of P(V) reagents. Thus, the Π-reagent platform clearly carries with it benefits from the standpoint of practicality and ideality in accessing difficult sectors of chemical space. In essence, the methodology presented herein serves as a formal surrogate for a chiral version of $POCl_3$ that can undergo nucleophilic substitution in a controllable sequential fashion. Studies in this area continue and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Detailed experimental procedures and analytical data (PDF)

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GRAPHICAL ABSTRACT