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Microreview

Anionic Cascade Reactions

Anionic Cascade Routes to Sulfur and Nitrogen Heterocycles Originating from Thio- and Aminophosphate Precursors

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Abstract: This micro-review attempts to comprehensively cover reported reactions employing thio- and aminophosphate precursors for forming sulfur and nitrogen heterocycles. All such reactions are triggered by initial formation of an alkoxide, most commonly by attack of a carbon or heteroatom nucleophile onto a carbonyl group. The alkoxide intermediate facilitates an intramolecular transfer of the phosphate group to form a thiolate or nitrogen atom anion, which then terminate the anionic cascade via an intramolecular O-phosphate displacement reaction to form the heterocyclic products.

Contents

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1. Introduction

Phosphates have emerged from the primordial soup as critical functional and structural components of many organic architectures essential to living organisms.[1] Shown in Figure 1 are selected examples of the most prominent members of this important family of organophosphates. This family most famously includes ribonucleic acid (RNA) and its deoxy counterpart (DNA), which are both polynucleotides wherein the phosphate plays the role of connecting the furanoses together at their 3- and 5-positions, while also adding a negative charge to each monomer added to the chain. Perhaps, the most significant of these monomers (nucleosides) is adenosine triphosphate (ATP), which participates in many biological processes. Gluconeogenesis is a critical metabolic pathway in which phosphates play a key role and involves the intermediacy of glucose-6-phosphate, and phosphoenolpyruvate along with other organophosphates. Pyridoxal phosphate is an example of a small important organophosphate used in many enzymatic processes. Isopentenyl pyrophosphate (IPP), which is assembled from acetyl Coenzyme A (CoA) via mevalonate-5-phosphate precursor, is a building block *en route* to many terpenes. Phosphocreatine is a rare ex-

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ample of a natural aminophosphate whose role is to donate a phosphate group, adenosine diphosphate (ADP). Phosphates also serve an important role as structural components of phospholipids, which are essential for the assembly of cell membranes.

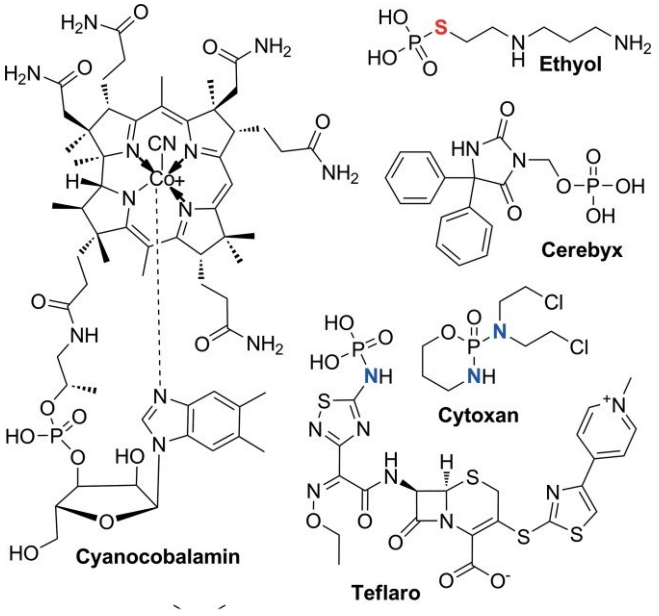


Figure 1. Examples of organophosphates significant in biological processes.

Not surprisingly, given the importance of organophophates in crucial biological processes, they have been employed as essential chemical substituents in pharmaceuticals[2] and agrochemicals (Figure 2). Many of these compounds have one or more of the phosphate group oxygen atoms replaced with either a nitrogen (blue) and/or sulfur (red) atom or both. The structures displayed in Figure 2 can be, based on their intended applications, broken down into pharmaceuticals (teflaro®, cerebyx, cyanocobalamin, cytoxan and ethyol), herbicides (bensulfide and butamifos) and pesticides (malathion, profenofos, acephate, monocrotophos, dimethoate and chlorpyrifos). Two of these compounds are natural product derivatives, the common vitamin(B/Z) cyanocobalamin and the cephalosporin antibiotic teflaro. The phosphate groups serve a variety of different roles in these compounds, ranging from tether or a prodrug functional group to essential structural component of the pharmaceutical or agrochemical agent.

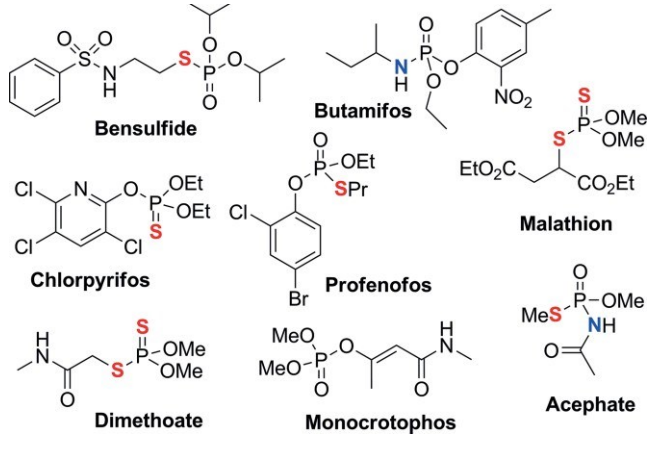


Figure 2. Phosphate group-containing pharmaceuticals and agrochemicals.

Phosphates are not only important structural components in biologically essential molecules, pharmaceuticals and agrochemicals but they also play a key role in many important reaction classes. In this microreview we present a class of reactions, which has previously not been reviewed or summarized, that employ either a thio- or aminophosphate precursor to access sulfur and nitrogen heterocycles, respectively, via a one-pot anion triggered cascade. Figure 3 summarizes the type of phosphates that have been used in these reactions, and the range of sulfur and nitrogen hetereocycles synthesized using such phosphate group enabled anionic cascades.

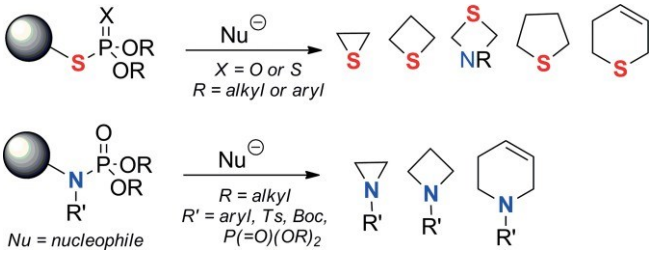


Figure 3. Summary of anionic cascade approaches presented.

We have selected to present this exciting science in two main sections focused on sulfur and nitrogen heterocycles respectively wherein synthesis of the smallest rings are presented first, followed progressively by discussions of syntheses of larger rings.

2. Synthesis of Sulfur Heterocycles

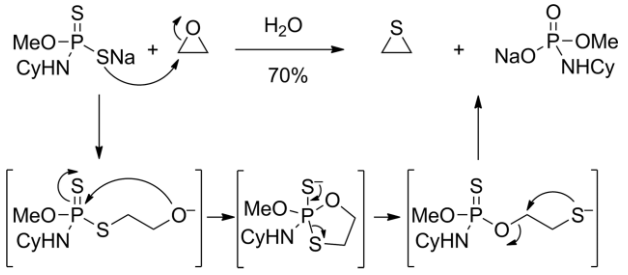
Sulfur heterocycles are important structural components of many natural products and pharmaceuticals.[2] In this section we present, chronologically, the earliest thiophosphate enabled contributions toward the synthesis of small sulfur heterocycles, which in the early years are almost exclusively focused on thiiranes, and how the field and approaches have evolved since.

2.1. Thiirane

Thiiranes (episulfides) are strained three-membered sulfur heterocycles, which, unlike their oxirane (epoxide) and aziridine counterparts, are challenging to make directly from double bonds. Furthermore, thiiranes are also relatively unstable and readily undergo desulfurization. Alternative methods for their preparation and their utilization as new synthetic gateways to double bonds have been some of the motivations for early thiophosphate reaction contributions.

N. K. Hamer reported in 1968 a single example of converting ethylene oxide into thiirane by employing sodium *N*-cyclohexylphosphoramidothioate nucleophile in water (Scheme 1).[3,4] This high-yielding transformation proceeds via initial oxirane ring opening, followed by intramolecular attack of the resulting alkoxide onto the weak P=S bond to form a pentavalent inter-

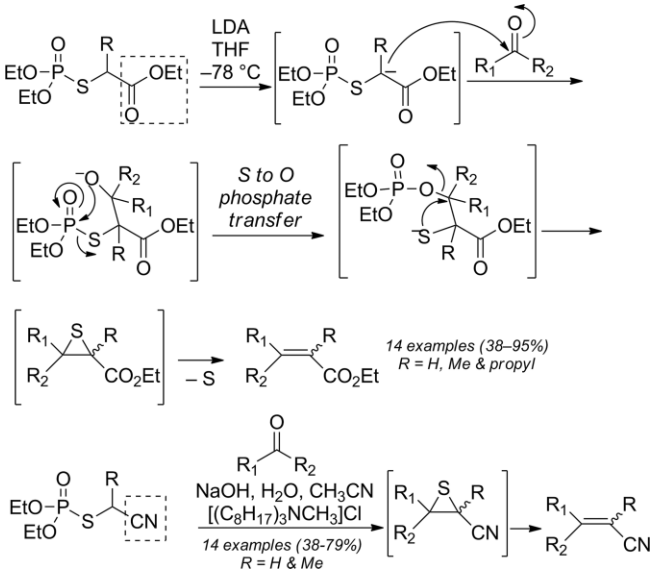
mediate, which then fragments to form a thiolate nucleophile. This thiolate then displaces the phosphate leaving group to afford the desired thiirane product.



Scheme 1. Hamer's 1968 thiirane synthesis.

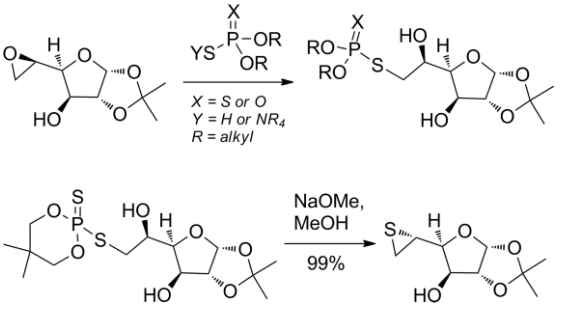
It is worth noting that thiophosphates are not the only such bi-functional nucleophiles capable of converting oxiranes into thiiranes. The most classical approach employs thiocyanate nucleophiles.[5]

Inspired by the contributions of his mentor, C. R. Johnson,[6] and A. I. Meyers[7] who had both shown that aldehydes react with sulfur-stabilized anions to form thiiranes in a single pot, K. Tanaka demonstrated that a similar transformation could be accomplished with an α-thiophosphate group (Scheme 2) instead of a heterocycle or a dithiocarbonate.[8] Employing α-thiophosphate carbanions stabilized by either an ester[9] or a nitrile,[10] aldehydes and ketones can be converted into enolate and acrylonitrile products in high yields via an intermediate thiirane. In both cases the thiirane undergoes a spontaneous extrusion of sulfur to form the double bond. This approach is similar to the Darzens and *aza*-Darzens approaches to oxiranes and aziridines, except a thiophosphate group, rather than a halogen, is used next to the ester. It is to be noted, that thiiranes cannot be made using classical Darzens approach because thiocarbonyls (C=S) are unstable and react differently than carbonyl and imine electrophiles. As discussed in later sections of this microreview, this new alternative approach, wherein a leaving group is made in situ, can also be adapted for other heteroatoms with the exception of oxygen.



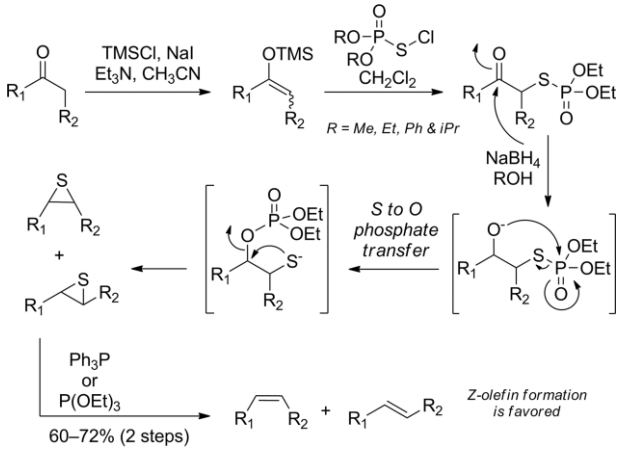
Scheme 2. Tanaka's 1979 thiirane enabled olefin syntheses.

M. Michalska has shown that a protected 5,6-epoxy furanose can undergo a ring-opening selectively at the 6-position with either thiophosphoric acids or their alkylammonium salts (Scheme 3).[11,12] Interestingly, he notes that dithiophosphoric acids react most rapidly of the phosphoric acid derivatives he explored. For one product he has further demonstrated that treatment with sodium methoxide quantitatively converts the phosphate adduct into a thiirane with the expected inversion of configuration at the C5-carbon.



Scheme 3. Michalska's 1980 thiirane furanose synthesis.

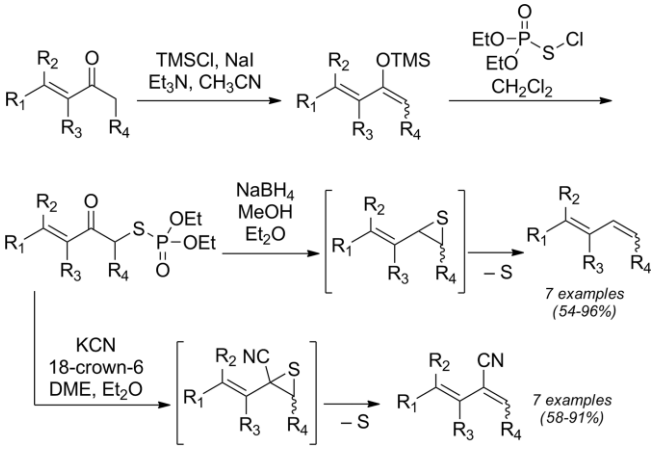
A. Skowronska's first contribution in this area focused on developing a stereoselective route to olefins (Scheme 4).[13,14] Toward that end, a ketone was converted into a silyl enol ether and then reacted with an electrophilic thiophosphate source to afford α-thiophosphate ketone. Treatment of this new ketone with sodium borohydride generated an alkoxide intermediate, which then underwent a phosphate group transfer from sulfur to oxygen, generating a thiolate nucleophile that displaced the phosphate to form a mixture of thiiranes. When this mixture was subjected to either a phosphine or a phosphite nucleophile a facile desulfurization ensued, resulting in a mixture of *E*- and *Z*-olefinic products reflective of the original diastereomeric mixture from the hydride nucleophilic attack according to Cram's model. In this case, *Z*-olefins are generally favored with ratios up to 3:1 for larger subsituents. Interestingly, when this same



Scheme 4. Skowronska's 1991 stereoselective olefin synthesis.

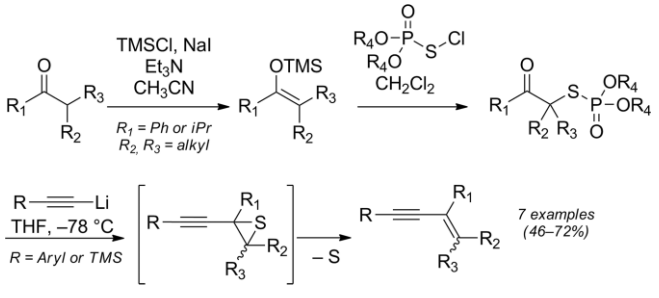
sequence is repeated for a selenophosphate, a selenirane intermediate with higher *Z*-selectivity is generated.

Skowronska has expanded his approaches to diene syntheses using enone precursors (Scheme 5).[15] The synthetic strategy is identical, but in this follow up study he demonstrates that the anionic phosphate hopping cascade can also be initiated with a carbon nucleophile, nitrile in this case. This is a significant evolution as it results in decoration of the double bond with a functionalized carbon atom. Reactions are primarily *Z*-selective, but this selectivity can be reversed by using a large phosphate group. This three-step approach (enol ether formation, thiophosphate group installation and anionic cascade) converts a ketone into a double bond.



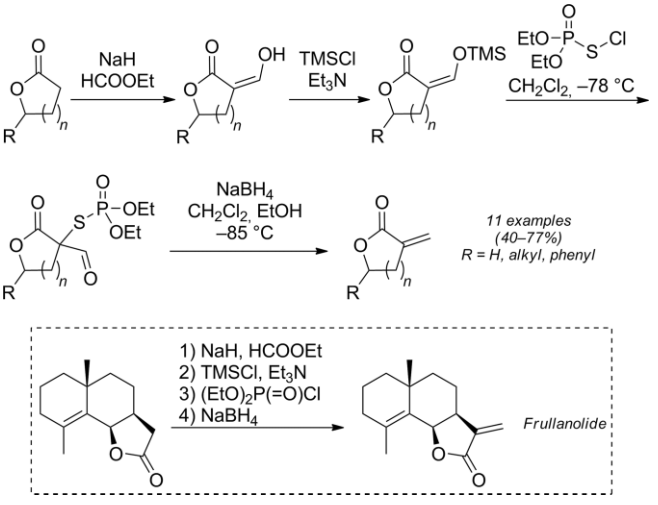
Scheme 5. Skowronska's 1999 vinyl thiirane synthesis.

Skowronska has shown that the phosphate mediated anionic cascade can be triggered by carbon nucleophiles other than a cyano group. Alkyne anions are compatible as well (Scheme 6) and allow construction of challenging enynes with a tetrasubstituted olefin component.[16] Although stereoeselectivity is low, it is important to emphasize how challenging tetrasubstituted olefins are to synthesize using conventional strategies.



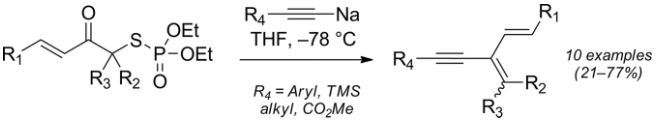
Scheme 6. Skowronska's 2000 enyne synthesis approach.

In the 1970's and 1980's there was great interest in the development of new methods for forming α-methylene lactones from lactones, fueled by many intriguing natural product targets such as vernolepin. Eschenmosher's methylenation reaction,[17] and other approaches emerged during this time. Skowronska has demonstrated that α-thiophosphates can be used to synthesize α-methylene lactones and ketones (Scheme 7).[18] In his four-step approach, lactones are first formylated, then converted to silyl enol ethers before being subjected to an electrophilic thiophosphate source. The resulting α-thiophosphate formylated lactones then enter the aforementioned thiirane forming anionic cascade upon treatment with sodium borohydride. Skowronska has applied his method in the total synthesis of frullanolide.



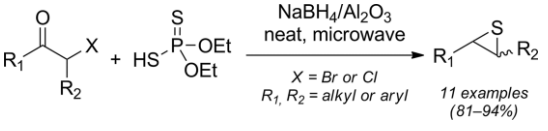
Scheme 7. Skowronska's 2000 α-carbonyl methylenation.

By combining lessons learned from his diene synthesis with latter success with alkyne nucleophiles, Skowronska has further demonstrated that α-thiophosphates can be used as starting materials to access dieneyne products (Scheme 8).[19] Again, one of the main synthetic strengths of this particular approach is the access it provides to tetrasubstituted double bonds.



Scheme 8. Skowronska's 2002 dieneyne synthesis.

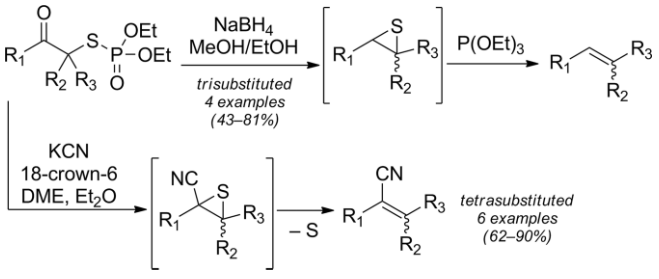
L. D. S. Yadav made an interesting improvement to Skowronska's thiirane synthesis approach wherein there is no need for the use of toxic electrophilic thiophosphate reagents (Scheme 9).[20] By mixing α-halo ketone precursors neat with diethyl dithiophosphoric acid and alumina supported sodium borohydride, under microwave irradiation in a domestic microwave oven, thiiranes were synthesized in one pot in high yields. This reaction also works thermally in the absence of any microwave irradiation, but yields are significantly lower.



Scheme 9. Yadav's 2002 one pot thiirane synthesis.

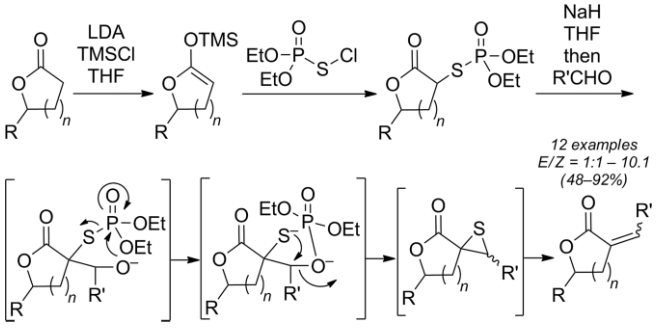
By combining lessons from his earlier thiirane/olefin syntheses, Skowronska chose to specifically synthesize tri- and tetrasubstituted olefins from a common precursor using his thiophosphate approach. These olefin classes are arguably more challenging to make than disubstituted olefins with standard

methods especially when all substituents on the olefin are unactivated. The approach is the same as before (Scheme 10),[21] wherein a hydride or cyano nucleophile attacks the ketone, thus initiating a cascade resulting in formation of a thiirane, which then either spontaneously loses sulfur (cyano scenario), or sulfur extrusion is assisted with a phosphite nucleophile.



Scheme 10. Skowronska's 2003 alkene synthesis.

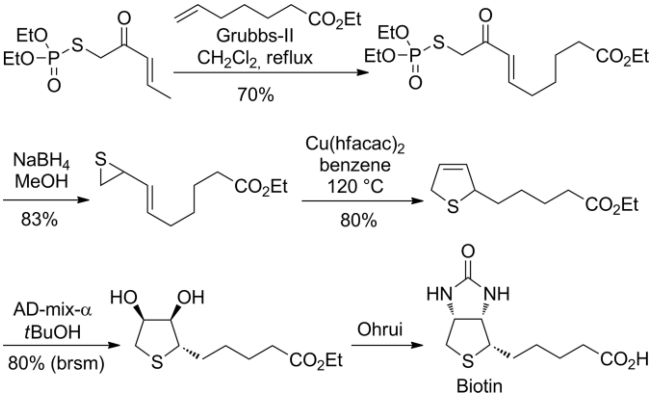
E. Krawczyk revisited Skowronska's methylenation approach. Instead of having a pre-installed formyl group followed by a reduction step, she has shown that the α-thiophosphate sodium enolate can be trapped with a variety of aldehydes to form tri-substituted olefins directly in one pot via a thiirane intermediate (Scheme 11).[22] Stereoselectivity is significantly impacted by the size of substituents (R and R').



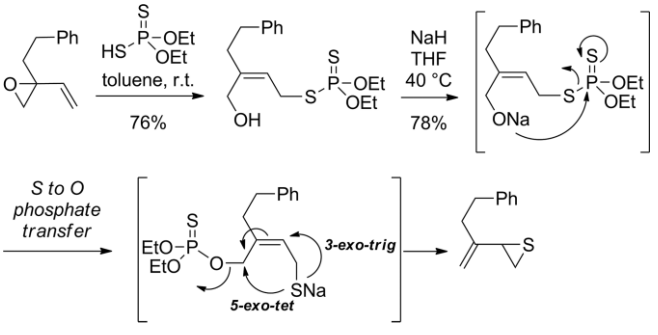
Scheme 11. Krawczyk's 2006 α-carbonyl olefination.

J. T. Njardarson[23] has used Skowronska's method to accomplish a short formal total synthesis of biotin[24] (Scheme 12). Following cross metathesis between thiophosphate enone and a terminal alkene, a vinyl thiirane was accessed by treating the product with sodium borohydride. Njardarson's copper-catalyzed ring expansion protocol[25] then converted the vinyl thiirane into a 2,5-dihydrothiophene. Careful chemo- and substrate controlled dihydroxylation of the double bond afforded the diol shown, which is an intermediate in Ohrui's[26] biotin synthesis. The S-based carbonyl starting materials are synthesized either via nucleophilic substitution on α or β-halo-substituted carbonyl compounds with S nucleophiles or via Michael addition on the α, β-unsaturated carbonyl compound with electrophilic sulfur. The required thiophosphate reagents are generally cheap and commercially available.[25,35]

Njardarson has developed a mild regio- and steroeselective ring opening of vinyl oxiranes with dithiophosphoric acid esters (Scheme 13).[27] The resulting products provided an excellent opportunity to evaluate whether a phosphate group could transfer over a longer distance (via a seven-membered ring intermediate) and if the resulting thiolate would then form a vinyl thiirane or a 2,5-dihydrothiophene product. Treatment of the alcohol product with sodium hydride and gentle heating in tetrahydrofuran triggered the expected anionic cascade, which was terminated exclusively via 3-*exo-trig* cyclization pathway to form a vinyl thiirane product.



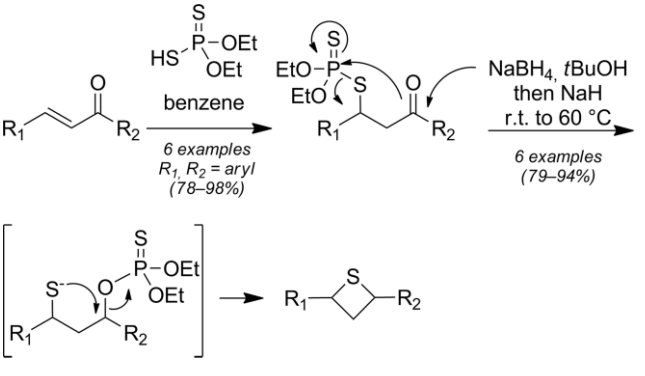
Scheme 12. Njardarson's 2007 biotin formal synthesis.



Scheme 13. Njardarson's 2014 vinyl thiirane synthesis.

2.2. Thietane

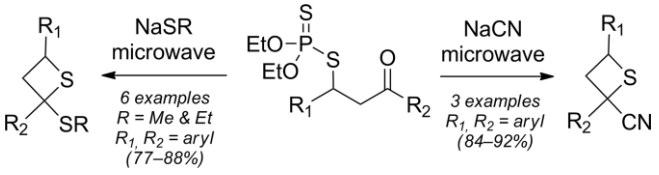
Y. Ueno was the first to demonstrate the thiophosphate hopping approach as a viable synthetic strategy to assemble thietanes (Scheme 14).[28] Using six different chalcone substrates as reactive Michael acceptors (R^1 and R^2 = aryl), he synthesized the requisite starting materials for his anionic cascades by reacting the chalcone electrophiles with dithiophosphoric acid es-



Scheme 14. Ueno's 1981 chalcone approach to thietanes.

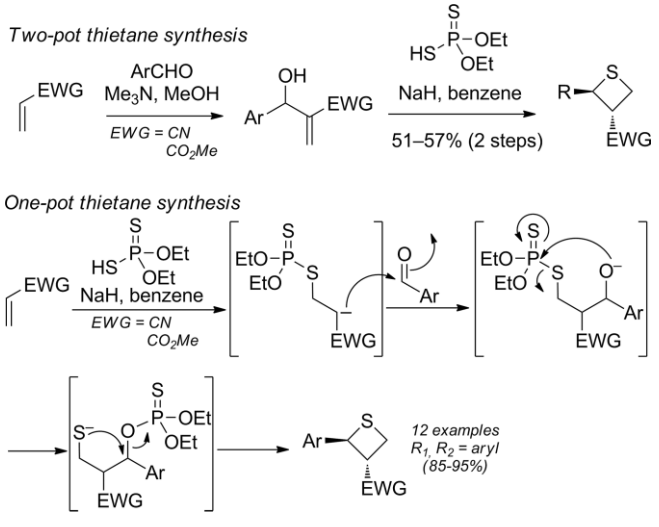
ters in benzene at room temperature. An anionic cascade was initiated with sodium borohydride (alkoxide formation), which proved not sufficient, required addition of sodium hydride and a thermal boost. These optimized reaction conditions, afforded the targeted thietane products in excellent yields.

Almost 20 years after working for Ueno on a chalcone approach to thietanes, L. D. S. Yadav revisited this approach (Scheme 15) with two new nucleophiles as anionic cascade triggers (cyano and alkyl thiolate instead of a hydride).[29] By subjecting a neat mixture of sodium cyanide or sodium alkyl thiolates and the dithiophosphate Michael adduct shown to microwave irradiation, thietanes can be formed directly in high yields.



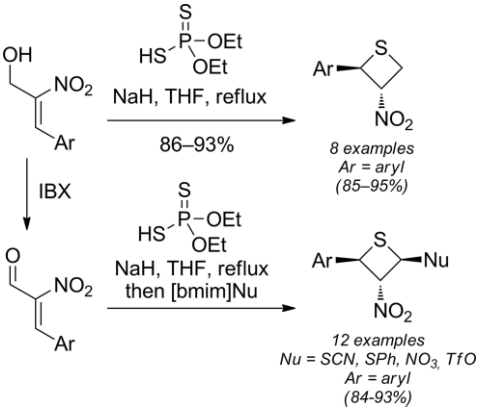
Scheme 15. Yadav's 2002 chalcone approach to thietanes.

Yadav has designed two routes to 2,3-substituted thietanes inspired by the Baylis–Hillman reaction (Scheme 16).[30] The first route utilizes modified Baylis–Hillman reaction conditions[31] to afford the classic adduct, which is then reacted with dithiophosphoric acid ester in the presence of sodium hydride to afford the desired thietane in the second step. Not satisfied, he developed a one-pot synthesis, which is triggered by initial dithiophosphate Michael-addition step, followed by trapping of the resulting stabilized carbanion with an aryl aldehyde, which then triggers the phosphate mediated cascade to form the thietane product.



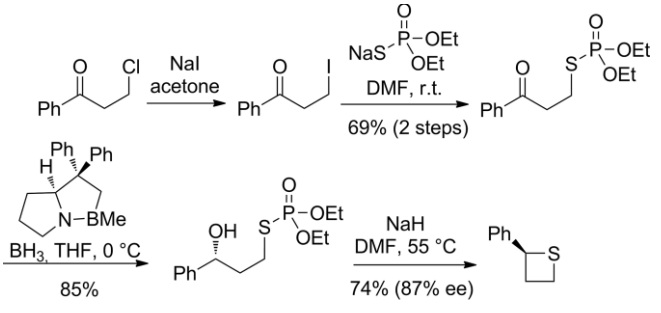
Scheme 16. Yadav's 2009 thietane Baylis–Hillman route.

The success of Yadav's Baylis–Hillman route led him to explore additional variations (Scheme 17).[32] His latest approaches use a reactive Michael acceptor (nitro group). In his first approach, a Baylis–Hillman adduct is used to afford 2,3-disubstituted thietanes in one-pot. The second scenario employs an even more reactive Michael acceptor wherein the alkoxy anion needed for the phosphate cascade is generated by the addition of a heteroatom nucleophile onto the aldehyde group. This attractive one pot route results in the formation of tri-substituted thietanes with three different functional group handles for further manipulations.



Scheme 17. Yadav's 2012 thietane Baylis–Hillman route.

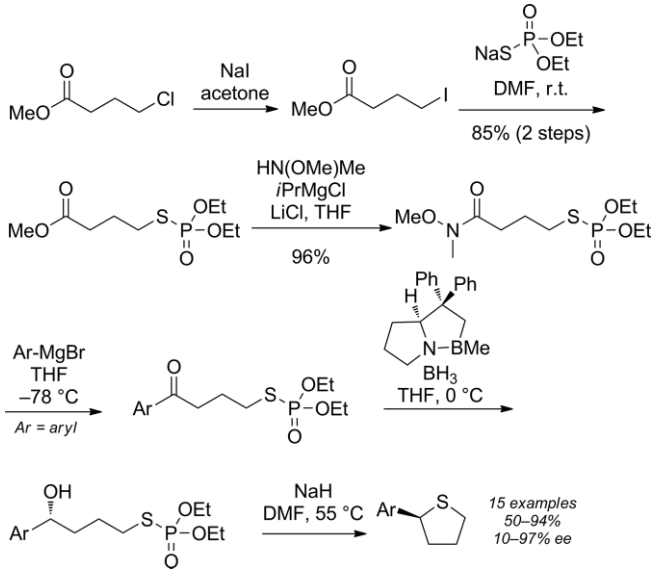
J. Wu has demonstrated that a chiral thietane can be synthesized using phosphate-mediated anionic hopping cascade (Scheme 18).[33] Finkelstein reaction on 3-chloro-1-phenylpropan-1-one affords an iodide, which can be carefully displaced with the sodium salt of diethyl thiophosphate in dimethylformamide. Chirality is installed using Corey–Bakshi–Shibata (CBS) carbonyl reduction protocol.[34] The resulting chiral alcohol then undergoes an inversion as the in situ formed thiolate displaces the phosphate formed in the anionic cascade. This strategy was only demonstrated with a single example.



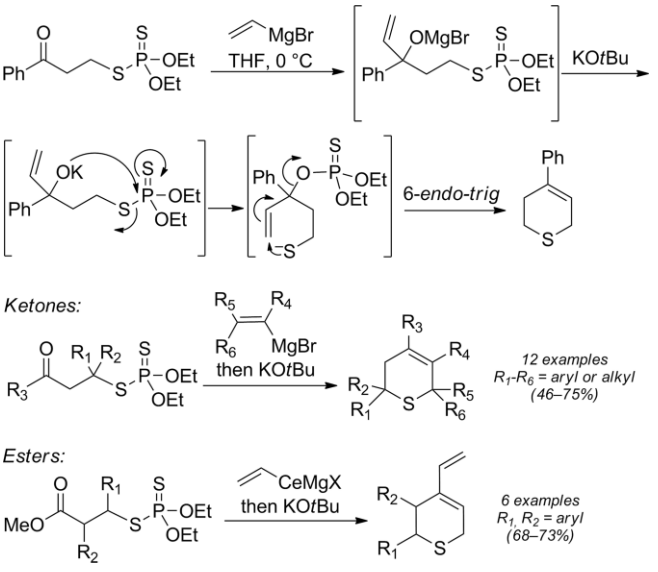
Scheme 18. Wu's 2012 asymmetric thietane synthesis.

2.3. Tetrahydrothiophane

Wu has developed an asymmetric route to chiral tetrahydrothiophenes containing an aryl group in the 2-position (Scheme 19).[32] The last two steps are the same as used in his thietane approach, namely an asymmetric CBS reduction to install the chiral secondary benzylic alcohol followed by an anionic cascade resulting in formation of the chiral tetrahydrothiophene. The main challenge with this approach is the number of steps it takes to make the starting material. In a typical approach a chloride is first substituted with an iodide followed by another substitution with thiophosphate. The ester group is then converted into a Weinreb amide, which allows late stage Grignard addition of all the aryl groups used in Wu's study.



Scheme 19. Wu's 2012 tetrahydrothiophene synthesis.

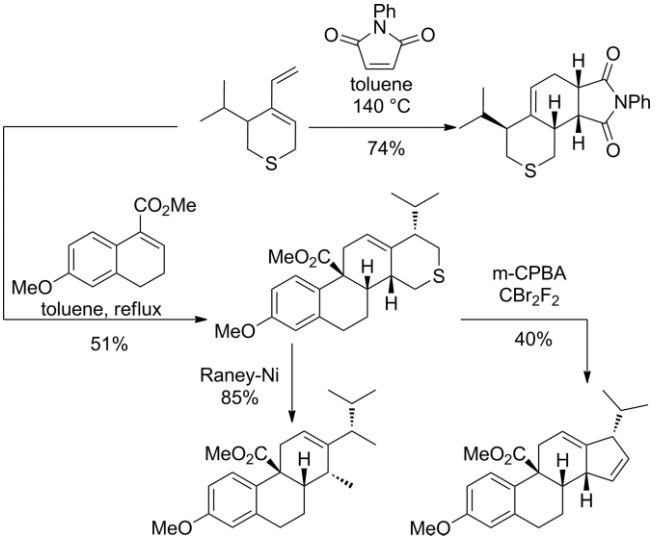


Scheme 20. Njardarson's 2012 thiopyran synthesis.

2.4. Tetrahydrothiopyran

Njardarson has explored leveraging in situ formed allylic phosphates to access larger ring structures via strategic S_N2'-type intramolecular cyclizations (Scheme 20).[35] By attacking γ-dithiophosphate ketones with vinyl nucleophiles a tertiary alkoxide is afforded, which then sets into motion the phosphate transfer from sulfur to oxygen forming an allylic phosphate wherein the phosphate group is located at a quaternary carbon atom. This substitution pattern favors *6-endo-trig* cyclization of the thiolate nucleophile over the sterically congested *4-exo-tet* pathway. Although Grignard reagents are the most attractive carbon nucleophiles for this cascade, Njardarson reports that the intermediate magnesium alkoxide hinders phosphate transfer. This temporary obstacle was solved by the addition of potassium *tert*-butyl alkoxide, which undergoes a *trans* metallation reaction thus allowing the cascade to proceed in one pot. Potassium is faster than sodium and lithium counterions and larger alkoxides are favored over smaller alkoxides. This new one-pot anionic cascade has been demonstrated for a variety of ketone substrates and vinyl Grignard nucleophiles. This new reaction also works for esters, but a more reactive carbon nucleophile is required for a successful cascade. Vinyl cerium reagents, made from the same Grignard reagents, were shown to be a good solution for this task.

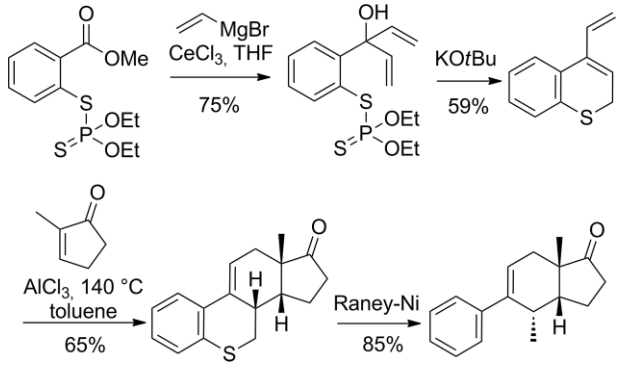
These deceptively simple looking thiopyran products are versatile synthetic intermediates that allow rapid access to useful products because of the sulfur atoms unique reactivity (Scheme 21). Njardarson showcased this with 1–2 step routes to "steroidal" motifs. Diels–Alder cycloadditions with a thiopyran diene accessed from the ester route are diastereoselective, allowing the starting isopropyl stereocenter to control the formation of three additional stereocenters to afford a "thio-steroid" product. The thioether can be reductively removed using Raney nickel or subjected to Ramberg–Backlund ring contraction reaction conditions to afford a steroid construct. These two step routes constitute a "traceless" approach to steroidal frameworks from a simple thiopyran starting material.



Scheme 21. Njardarson's 2012 thiopyran target syntheses.

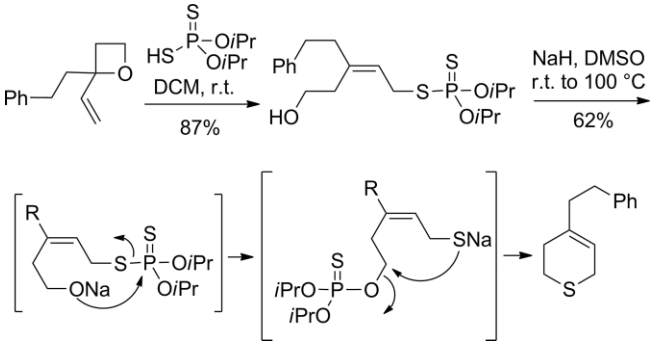
Njardarson has established that his novel thiopyran route can also be expanded to thiochromenes, thus demonstrating that aryl thiopsphates also participate productively in the anionic cascade (Scheme 22). Diels–Alder cycloaddition then affords a "thio-steroid" product in one additional step, which in turn can be further reduced to yield a fused ring system with three stereocenters and useful handles for further funcationalization.

Njardarson has reported that vinyl oxetanes undergo a regio- and stereoselective ring opening of vinyl oxetanes with dithiophosphate acid esters (Scheme 23),[36] which is consistent with how vinyl oxiranes reacted with a similar nucleophile (Scheme 13). The *cis*-relationship between the dithiophosphate group and the homo-allylic alcohols provided an excellent opportunity to learn if the phosphate group could hop even fur-



Scheme 22. Njardarson's 2012 thiochromene synthesis.

ther, via an eight membered intermediate, to form a phosphate and a thiolate. This is indeed possible, and not surprisingly higher temperatures and a more polar solvent are required to facilitate the phosphate transfer and cyclization. Using this unorthodox approach, thiopyran products can be synthesized.



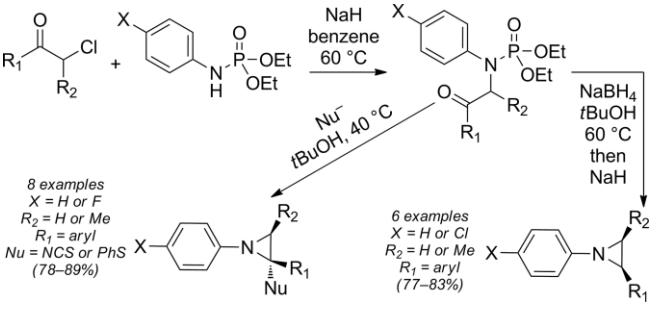
Scheme 23. Njardarson's 2012 thiopyran synthesis.

3. Synthesis of Nitrogen Heterocycles

Nitrogen heterocycles are important structural components of majority of approved pharmaceuticals[37] and countless natural products. Anionic phosphate hopping approaches to nitrogen heterocycles have only been investigated more recently. The main difference and challenge associated with these synthetic efforts is the selection of a suitable nitrogen capping group capable of protecting and electronically stabilizing the nitrogen atom to make it a well matched nucleophile.

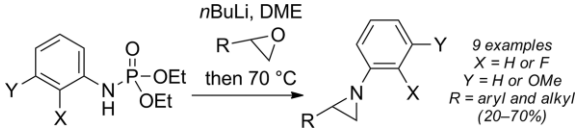
3.1. Aziridine

Yadav has extended his thiirane synthesis investigations (Scheme 9) to also include aziridines (Scheme 24).[38] For this proof of concept he chose an aryl substituent for the nitrogen atom to avoid any competing pathways. Alkylation of these aryl amino phosphates affords the anionic cascade precursors. Treatment of this precursors with sodium borohydride in presence of *t*BuOH triggers the proposed phosphate mediated cascade to form aziridines with help from sodium hydride. This same precursor can also be converted into aziridines using either potassium thiocyanate or sodium thiophenolate nucleophiles. In all examples, *cis*-aziridines are favored.



Scheme 24. Yadav's 2008 aziridine synthesis.

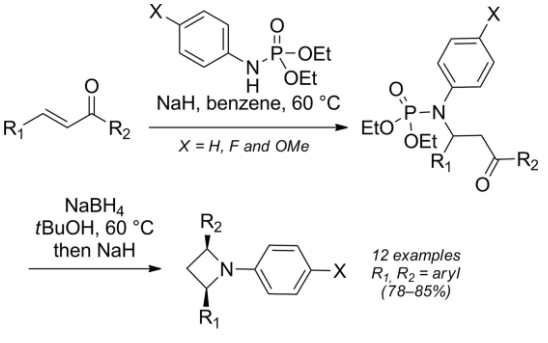
Revisiting the earliest thiophosphate syntheses of thiiranes, C. D. Bray has developed an aziridine synthesis variation (Scheme 25).[39] Lithiated aryl aminophosphates can be used to convert oxiranes into aziridines in one pot with help from a polar aprotic solvent and gentle heating, yields range from poor to very good. Although aminophosphates are not involved, an aziridine synthesis by K. A. Jorgensen employing iminophosphoranes and epoxide substrates is worth noting in this context.[40]



Scheme 25. Bray's 2014 aziridine synthesis.

3.2. Azetidine

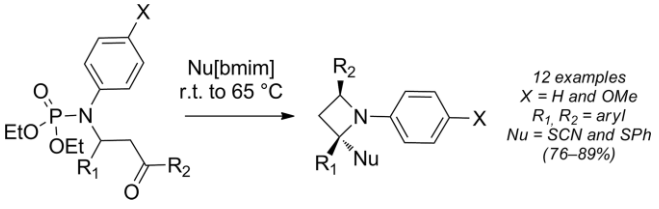
Yadav has adapted the thietane synthesis he developed with Ueno (Scheme 14) to azetidines (Scheme 26).[41] The first step in the synthesis involves the addition of the sodium anions of aryl amino phosphates in a 1,4-fashion to chalcones. The resulting products are then reduced with sodium borohydride and the anionic cascade to azetidine products is driven to completion with the aid of sodium hydride and thermal input, yields of aryl *N*-protected 2,4-substituted azetidines are high and there is a preference for the formation of the *cis*-isomer.



Scheme 26. Yadav's 2007 azetidine synthesis.

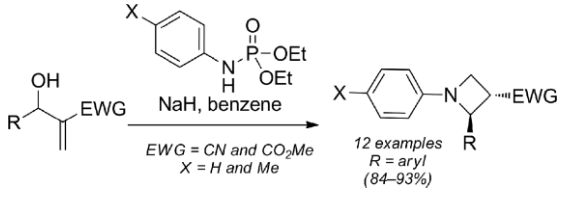
Yadav has shown that his azetidine synthesis can be expanded to other nucleophilic anionic triggers (Scheme 27).[42]

In this study he established that thiocyanate and thiophenolate nucleophiles were well-suited anionic triggers for forming azetidine products as single diastereomers.



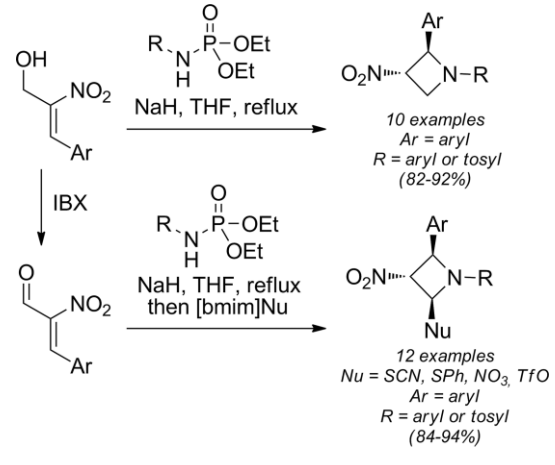
Scheme 27. Yadav's 2008 azetidine synthesis.

Yadav has also demonstrated that azetidines can be assembled in one pot from Baylis–Hillman adducts (Scheme 28).[43] As before, the sodium anion of aryl aminophosphates serves as the nucleophilic trigger for the anionic cascade. Only aryl-substituted Baylis–Hillman adducts have been evaluated to date.



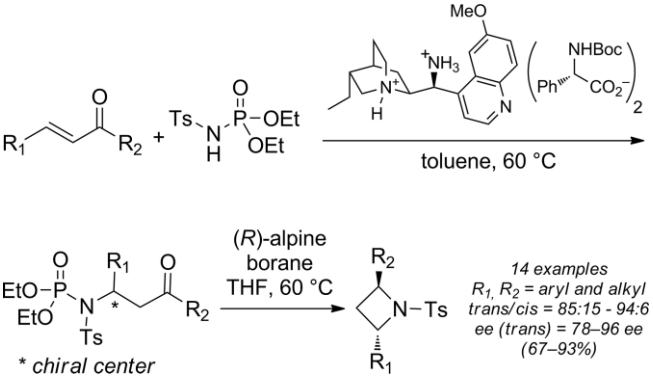
Scheme 28. Yadav's 2008 azetidine Baylis–Hillman route.

Yadav has further expanded the use of Baylis–Hillman adducts as starting materials for the anionic cascade (Scheme 29) with his most recent explorations focused on nitro substituted olefin Michael acceptors.[44] Two scenarios are presented, where in both the amino phosphate attacks first followed by either no intervention or addition of an external heteroatom nucleophile. These phosphate group mediated anionic cascades are high yielding and highly diastereoselective. It is worth noting that in this paper Yadav does report the usefulness of nitrogen atom protecting group (Ts = tosyl).



Scheme 29. Yadav's 2011 azetidine Baylis–Hillman route.

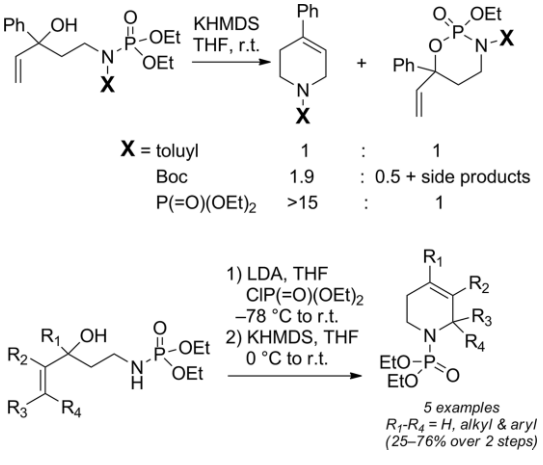
Yadav's most recent efforts have been dedicated to the synthesis of enantiopure azetidines (Scheme 30).[45] He has demonstrated that Melchiorre's organocatalyst[46] can be used to access aminophosphate Michael adducts in high yields. Intramolecular borane reduction of the ketone with (*R*)-alpine borane followed by reflux affords 2,4-*trans* tosyl-protected azetidines in high yields and good enantiopurity.



Scheme 30. Yadav's 2012 asymmetric azetidine synthesis.

3.3. Tetrahydropiperidine

Njardarson has expanded his anionic cascade efforts to also include tetrahydropyridine syntheses (Scheme 31).[47] These studies built upon his successful thiopyran synthesis efforts (Scheme 20). The nitrogen variant proved challenging, particularly the synthesis of anionic phosphate hopping precursors. The Njardarson group revealed interesting insights into how the nature of the nitrogen atom protecting group can impact the cascade. For example, for aryl and *N*-Boc substituents one of the alkoxide substituents is extruded instead of the nitrogen atom in the anionic hopping step to afford an unwanted phosphate containing heterocycle. This competing side reaction can be suppressed by employing a *N*-amino bis-phosphate group. The problem with this solution is that it is quite challenging to add a second phosphate group to the deactivated and sterically hindered nitrogen atom. The N-based carbonyl starting materials are commonly synthesized using the Atherton–Todd reaction,[48] which employs dialkyl phosphite and secondary amines, or alternatively a recent procedure developed by Ham-



Scheme 31. Njardarson's 2015 tetrahydropyridine synthesis.

merschmidt.[49] These same products can alse be synthesized by Staudinger reaction variation,[50,51] that uses phosphite instead of phosphine nucleophiles to attack the azido carbonyl compound precursor.

4. Synthesis of Other Heterocycles

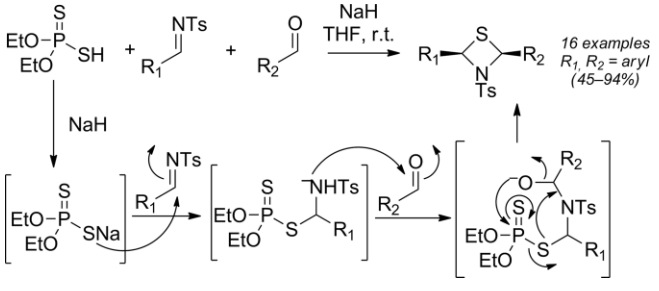
This same approach has been extended to two other heterocyclic motifs (selenirane and thiazetidine).

4.1. Selenirane

Skowronska has reported that the selenium variant of a thiirane (selenirane) can be synthesized using the chemistry detailed in Schemes 4 and 10.

4.2. Thiazetidine

Yadav has designed a clever one-pot three-component route to 2,4-*syn*-disubstituted thiazetidines (Scheme 32).[52] Deprotonation of dithiophosphoric acid ester with sodium hydride initiates the cascade. This thiolate nucleophile then attacks the tosyl protected imine resulting in a nitrogen anion, which then proceeds to attack the aryl aldehyde to form an alkoxide. This alkoxide accepts the phosphate group, forms a thiolate that then displaces the newly formed phosphate to yield the thiazetidine product.



Scheme 32. Yadav's 2011 synthesis of thiazetidines.

Conclusions and Outlook

This microreview presents all of the reported anionic cascades that utilize thio- or amino-phosphate groups for the purpose of facilitating formation of three to six-membered heterocycles. In the early days, there were only a handful of investigators and the focus was almost exclusively on the formation and applications of thiiranes (episulfides), which were typically assembled by addition of a nucleophile to α-thiophosphate carbonyl groups. In the last ten years this research area has gathered momentum as evident from the number and diversity of new contributions. These phosphate group enabled anionic cascades are particularly powerful for assembling strained three and four membered heterocycles. This class of anionic cascades can be initiated by the heteroatom phosphate group itself or by a variety of nucleophiles onto an electrophilic scaffold with a strategically placed heteroatom phosphate group nearby. It is worth noting that the thio- and amino-phosphate groups are remarkably stable, their ability to tolerate a great range of carbon and heteroatom nucleophiles, which provides synthetic design opportunities that carbonyl based protecting groups would not survive.

It is our sincere hope that this comprehensive coverage of heterocyclic methods enabled by the addition of a nucleophile to thio- or amino-phosphate containing substrates will stimulate new exciting contributions in this interesting but surprisingly neglected area of research. There are still many unanswered questions and countless opportunities for new reaction designs and target focused applications. For example, a) no one has systematically evaluated how varying the phosphate substituent impacts the anionic cascade, b) asymmetric contributions are almost nonexistent despite multiple promising scenarios for assembling heterocycles, c) the search for the "optimal" accompanying nitrogen atom protecting group is still not complete and d) there is certainly a need for new methods to assemble amino-phosphate substrates which are generally harder to make than their thio-phosphate counterparts.

Acknowledgments

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Keywords: Cascade reactions · Sulfur heterocycles · Nitrogen heterocycles · Thiophosphates · Aminophosphates

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