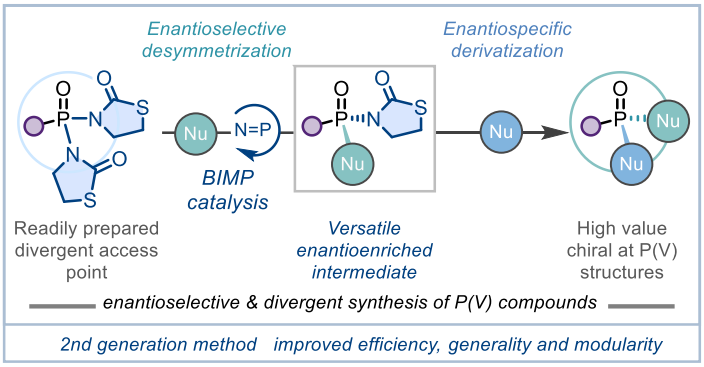
Second Generation Catalytic Enantioselective Nucleophilic Desymmetrization at P(V): Improved Generality, Efficiency and Modularity

Michele Formica,[‡1] Branislav Ferko,[‡1] Thomas Marsh,[1] Timothy A. Davidson,[1] Ken Yamazaki[2]* and Darren J. Dixon[1]*

Affiliations: [1]Department of Chemistry, Chemistry Research Laboratory, University of Oxford, 12 Mansfield Road, OX1 3TA, Oxford, UK. [2] Division of Applied Chemistry, Okayama University, Tsushimanaka, Okayama 700-8530, Japan.

ABSTRACT: A second generation catalytic two-phase strategy for the enantioselective synthesis of chiral at P(V) compounds is described. This protocol, consisting of a bifunctional iminophosphorane (BIMP) catalyzed nucleophilic desymmetrization of prochiral, bench stable P(V) precursors and subsequent enantiospecific substitution allows for divergent access to a wide range of *C*-, *N*-, *O*- and *S*- substituted P(V) containing compounds from a handful of enantioenriched precursors. A new catalyst/leaving group combination allowed for a far wider substrate scope and increased reaction efficiency and practicality over previously established protocols. The resulting enantioenriched intermediates could then be converted to an even greater range of distinct classes P(V) of compounds by displacement of the remaining leaving group as well as allowing for even further diversification downstream. Density functional theory (DFT) calculations were performed to pinpoint the origin of enantioselectivity for the BIMP-catalyzed desymmetrization, to rationalize how a superior catalyst/leaving group combination leads to increased generality in our second-generation catalytic system, as well as to shed light onto observed retention and inversion pathways when performing late-stage enantiospecific S_N2@P reactions with Grignard reagents.

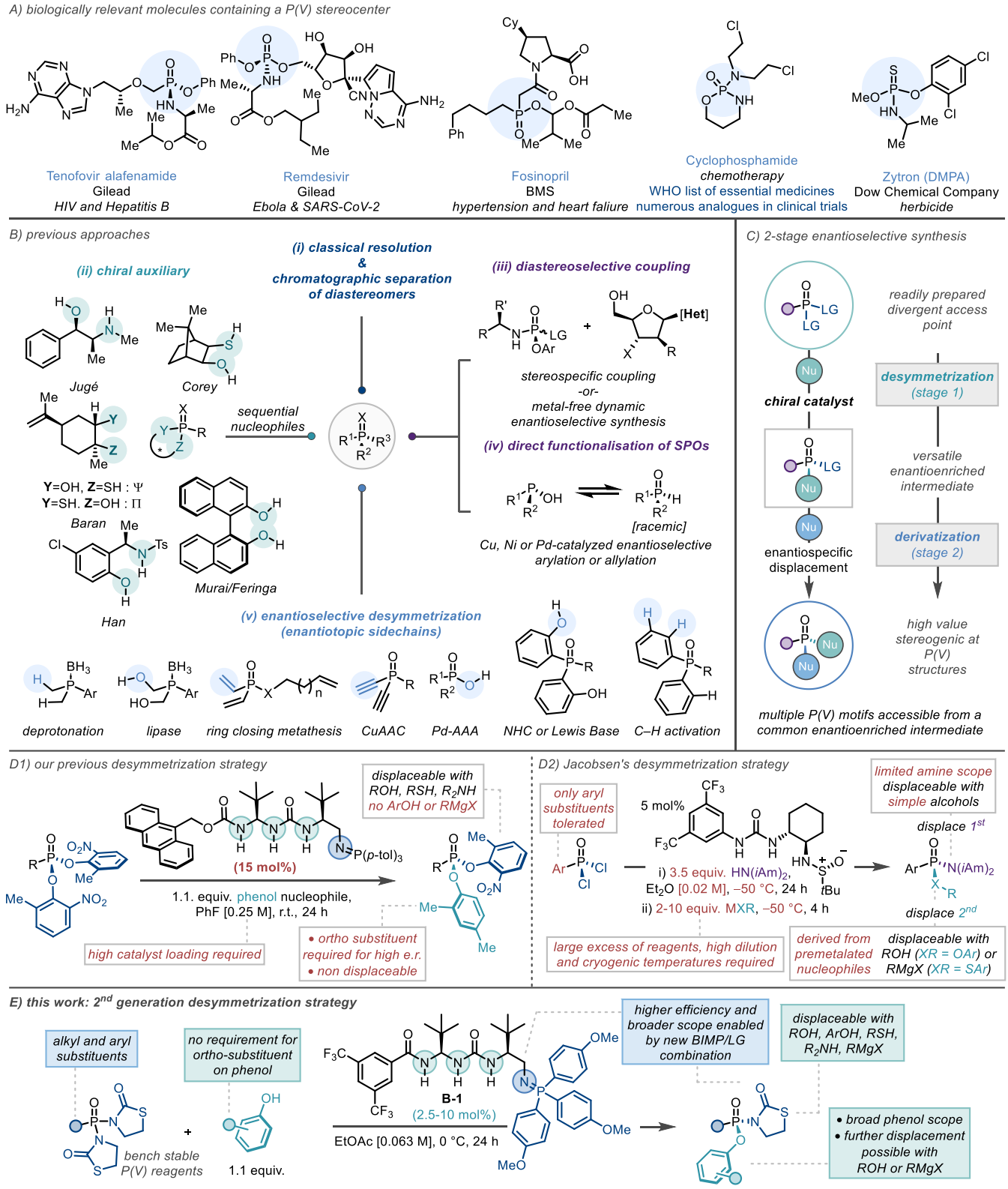


INTRODUCTION:

Compounds containing one or more phosphorus atoms in the P(V) oxidation state are important to chemistry, biology, and medicine (**Scheme 1A**).[1,2] These include marketed antiviral drugs such as such as Tenofovir alafenamide[3] and Remdesivir, the latter being an effective treatment for the Ebola virus[4] which was also approved for use against SARS-CoV-2.[5,6] Other relevant compounds include Fosinopril,[7] a compound used to treat hypertension and heart failure and WHO essential medicines listed chemotherapy agent Cyclophosphamide.[8] In addition to being common APIs, P(V) containing compounds are also highly relevant motifs in agrochemistry.[9] A representative example is the herbicide Zytron developed by Dow.[10] As such, the development of efficient methods for the preparation of enantioenriched P(V) containing compounds is crucial.

Synthetic approaches to enantiopure P(V) compounds can be subdivided into five categories (**Scheme 1B**).[11–16] The first approach is classical resolution and/or separation of diastereomers or enantiomers by chromatography (**Scheme 1B**, **i**).[17–23] A second approach revolves around the use of labile chiral auxiliaries which can be displaced by sequential diastereoselective nucleophilic additions to afford enantioenriched P(V) species (**Scheme 1B**, **ii**).[24–54] Thirdly, chiral, yet racemic at P(V) electrophiles bearing a single leaving group (and often possessing a chiral sidechain) can be coupled diastereoselectively to enantiopure nucleophiles employing chiral catalysts (**Scheme 1B**, **iii**).[55–64] A subsequent approach involves the direct functionalization of secondary phosphine oxides (SPO) by means of a metal catalyst bearing chiral ligands to obtain tertiary phosphine oxides.[65–92] To date, however, this approach has been limited to the synthesis of all carbon substituted phosphine oxides (**Scheme 1B**, **iv**). The final strategy is an enantioselective desymmetrization by which prochiral groups linked to a phosphorus center are differentiated by a chiral catalyst (**Scheme 1B**, **v**). Multiple reactions have been developed using this strategy, however, until recently none have involved chemistry occurring at the P atom directly, but rather generate the P stereocenter indirectly (through manipulation of enantiotopic side chains) inherently limiting their scope.[93–145]

A strategically distinct enantioselective desymmetrization of P(V) species would involve an enantioselective nucleophilic substitution of enantiotopic leaving groups. By judicious choice of leaving group, nucleophile, and catalyst the desired enantioenriched species could be obtained in high yield and with excellent enantioselectivity (stage 1). The desymmetrized substrate would then still possess another leaving group, poised for a second (potentially enantiospecific) nucleophilic substitution reaction enabling diverse downstream derivatization opportunities (stage 2). This two-phase strategy would allow for a wide range of P(V) compounds to be accessed from a common intermediate, overcoming one of the main limitations of current enantioselective desymmetrization approaches (**Scheme 1C**).



Scheme 1. [**A**] Biologically relevant molecules containing a P(V) stereocenter; Cy = cyclohexyl [**B**] Classical and modern approaches to enantioenriched P(V) compounds; SPO = secondary phosphine oxide; CuAAC = copper catalyzed azide-alkyne cycloaddition; PdAAA = palladium catalyzed asymmetric allylic alkylation [**C**] A distinct catalytic two-phase strategy for the modular synthesis of enantioenriched P(V) compounds; [**D**] Complementary two-phase strategies developed by our own group (D1) and that of Jacobsen (D2), with the limitations of each method highlighted in red; [**E**] This work: an improved, second generation desymmetrization/derivatization strategy for the synthesis of enantioenriched P(V) compounds enabled by a new BIMP catalyst/thiazolidinone leaving group combination.

Two complementary methods employing this two-phase strategy have now been developed, one by our group[146] and the other by that of Jacobsen.[147] While both methods allow for the enantioselective synthesis of a wide range of enantioenriched chiral at P(V) compounds, neither is without limitations.

In our own work (**Scheme 1**, **D1**), phenol nucleophiles were used in the desymmetrization step under ureidopeptide[148–154] bifunctional iminophosphorane (BIMP) catalysis,[155–168] however, to obtain high levels of enantioselectivity, phenol nucleophiles bearing an *ortho*-substituent were required, inherently limiting the scope of the reaction. Additionally, the optimal leaving group, 2-nitro-6-methyl-phenolate,[169] is a relatively weak Brønsted base, rendering the turnover of the optimal superbasic BIMP catalyst inefficient, which, in turn, forces an excessive 15 mol% catalyst loading to ensure high conversion of the starting material to product. The second stage enantiospecific displacement was also not without its limitations. While the remaining nitrophenol leaving group could be smoothly displaced with a variety of biologically relevant alkyl alcohols, thiols and amines, reactions with biologically relevant aromatic alcohols as well as displacement with carbon-based nucleophiles was either inefficient or led to the formation of significant amounts of byproducts. Finally, the *ortho*-substituted phenols introduced in the first stage could not be easily displaced, most probably due to a combination of steric effects and decreased electrophilicity at the now alkyl alcohol derived phosphonate esters.

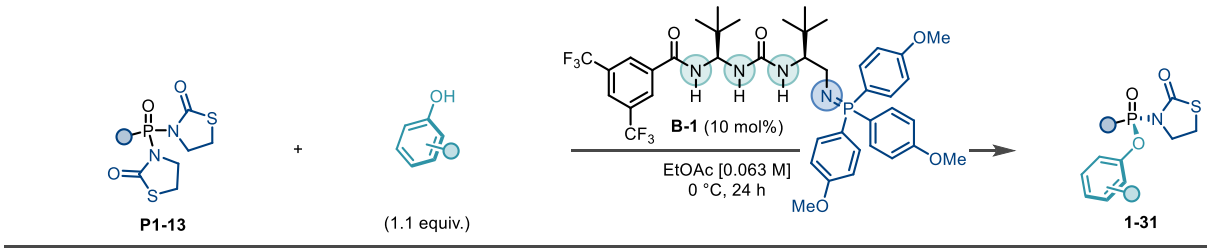
Jacobsen offered an elegant and complementary approach employing phosphoryl dichlorides (**Scheme 1**, **D2**). Under thiourea catalysis, the Jacobsen group was able to displace one of the enantiotopic chlorine atoms with specific amine nucleophiles, then, in the same pot a second enantiospecific substitution could take place using a large excess of alkoxide, phenoxide, thiolate or organomagnesium nucleophiles, with both steps taking place under high dilution and at cryogenic temperatures. Notably, only aryl substituted phosphoryl dichlorides were competent substrates for this transformation, while alkyl substituted phosphoryl dichlorides were inefficient substrates under the optimized conditions. The amine substituent of the phosphorus stereocenter could then be displaced enantiospecifically with solvent quantities of simple alkyl alcohols (MeOH, EtOH, allyl alcohol) under Brønsted acidic conditions. Only after this second, enantiospecific step, the resulting enantioenriched P(V) product could be further functionalized enantiospecifically with a variety of nucleophiles depending on the nucleophile previously used to displace the second chloride substituent. For example, if phenyl thiolate was employed, it could be replaced by more complex alkyl alcohols, if *para*-CF_3-phenoxide was used, it could then be replaced by a Grignard reagent.

RESULTS & DISCUSSION:

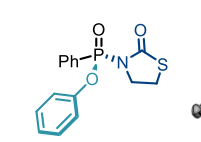
Cognizant of the strengths and limitations of both systems, the need for an improved second-generation approach was apparent. An improved method would consist of a desymmetrization step employing a wide range of (medicinally relevant) phenol nucleophiles (not only those which are *ortho*-substituted) and a derivatization step whereby the second leaving group could be displaced directly by complex, biologically relevant nucleophiles (avoiding the need for sequential enantiospecific displacements). Ideally, the phenol substituent could itself be replaced to provide access to an even wider range of enantioenriched P(V) compounds.

To achieve this, a full re-optimization of our first-generation method was required employing *para*-cresol as a model nucleophile for non-*ortho*-substituted phenols. Following an extensive evaluation of new leaving group/ureidopeptide BIMP catalyst combinations, the use of thiazolidinone[170–173] and **B-1** was found to be optimal, utilizing EtOAc as solvent and carrying out the reaction at 0 °C (see Supporting Information for full details). The thiazolidinone mimics the previous nitrophenol leaving group in that it also bears a Lewis basic functionality which can interact with the ureidopeptide through an analogous H-bonding network to obtain the desired products in high enantioselectivity. In addition, due to the higher basicity of the thioazolidinone conjugate base ($pK_{a[DMSO]} \approx 20$ vs $pK_{a[DMSO]} \approx 12$ for the nitrophenol),[174] higher reaction efficiency was observed, allowing for lower catalyst loadings (**Scheme 1**, **E**).

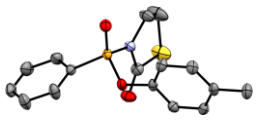
With the newly optimized conditions in hand, the scope with respect to both the phenol nucleophile and the bis-thiazolidinone derived P(V) electrophile was assessed (**Scheme 2**). Pleasingly, and in contrast to our previously reported method , when using phenyl-substituted P(V) electrophile **P1**, unsubstituted phenol (**1**, 75% yield, 99:1 e.r. vs 57% yield, 53:47 e.r. under the first-generation conditions), as well as a wide range of electron donating substituents at the phenol *para*-position were well tolerated, providing desired products (**2**-**4**) with high levels of yield and enantioselectivity. When *para*-fluoro-phenol was employed, 2.0 equivalents of the nucleophile were required to obtain desired product **5** in 48% yield and 93.7 e.r. Most noticeably, nucleophiles bearing additional Lewis basic substituents which could disrupt the non-covalent interactions between the substrate and catalyst were well tolerated, namely products derived from phenols bearing a benzylic ester (**6**) and a pyridine (**7**) were obtained in 74% and 53% yield, and 97.5:2.5 e.r. and 92:8 e.r., respectively. Single crystal X-ray diffraction analysis of a suitable crystal of **2** established the absolute configuration of the desymmetrised products as (*R*).



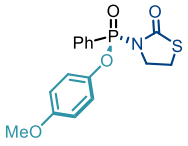
A) phenol nucleophile scope



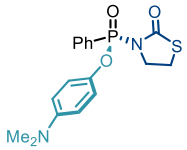
1 75% yield, 99:1 e.r.
[57% yield, 53:47 e.r. with Gen 1 system]



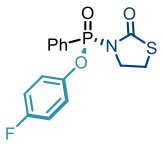
2 99% yield, 98:2 e.r.
[from *p*-cresol]



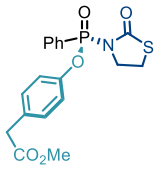
3 93% yield, 96:4 e.r.



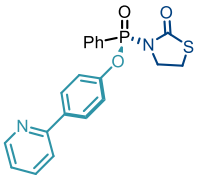
4 88% yield, 92:8 e.r.



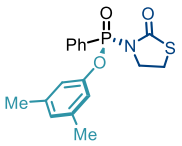
5 48% yield, 93:7 e.r.
(2 eq. of phenol used 48 h, 0.3 mmol)



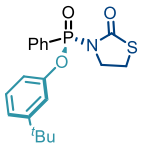
6 74% yield, 97.5:2.5 e.r.



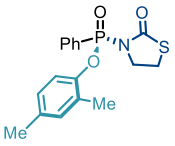
7 53% yield, 92:8 e.r.



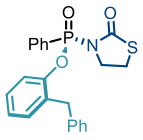
8 98% yield, 98:2 e.r.



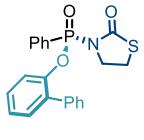
9 76% yield, 96:4 e.r.
[47% yield, 59.5:40.5 e.r. with Gen 1 system]



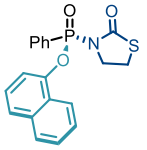
10 99% yield, 97:3 e.r.



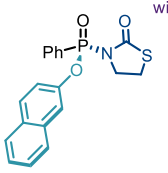
11 75% yield, 92:8 e.r.



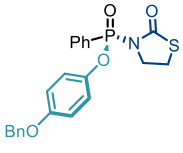
12 99% yield, 86:13 e.r.



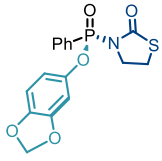
13 95% yield, 88:12 e.r.



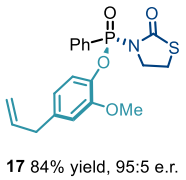
14 64% yield, 98:2 e.r.
[<10% conv. with Gen 1 system]



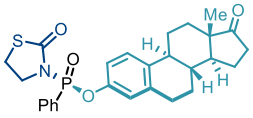
15 97% yield, 96:4 e.r.
[from monobenzone]



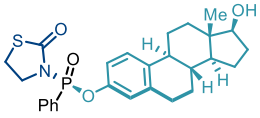
16 66% yield, 96:4 e.r.
[from sesamol]



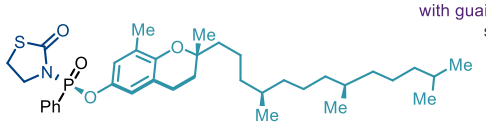
17 84% yield, 95:5 e.r.
[from eugenol]
[81% yield, 55.5:45.5 e.r. with guaiacol with Gen 1 system]



18 97% yield, 97:3 d.r.
[from estrone]

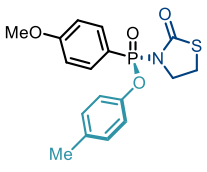


19 80% yield, 97:3 d.r.
[from estradiol]

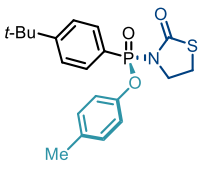


20 98% yield, 94:6 d.r.
[from δ-tocopherol]

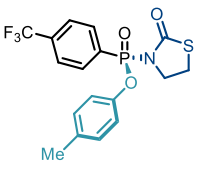
B) P(V) electrophile scope



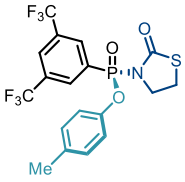
21 73% yield, 96:4 e.r.



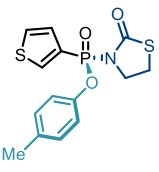
22 77% yield, 98:2 e.r.



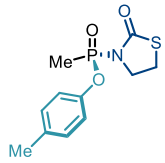
23 63% yield, 95:5 e.r.



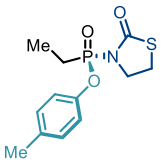
24 69% yield, 86:14 e.r.
(–20 °C, 72 h)



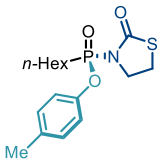
25 90% yield, 95:5 e.r.



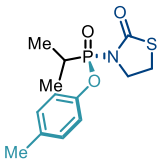
26 97% yield, 90:10 e.r.



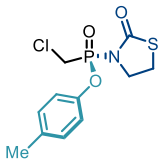
27 95% yield, 93:7 e.r.



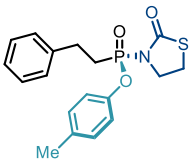
28 88% yield, 92:8 e.r.



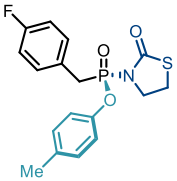
29 79% yield, 94:6 e.r.
[7% yield, 77:23 e.r. with Gen 1 system]



30 46% yield, 89:11 e.r.



31 69% yield, 94:6 e.r.



32 65% yield, 91:9 e.r.

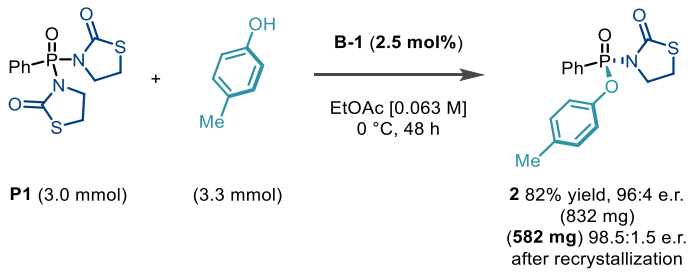
Scheme 2. [A] Phenol nucleophile scope **[B]** P(V) electrophile scope reactions were carried out on 0.1 mmol scale; all yields are isolated yields; yields for related products employing our first-generation method are reported in purple under the relevant examples; e.r. determined by HPLC analysis; **2** is a single crystal X-ray structure, H-atoms omitted for clarity; d.r. was determined by $^{31}P\{^{1}H\}$ NMR or ^{1}H NMR.

Phenols with alternative substitutions patterns were then examined as nucleophiles. Products **8** and **9** bearing only *meta*-substituents were obtained in 98% and 76% yield, and 98:2 e.r. and 96:4 e.r., respectively (the corresponding 2-nitro-6-methyl-phenol analog of **9** was obtained in only 47% yield and 59.5:40.5 e.r. when using our previous method). As with our previously described method, *ortho*-substituted phenols could also be employed, with the derived products (**10**-**12**) being obtained in high yield and good enantioselectivity. Naphthols could also be employed as nucleophiles (**13**-**14**), noticeably **14** was obtained in 64% yield and 98:2 e.r. representing a drastic improvement compared to our first-generation method where less than 10% conversion to product was observed.

Next, we turned our attention to more complex phenol nucleophiles derived from naturally occurring compounds or pharmaceuticals (**15**-**17**). Products **15** and **16** derived from monobenzone and sesamol, respectively, were obtained in 97% yield and 66% yield, and both in 96:4 e.r. **17** derived from eugenol was obtained in 84% yield and 95:5 e.r. (vs. 81% yield, 55.5:45.5 e.r. using related guaiacol (2-methoxyphenol) with the first-generation system). Finally, diastereoselective phosphorylations were conducted using structurally complex, enantiomerically pure phenol nucleophiles (**18**-**20**). Estrone derived product **18** was obtained in 97% yield and 97:3 d.r. while estradiol derived product **19** was obtained in 80% yield and 97:3 d.r. with phosphorylation occurring exclusively at the phenolic site. Compound **20** was obtained from δ-tocopherol in 98% yield and 94:6 d.r. Importantly, when these reactions were conducted using an achiral phosphazene base (BEMP; 2-tert-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine) the resulting d.r. was always ~1:1 indicating full catalyst control in the diastereoselective examples.

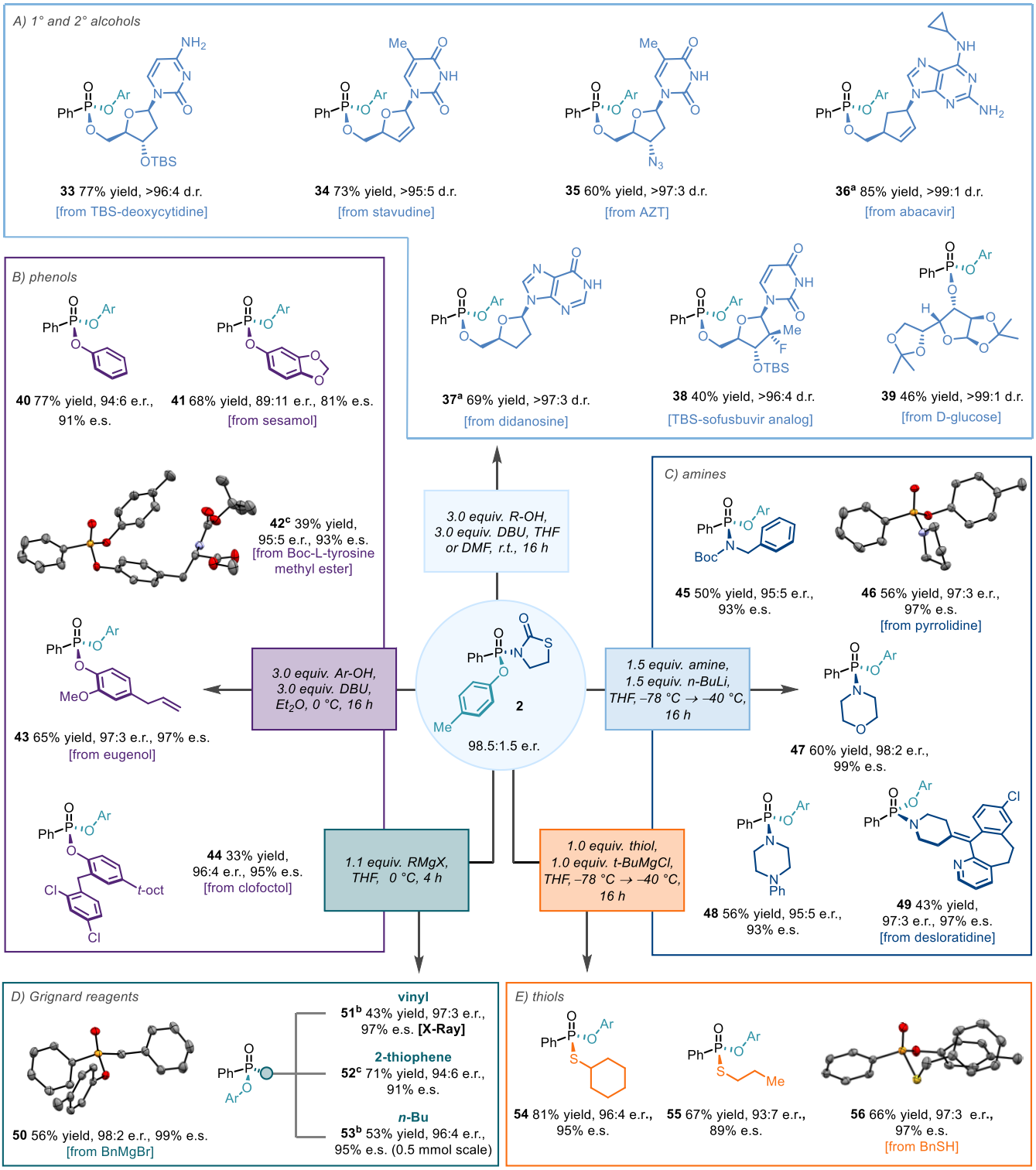
Having explored the scope with respect to the phenol nucleophiles, the scope of the P(V) electrophile was then assessed (**Scheme 2**, **B**). Electron donating (**21**-**22**) and electron withdrawing (**23**) substituents on the aromatic group were well tolerated with the desired products being obtained in 63-77% yield and >95:5 e.r. When a very electron poor aromatic group was introduced (**24**), however, lower temperature (−20 °C) and a 72 h reaction time was required to obtain the desired product in appreciable yield and 86:14 e.r. On the other hand, when a thiophene substituted electrophile was employed, the desired product **25** was obtained in 90% yield and 95:5 e.r. Subsequently, P(V) electrophiles bearing alkyl substituents were submitted to the optimized desymmetrization conditions. Methyl, ethyl, and *n*-hexyl derived substrates were all competent electrophiles in the desymmetrization with the desired products (**26**-**28**) being obtained in 88-97% yields and 90:10-93:7 e.r. Interestingly even more sterically demanding substituents on P, such as *iso*-propyl, could also be accommodated with the resulting enantioenriched product (**29**) being obtained in 79% yield and 94:6 e.r. This result is in stark contrast to the 7% yield and 77:23 e.r. obtained under the first-generation conditions, which most likely resulted from the steric repulsion arising between the hindered *ortho*-substituted phenol nucleophile and an encumbered electrophile. Use of a substrate bearing a chloromethyl substituent afforded the corresponding desymmetrised product **30** in 49% yield and 89:11 e.r., a result of diminished reactivity as opposed to the formation of side products. A phenylethyl-derived substrate was also well-tolerated, forming desymmetrised product **31** in 69% yield and 94:6 e.r. Benzylic substrates were also compatible with **32** being obtained in 65% yield and 91:9 e.r.

For the two-stage strategy to be broadly useful the synthesis of the enantioenriched desymmetrized P(V) compounds would also need to be scalable. To our delight, our second-generation protocol could be carried out on gram scale employing just 2.5 mol% of **B-1**. After 48 hours, enantioenriched **2** was obtained in 82% yield and 96:4 e.r. which could be further boosted to 98.5:1.5 e.r. after a single recrystallization (**Scheme 3**).



Scheme 3. Synthesis of **2** on 3.0 mmol scale with reduced catalyst loading.

With a considerable amount of enantioenriched **2** (98.5:1.5 e.r.) in hand, the scope of the second stage of the strategy, namely the enantiospecific substitution of the second thiazolidinone leaving group, could then be explored. In the first instance the thiazolidinone was smoothly displaced with a series of complex, medicinally relevant 1° and 2° alcohols (**Scheme 4**, **A**). Employing 3.0 equiv. of nucleophile and 3.0 equiv. of DBU in THF or DMF at room temperature, the remaining leaving group could be displaced with: TBS-deoxycytidine (**33**), the anti-HIV drugs[175] stavudine (**34**),[176] AZT (**35**), abacavir (**36**) and didanosine (**37**), the nucleoside fragment of anti-hepatitis C drug sofosbuvir (**38**)[177,178] and the secondary 3'-OH of acetal protected D-glucose (**39**), all in good to excellent yields and with over >95:5 d.r.



Scheme 4. Reaction scope for derivatization of enantioenriched P(V) phosphonate. Reactions carried out between 0.05 and 0.15 mmol scale (see supporting information for more details); All yields are isolated yields; d.r. determined by $^{31}P\{^{1}H\}$ NMR; e.r. determined by HPLC analysis. All non-line structures (**42**, **46**, **50**, **56**) are single crystal X-ray structures, H-atoms omitted for clarity. [a]Reaction carried out using DMF as solvent; [b]–78 °C, 2 h; [c]–78 °C to –40 °C, 16 h.

Subsequently, the use of phenols as nucleophiles in the second stage enantiospecific nucleophilic substitution was then investigated (**Scheme 4**, **B**). This was of particular importance as the resulting enantioenriched diaryl phosphonate esters represent a class of P(V) compounds previously inaccessible by both our first-generation method and that described by Jacobsen. When using 3.0 equivalents of nucleophile and 3.0 equivalents of DBU at in Et_2O at 0 °C for 16 hours the remaining thiazolidinone could be replaced with a suite of phenols, including medicinally relevant ones. Carrying out the displacement with phenol afforded desired product **40** in 77% yield and 94:6 e.r. (91% enantiospecificity). When using sesamol as nucleophile the desired product **41** was obtained in 68% yield but with a minor erosion of enantiopurity (81% e.s.). Other

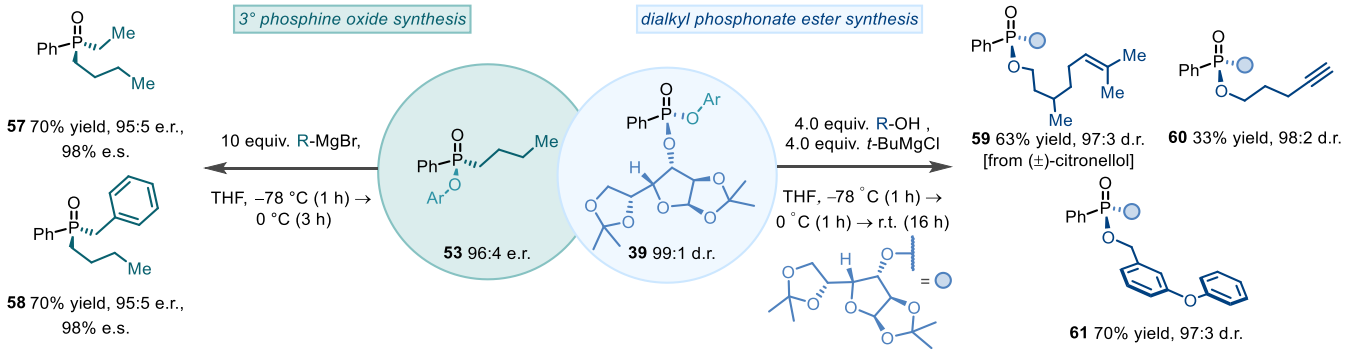
biologically relevant nucleophiles were instead better tolerated, with the products derived from Boc-L-tyrosine methyl ester (**42**), eugenol (**43**) and the antibiotic clofoctol (**44**), which also exhibits considerable antiviral activity in Vero 81 cells against SARS-CoV-2[179,180] being isolated in 33-65% yield and ≥ 93% e.s. Product **42** was recrystallized to enantiopurity, and single crystal X-ray diffraction analysis revealed that the nucleophilic substitution proceeded with inversion of stereochemical configuration at the P(V) center.[181,182]

Following the displacement with alkyl alcohols and phenols, the use of amines to displace the thiazolidinone was examined (**Scheme 4**, **C**). When employing 1.5 equiv. of nucleophile (generated from 1.5 equiv. each of the amines and *n*-BuLi as base at −78 °C in THF) at −40 °C a range of phosphonamidates derived from acyclic (**45**) and cyclic amines (**46-48**) could be obtained in 50-60% yield and ≥ 95:5 e.r. In addition, the enantiospecific substitution could also be carried out with tricyclic H_1 inverse agonist desloratadine, with resulting product **49** being obtained in 43% yield and 97:3 e.r. (97% e.s.). X-Ray diffraction analysis of a single crystal of **46** revealed that nucleophilic substitution with amines proceeded with inversion of the P(V) stereocenter as well.

Our attention then turned to the enantiospecific synthesis of phosphinate esters (**Scheme 4**, **D**) employing Grignard reagents as nucleophiles in the second step. Pleasingly, and in complete contrast to our first generation method where addition of Grignard reagents were unproductive and led to the exclusive formation of byproducts, the thiazolidinone leaving group could be smoothly displaced by employing 1.1 equiv. of organomagnesium halides in THF at 0 °C for 4 h. Products derived from BnMgCl (**50**), vinyl-MgCl (**51**), 2-thiophene-MgBr (**52**) could be obtained in moderate to good yields and ≥ 91% e.s. with only minor adjustments to the reaction temperature and time while the enantiospecific displacement with *n*-BuMgCl could be carried out on 0.5 mmol scale affording phosphinate ester **53** in 53% yield and 96:4 e.r. (95% e.s.). Both **50** and **51** were recrystallized to enantiopurity and single crystals from these samples were analyzed by X-Ray diffraction. Unlike displacement with heteroatom-based nucleophiles, displacement with Grignard reagents took place with retention of stereochemical configuration at the P(V) center.[183]

Finally, a collection of enantioenriched phosphonothioates was prepared by displacing the thiazolidinone leaving group with thiol nucleophiles (**Scheme 4**, **E**). Employing 1.0 equiv. of thiol with 1.0 equiv. of *t*-BuMgCl in THF at −40 °C phosphonothioates bearing cyclohexyl (**54**), *n*-propyl (**55**) and benzyl (**56**) substituents in good yields and with high enantiospecificity. X-Ray diffraction analysis of a single crystal of **56** revealed that, as with alcohols and amines, nucleophilic substitution with thiols proceeded with inversion of the P(V) stereocenter.

The possibility of displacing the phenol substituent (introduced in the first step) on **53** by means of a second substitution with a different Grignard reagent was then probed, as this would allow access to yet another class of P(V) compounds, namely tertiary phosphine oxides. To our delight, when **53** was treated with an excess of Grignard reagent in THF the *para*-cresol substituent on phosphorus could indeed be displaced, affording compound **57** and **58** in 70% yield and 95:5 e.r. (98% e.s.) (**Scheme 5, left**). Interestingly, and in contrast to when Grignard reagents were employed to displace the thiazolidinone leaving group, this substitution was found to proceed with inversion of configuration at P (see Supporting Information for further details).



Scheme 5. Synthesis of enantioenriched 3° phosphine oxides (left) and dialkyl phosphonate esters (right). All yields are isolated yields; d.r. determined by $^{31}P\{^1H\}$ NMR; e.r. determined by HPLC analysis. Ar = 4-Me-C_6H_4.

Encouraged by the successful displacement of the *para*-cresol substituent on phosphorus with Grignard reagents, we considered if the products derived from substitution with alkyl alcohols in the second step could be converted to enantioenriched bis-alkyl phosphonate esters by means of another stereospecific substitution with biologically relevant alcohols. Indeed, employing glucose bearing phosphonate ester **39** as a substrate, the *para*-cresol substituent could be swiftly exchanged with a variety of alkyl alcohol nucleophiles with high levels of enantiospecificity (with inversion of configuration

at P). Phosphonate **59**, derived from (±)-citronellol was obtained in 63% yield and 97:3 d.r. while **60**, which bears an alkyne handle for further functionalization through click chemistry[184] could be obtained in 33% yield and 98:2 d.r. Finally, **61**, derived from 3-phenoxy benzyl alcohol (a common motif in agrochemicals)[185] was obtained in 70% yield and 97:3 d.r. (**Scheme 5, right**).

COMPUTATIONAL STUDIES

To elucidate the origin of enantioselectivity in the catalytic nucleophilic desymmetrization of the prochiral P(V) substrates, a density functional theory (DFT) study was performed (**Figure 1**). As the rate- and enantio-determining step in our previous report was the formation of a pentacoordinate anionic intermediate,[146] the kinetic preference for the nucleophilic attack was examined in this computational study, using the model catalyst **B-2**, phosphonate ester **P1** or **P7**, and phenol nucleophile. Among the located transition states (TSs), the lowest TS structures for the formation of (*R*)- and (*S*)-products from **P1** were **TS1-(*R*)** and **TS2-(*S*)**, respectively (**Figure 1**, middle). The more favored transition state (**TS1-(*R*)**) agrees with the experimentally confirmed absolute stereochemical configuration obtained by single crystal X-ray diffraction analysis and is computed to be 3.3 kcal mol^{-1} lower in energy than **TS1-(*S*)**. Both transition structures engage in several stabilizing non-covalent interactions (NCIs) such as hydrogen bonding, CH–π, and π–π interactions between the catalyst and the reactants. The simultaneous activation of the P(V) electrophile and the phenol nucleophile is promoted by multiple hydrogen bonding interactions with the BIMP catalyst. The notable difference which contributes to increasing the energy barrier of **TS2-(*S*)** is the repulsive interaction between oxygen lone pairs of the phosphonate and thiazolidinone in the substrate. The favored TS benefits from dipole minimization rather than being affected by the substituent on the phosphorus atom. This is evidenced by the minimal change in energy trend ($\Delta\Delta G^{\ddagger}$ = 3.1 kcal mol^{-1}) when a phenyl substituent is replaced by a methyl group (**Figure 1**, right).

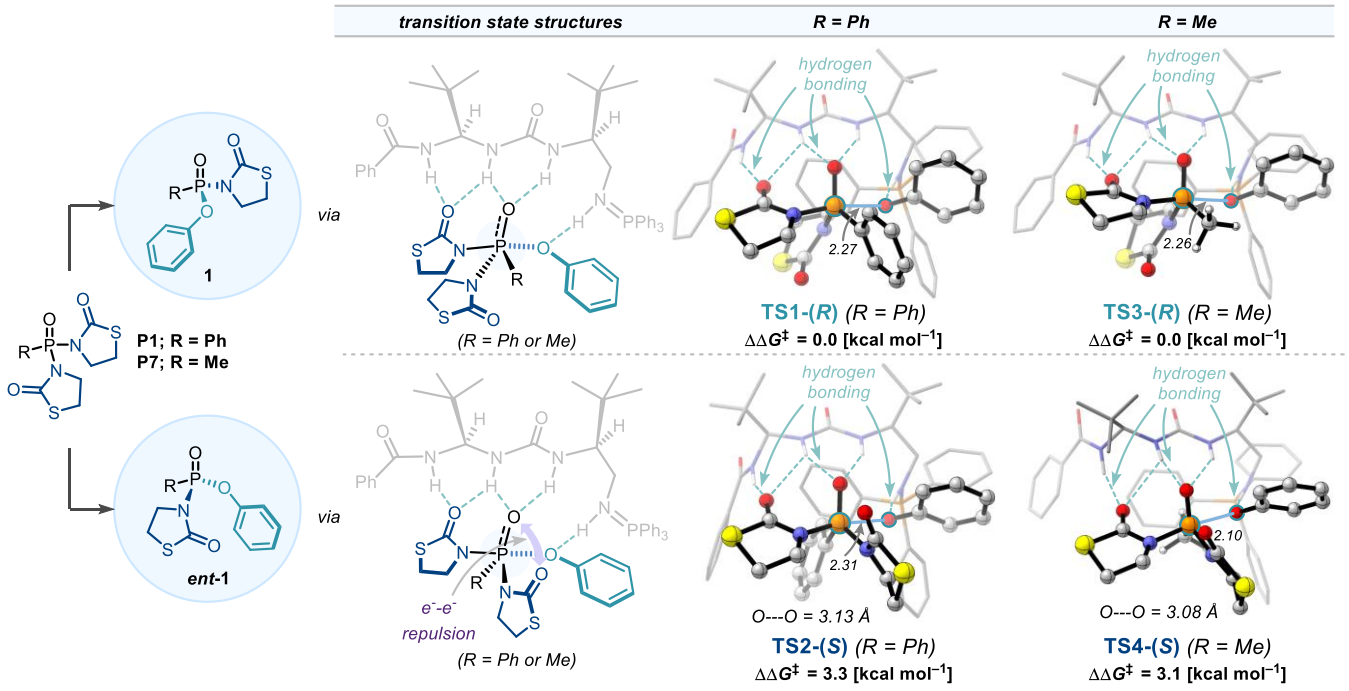


Figure 1. Nucleophilic attack transition state structures (relative Gibbs free energies [kcal mol^{-1}]) for the formation of the (*R*)- and (*S*)-products from **P1** and **P7** computed at SMD/M06-2X/def2TZVP//SMD/M06-2X/def2SVP level of theory. Bond lengths (Å) of the TS geometries are provided in the Supporting Information.

A major limitation of our first-generation catalytic method was the requirement for an *ortho*-substituent on the phenol nucleophiles to achieve high levels of enantioselectivity. Our second-generation method, on the other hand, does not. DFT calculations were thus utilized to pinpoint the reason for why an *ortho*-substituent was required in the first-generation method but not for our newly established system (**Figure 2**). In the computed TSs for the first-generation catalytic system, a high enantioselectivity is obtained with 2,4-dimethylphenol ($\Delta\Delta G^{\ddagger}$ = 2.4 kcal mol^{-1}),[146] while a dramatic decrease in the energy difference is observed in the absence of a 2-methyl substituent ($\Delta\Delta G^{\ddagger}$ = 0.9 kcal mol^{-1}). The superimposed structures for both TSs in **Figure 2A** strongly imply that there is almost no geometry change with or without an *ortho*-methyl group in **TS5-(*R*)-Me** and **TS5-(*R*)-H** (RMSD = 0.15; RMSD = root mean square deviation), but there is an obvious geometrical distinction for the phenol nucleophile in the disfavored transition states **TS6-(*R*)-Me** and **TS6-(*R*)-H** (RMSD = 0.25). This indicates that the steric repulsion between the catalyst and the *ortho*-substituent of the phenol nucleophile further destabilizes the disfavored

transition state structure (**TS6-(*S*)-Me**) leading to high levels of enantioselectivity. In comparison, the second-generation catalytic system has sufficient space to accommodate the phenol nucleophile approaching the phosphorus atom (**Figure 2, B**). As evidenced by the similar RMSD values in both favored and disfavored TSs with and without the *ortho*-methyl group (RMSD = 0.39 and 0.32), along with the maintained large energy barrier difference in the presence of an *ortho* substituent ($\Delta\Delta G^{\ddagger}$ = 2.5 kcal mol^{-1}), the origin of high enantioselectivity relies soley on positive non-covalent interactions between the BIMP catalyst and the P(V) electrophile in the transition state leading to the major enantiomer, rather than relying on an additional destabilization between the catalyst and the nucleophile in the disfavored transition state. These insights from the DFT calculations shed light on the origins of enantioselectivity for both first- and second-generation catalytic systems in the enantioselective nucleophilic substitution at P(V) and provide insight as to why the second-generation system was found to be far more general.

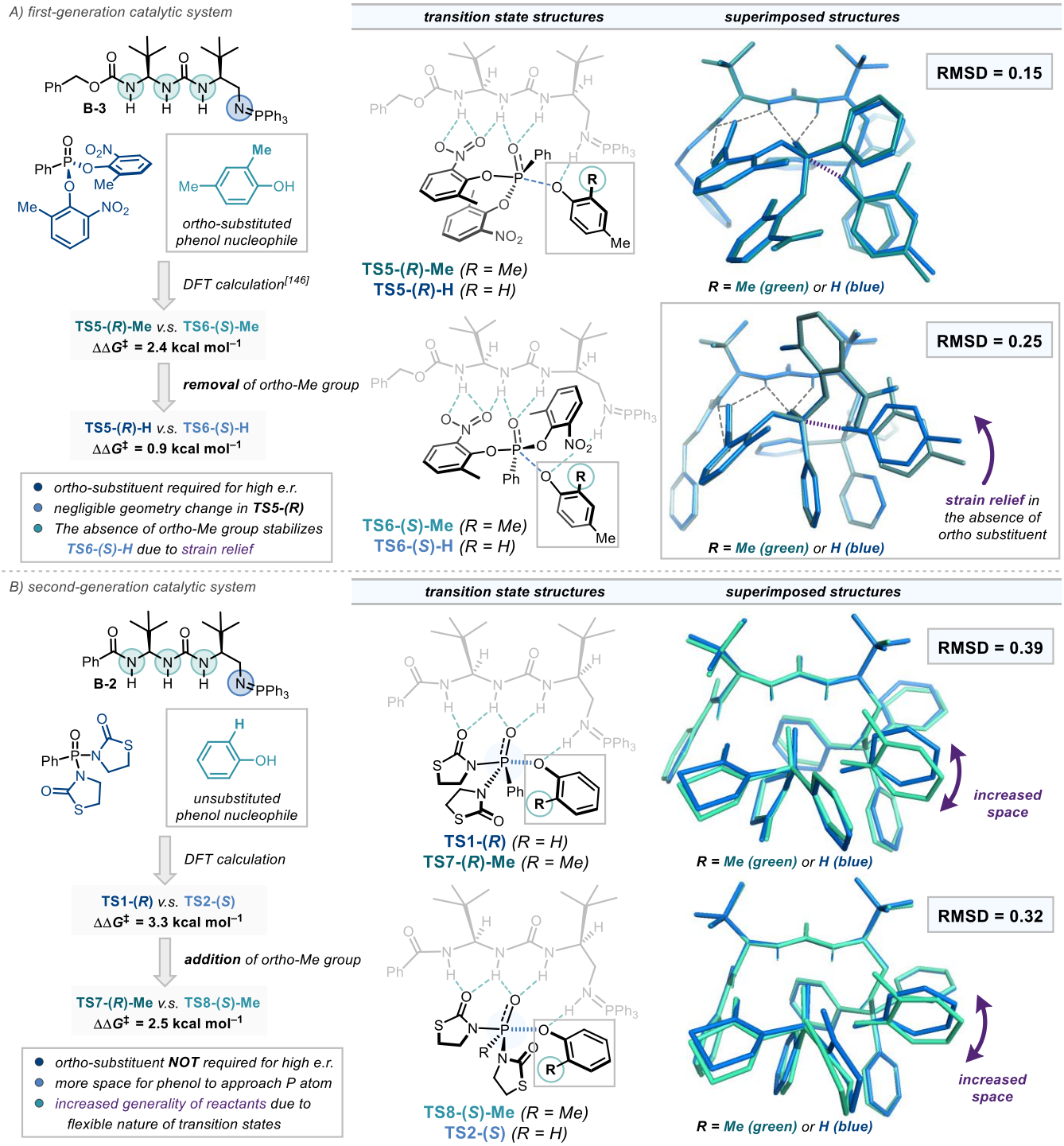


Figure 2. Impact of *ortho*-substitution in the first- and second-generation systems computed at SMD/M06-2X/def2TZVP//SMD/M06-2X/def2SVP level of theory. RMSD = root mean square deviation. RMSDs were calculated by replacing the *ortho*-methyl groups with hydrogens.

An interesting trend was observed when Grignard reagents were examined as nucleophiles for enantiospecific S_N2@P reactions (**Schemes 4 & 5**).[181-183,186-189] The displacement of the thiazolidinone leaving group took place with retention of stereochemical configuration at the P(V) center, whereas phenol displacement took place with inversion of configuration. Thus, we utilized DFT calculations to elucidate the origin of these unique pathways using *n*-BuMgCl as a representative nucleophile (**Figure 3**). First, the substrate **2** chelates the Grignard reagent and generates a stable complex **Int1**, which undergoes a nucleophilic attack at phosphorus center (S_N2@P) through the transition state structure **TS9** ($\Delta G^{\ddagger}$ = 19.7 kcal mol^{-1}, **Figure 3, A**). Once the P−C bond is formed, the thiazolidinone leaving group is dissociated simultaneously without the formation of a pentacoordinate P(V) intermediate. This pathway is referred to as a double-well potential energy surface (PES), and the process, also known as the frontside bimolecular nucleophilic substitution at phosphorus (S_N2@P4-f), is the favored pathway compared to the backside S_N2@P4-b.[187] Interestingly, the P−C bond formation preferably occurs opposite to the phenoxy group when comparing **TS9** and **TS10**, and this is due to the stabilization of electron density localized at the apical oxygen atom which can further promote the substitution process. In stark contrast, nucleophilic substitution with the Grignard reagent in the absence of thiazolidinone leaving group occurs by S_N2@P4-b through the most preferred transition state structure **TS12** (**Figure 3, B**). Again, the phenoxy group tends to be placed at the apical position at the transition state, and in this case the dissociation of the leaving group through the concerted process leads to the formation of the stereochemically inverted product. Taken together, the in-depth analyses into both catalytic enantioselective and stoichiometric enantiospecific nucleophilic substitution reactions at the P(V) center revealed the origin of improved generality and diversifiability of our second-generation protocol.

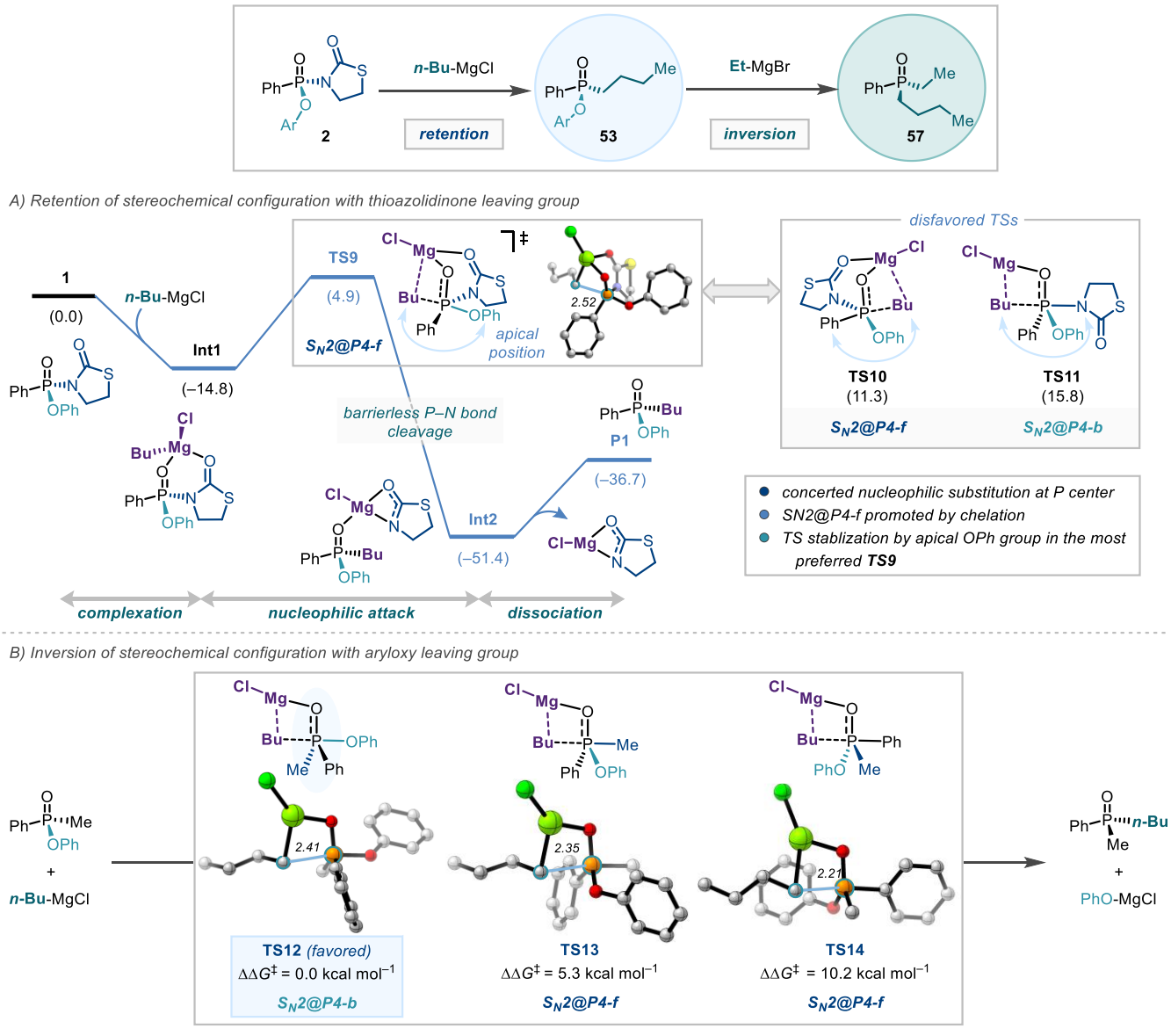


Figure 3. Rationalization of stereochemical retention [**A**] and inversion [**B**] pathways upon nucleophilic substitution with Grignard reagents (relative Gibbs free energies [kcal mol^{-1}]) computed at SMD/M06-2X/def2TZVP//SMD/M06-2X/def2SVP level of theory.

CONCLUSIONS

A more practical, general, and efficient second-generation enantioselective desymmetrization at P(V) has been developed. Through the use of thiazolidinone leaving groups on the P atom and fine tuning of the ureidopeptide BIMP catalyst numerous drawbacks of previously established methods have now been overcome. Phenols with a wide array of substitution patterns can be readily employed as nucleophiles in the desymmetrization step (vs. only *ortho*-substituted phenols previously) with both aryl and alkyl derived P(V) electrophiles as substrates. The remaining thiazolidinone leaving group can be readily displaced by medicinally relevant alkyl and aryl alcohols, amines, Grignard reagents and thiols, providing divergent access to a wide range of enantioenriched P(V) species through a single two-phase catalytic platform. In contrast to our first-generation approach the nucleophile employed for the desymmetrization could also be displaced enantiospecifically with either Grignard reagents to access tertiary phosphine oxides or with alkyl alcohols to access complex enantioenriched dialkyl phosphonates. DFT studies were then carried out to investigate the origins of enantioselectivity in the catalyst controlled desymmetrization step and to rationalize the superior enantioselectivities arising from the newly established pairing of the ureidopeptide BIMP catalyst and the thiazolidinone leaving group compared to the previously employed nitrophenol. Additionally, subsequent second and third stage enantiospecific nucleophilic substitutions progressing through either stereoinversive or retentive processes were also rationalized. Taken together, the newly developed catalytic platform, and computational insights obtained in this study provide a toolbox for the preparation and utilization of enantioenriched stereogenic at P(V) compounds as well as a road map for the development of even more general catalytic strategies to access this ever more important class of compound.

ASSOCIATED CONTENT

Supporting information

The Supporting Information is available free of charge at XX.

Further optimization and DFT studies, experimental procedures, characterization data, NMR spectra, HPLC traces, single crystal X-ray data and xyz coordinates (PDF).

Accession Codes

CCDC 2292138 (compound **2**), 2292139 (compound **42**), 2292140 (compound **46**), 2292141 (compound **50**) , 2292142 (compound **51**), and 2292143 (compound **56**) contain the supplementary crystallographic data for this paper. These data can be obtained free o of charge via www.ccdc.ca-m.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: +441223336033.

AUTHOR INFORMATION

Corresponding Authors

Darren J. Dixon *Department of Chemistry, Chemistry Research Laboratory, University of Oxford, 12 Mansfield Road, OX1 3TA, Oxford, UK. Email: darren.dixon@chem.ox.ac.uk*

Ken Yamazaki *Division of Applied Chemistry, Okayama University, Tsushimanaka, Okayama 700-8530, Japan. Email: k-yamazaki@okayama-u.ac.jp*

Authors

Michele Formica *Department of Chemistry, Chemistry Research Laboratory, University of Oxford, 12 Mansfield Road, OX1 3TA, Oxford, UK.*

Branislav Ferko *Department of Chemistry, Chemistry Research Laboratory, University of Oxford, 12 Mansfield Road, OX1 3TA, Oxford, UK.*

Thomas Marsh *Department of Chemistry, Chemistry Research Laboratory, University of Oxford, 12 Mansfield Road, OX1 3TA, Oxford, UK.*

Timothy A. Davidson *Department of Chemistry, Chemistry Research Laboratory, University of Oxford, 12 Mansfield Road, OX1 3TA, Oxford, UK.*

Notes

‡These authors contributed equally.

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