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Recent Progress in the Horner-Wadsworth-Emmons Reaction

Juan Á. Bisceglia and Liliana R. Orelli*

Departamento de Química Orgánica. Facultad de Farmacia y Bioquímica. Universidad de Buenos Aires. CONICET. Junín 956, (1113) Buenos Aires, Argentina

Liliana R. Orelli

Abstract: The Horner-Wadsworth-Emmons reaction is one of the most reliable and widespread synthetic tools for the stereocontrolled construction of ethylenic bonds. The versatility of the reaction makes it a valuable synthetic tool to prepare simple as well as densely functionalized and complex molecular scaffolds. This review is devoted to the recent evolution of the reaction, which considerably widens its product scope and synthetic potential. The main recent developments on the HWE reaction presented in this work comprise novel phosphonate reagents and sequential reactions involving the HWE olefination. Interesting applications, including access to challenging or complex synthetic targets, relevant organic compounds and natural products are also highlighted.

Keywords: Horner-Wadsworth-Emmons reaction, carbonyl olefinations, functionalized phosphonate reagents, functionalized olefins, one-pot reactions, tandem reactions.

1. INTRODUCTION

The Horner-Wadsworth-Emmons reaction (HWE) is one of the most employed methods for carbonyl olefination [1]. Its popularity is due to a combination of factors which include absolute positional selectivity, robustness, availability of starting materials and synthetic versatility of the reactions products. A shallow inspection of the literature on the subject reveals that the number of publications concerning HWE reaction is constantly growing (Fig. **1**) [2].

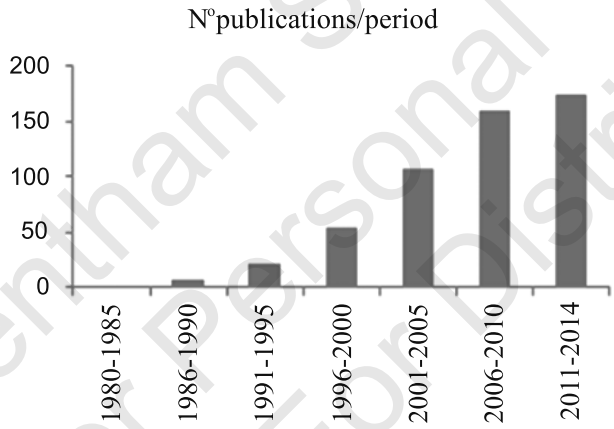

Fig. (1). Number of publications/year containing the term "Horner-Wadsworth-Emmons" for the shown periods

Depending on the starting materials, reaction products may be mono, di, tri or tetrasubstituted electron deficient alkenes, such as α,β–unsaturated esters, ketones and nitriles. These kind of products, being themselves valuable, are also important synthetic intermediates since they provide a convenient arrangement of three consecutive and diversely functionalized carbon atoms. Besides reactions affecting other pending groups, basic HWE products offer a wide range of reactivity. The electron withdrawing group can be subjected to hydrolysis, redox reactions or organometallic additions, while the newly formed double bond is susceptible to electrophilic and pericyclic additions as well as various allylic-type rearrangements. Finally, the EWG substituted alkene as a whole is generally a good Michael acceptor.

Several features make the HWE reaction a good choice for organic chemists of many different areas. First of all, HWE is a much studied reaction, offering a handful of literature examples that address distinct situations. The reaction is chemoselective, differentiating aldehydes from ketones and offers complete positional selectivity of the newly formed olefin. Its stereoselectivity has also been intensively studied, and several factors affecting the stereochemical outcome of a HWE reaction, such as base, solvent, counterion, temperature, catalysts, additives, nature of phosphonate ester and use of modified and chiral substrates are well known. The most accepted rationalization on the reaction mechanism, which implies an equilibrium between the anion, the diastereomeric carbonyl addition adducts and the corresponding oxaphosphetanes, has been tested to the point that the stereochemistry of the products can be selected just by altering the heating rate of the reaction (kinetic *vs.* thermodynamic products) [3].

In addition, HWE is a versatile reaction and accepts a variety of diversely substituted phosphonate and carbonyl partners, which makes it fit for convergent and linear synthetic designs. The required reagents are accessible by a variety of methods, either by inclusion of the phosphonate group in an existing molecule framework or by modification of an already formed stabilized HWE reagent, since these can participate in reactions that are common within dicarbonyl compounds such as α–alkylation, halogenation, Claisen-type acylation and Knovenagel reactions, among others.

Finally, HWE olefination is a robust reaction, allowing the practitioner to choose among a wide assortment of solvents, bases, additives and reaction conditions, a possibility that clearly broadens the substrate scope and simplifies synthetic planning. Solvents of almost every type have been used as the reaction milieu: water, alcohols, acetonitrile, halogenated solvents, ethers, aromatic hydro-

*Address correspondence to this author at the Departamento de Química Orgánica. Facultad de Farmacia y Bioquímica. Universidad de Buenos Aires. CONICET. Junín 956, (1113) Buenos Aires, Argentina; Tel/Fax: +541149648252;
E-mail: lorelli@ffyb.uba.ar

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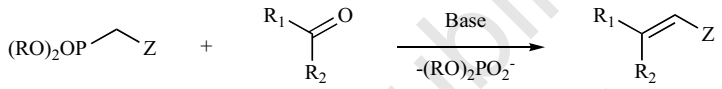
Table 1. HWE reaction protocols frequently found in the literature.

Protocol	Main Features	Applications
Traditional	THF, NaH, BuLi (or other strong base)	Synthesis of *E* olefins
Still-Genari	DCM, THF, use of bis(CF_3CH_2O) phosphonate	Synthesis of Z olefins
Ando	DCM, THF, use of bis (ArO) phosphonate	Synthesis of Z olefins
Masamune-Roush	DCM, THF, MeCN, organic base + Li^+ salts	Base sensitive substrates
Paterson	"wet" THF (ca. 40:1 THF/water), $Ba(OH)_2$	Macrocyclizations
Helquist	DCM, MeCN, organic base, $Zn(TfO)_2$	Diprotic phosphonate reagents
Schmidt	DBU, "salt free"	Synthesis of Z olefins



R= alkyl, aryl R_1, R_2 = H, alkyl, (Het)aryl Z = EWG or unsaturated

Scheme 1.

carbons, ionic liquids, and solvent free reactions are also known. Bases of all kinds and strengths, such as strong ionic bases (alkyl lithiums, metallated hexamethyldisilazane, LDA, sodium hydride and alkoxides), alkali metal hydroxides and carbonates and organic bases (trialkylamines, amidines and guanidines) are also routinely used in this reaction. The use of different additives is also frequent in order to improve the reactivity or stereoselectivity of the reaction, common examples being the use of lithium salts in combination with organic bases, and phase transfer catalysts such as crown ethers which improve the solubility of Na/K bases in organic media.

This myriad reaction possibilities makes the HWE reaction compatible with a large amount of additional functional and protecting groups (ether, silylether, acetal/ketal, amide, ester and even halogen, OH and NH groups), which explains its ubiquity in natural product's synthesis.

Its wide use has determined the emergence of several named protocols with well established use in certain known situations. Some of the more helped are listed in Table **1**.

Being a long term much used reaction, the HWE olefination has not been the sole specific subject of reviews in the last 37 years. In spite of this, revision work on carbonyl olefinations [4], Wittig and related reactions [5], and phosphorus-stabilized carbanions has been published covering the reaction general applications, mechanism and stereochemistry [6]. Specific applications, as in the field of natural products synthesis [7] and green chemistry have also been revised [8].

The present review covers the period 2000-2014 and focuses on the recent evolution of the HWE reaction, which has largely expanded its ability to address synthetic problems related to diverse functionality, improved stereochemistry and molecular complexity. It comprises two main areas: the development and applications of novel functionalized phosphonate reagents and the use of the HWE olefination in one-pot, MCR and tandem reactions.

2. MODIFICATIONS IN THE REACTION PARTNERS

2.1. The Electron Withdrawing Group of the Phosphonate (Z)

Although ketone, ester and nitrile are by far the most frequently used stabilizing groups in HWE reagents, many other EWGs have been employed for this purpose. The following subsection is devoted to non classical and also less frequent Z groups (Scheme **1**), which expand the product scope attainable through the reaction and lead to a wider structural diversity.

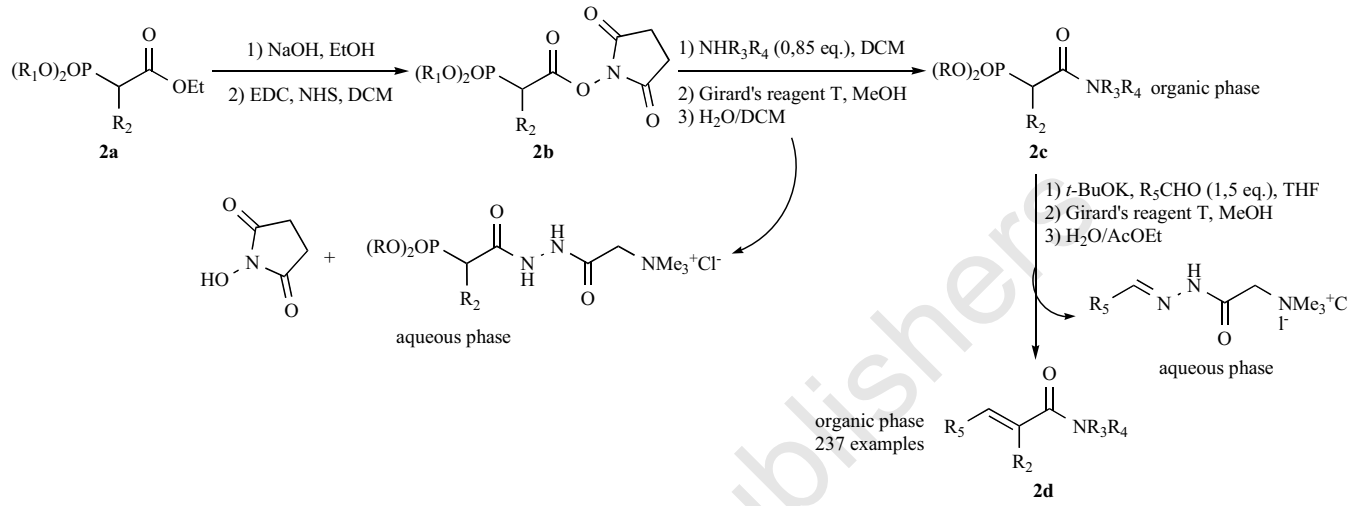
2.1.1. C-based Z Groups

While simple alkyl esters of phosphonoacetic and phosphonopropionic acid are the most widely used HWE reagents, other acyl derivatives have also been used in olefination reactions. More complex esters are frequently employed in the synthesis of macrolactone natural products when HWE is involved as the cyclization step, and their use has been revised elsewhere [7b].

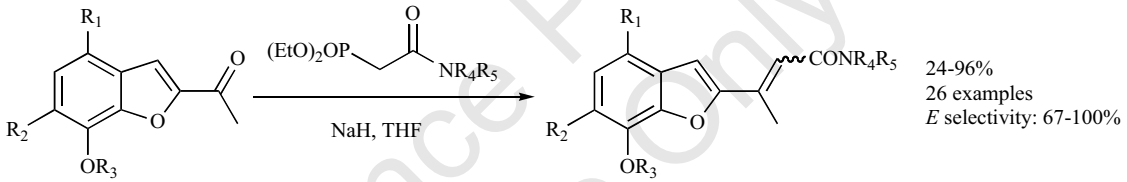
Nagao has shown that hydrolysis of the ester to carboxylic acid in Still phosphonates has a deep impact on the stereochemical outcome of the reaction. The reaction with simple alkyl, aryl, unsaturated and α–branched aldehydes yields the olefinated products with *E/Z* ratios > 9:1 when performed with *i*-PrMgBr as the base [9]. The unexpected stereochemistry of the resulting olefins was attributed to thermodynamic control, due to the presence of Mg (II), since diastereoselectivity was diminished by employing BuLi as the base, but not by lowering the reaction temperature.

Phosphonoacetamides are also used as HWE reagents, allowing for the direct preparation of α,β–unsaturated amides, thus avoiding the need of functional group manipulation of the otherwise resulting ester moiety. These reagents are usually prepared by carbamylation of phosphonate anions [10], phosphorylation of amide carbanions, Michaelis-Arbuzov reaction [11], or amine acylation with α–phosphonocarboxylic acid derivatives, being the two latter the most used. Although different coupling reagents have been employed for the synthesis of phosphonoacetamides from the parent acid, T3P was found to be more efficient than DCC, boric and boronic acids [12].

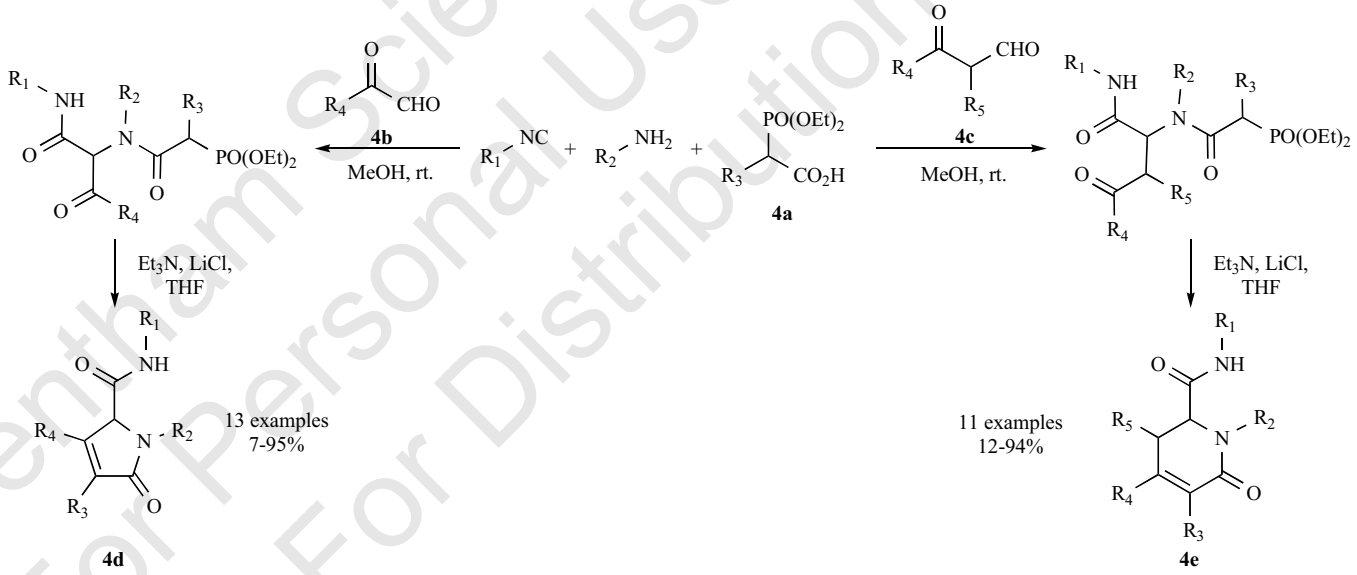
Kim employed an activated phosphonoacetic ester in a solution-phase combinatorial synthesis of piperamide-like compounds (Scheme **2**) [13]. The acylating agent **2b** was reacted with different amines and the resulting phosphonoalkylamides **2c** were submitted to HWE reaction with various aldehydes in a combinatorial manner. Since Girard's reagent T (betaine hydrazide hydrochloride) is capable of acting both as acyl and carbonyl scavenger, it was used to remove the excess activated ester and aldehydes from the organic layer. The reaction products (**2d**) were obtained, with a few excep-



Scheme 2.



Scheme 3.



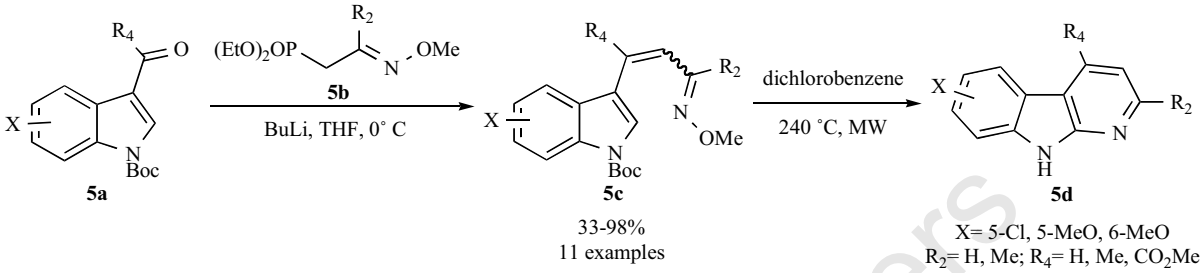
Scheme 4.

tions, with high yields, mainly *E* diasteroselectivity and high purity without further purification.

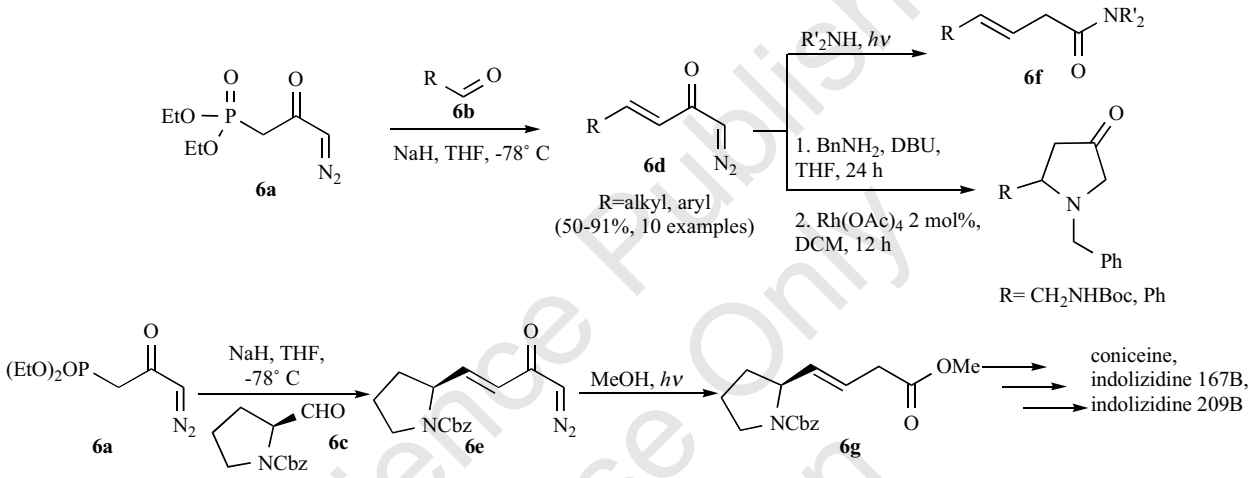
Reaction between phosphonoacetamides and ketones is less consistent in terms of yields and diastereoselectivity, as shown in the example presented in Scheme **3** [14].

Suitably *N*-substituted phosphonoacetamides can also react in an intramolecular fashion. Dömling developed a four component Ugi reaction (Scheme **4**) in which the aldehyde component was replaced by a 2- (or 3)-oxo aldehyde (**4b** and **4c**), and the acid component by a diethylphosphonoacetic acid derivative (**4a**). The adduct of such MCR is ready for intramolecular HWE reaction, leading to highly substituted pyrrolidinones **4d** and pyridines **4e** [15]. Although some of the (unoptimized) yields are low, and certain substrates fail to give the desired transformation or react poorly, the sequence gives high purity products after filtration and is adaptable to a 96 well plate format.

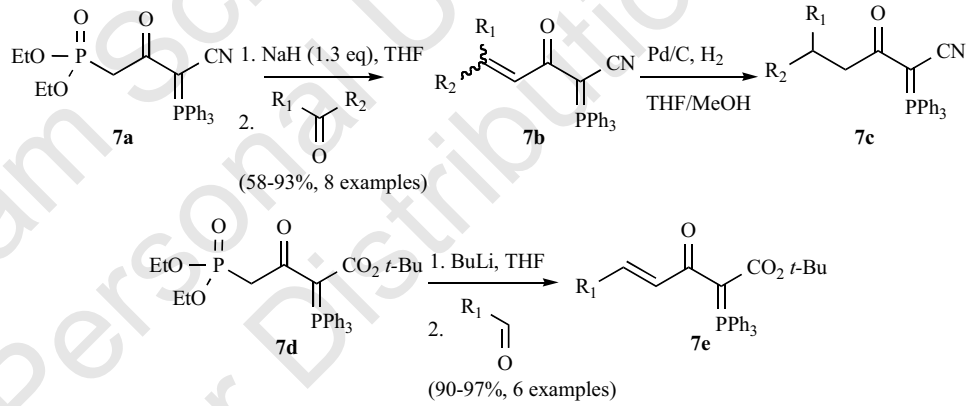
Ketones are customarily found as anion stabilizing groups, since their low reactivity allows for their coexistence with the phosphonate group in HWE reagents. Due to their higher reactivity, formyl phosphonates are not found as HWE reagents, although the precursor diethyl (2,2-diethoxy)ethylphosphonate is a commercially available compound. Interestingly, certain imino derivatives are



Scheme 5.



Scheme 6.

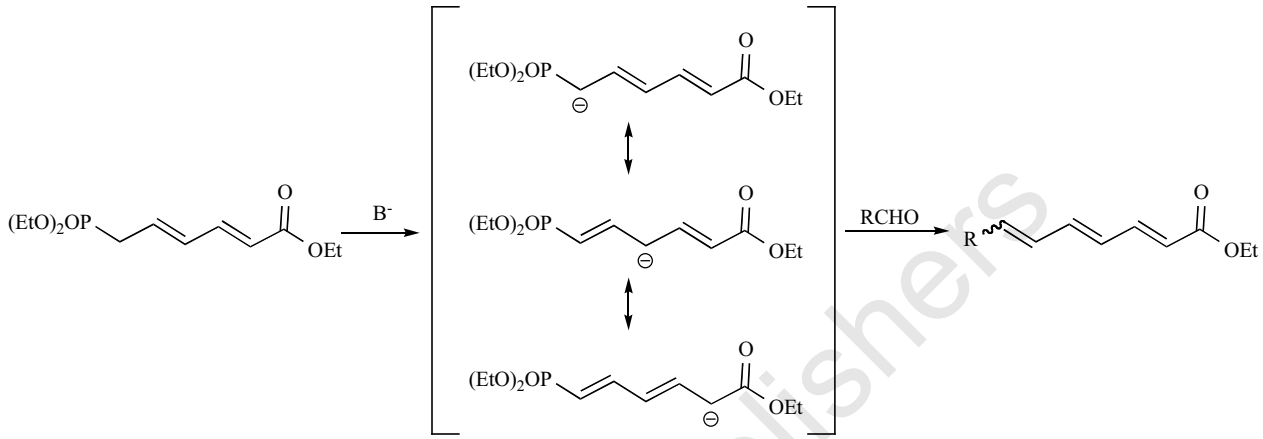


Scheme 7.

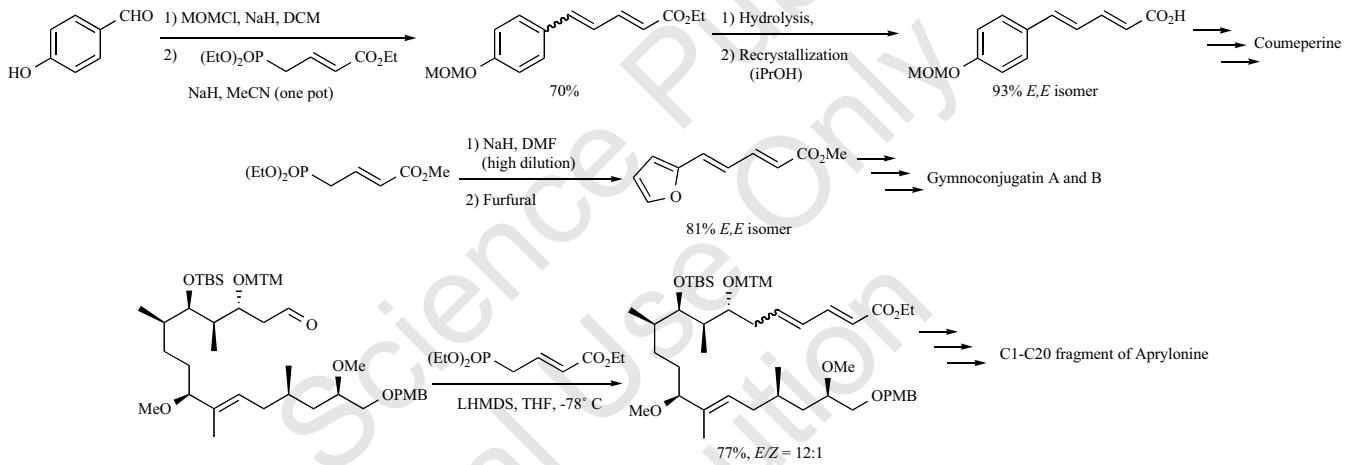
stable enough to be used in HWE olefinations. One such example is 2-diethoxyphosphoryl-1-dimethylhydrazonopropane, a modified phosphonate reagent developed by Petrosky. The hydrazone moiety acts in this case both as an anion stabilizing and a protecting group, bringing about a simplified homologation of polyunsaturated aldehydes [16]. More recently, methoxyimino phosphonates **5b** were used in the synthesis of α–carbolines **5d** [17]. The fact that **5b** reacts with 3-acetylindole **5a** instead of self reacting shows the limited electrophilicity of the oxime group in this context (Scheme **5**).

A new HWE diazo reagent, 3-diazo-2-oxopropylphosphonate (**6a**), was evaluated for the olefination of aliphatic, aromatic and *N*-protected amino aldehydes (**6b,c**) [18]. After suitable choice of the base and solvent, α,β–unsaturated diazoketones **6d,e** were obtained with high yields and complete *E*-selectivity (Scheme **6**). These valuable unsaturated diazocarbonyl compounds were then transformed, *via* Wolff rearrangement, to the corresponding β,γ–unsaturated amides **6f** and esters **6g** [19], advanced precursors of different alkaloids [20] (Scheme **6**).

α-Keto (cyanomethylene)triphenylphosphoranes **7b** are key intermediates in the preparation of α–keto amides and esters, structural motifs present in many bioactive natural products and synthetic peptides. Lee [21] reported an alternative synthesis of compounds **7b**, by HWE reaction of simple and functionalized aldehydes with diethyl (3-cyano-2-oxo-3-(triphenylphosphoranylidene)-propyl)phosphonate **7a**, a novel HWE reagent (Scheme **7**). The olefinated products can be hydrogenated to yield **7c** without affecting the β–oxo-α–phosphoranylidenenitrile. The same author, in a more recent paper [22], extended this synthetic approach to a phosphorane containing a *t*-butoxycarbonyl moiety (**7d**). HWE olefination of aldehydes with **7d** led to excellent yields of the correspond-



Scheme 8.



Scheme 9.

ing functionalized olefins **7e** with complete *E* selectivity (Scheme **7**).

Application of the vinylogy principle to simple HWE reagents such as TEPA or diethoxyphosphorylmethylketones leads to phosphonate reagents that can be generally used as C_{2n} building blocks. *ω*–Phosphono crotonic, sorbic and octatrienoic acid derivatives are generally used. Despite of the large charge delocalization expected from the resulting anions, the HWE product distribution obtained through these reagents reflects a clear preference for the longest linear conjugated chain (Scheme **8**).

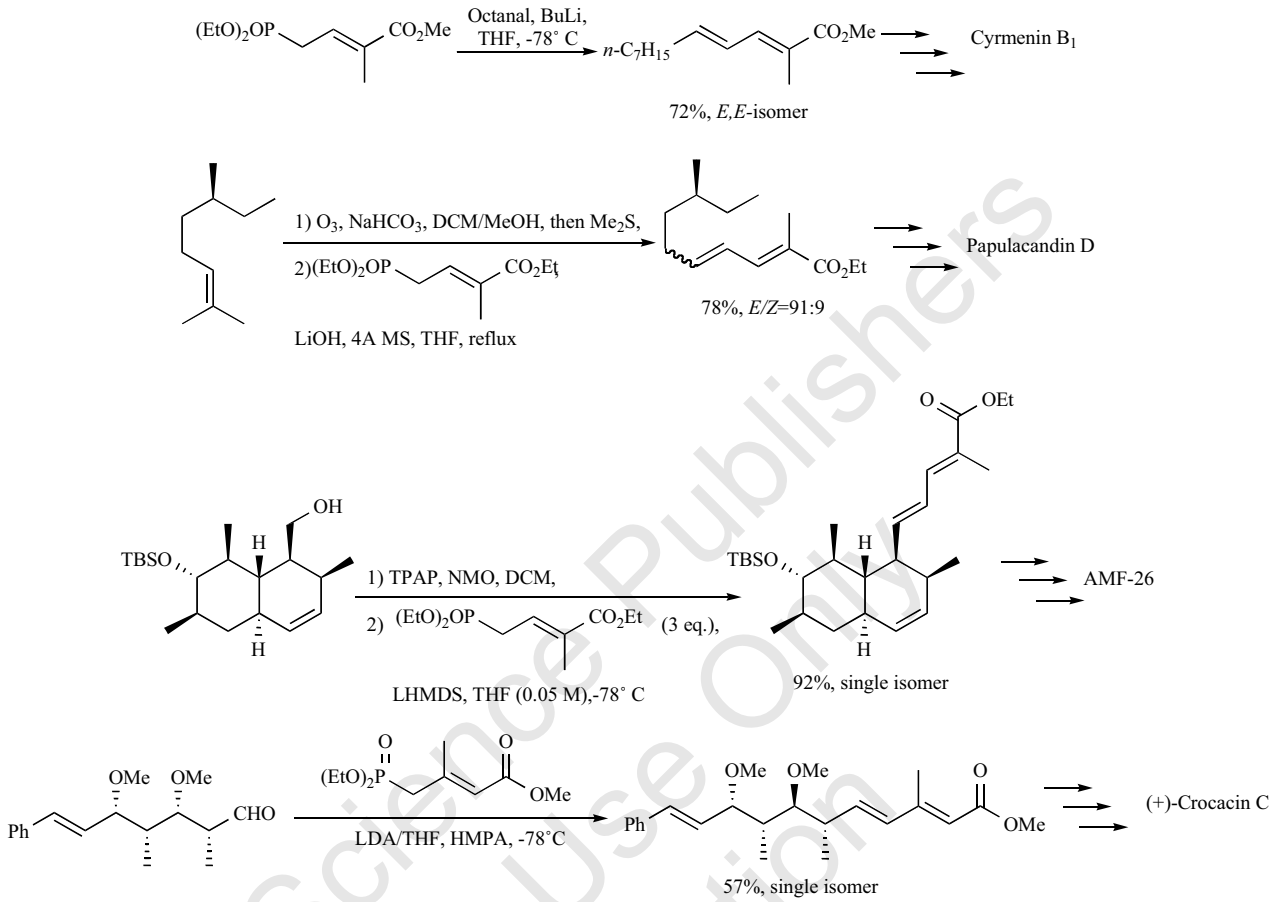
Simple dienylation of aldehydes using alkyl 4-(diethoxyphosphoryl)crotonate is generally performed in THF for sodium or lithium bases or in acetonitrile for organic bases. This approach has been used for the preparation of some intermediates in the total synthesis of Coumeperine [23], Gymnoconjugatins A and B [24], and the C1-C20 fragment of Aprylonine [25] (Scheme **9**).

Methyl phosphonocrotonic acid derivatives also find application in the synthesis of natural products (Scheme **10**). Although the *E/Z* selectivity achieved with such reagents is often poor and/or unpredictable, high stereoselectivity was achieved in some cases. Chakor reported the reaction of methyl 2-methyl-4-diethoxyphosphorylcrotonate with octanal with complete *E*-selectivity in his synthesis of Cyrmenin B_1 [26]. The same phosphonate was employed in the HWE olefination of a chiral aldehyde towards the synthesis of Papulacandin D by Denmark [27]. In 2013, Shiina reported the first total synthesis of AMF-26, an anti-cancer drug candidate [28], which also includes a dienylation step using the same reagent. A *β*–substituted vinylogous phosphonate was employed for the construction of a precursor of (+)-Crocacin C, an antifungal agent [29]. Also in this case, complete *E* selectivity was reported. It is noteworthy that despite the different experimental conditions employed in these examples, all of them achieve the desired transformation with good yields and diastereoselectivity.

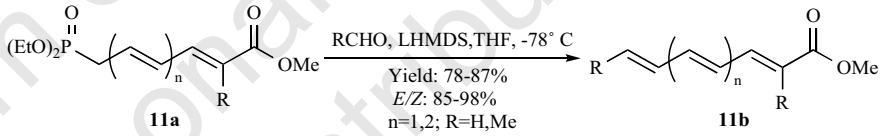
Olefination of aldehydes with *ω*–phosphonooligoenoic acid derivatives **11a** was recently studied by Wang [30] (Scheme **11**). High yields and complete *E*-selectivity were achieved with benzaldehyde. Aliphatic aldehydes, regardless of the presence or absence of proximal branching groups and/or free and protected OH groups, exhibited *E*-selectivities of 85-90%, while conjugated aldehydes gave poorer yields of **11b**.

Phosphoryl derivatives of sorbic acid have also been used in Srinivasarao's synthesis of Apoptolidin D core [31]. The functionalized vinylogous phosphonate **12b**, which is also a diethyl phosphonoacetylacetate derivative, was developed to produce the conjugated triene system present in (-)-tirandamicyn C (**12d**) [32] (Scheme **12**).

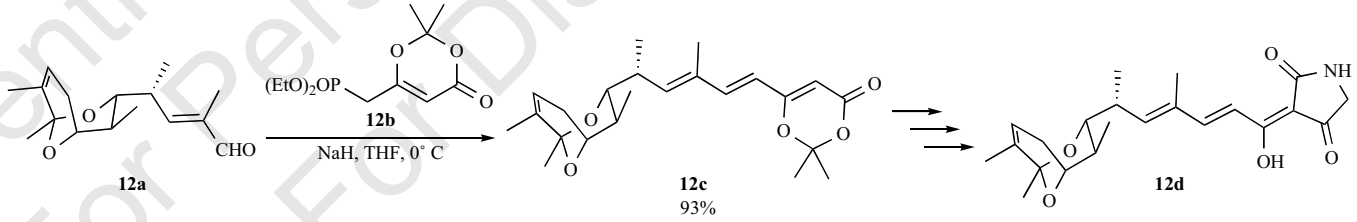
Benzylic an allylic phosphonates are considered as *semi*-stabilized HWE reagents [5c]. These reagents are usually prepared by the Arbuzov reaction of the corresponding bromides, although an interesting variation of this method involving the corresponding alcohols and a Lewis acid promoter was recently reported (Scheme **13**) [33]. The method gives fair yields, except with strong EWGs in



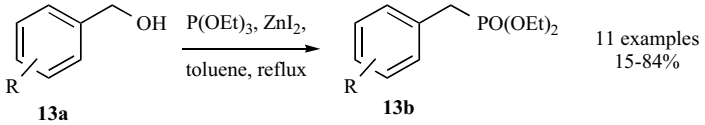
Scheme 10.



Scheme 11.



Scheme 12.

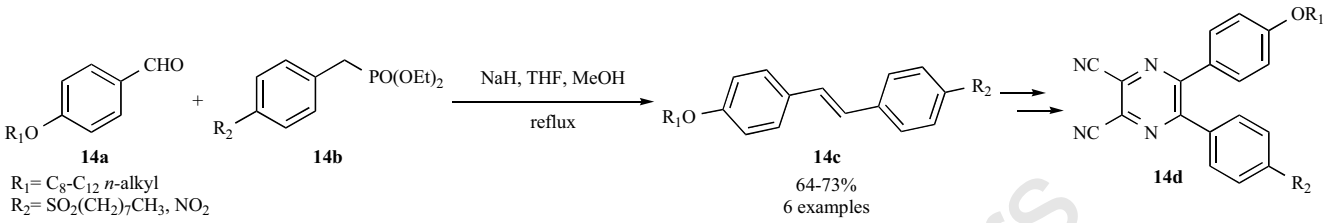


R= Br, Me, MeO, NO_2, CO_2Me, MOMO, TBS, vinyl

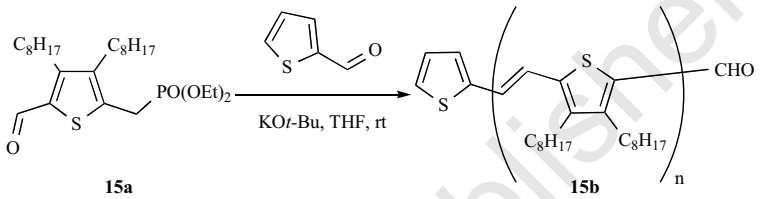
Scheme 13.

the aromatic ring and is compatible with some important protecting groups such as MOM, which decomposes under Arbuzov's conditions. The reaction was rationalized as an acid promoted nucleophilic substitution, and was extended to allylic alcohols.

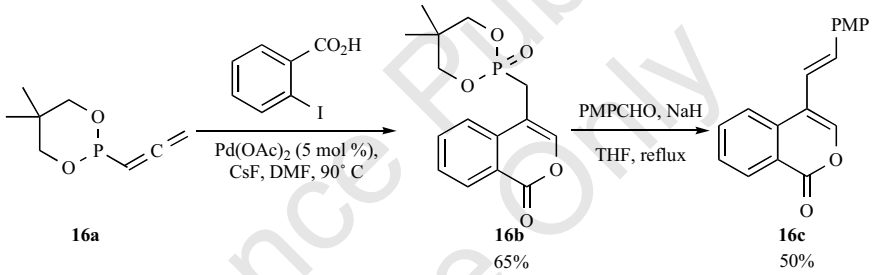
Reaction of benzylic phosphonates and benzaldehydes is an established method for the synthesis of substituted stilbenes and other molecules with extended π systems with many applications as molecular wires, OLEDS and fluorescent probes, among others. A typical example is found in the synthesis of precursors of push-pull tetrapyrazinoporphyrazines [34]. The requisite stilbenes **14c** were prepared by HWE reaction between an electron rich benzaldehyde (**14a**) and an electron deficient phosphonate (**14b**) and, after oxida-



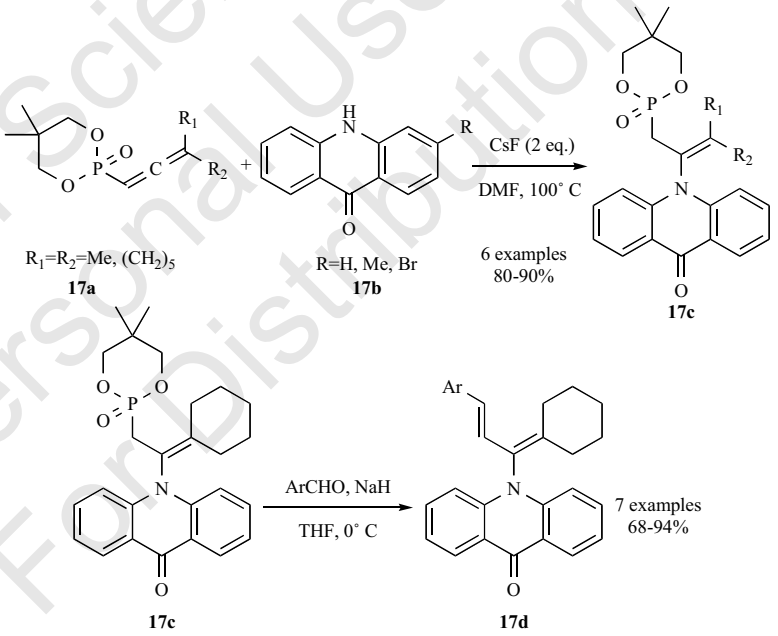
Scheme 14.



Scheme 15.



Scheme 16.

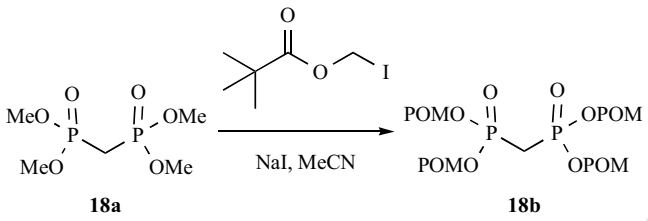


Scheme 17.

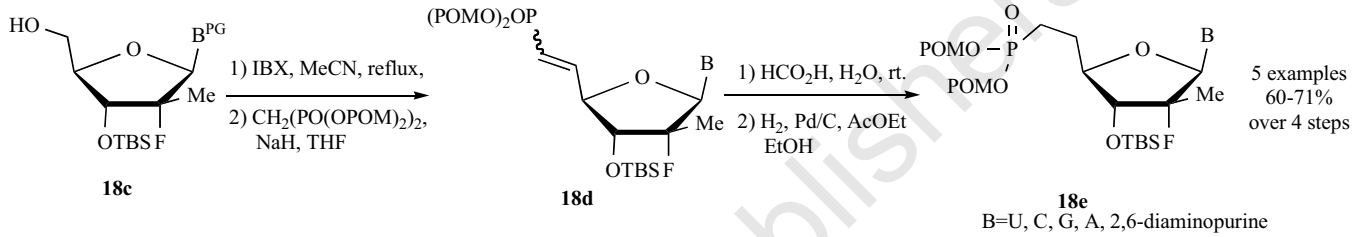
tion and condensation with diaminomaleonitrile, afforded the corresponding push-pull pyrazines **14d** (Scheme **14**).

This reaction also finds application in the elaboration of polymers by means of bifunctional starting materials. Hadziioannou informed the synthesis of a low bandgap macroinitiator by polymerization of tiophenecarbaldehyde **15a** (Scheme **15**) [35], in which the degree of polymerization was modulated by addition of variable quantities of a monofunctional 2-formylthiophene as end-capping agent.

Allylic phosphonates can be prepared from allenyl phosphonates. Swamy studied the $Pd(AcO)_2$ catalyzed reactions between allenyl phosphonates and aryl iodides (Scheme **16**). Reaction between **16a** and 2-iodobenzoic acid yielded a 4-phosphonomethyl isocoumarin (**16b**), an allyl phosphonate reagent [36]. When reacted with anisaldehyde, the olefinated product **16c** was produced in fair yield. In 2013, the same group presented an alternative method for the preparation of allylic phosphonates trough a CsF-mediated 1,2 addition of NH heterocycles **17b** to allenyl phosphonates **17a** [37] (Scheme **17**). The resulting HWE reagent **17c** was coupled with a series of 4-substituted benzaldehydes providing access to 10-(1-cyclohexylidene-3-arylallyl)acridinones **17d**.



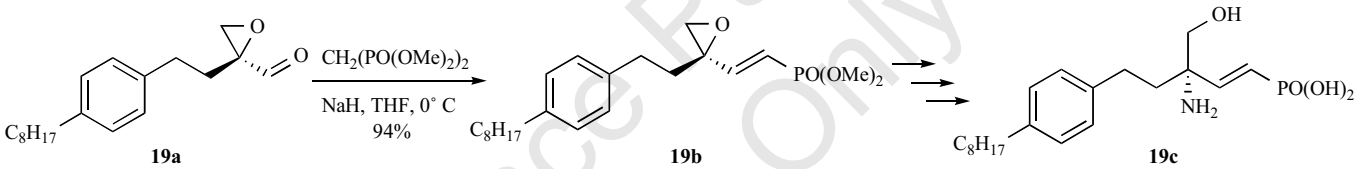
18a **18b**



18c **18d** **18e**

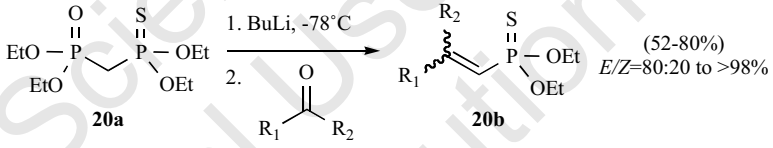
B=U, C, G, A, 2,6-diaminopurine

Scheme 18.



19a **19b** **19c**

Scheme 19.



20a **20b**

Scheme 20.

2.1.2. Phosphorus, Sulfur and Nitrogen-based Z Groups

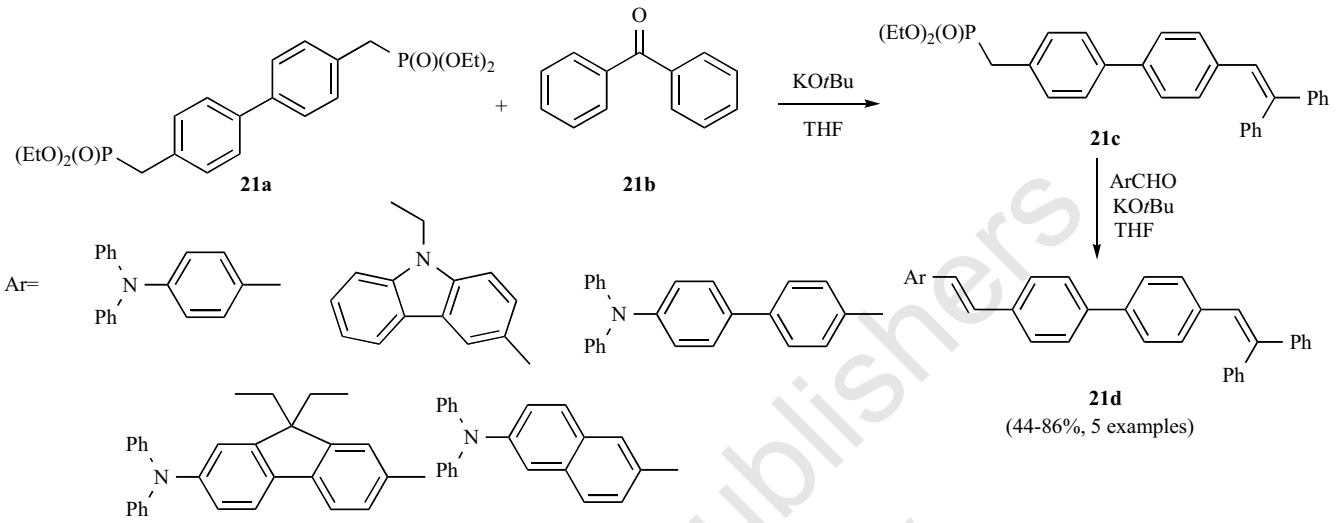
The phosphonate moiety can serve both as the leaving group in the elimination step of the HWE reaction and as the stabilizing group within the intermediate carbanion. Such biphosphonate reagents are generally prepared in connection to their biological properties, since they are isosteres of naturally occurring phosphate sugars, nucleotides and lipids [38]. Schinazi presented a practical synthetic route to furanonucleoside prodrugs containing the pivaloyloxymethyl phosphonate group (**18e**) by means of a methylenebis phosphonate salt derived from **18b** [39], which was reacted with fluorinated nucleoside **18c** under standard HWE reaction conditions (Scheme **18**) [40].

Aminophosphonic acid **19c** was designed by Bittman as a modification of FTY720, to be an allosteric inhibitor of sphingosine kinase 1, which is overexpressed in some cancer types. A key step in its synthesis was the olefination of the oxyrane containing aldehyde **19a** with tetramethyl methylenediphosphonate, a commercially available reagent (Scheme **19**) [41].

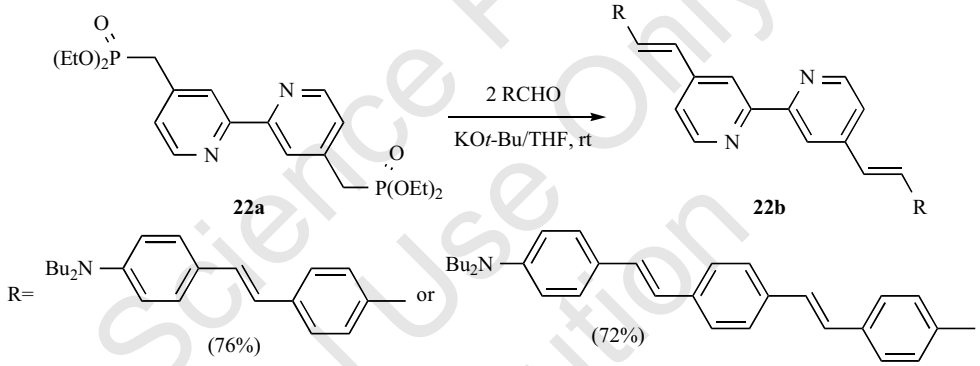
Mixed phosphorus compounds such as **20a** were synthesized by Ortial [42], and their reaction with aldehydes and ketones was investigated. A variety of olefination products **20b**, not easily accessible via any other process, were obtained with high *E*-stereoselectivity (Scheme **20**).

Non-geminal bisphosphonates can be used when the HWE reaction is intended to occur twofold, particularly in semistabilized (*i.e.* benzyl) HWE reagents. Selective HWE reaction of bisphosphonates with carbonyl compounds afford new phosphonate reagents, which can then undergo a second HWE olefination. This enables the preparation of nonsymmetrical diene derivatives, extending the product scope of the reaction. A recent example of this approach was reported by Lee [43], who synthesized a novel class of blue organic light-emmitting diodes (OLEDs) **21d** based on biphenyl phosphonates **21a** (Scheme **21**).

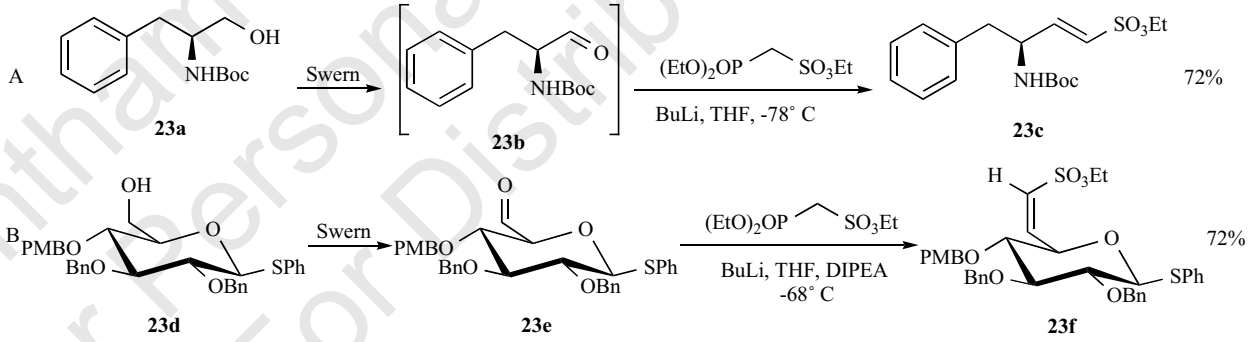
Bipyridine-based bisphosphonates are useful starting materials for the synthesis of organic molecules bearing extended π–conjugated systems. Among them, oligophenylenevinylene (OPV) derivatives have been extensively investigated due to their applications in the fields of photo- and electroluminescence, photovoltaism and nonlinear optics, among others. For example, Viau [44] reported the synthesis of new bipyridyl-based chromophores featuring extended oligophenylenevinylene π–conjugated backbones. After attempting different synthetic approaches, the best choice was a double HWE olefination of stilbene-derived aldehydes with bisphosphonate **22a** (Scheme **22**). Two novel derivatives **22b** were thus prepared with high yields and complete *E*-selectivity. The same approach was employed to prepare some novel examples of such "push-pull" molecules [45]. Klein further enlarged the scope of the reaction to develop a novel series of functionalized 2,2´-bipyridine ligands with either electron-withdrawing or donating end-capping groups designed for dye-sensitized solar cell applications [46].



Scheme 21.



Scheme 22.

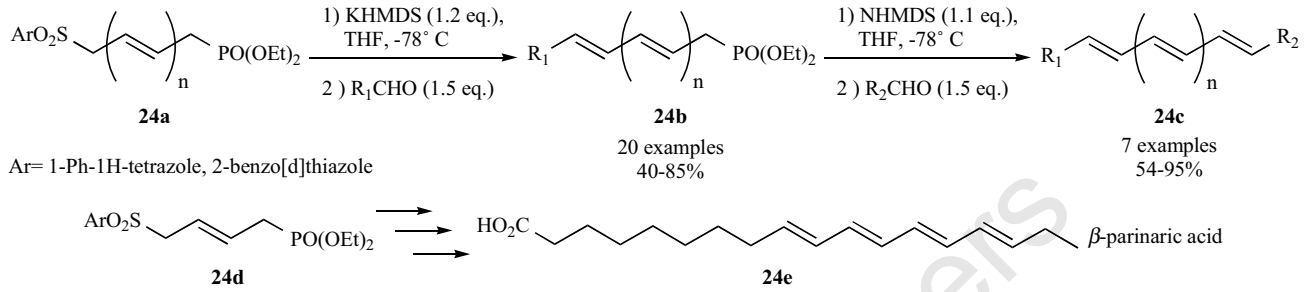


Scheme 23.

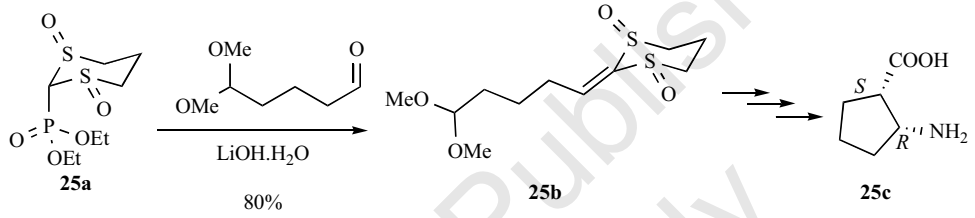
Stabilizing groups for HWE reagents also include sulphur functionalities, where the S atom may adopt several oxidation states. Alkyl phosphoryl sulfonates have been used to introduce an alkoxysulfonylvinyl group in Abouzid's synthesis of peptidomimetics **23c,** with potential antiviral activity, from phenylalaninol **23a** (Scheme **23, A**) [47]. The same reagent was used as an ethoxysulfonylethyl precursor of bioisosteres of sulphate esters in the synthesis of analogues of the antithrombin-binding pentasaccharide domain of heparin. In this case, HWE was chosen because an alternative strategy relying on a radical mediated reaction was not compatible with the phenylthioglycoside present in precursor **23d** [48] (Scheme **23, B**).

In 2012, Nagorny developed sulfonylphosphonates **24a** to be used in the synthesis of polyenes by two-step sequential condensations (Scheme **24**). Reaction of phosphonate **24a** led to allylic phosphonate **24b**, *via* a modified Julia olefination. The observed chemoselectivity was due to the higher acidity of sulfonyl group α–protons. The resulting semistabilized HWE reagent underwent olefination under standard conditions affording **24c**. The authors further exploited this sequence in the synthesis of β–parinaric acid [49]. A vinylogous diethylphosphonophenylsulfone was used to access a dienyl sulfone moiety in Srinivasarao's studies towards the synthesis of Apoptolidin D core [31], showing how the nature of the sulfone substituent affects its reactivity.

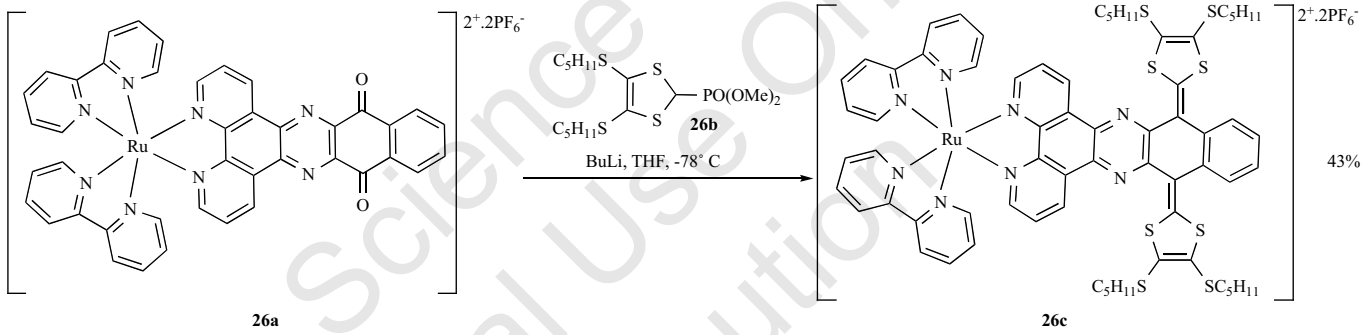
The cyclic bis-sulphoxide derived phosphonate **25a** was used as HWE reagent for the olefination of functionalized aldehydes in a novel synthesis of *ent*-cispentacin **25c** (Scheme **25**) [50].



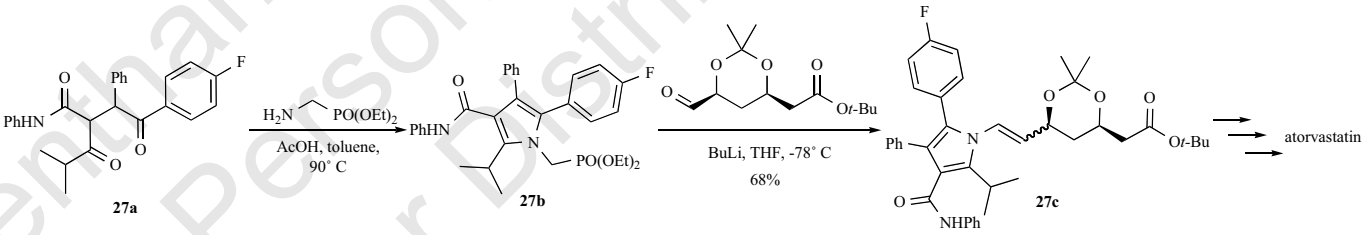
Scheme 24.



Scheme 25.



Scheme 26.



Scheme 27.

A further example of sulphur-phosphonate reagents versatility is given by the use of a 1,3-dithiol-phosphonate in the synthesis of ruthenium complex **26c**. Despite its resemblance with an umpolung compound, **26b** behaves clearly as a HWE reagent, reacting with the quinoxalinquinone acceptor **26a** with expulsion of dimethylphosphate (Scheme **26**) [51].

N-Vinylpyrrole **27c** was employed by Xiang for the synthesis of atorvastatin, a well known HMG-CoA reductase inhibitor. Phosphonate **27b**, in which the N atom is part of a heteroaromatic nucleus, was prepared from diethyl aminomethylphosphonate and diketone **27a**, through a Paal-Knorr synthesis [52] (Scheme **27**).

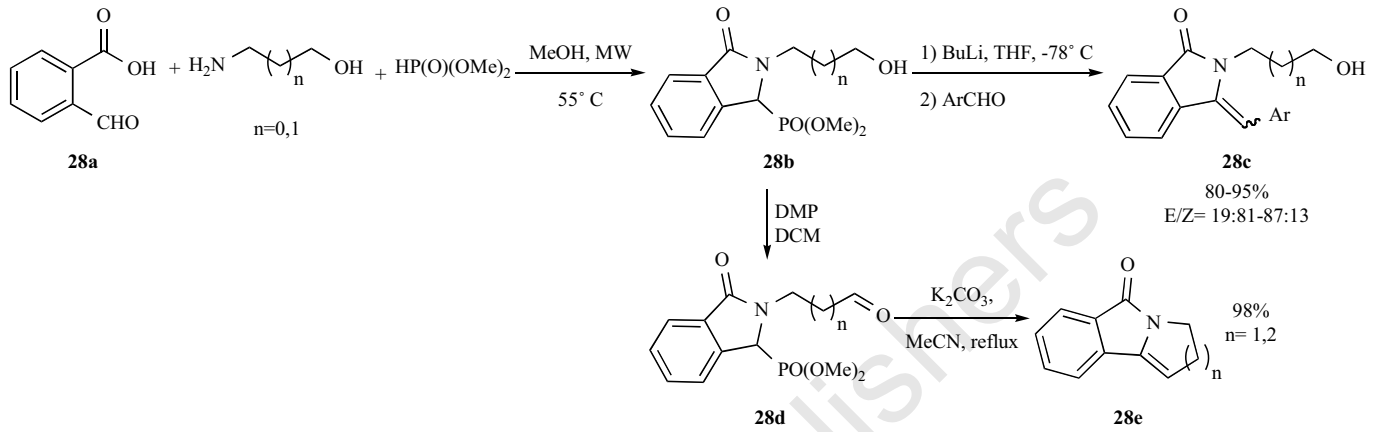
Another example is found in isoindolinone phosphonate reagent **28b**. This amidomethylphosphonate reacts with aldehydes either inter or intramolecularly, according to the chosen base/solvent system (Scheme **28**) [53].

2.2. α-Substituted Phosphonates

Another source of diversity in HWE reagents is the introduction of an additional substituent on the phosphonate α–carbon (W group, Scheme **29**). Introduction of a heteroatom or a functionalized carbon substituent leads to polyfunctionalized olefins and also allows intramolecular reactions to take place. Both possibilities widen the scope of the reaction and provide access to more complex synthetic targets.

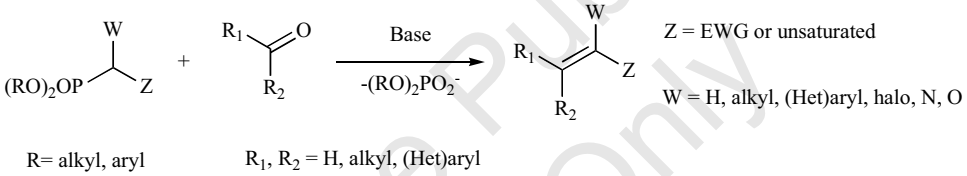
2.2.1. α-Halophosphonates

Halo compounds are valuable both as synthetic intermediates and as biologically active compounds. Stabilized phosphonates possessing a α–halogen represent a practical approach for the synthesis of halogenated olefins. *(E)*-α–bromoacrylates are useful synthetic precursors of trisubstituted alkenes, whose stereocontrolled preparation is a challenge in synthetic organic chemistry. A novel

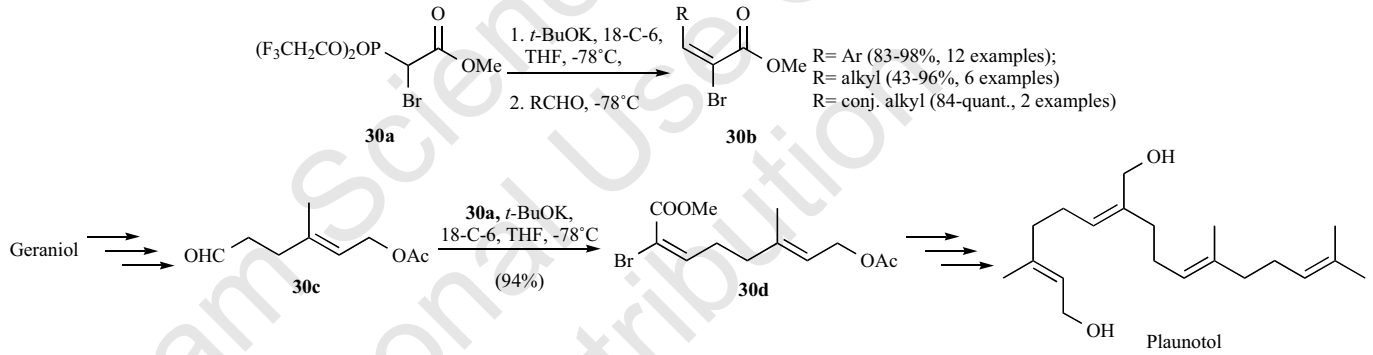


28a **28b** **28c** **28d** **28e**

Scheme 28.

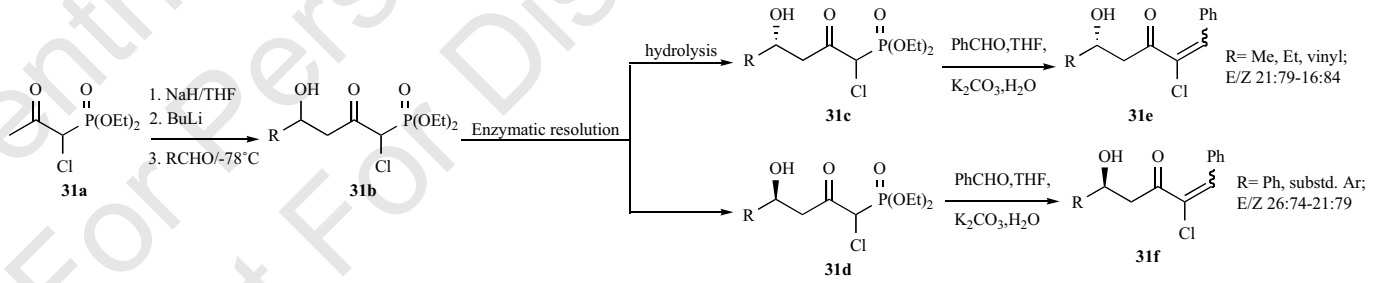


Scheme 29.



30a **30b** **30c** **30d**

Scheme 30.



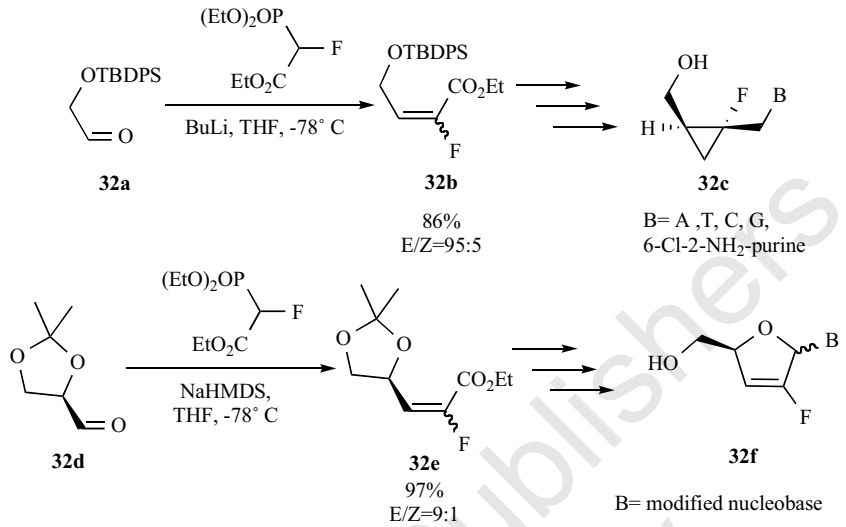
31a **31b** **31c** **31d** **31e** **31f**

Scheme 31.

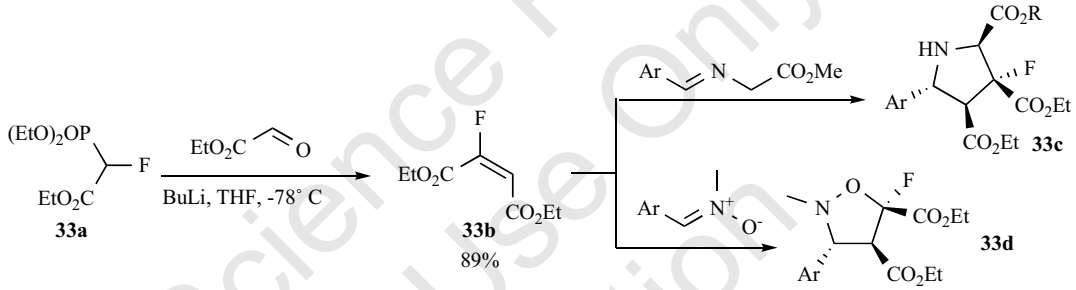
reagent, methyl bis(2,2,2-trifluoroethoxy)bromophosphonoacetate **30a**, was developed by Kogen for the synthesis of such compounds (Scheme **30**). HWE olefination of aromatic, aliphatic and conjugated aldehydes with **30a** yielded the corresponding α–bromoacrylates **30b**. By a suitable choice of the reaction conditions, high *E* selectivity (which in this case corresponds to a *cis* disposition of the hydrocarbon chain) was achieved [54]. This methodology, together with Suzuki cross coupling, allowed for a new, concise synthesis of plaunotol, a natural product with antibacterial activity against *Helicobacter pylori*. Geraniol-derived aldehyde **30c** was converted to *E*-bromide **30d**, a direct precursor of the C1-C7 fragment of the target compound, with the desired stereochemistry [55] (Scheme **30**).

Chiral α,β–unsaturated ketones are compounds with many applications in organic synthesis. Xu reported the synthesis of **31b** and its enzymatic resolution to novel chiral α–chloro-δ–hydroxy-β–ketoalkanephosphonates **31c,d**. Their HWE reaction with benzaldehyde enabled the preparation of several α–chloro-δ–hydroxy-α,β–unsaturated ketones **31f,e** with high enantiomeric purity [56] (Scheme **31**).

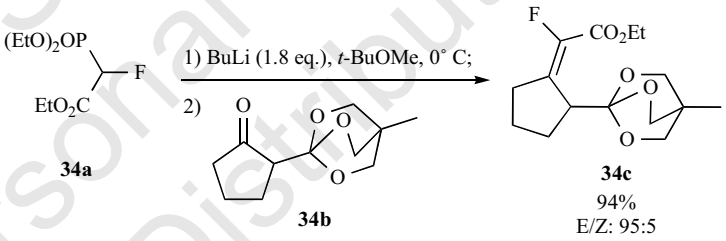
Triethyl α–fluorophosphonoacetate (F-TEPA) is employed in the preparation of *(E)*-α–fluoro-α,β–unsaturated esters [57], which



Scheme 32.



Scheme 33.



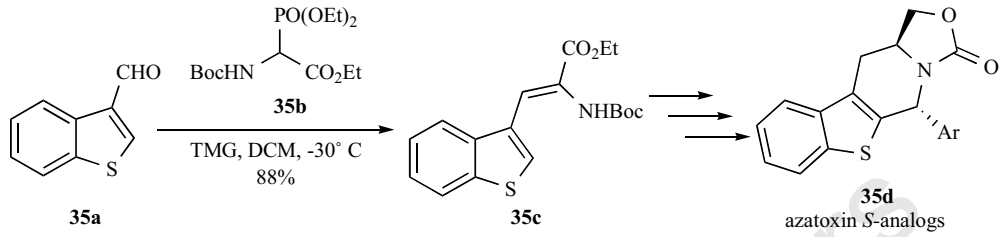
Scheme 34.

play an important role in the synthesis of various biologically active fluorinated compounds [58].

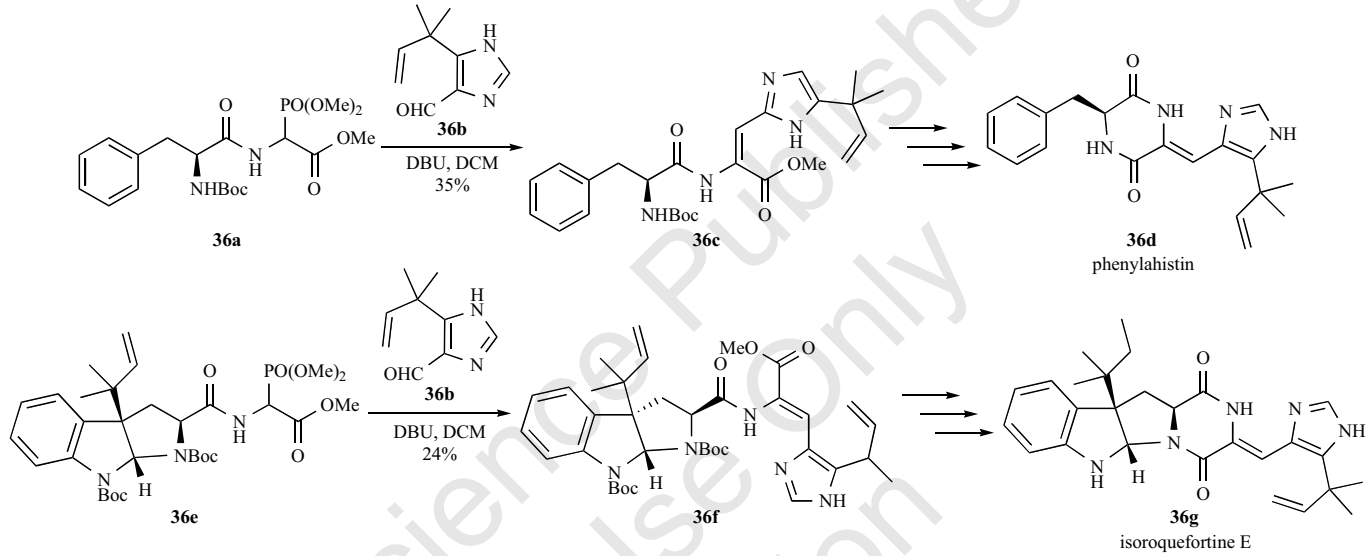
Nucleosides containing one or more fluorine atoms either in the sugar moiety or in the base have drawn increasing attention, due both to their antiviral and anticancer activity and to the improvement in the bioactivity and stability of the corresponding compounds as a consequence of fluorine substitution [59], since isosteric replacement of hydrogen by fluorine atom in bioactive molecules usually has a dramatic effect on their properties [60]. The HWE reaction of α–fluorophosphonates has been widely applied to the synthesis of fluorinated nucleosides, being the key step for the introduction of a fluorine atom in the normal or modified sugar moiety [59], generally with *E* stereoselectivity [61]. Two recent examples of such modifications are shown in Scheme **32**. Lee designed a series of fluorocyclopropanoid nucleosides **32c** as conformationally restricted analogues of acyclic nucleosides such as acyclovir [62]. These compounds where synthesized from **32b**, which was obtained by fluoroolefination of silyloxy aldehydes **32a**. Fluorinated dideoxynucleosides are also compounds with improved antiviral activity as reverse transcriptase inhibitors. Chu reported in 2002 the synthesis of a series of unsaturated nucleosides starting with **32e**, which was obtained as the HWE product between F-TEPA and isopropylidene D-glyceraldehyde **32d**. A deprotection-lactonization-reduction-acylation sequence (not shown) converted **32e** to an appropriate glycosyl donor for the synthesis of **32f** [63] (Scheme **32**).

In 2012, Patrick informed the preparation of diethyl-2-fluormaleate **33b** and its cycloaddition reactions with azomethine ylides and nitrones as a straightforward method for the synthesis of ring-fluorinated heterocycles **33c,d**. The fluoro olefin was synthesized in a single step from ethyl glyoxylate and F-TEPA (Scheme **33**) [64].

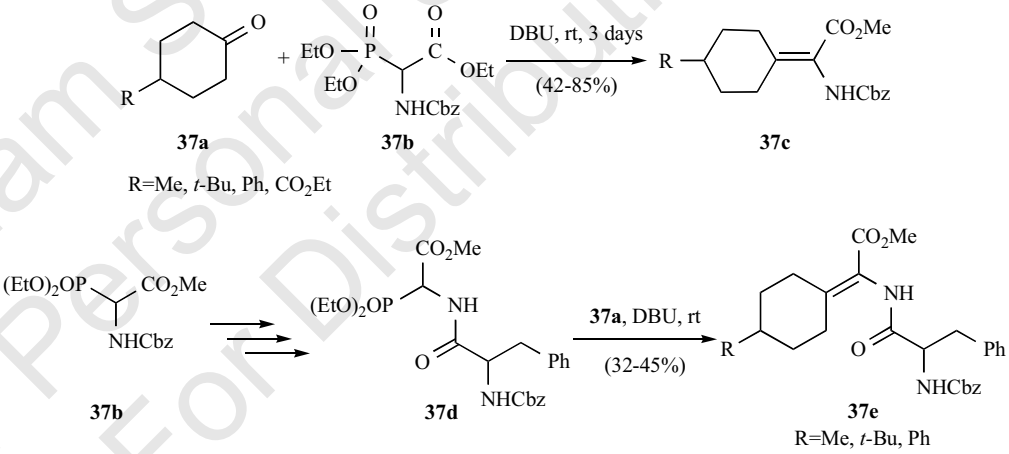
Fluoro olefins behave as isoelectronic and isosteric replacements for amides [65]. In 2014, Sano reported the synthesis of *rac*-**34c** as a surrogate for Cbz-Gly-ProOH dipeptide with a stereostable *E* amide linkage [66]. The key step was the HWE reaction between 2-F-TEPA and 2-OBO-cyclopentanone (**34b**), which afforded **34c** with high yield and stereoselectivity (Scheme **34**).



Scheme 35.



Scheme 36.



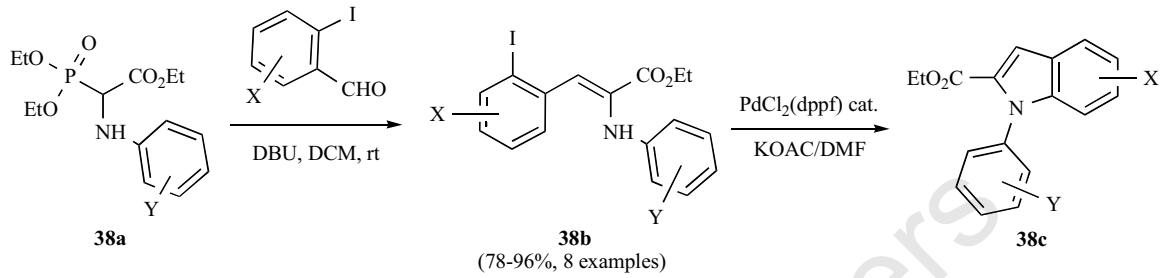
Scheme 37.

2.2.2. α-Aminophosphonates

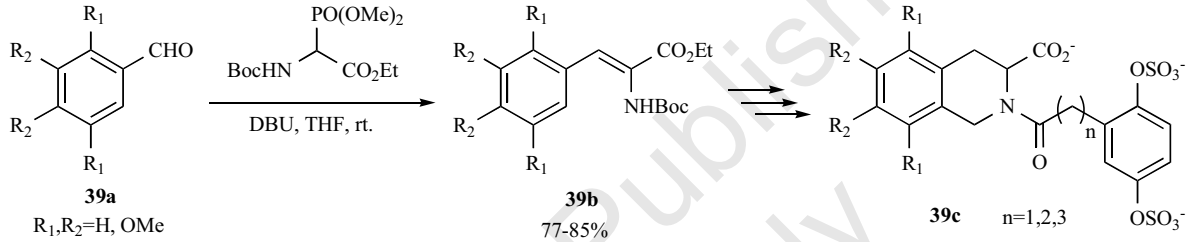
Stabilized phosphonates bearing a α–amino group are useful HWE reagents that allow for the direct synthesis of dehydroaminoacids and α–aminoacids through reduction of the latter. This strategy was applied for the synthesis of azatoxin *S*-analogs **35d**. Benzo[*b*]thiophene **35a** was olefinated using *N*-boc-triethylphosphonoglycinate **35b**, yielding dehydroaminoacid **35c**. Asymmetric reduction was then used to establish the stereochemistry of the pyrido-oxazole ring fusion [67] (Scheme **35**).

Trimethyl phosphonoglycinate derivatives **36a,e** were employed as the key step to build the dehydroamino acid moiety of the alkaloids phenylahistin (**36d**) and isoroquefortine E (**36g**), respectively, from a common aldehyde precursor [68] (Scheme **36**). Both *N*-(α–aminoacyl) dehydroaminoacids **36e,f** where then elaborated into the diketopiperazine moieties common to both alkaloids.

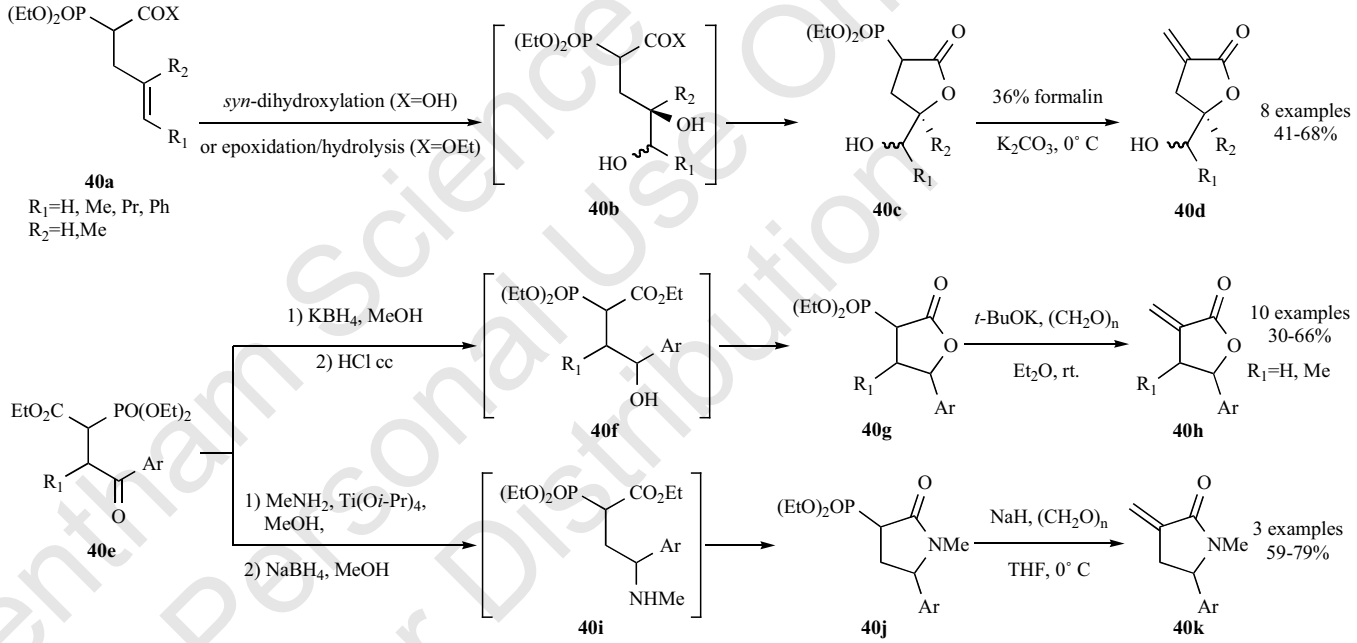
α,β–Didehydroaminoacids have received considerable attention after their discovery in some naturally occurring oligopeptides [69]. Their presence within peptide sequences introduces conformational constraints, leading to applications in the study of enzyme mechanisms and binding. The development of synthetic strategies for natural and unnatural α,β-didehydroamino acids is thus desirable. On the basis of the method developed by Schmidt [70], Cativiela investigated the HWE olefination of several 4-substituted cyclohexanones with commercially available **37b** as a method for the synthesis of novel α,β-didehydroamino esters **37c** [71] (Scheme **37**). Such derivatives display axial chirality and were obtained as race-



Scheme 38.



Scheme 39.



Scheme 40.

mic mixtures. The method was then extended to the synthesis of model dipeptides **37e** containing an axially chiral *α,β*-didehydroamino acid moiety.

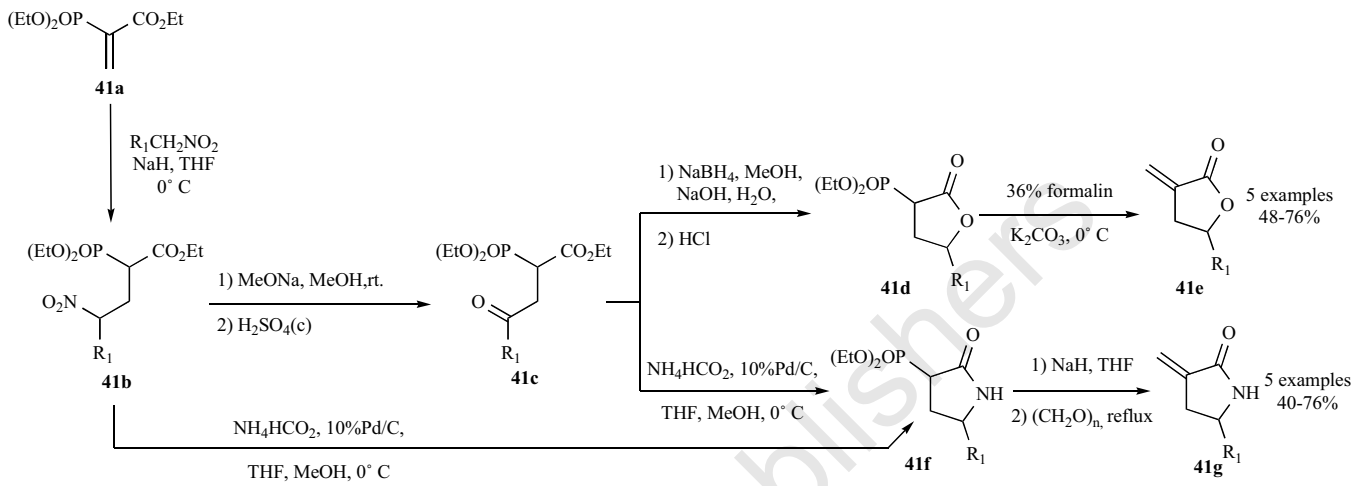
Z-Stereoselectivity had previously been observed in the HWE olefination of 2-iodobenzaldehydes with *N*-aryl-*α*–phosphonylglycines (**38a**) [72]. The resulting didehydrophenylalanine derivatives **38b** were subjected to Pd-catalyzed amination yielding *N*-aryl indole-2-carboxylates (**38c**). The specific formation of *Z* isomers in the HWE reaction was crucial to the success of the process. The reaction was also efficient for the preparation of *N*-acyl indole derivatives from the corresponding *N*-acyl–*α*–phosphonylglycines (Scheme **38**).

Dehydroaminoacids **39b** derived from benzaldehydes give access to isoquinolines through Pictet-Spengler reaction, as demonstrated by Desai's synthesis of sulphated tetrahydroisoquinoline antithrombin activators (**39c**) [73] (Scheme **39**).

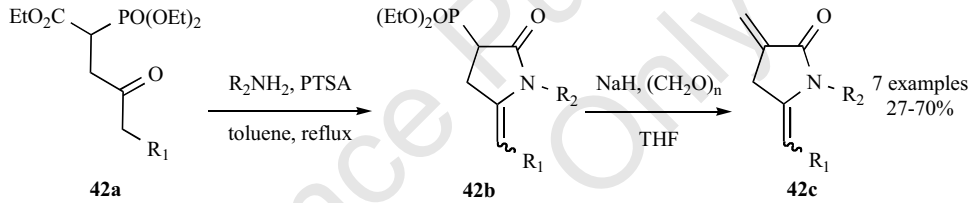
2.2.3. Polyfunctionalized Phosphonates

HWE reaction is especially suited for the construction of exocyclic double bonds. In such cases, the olefinating reagent is generally a cyclic core bearing a phosphonate group. This reaction has found use in the preparation of *α*–methylene lactones and lactams with cytostatic activity. The olefinations were performed using 3-phosphorylated lactones and lactams, which in turn could be accessed through functionalized phosphonoacetate derivatives.

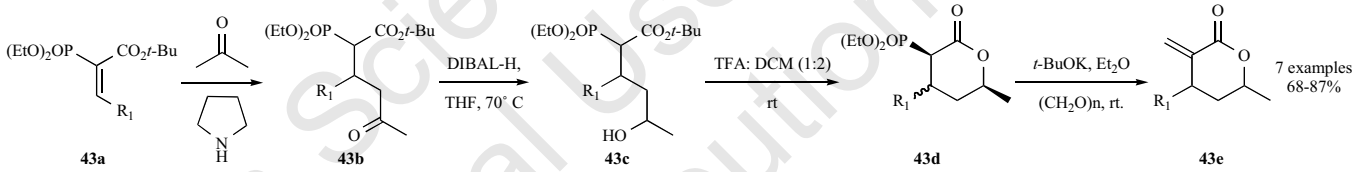
Janecki reported the synthesis of 5-hydroxymethyl-3-methylidene butyrolactones **40d** employing this approach (Scheme **40**). Stabilized phosphonates resemble dicarbonyl compounds as they can be alkylated by suitable halides. Thus, the requisite 5-substituted-3-(diethylphosphono)butyrolactones **40a** were readily prepared by alkylation of TEPA and subsequent oxidation to diols **40b**, which were cyclized to phosphonolactones **40c** [74]. In 2008, the same author prepared ethyl 3-diethylphosphono-4-aryl-4-oxo-



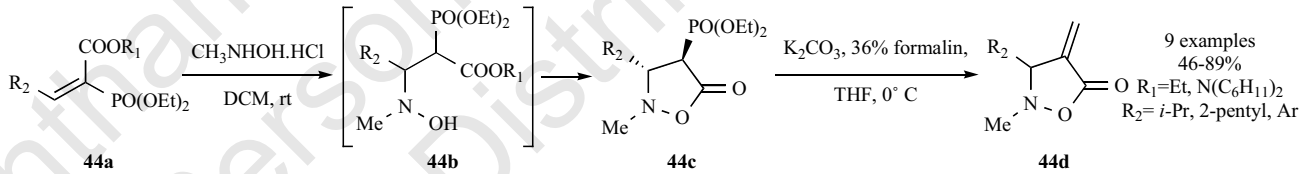
Scheme 41.



Scheme 42.



Scheme 43.



Scheme 44.

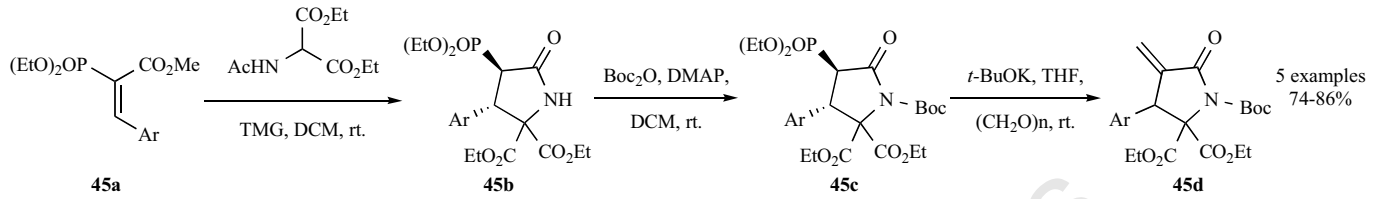
butanoates **40e** by alkylation of TEPA with various 2-bromoaceto(or propio)phenones. This versatile HWE reagent was converted not only to 3-phosphoryl lactones **40g** through reduction and cyclization, but also to 3-phosphoryl-lactams **40j** by reductive amination. Both cyclic products afforded the corresponding 3-methylidene derivatives (**40h,k**) by reaction with formaldehyde polymer [75].

An alternative for the generation of 3-methylidene lactones and/or lactams relies on the fact that derivatives of 2-phosphonoacrylic [76] acid **41a** readily engage in Michael-type additions, behaving as the acceptor. Addition of nitroalkane salts to **41a** followed by Nef reaction of **41b** yields 4-keto-2-phosphonobutyrates **41c** [77]. Reduction of **41c** affords phosphonofuranones **41d**, which were olefinated to α-methylidene lactones **41e** [78] (Scheme **41**). α-Methylidene lactams **41g** were available employing the same precursors, except that reductive amination was employed to obtain compounds **41f**, also accessible by direct reduction of the nitroalkanoate [79]. The method also allows for the preparation of *N*-substituted enamides **42c** if a primary amine is condensed with the carbonyl precursor (**42a**) and the reduction step is omitted [80] (Scheme **42**).

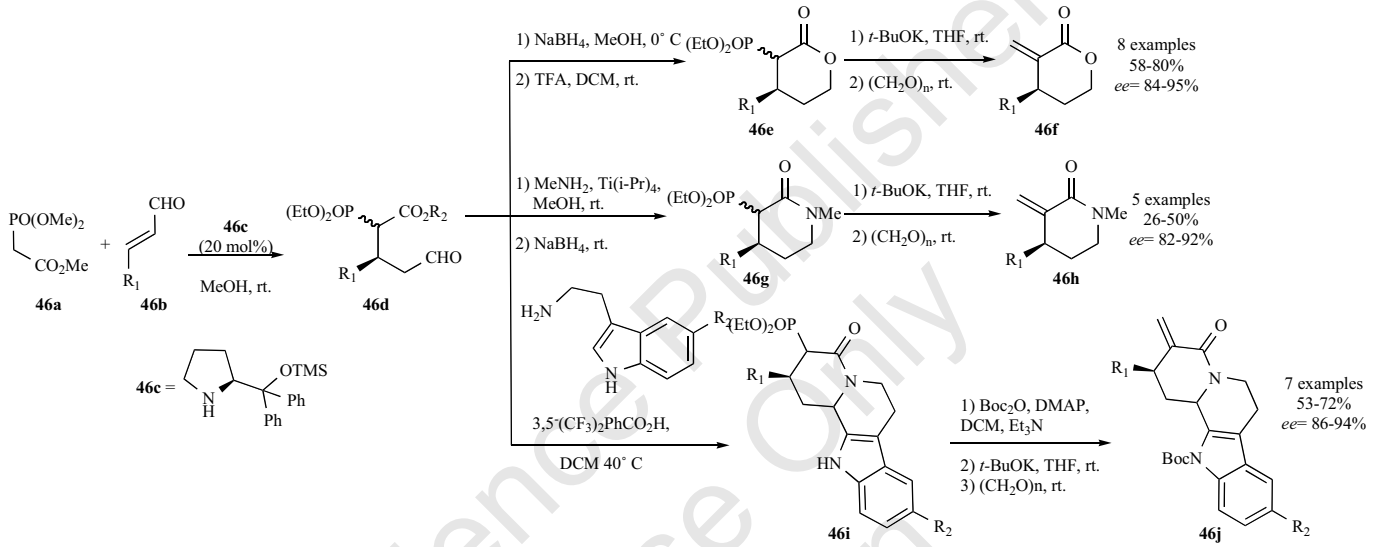
Finally, enamine-mediated Michael addition to **43a** affords 5-keto derivatives **43b** which, after a reduction-acylation sequence (**43b-d**) lead to the higher homologues (δ-lactams **43e**), further demonstrating the versatility of acrylic phosphonate precursors [81] (Scheme **43**).

3-Substituted phosphonoacrylate derivatives also find application in the synthesis of other alkylidene heterocycles, using bidentate nucleophiles. An example of this is the reaction of **44a** with *N*-methylhydroxylamine affording 3-methylideneisoxazolinone derivatives (**44d**) [82], depicted in Scheme **44**.

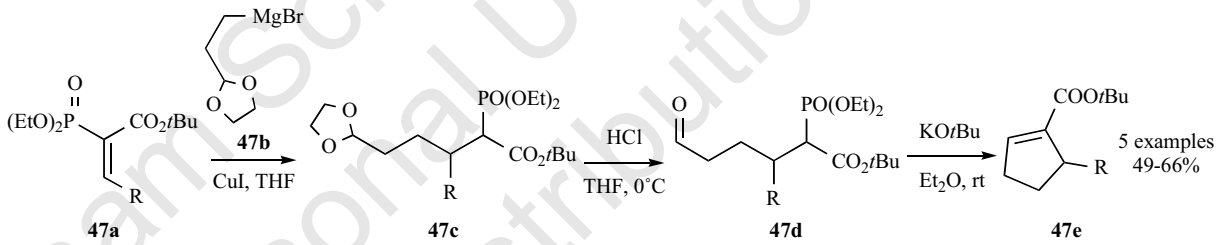
Acetamidomalonate (**45a**) shows a similar behavior, leading to cyclic products **45d** through nucleophilic addition followed by intramolecular acylation to **45b** [83] (Scheme **45**). Nitroalkane conjugate addition followed by reduction has also been used with these precursors [84].



Scheme 45.



Scheme 46.



Scheme 47.

Additionally, trialkylphosphonoacetates may also behave as Michael donors, giving straightforward access to α-phosphoryl-δ-lactones and lactams. Jørgensen described an organocatalyzed asymmetric version of this reaction (Scheme **46**) which allowed for the straightforward synthesis of various substances embodying the 3-methylidene-2-oxo heterocycle motif, leading to lactones (**46e**), lactams (**46g**) and polycyclic lactams (**46i**) [85].

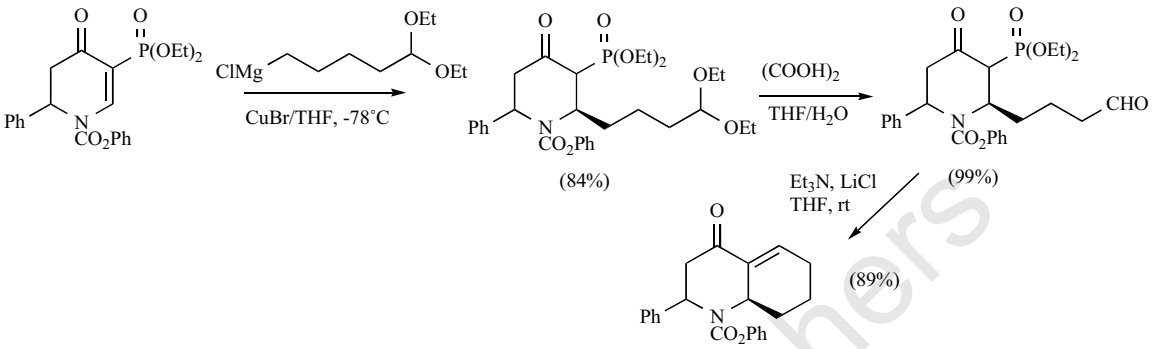
Intramolecular HWE reaction is a well established synthetic method to construct cyclic unsaturated systems. The synthesis and reactions of phosphorylated aldehydes have been reviewed earlier [86]. Several reports are available on the synthesis of substituted cyclohexene derivatives, while the cyclization of 2-diethoxyphosphoryl-6-oxoalkanoates leading to the corresponding five-membered analogues is less documented. This may be due to the lack of efficient preparative methods for the necessary precursors. Krawczyk [87] reported a general method for the required *t*-butyl 2-diethoxyphosphoryl-5-formyl pentanoates (**47d**), by Michael addition of Grignard reagent **47b** to vinyl phosphonoacetates. Intramolecular HWE alkenylation of such precursors afforded 5-substituted cyclopentene carboxylate esters (**47e**) in good yields (Scheme **47**).

α-Phosphoryl cyclic ketones can also be employed to establish an exocyclic double bond and react with aldehydes without any noticeable self condensation side reactions. An intramolecular example of this approach employing a masked aldehyde moiety allowed for the facile preparation of a *trans*-bicyclic enone in a highly stereocontrolled fashion (Scheme **48**).

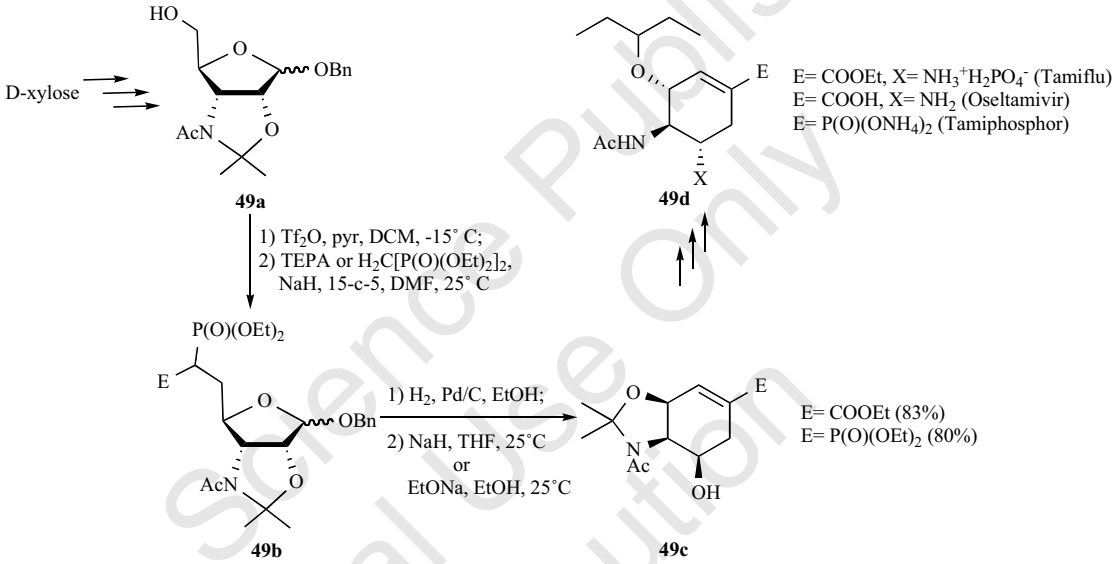
Phosphonates including an acetal moiety can also be used as precursors of the more reactive phosphonoaldehydes in intramolecular HWE reactions leading to cyclic alkenes. A recent example was reported by Fang [88], in which phosphonate **49b**, derived from D-xylose, reacts in an intramolecular fashion to give the corresponding cyclohexene carboxylate derivative (**49c**), an intermediate in the synthesis of Tamiflu and Oseltamivir (Scheme **49**). Interestingly, this approach was extended to the synthesis of structurally related new phosphonates, with enhanced antiviral potency (**49d**).

2.3. Miscelaneous Phosphonates

In a recent paper, Beier developed a new HWE reagent, diethyl 1-fluoro-1-nitro-methylphosphonate **50b**, and studied its olefination reactions (Scheme **50**). This acidic reagent is unstable to air and

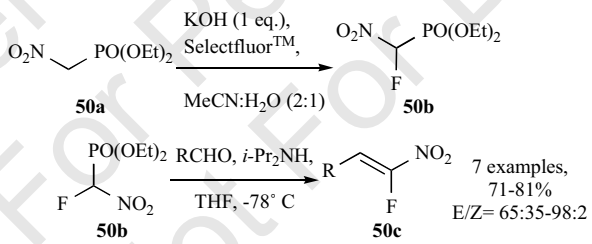


Scheme 48.



Scheme 49.

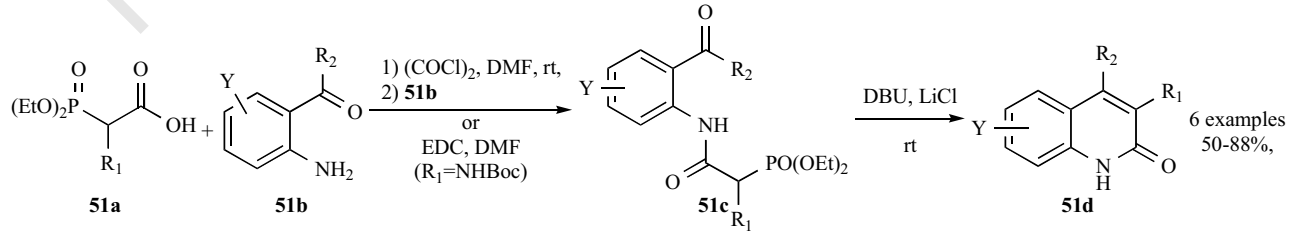
bases and reacts with aldehydes in the presence of diisopropylamine even at -78 ºC. Reaction with ketones is sluggish or does not occur, while olefination of aldehydes proceeds with good yields. The resulting 1-fluoro-1-nitroolefins **50c** can be reduced to 1-fluor-1-nitroalkanes easily [89]. Reagent **50b** can also be alkylated with reactive halides or Michael acceptors.



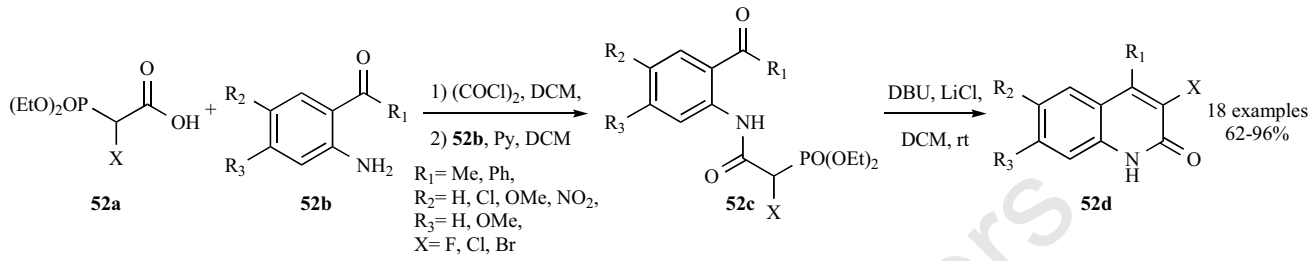
Scheme 50.

Peters developed a HWE-based approach towards substituted 2-quinolones (**51d**), a heterocyclic nucleus present in biologically active compounds and also a starting material of synthetic value. The method, depicted in Scheme **51**, involves *N*-acylation of *o*-aminophenylketones (**51b**) followed by intramolecular HWE olefination of amidoketones **51c**. The procedure involves mild reaction conditions, good yields, and can be performed either in two steps or as a one-pot procedure. An additional advantage is its applicability to certain derivatives which were not readily accessible through previously reported methods. This procedure, however, could not be applied to 2-unsubstituted phosphonates, which yield the corresponding Knoevenagel products [90].

Zhao and co-workers developed a similar method for the synthesis of 4-substituted-3-halo-2-quinolones (**52d**) starting from 2-halo diethylphosphonoacetic acids (**52a**, X= F, Cl, Br) and *o*-aminophenylketones (**52b**) [91] (Scheme **52**).

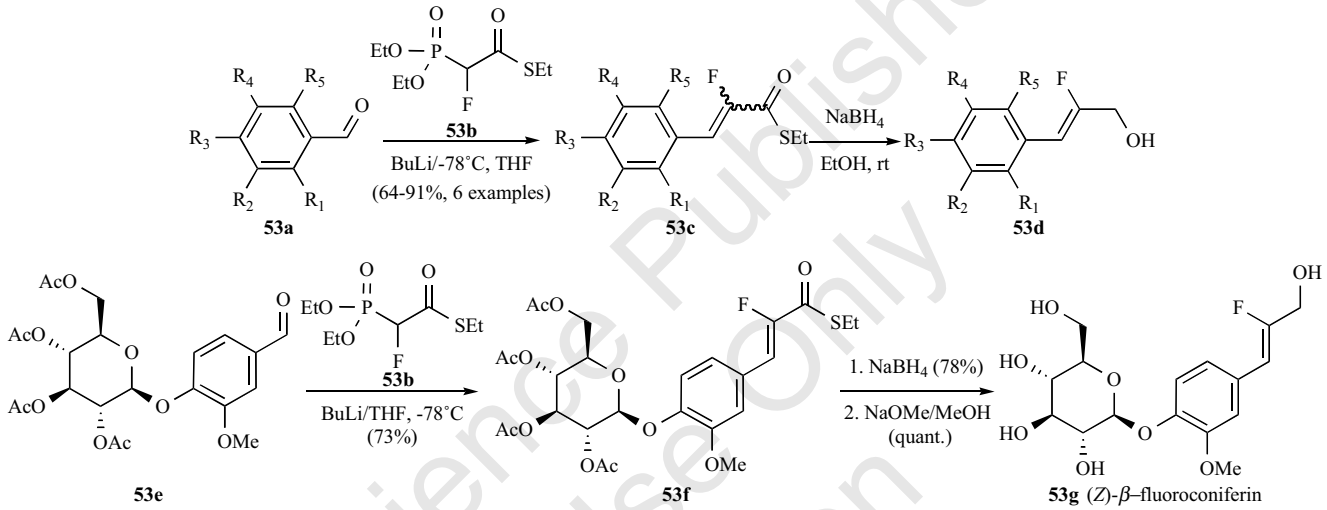


Scheme 51.



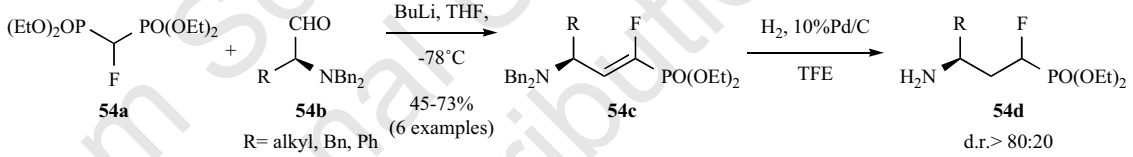
52a **52b** **52c** **52d**

Scheme 52.



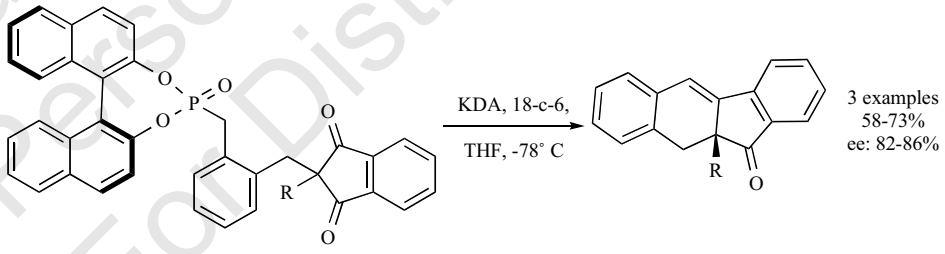
53a **53c** **53d** **53e** **53f** **53g** (*Z*)-*β*–fluoroconiferin

Scheme 53.



54a **54b** **54c** **54d**

Scheme 54.



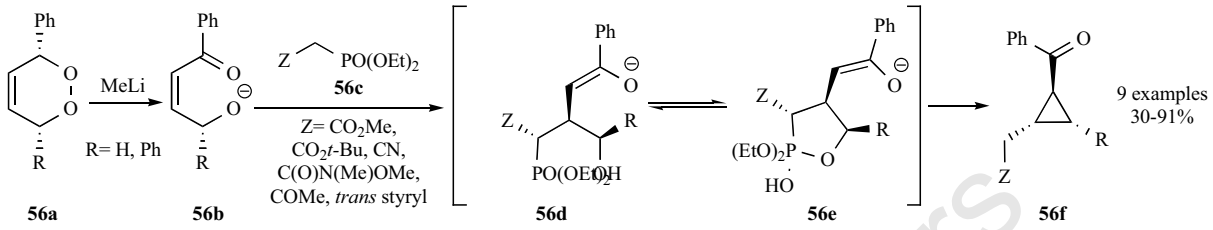
55a **55b**

Scheme 55.

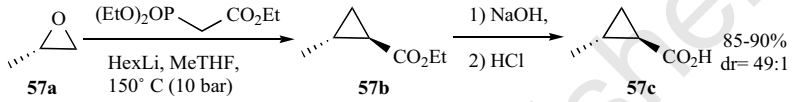
2-(Diethoxyphosphoryl)-2-fluoro-ethanethioic acid S-ethyl ester (**53b**) was developed by Kajjout [92], and employed in the HWE olefination of aromatic aldehydes (Scheme **53**). The resulting *α*–fluoro–*α,β*–unsaturated thioesters (**53c**) were then reduced to the corresponding *(Z)-β*–fluoroallyl alcohols (**53d**). The *E/Z* selectivity of the olefination step varies according to the nature of the substituents, but the *E/Z* mixtures obtained undergo isomerization during the ester reduction step, yielding exclusively the *Z* final products. This methodology, applied to *O*-glucosylated vanillin (**53e**), provided easy access to *(Z)-β*–fluoroconiferin (**53g**), a strong lignin polymerization inhibitor.

Fluorinated aminophosphonates are mainly sought for their applications in bioorganic chemistry and because of the biological activities displayed by some of them. A straightforward two-step method to access such compounds (**54d**) is depicted in Scheme **54**, and involves reduction/deprotection of fluorinated vinylphosphonate **54c**. The olefin substrates were prepared from fluoromethylene bisphosphonate **54a** and chiral *α*–(dibenzylamino)aldehydes **54b** [93].

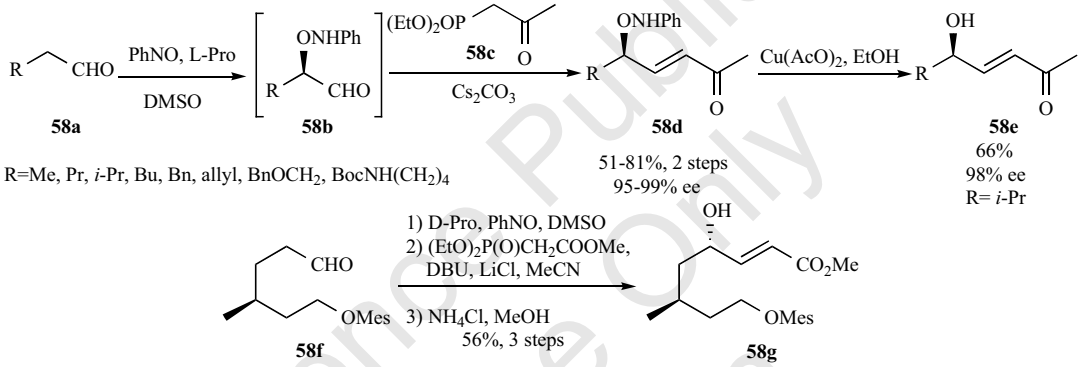
Although asymmetric HWE reactions are scarce, some examples can be found in the literature. In 2002, Tanaka reported the synthesis of chiral 10-substituted benzo[*b*]fluorenones **55b** by intramolecular HWE olefination from axially chiral phosphonate **55a** (Scheme **55**). Other diketones gave poorer results in terms of yield and asymmetric induction [94].



Scheme 56.



Scheme 57.



Scheme 58.

2.4. Other Electrophiles

Although the vast majority of HWE reactions proceed through *β*–oxiphosphonate→1,2-oxaphosphetane intermediates, in some cases the homologous *γ*–oxi phosphonate→1,2-oxaphospholanes can lead to cyclopropane derivatives. This behavior can be observed when an epoxide or a dioxine are used as the elecrophile instead of an aldehyde or ketone.

Dioxines (**56a**) behave as masked 3-hydroxy-enones (**56b**), since they can be isomerized to the latter either by cobalt or base catalysis. In 2002, Taylor studied the reaction between **56a** and various HWE reagents **56c**, obtaining moderate to excellent yields of the desired cyclopropanes **56f** with the shown stereochemistry [95] (Scheme **56**). The reaction has some limitations and fails when *Z* is a methyl ketone or a styryl group. The lowest yields were obtained for triethylphosphonopropionate, which afforded a diastereomeric mixture of the products (not shown).

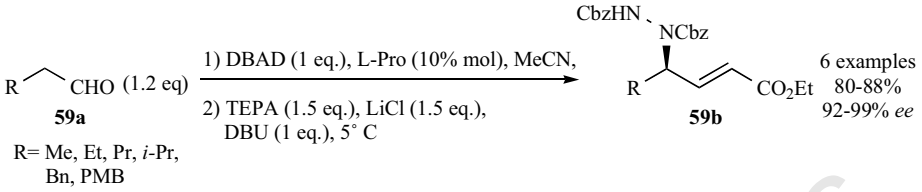
Synthesis of cyclopropanes by HWE methodology employing oxiranes as the starting materials is a known procedure, although some practical drawbacks are found in large scale preparations when alkyl oxiranes are used as the substrates [96]. Merschaert developed an efficient synthesis of *(R,R)*-2-methylcyclopropanecarboxylic acid (**57c**) from *(S)*-2-propylene oxide and TEPA (Scheme **57**). The authors informed that the reaction outcome was highly dependent on the reaction conditions. The harsh conditions required to bring about reaction in **57a** are in agreement with the chemoselectivity previously observed in the reaction of **19a** (Scheme **19**).

3. CONSECUTIVE REACTIONS

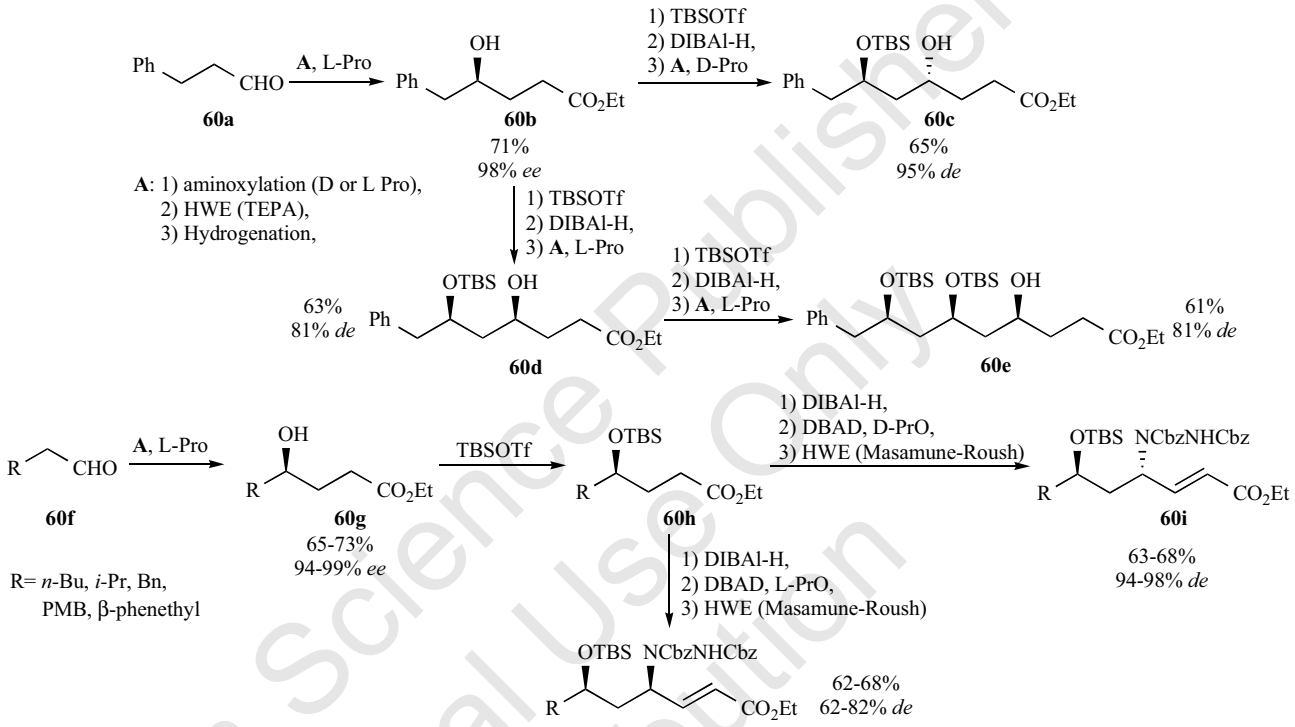
3.1. Sequential Reactions

Sequential reactions introduce a significant modification in a chemical compound by means of a series of high yielding reactions with a predictable outcome and without the need of step by step purification. In spite of this, product isolation, solvent replacement and/or changes in the reaction conditions are often needed. It is a prerequisite for each step to deliver a high purity product in order to comply for the needs of a practical sequential reaction. HWE reaction fulfills these requirements and finds use in some well established sequential reactions.

Asymmetric organocatalyzed functionalizations of aldehydes are important transformations. Among them, reaction of enols, enolates, enol ethers and enamines with nitrosobenzene, in the presence of a Lewis acid catalyst, lead to *α*–aminoxy derivatives, which can in turn be converted to highly valuable *α*–hydroxy compounds through N-O bond scission [97]. Although asymmetric aminoxylation-reduction of trialkyltin enolates using nitrosobenzene as the oxidant and BINAP-Ag^+ complexes as catalysts had previously been reported [98], truly organocatalytic chiral *α*–aminoxylation of aldehydes was first described in 2003. Since then, it has been linked to consecutive reactions because *α*–(phenylaminoxy)aldehydes are highly unstable compounds, whose isolation and purification are cumbersome [99]. The aminoxylation/HWE sequence was developed by Zhong *et al*. with the aim of providing an expeditious access to secondary chiral allylic alcohols [100]. The sequence, depicted in Scheme 58, involves the reaction between *in situ* generated *α*–aminoxyvaleraldehyde **58b** and diethyl (2-oxopropyl)phosphonate, yielding the desired *γ*–aminoxyenone **58d**. The high optical purity of the resulting material indicated that racemization was a negligible process in the chosen experimental conditions, probably due to the different acidities of the oxidized aldehyde and phosphonate reagent. The resulting aminoxy compounds yield the corresponding alcohols **58e** after treatment with cupric acetate. This methodology was further refined by McMillan [101], who included the deamination step in the reaction work-up. In his syntheses of Brasoside and Littoralisone (Scheme **58**), aldehyde **58f**, derived



Scheme 59.



Scheme 60.

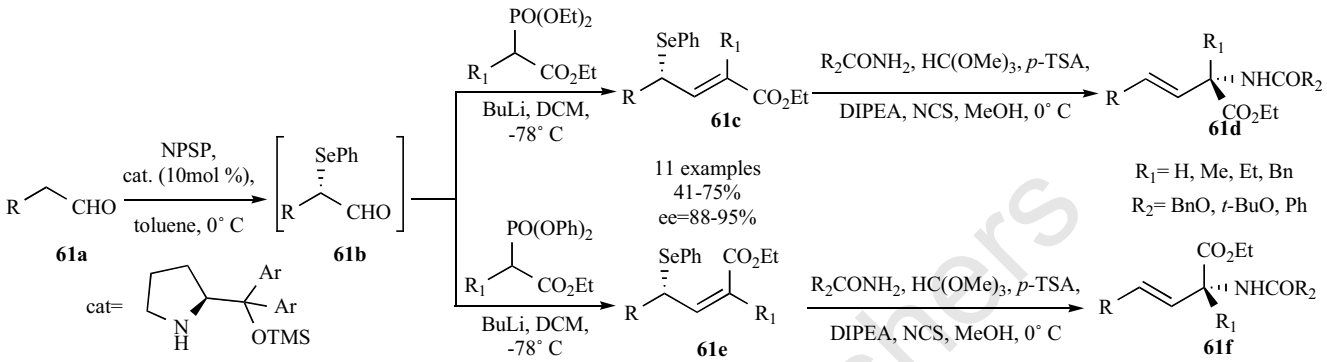
from (-)-citronellol, was subjected to *D*-Proline-catalyzed oxidation and olefinated in Masamune-Roush conditions. Subsequent deamination took place during NH_4Cl/MeOH workup of the reaction, delivering γ–hydroxy–α,β–unsaturated ester **58g** in 56% yield over three steps.

Since then, asymmetric organocatalyzed aminoxylation/HWE/reduction sequences have found much use in the synthesis of natural products, where polyfunctionalized carbon chains with definite stereochemistry are often needed [102]. In addition, the hydrolytic deamination step can be omitted when the desired product is the saturated γ–hydroxy ester, since N-O bond cleavage occurs readily under heterogeneous hydrogenation conditions [103].

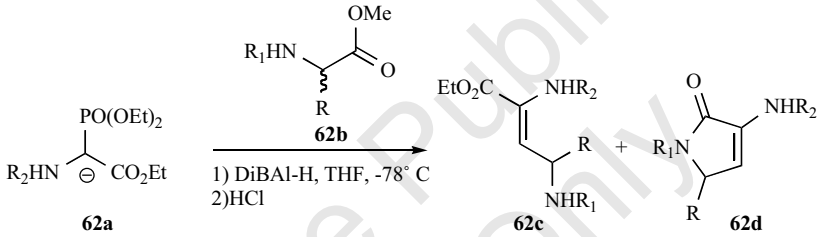
Enantioselective α–amination of aldehydes is also a well established synthetic procedure [104]. From the beginning it has been linked to one pot sequential processes, since the aminoaldehyde products are even more prone to racemization than the α–aminoxy compounds [105]. The reaction is conducted with *D*- or *L*-proline as the organocatalyst and DBAD (and other azodicarboxylates) as the electrophilic nitrogen source, leading to *N,N'*-bis(Cbz) protected α–hydrazino aldehydes and ketones. In 2007, Kotkar reported the first HWE trapping of these reactive derivatives [106] (Scheme **59**). The amination/HWE product **59b** was obtained in 80% yield, although with 22% ee, showing the instability of the chiral centre in the intermediate aminoaldehydes. Different bases were assayed in order to decrease the racemization rate, and the Masamune-Roush protocol was identified as the optimal condition, working at low temperature and decreasing the exposure time without seriously affecting the chemical yield.

The scope of these reaction sequences was further extended by the addition of an ester to aldehyde reduction step and by submitting the resulting chiral γ–substituted aldehyde to an additional α–functionalization/HWE/reduction protocol, iteratively (Scheme **60**). Since either antipode of *Pro* can be used as the catalyst, this extension of the method gives access to both *anti* and *syn* 1,3-diols and 1,3-aminoalcohols. It should be noted, however, that diasteroselectivities can be lowered due to matched-mismatched effects on successive iterations (compare **60c** and **60d**) and that careful selection of protecting groups is necessary in order to avoid diminished aldehyde reactivity [103a]. The strategy was investigated by Kumar, who examined the stereochemical outcome of successive iterations [107]. In 2010, the same author reported an extension of this concept by combining aminoxylation and amination sequences in order to obtain *syn* and *anti* 1,3-aminoalcohols [108] (Scheme **60**). Chemical yields for aminoalcohols **60i** and **60j** were similar but, also in this case, the *syn* series showed a lower degree of asymmetric induction, behaving as the mismatched pair. More recently, various azabicyclic ring systems were synthesized by this approach [109].

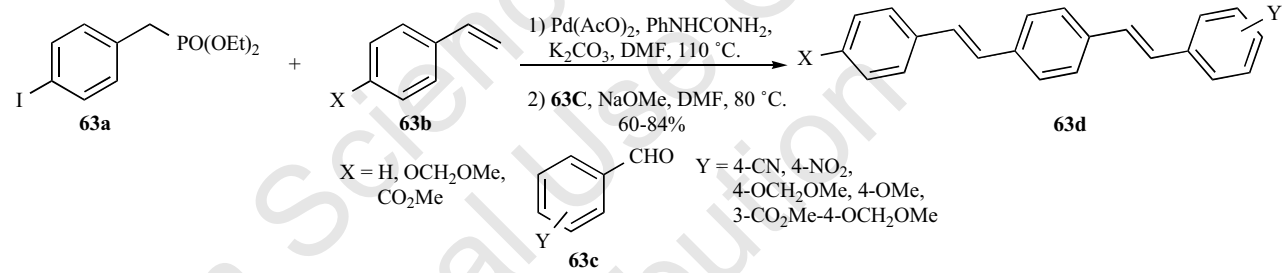
Organocatalyzed α–functionalization of aldehydes followed by HWE reaction was also employed in Armstrong's synthesis of qua-



Scheme 61.



Scheme 62.



Scheme 63.

ternary α–vinyl-α–aminoacids (Scheme **61**). In this case, the electrophile **61b** was generated from *N*-(phenylseleno)phthalimide, and the resulting α–chiral aldehyde **61b** was trapped as the *E* (**61c**) or *Z* (**61e**) HWE adduct by employing either diethyl or diphenyl phosphonoacetate, respectively. The resulting allylic phenylselenides were transformed to the corresponding selenimides, which rearranged spontaneously to the chiral α–aminoacids **61d** and **61f**. HWE reaction's stereoselectivity was crucial in order to obtain both optical antipodes of the desired products employing *L*-Pro as the only precursor of the asymmetric induction agent [110].

3.2. One Pot, Tandem and MCR Procedures

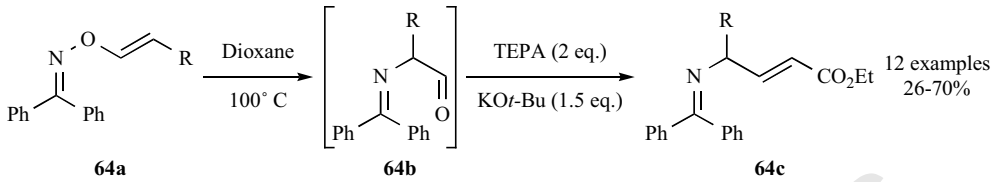
One pot, MCR and tandem reactions represent the acme of chemical pragmatism, since they allow for consecutive reactions to take place without isolation and purification of synthetic intermediates, thus saving time and effort. Both tandem and multicomponent reactions are "one pot operations" being distinguished by the intramolecular character of the former. The reverse, however, is not true, and many one pot reactions require modifications (temperature, solvent, catalyst addition) during their implementation. Although all the examples discussed in the present section fall in one of these categories, a stern subdivision based on them would be both impractical and artificial. According to this, the sorting of the following examples is based on whether the modification of the reaction partners takes place before or after the HWE reaction, and the type of the accompanying reaction.

HWE reaction can be performed with *in situ* generated aldehydes. In the example shown in Scheme **62**, the preformed stabilized phosphonate carbanion **62a** is treated with an aminoacid ester (**62b**) in the presence of DIBAl-H at low temperature to produce *Z*-dehydroaminoacids **62c**. Lack of stereoselectivity led in this particular case to the unexpected compound **62d**, as a result of nucleophilic cyclization of the *E* product during workup [111].

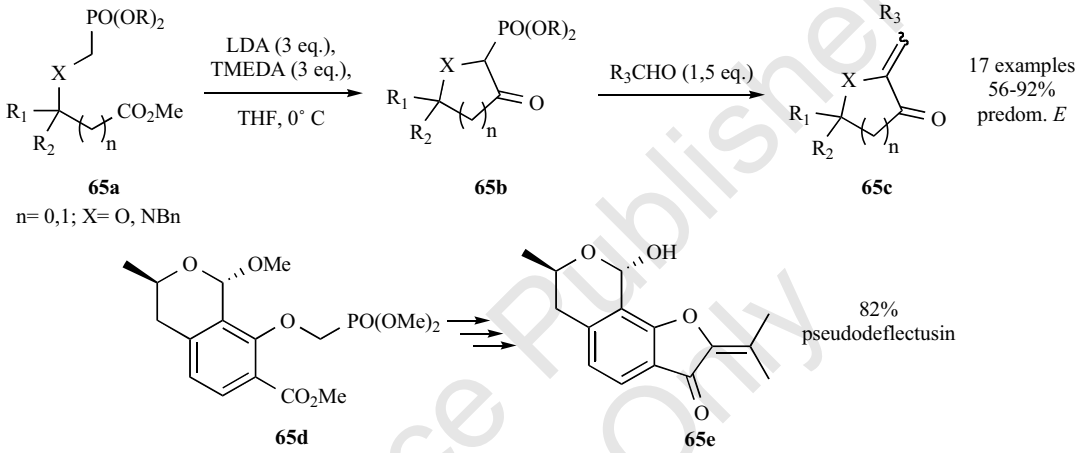
In 2009, a one-pot synthesis of 1,4-bis-styrylbenzenes was developed, involving Heck coupling of diethyl 4-iodobenzylphosphonates (**63a**) with substituted styrenes (**63b**) followed by HWE reaction with benzaldehydes (**63c**) [112] (Scheme **63**). The inverse two step sequence, starting with the HWE reaction and performing the chromatographic purification before the Heck coupling, led to lower overall yields (50-65%) of **63d**. The one pot version of the HWE/Heck sequence afforded even lower yields (43-60%).

Anderson prepared α–iminoaldehydes **64b** through a 1,3-rearrangement of *O*-alkenyloximes **64a**. The reaction products were trapped by TEPA anion to yield γ–imino-α,β–unsaturated esters **64c** [113], which were then hydrolyzed to the corresponding amines (Scheme **64**).

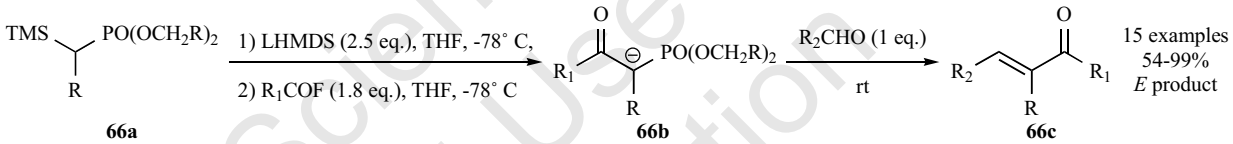
Fujioka presented a two step reaction sequence, depicted in Scheme **65**, for the synthesis of four and five-membered heterocycles **65c** bearing a α–exocyclic double bond. The first step, a base induced Claisen-like acylation affords the stabilized cyclic phos-



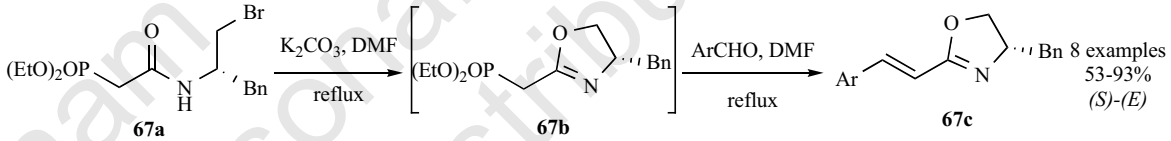
Scheme 64.



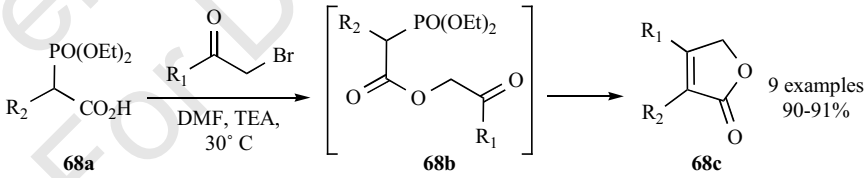
Scheme 65.



Scheme 66.



Scheme 67.



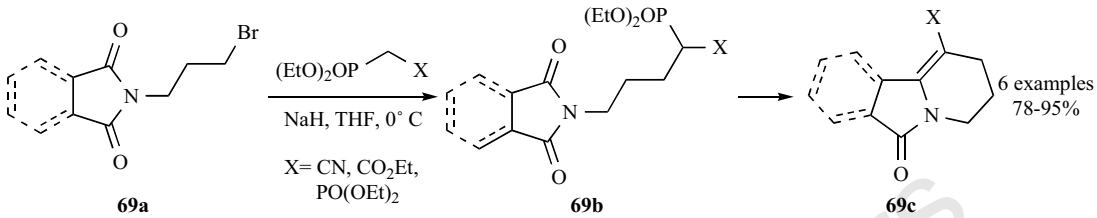
Scheme 68.

phonate **65b**, and HWE reaction between the latter and an aldehyde ensues. The equivalent two step synthesis led to similar yields and stereoselectivity. The authors employed this protocol for the expeditious synthesis of (±)-pseudodeflectusin from phosphonate ester **65d** [114].

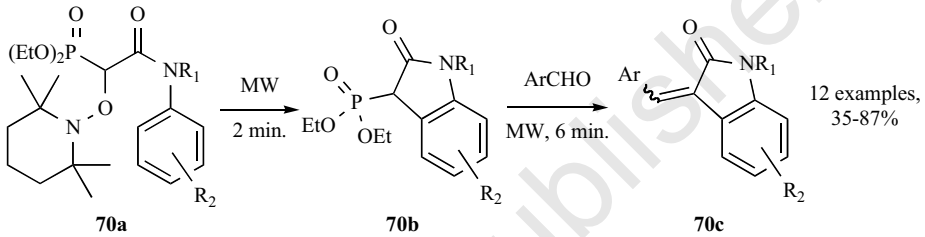
Umezawa developed a protocol for the one pot generation of a HWE reagent salt followed by HWE olefination in a three component reaction mode (Scheme **66**). Base-induced reaction of trimethylsilylmethyl phosphonate **66a** with an acyl fluoride generates a α–TMS phosphonoketone, which after fluoride-induced loss of the TMS group generates the corresponding stabilized anion **66b**. Addition of an aldehyde allows the HWE reaction to proceed to the desired enones **66c** [115].

Base-induced heterocyclization of diethyl *N*-(2-bromo-1-benzyl)phosphonoacetamides **67a** followed by one pot HWE reaction of the resulting oxazolines **67b** was a more effective route to (*S,E*)-2-(2-arylvinyl)-4-benzyl-4,5-dihydrooxazoles **67c** than stepwise approximations (Scheme **67**). In all cases the products were isolated as single diastereomers and without loss of enantiomeric purity [116].

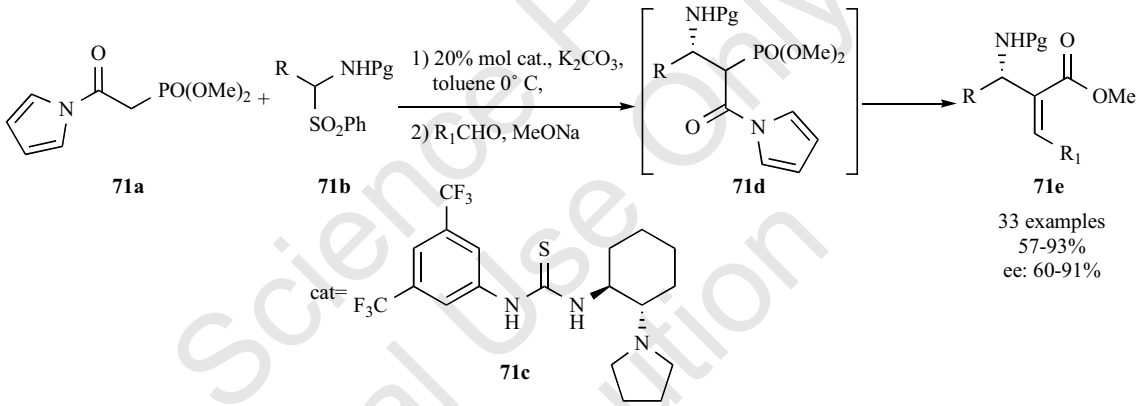
Argade presented a one pot synthesis of 3,4-diaryl-2-(5*H*)-furanones **68c** involving a displacement reaction followed by tandem HWE reaction (Scheme **68**). This very convenient procedure employs triethylamine as the base and gives high purity products (>97%) with excellent yields. The intermediate phosphonoester **68b** was isolated in 92% yield performing the reaction in DCM at 0º C.



Scheme 69.



Scheme 70.



Scheme 71.

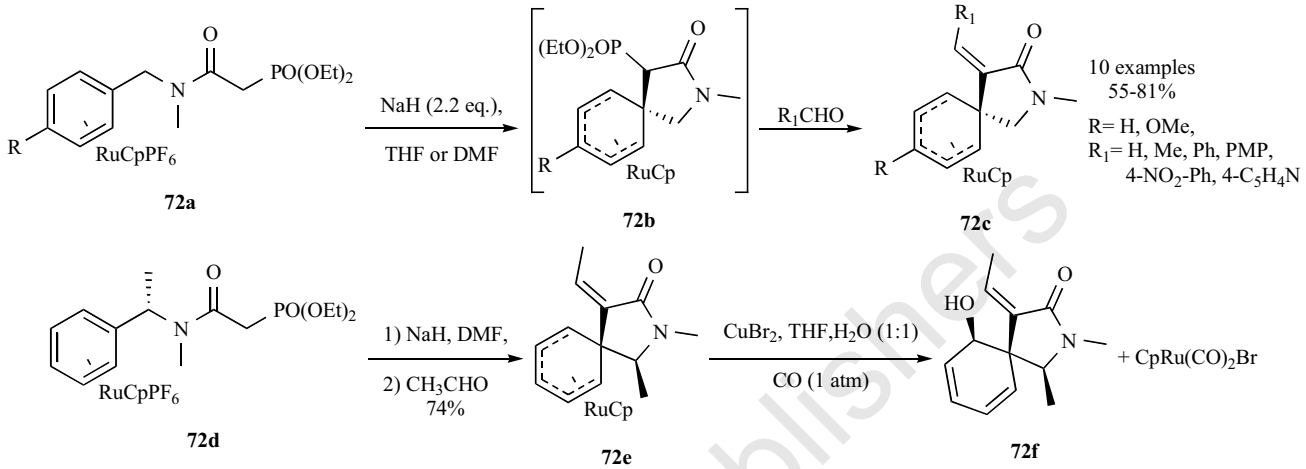
This sequence was employed for the synthesis of *Cox-2* inhibitor Rofecoxib (R_1=4-$MeSO_2Ph$, R_2=Ph) in multigram scale with 92% yield [117].

HWE reaction is mostly related to aldehyde or ketone olefination. Although phosphonate anions are capable of reacting with other electrophiles, such as esters, amides and amidines [118], these reactions proceed presumably through a nucleophilic acyl displacement mechanism, leading not to olefinated products but to acyl phosphonates. Although amides are known not to participate in HWE reactions, some imides (**69a**) do. Couthon described some examples of this reaction (Scheme **69**), which occurs spontaneously in the conditions leading to **69b** [119], and extended this methodology to other HWE reagents (Scheme **69**, X= CN, CO_2Et). Simple amides and more sterically hindered imides could not be olefinated in the same conditions.

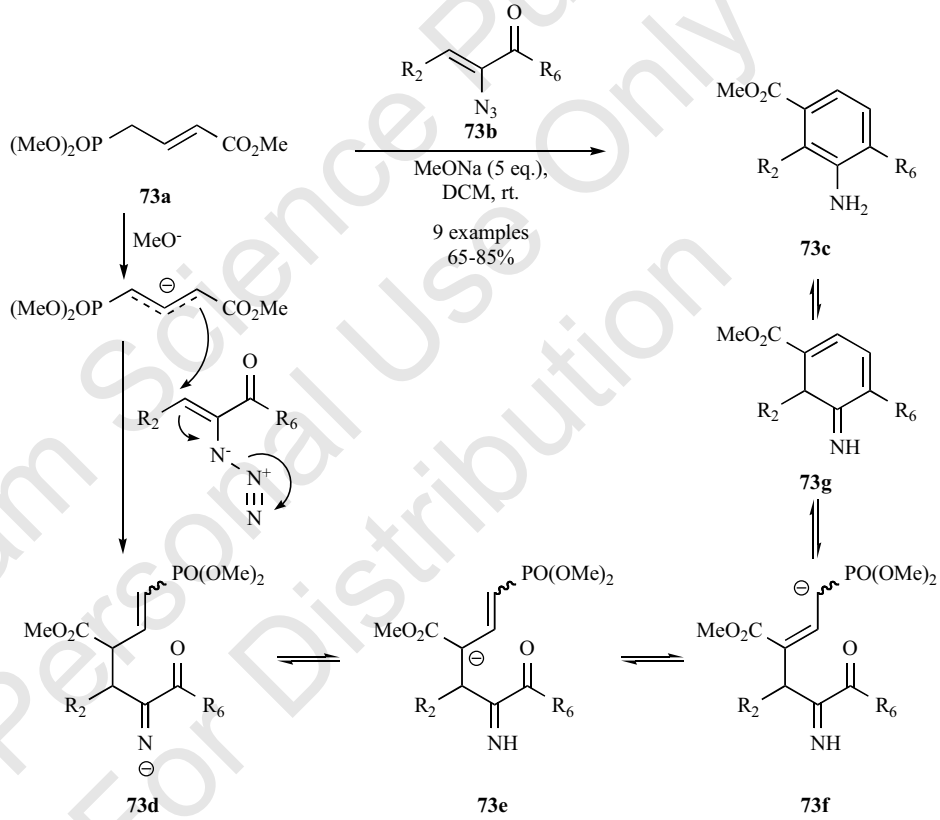
Some alkoxylamine-substituted phosphonates **70a** can undergo microwave-assisted radical aromatic substitution leading to novel oxindole phosphonates **70b**. Microwave-assisted HWE alkenylation of such compounds with aromatic aldehydes provides an easy access to the corresponding alkenyl heterocycles **70c** in good to high overall yields in short reaction times and with predominant *E*-selectivity [120] (Scheme **70**).

Stabilized phosphonate carbanions can also act as Mannich donors. In the example depicted in Scheme **71**, Wang demonstrated that the highly reactive 1-diethoxyphosphorylacetyl pyrrole **71a** can be used in the stereoselective addition to protected imines (generated *in situ* from α–amidosulfones **71b**) when the reaction is catalyzed by a bifunctional chiral thiourea (**71c**). The resulting phosphono-Mannich bases **71d** reacted with aldehydes in the presence of sodium methoxide, yielding the corresponding *Z*-aminoolefins **71e**, generally with high degrees of asymmetric induction. Interestingly, the *N*-acylpirrole served both to enhance the reactivity of the phosphonate reagent and as a leaving group, being replaced by methoxyl under the reaction conditions [121]. *E*-olefins were obtained when proazaphosphatrane ($P(i\text{-}BuNCH_2CH_2)_3N$) was used as the base [122].

Aromatic Ru complexes are prone to nucleophilic attack by phosphonate anions, as demonstrated in Dalvi's synthesis of *Z*-enamide spirocyclic compounds **72c** [123] (Scheme **72**). *N*-benzyl-*N*-methyl (diethylphosphono)acetamide was converted to its η^6-$RuCp^+$ complex **72a** by simple ligand exchange with $[(MeCN)_3RuCp][PF_6]$. Treatment of **72a** with NaH gave rise to **72b**, which, after exposure to various aldehydes, led to **72c**. The stereochemical outcome of the reaction is ruled by the presence of the CpRu group, leading to nucleophilic attack exclusively from the opposite face. The authors also explored an asymmetric version of the reaction by using the chiral α–substituted benzylamine precursor **72d**. Facial selectivity of the spirocyclization step led to the desired lactam **72e** as a single stereoisomer. The reaction was unsuccessful with acetone and cyclohexanone, and other ketones were not investigated. A decomplexation protocol leading to oxygenated functionalities in the cyclohexadiene ring (**72f**) was also employed.



Scheme 72.

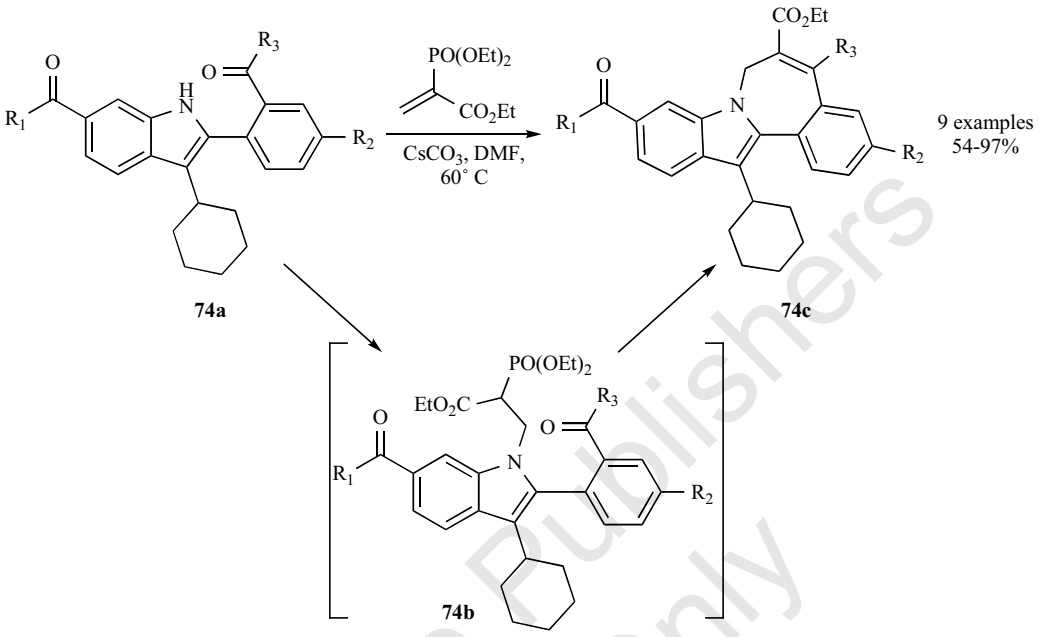


Scheme 73.

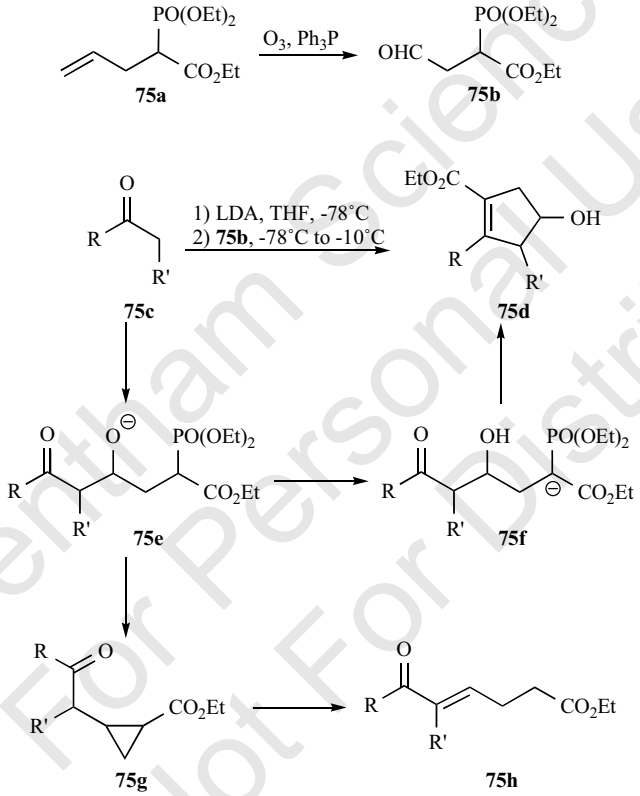
Yu presented a synthesis of polysubstituted anilines in which trimethyl 4-phosphonocrotonate (**73a**) acts both as a Michael donor and HWE reagent, leading to a tandem addition-elimination-annulation sequence (Scheme **73**). The authors rationalized this reaction assuming an initial attack by phosphonocrotonate anion, leading to the expulsion of molecular nitrogen from azide **73b**, followed by intermolecular proton shift (**73d-f**), HWE reaction and aromatization to **73c** [124]. The reaction was inhibited when R_6= *t*-Bu or OEt, due to diminished reactivity of the carbonyl, and when R_6=H, probably because of competitive direct HWE reaction of the aldehyde. Analogous results were obtained when the corresponding 4-triphenylphosphonium reagent was used instead of the phosphonate.

As previously mentioned, phosphonoacrylates behave as Michael acceptors, thus providing an easy way of attaching the phosphonoacetate group to a nucleophilic molecule. This feature was exploited for the synthesis of benzazepine-10-carboxylic acid derivatives (**74c**) [125] depicted in Scheme **74**. The overall transformation consists of deprotonation of indole **74a** NH followed by aza-Michel conjugated addition leading to a 3-indolyl-2-phosphonopropionate **74b** which then engages in an intramolecular HWE olefination.

Despite their lower reactivity and poorer stereoselectivity in the HWE olefination, ketones can be useful in intramolecular HWE reactions. Kraus reported a tandem aldol addition/intramolecular HWE reaction that afforded polysubstituted cyclopentenols in a



Scheme 74.



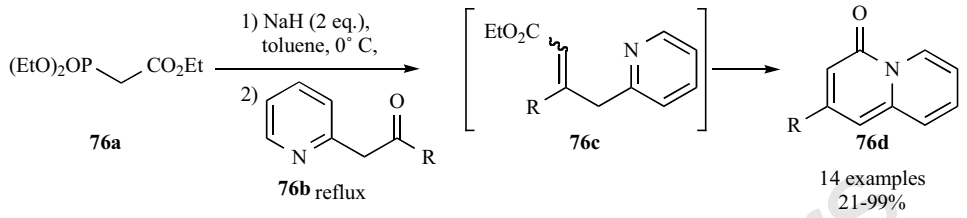
Scheme 75.

single operation (Scheme **75**) [126]. To meet this purpose they prepared the versatile aldehyde-containing phosphonate **75b** (ethyl 2-(diethoxyphosphoryl)-4-oxobutanoate) by ozonolysis of ethyl 2-(diethoxyphosphoryl)pent-4-enoate **75a**. When reagent **75b** was allowed to react with the preformed kinetic lithium enolate of various ketones (**75c**), 2,3-disubstituted ethyl 4-hydroxycyclopentenecarboxylates **75d** were obtained as the main products. The reaction showed diasteroselectivities ranging from 5.5:1 to 10:1, always favouring the 3,4-*trans* isomer. In some cases, the authors evidenced the presence of up to 5% of a secondary product in the reaction mixture, with the general structure **75h**. Interestingly, **75h** is the only product when the starting ketones are α–tetralone or methyl cyclopropyl ketone. Products **75h** would arise from the base-promoted ring opening of intermediate cyclopropanes **75g**, which would in turn been formed by the rare 1,3 elimination of diethyl phosphate anion from alkoxide **75e** [127].

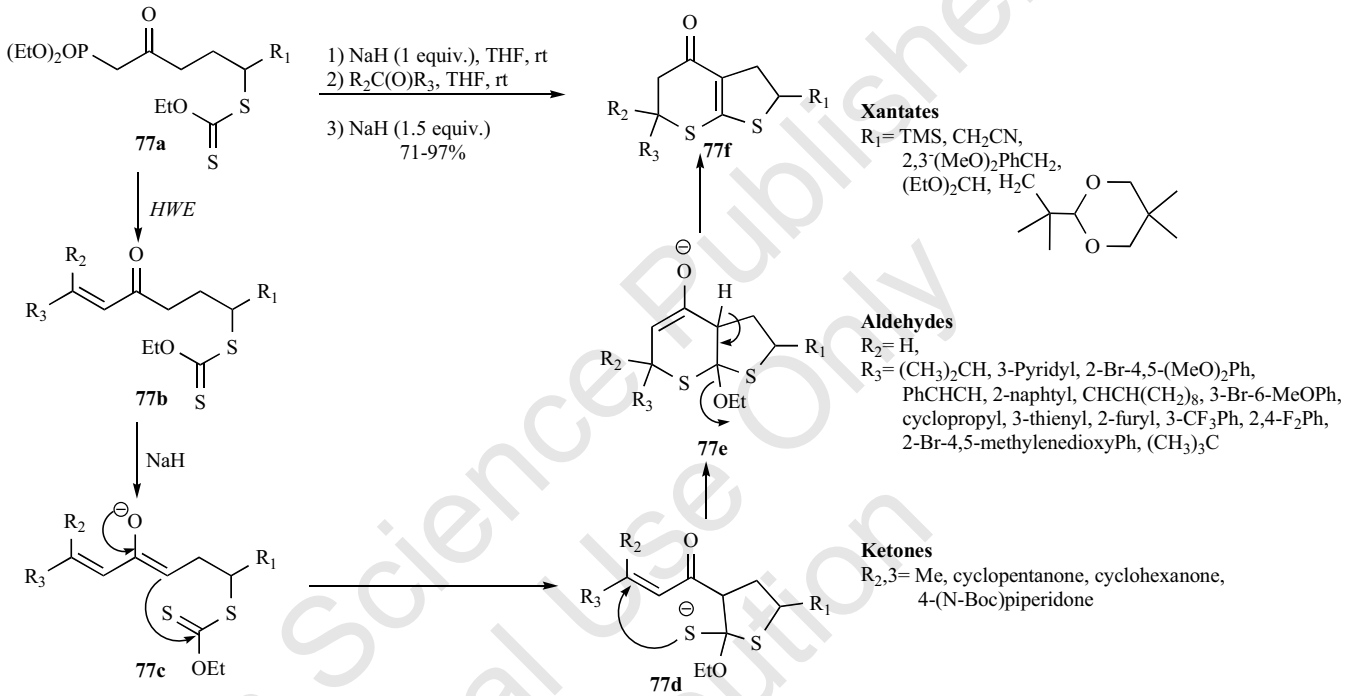
Watson developed a method for the synthesis of (4*H*)-quinolizin-4-ones **76d** comprising olefination of β–ketopyridines (**76b**) followed by tandem acylation of the 3-(2-pyridyl)-propenoate intermediate (**76c**, Scheme **76**). The desired quinolizinones **76d** were isolated in good to excellent yields with the exception of R=4-NO_2Ph, which led to decomposition products and R=4-TBSOPh, which was partially desilylated during the reaction [128].

Corbet reported a one-pot sequence leading to thieno[2,3-*b*]thiopyranones using β–keto-ε–xanthylphosphonates as the starting materials [129] (Scheme **77**). The one-pot procedure involves an initial HWE reaction followed by a base-promoted domino reaction comprising intramolecular Claisen-type cyclization, thia-Michael addition and β–elimination. According to the authors, after initial HWE reaction, deprotonation of adduct **77b** by NaH generates carbanion **77c**, which starts the reaction cascade by nucleophilic addition to the xantate group. This generates anion **77d**, which takes part of the Michael addition step leading to the bicyclic system **77e**. Base-promoted elimination of EtOH then generates the isolated product **77f**. Since the starting ε–xanthylphosphonates can be easily prepared from γ–xanthylphosphonates, the sequence provides facile access to 2,6-di and 2,6,6-trisubstituted 5,6-dihydro-2*H*-thieno[2,3-b]thiopyran-4(3*H*)-ones. Reaction with aliphatic (including cyclopropyl), unsaturated and (hetero)aromatic aldehydes led to heterocycles **77f** with very good to excellent yields in general. Reaction with cyclic ketones allowed for the synthesis of spirocyclic systems, although with poorer yields (24-55%) and longer reaction times, being the HWE reaction the rate-determining step.

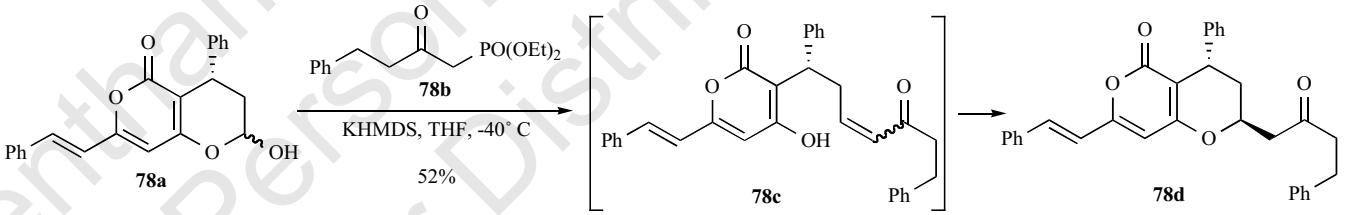
As previously mentioned, HWE olefination products behave as Michael acceptors, providing direct access to cyclic compounds.



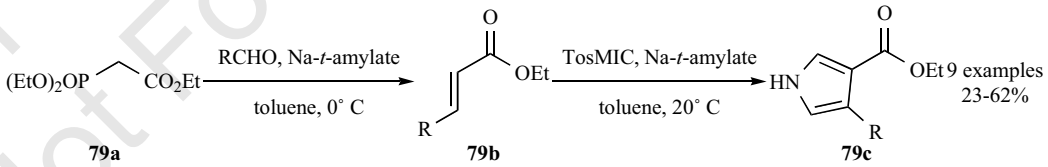
Scheme 76.



Scheme 77.



Scheme 78.

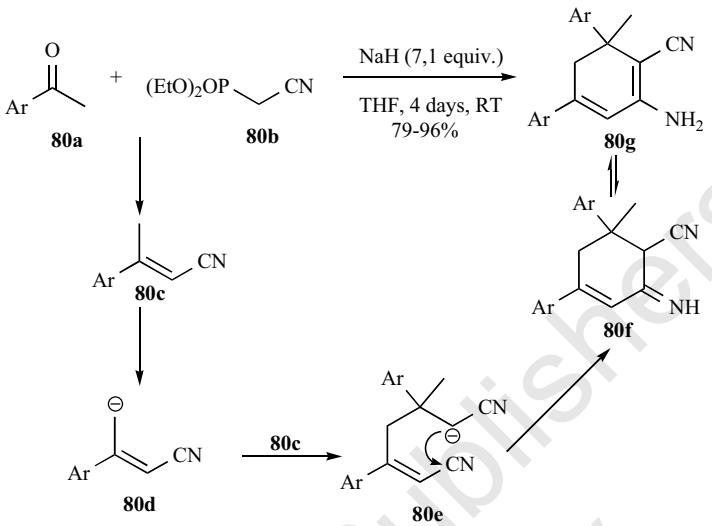


Scheme 79.

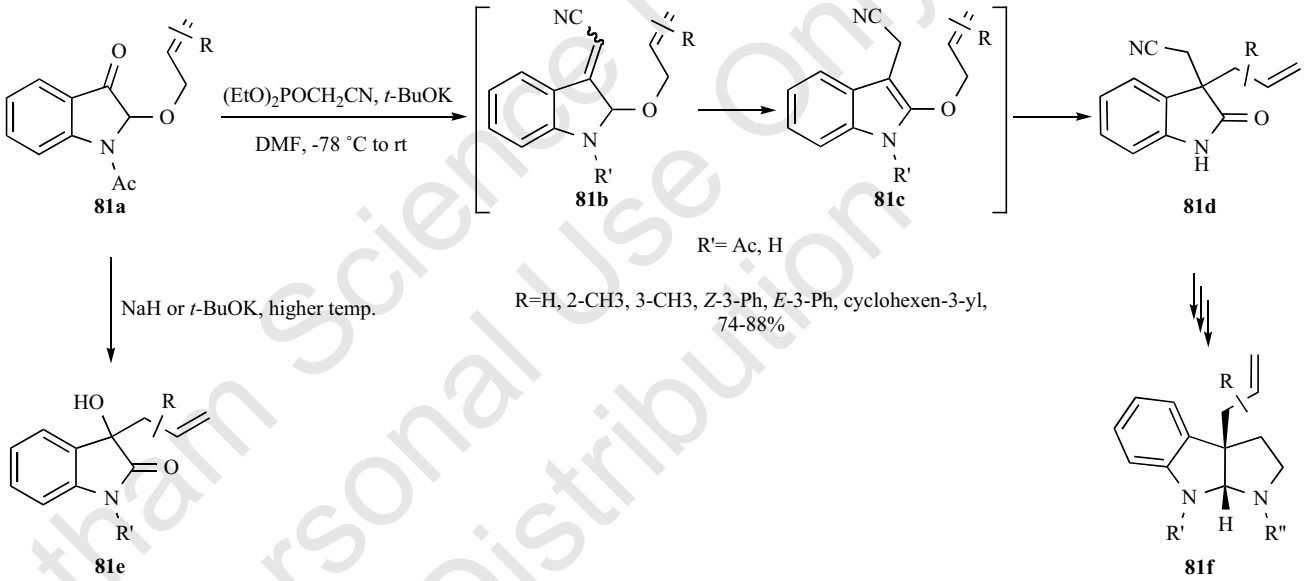
Tang used this approach in his bioinspired synthesis of the pyrano[4,3-*b*]pyranone core of katsumadain A [130], depicted in Scheme **78**. In this case, after HWE olefination of hemiacetal **78a** with phosphonoketone **78b**, the resulting enone **78c** undergoes a tandem oxa-Michael reaction to furnish **78d**.

Shin demonstrated that HWE reaction products can be used for the large-scale production of pyrroles in a sequential manner employing the van Leusen pyrrole synthesis [131] (Scheme **79**). In this case, judicious choice of the base allowed for the two steps to be performed in the same solvent, which was also used for the crystallization of the products. The fair yields obtained in most cases with this reaction sequence are compensated by the fact that it renders valuable α–unsubstituted pyrroles **79c** on a kilogram scale from nonexpensive starting materials [132].

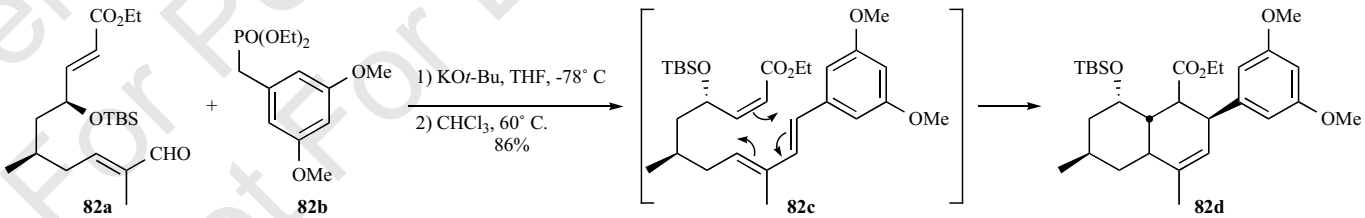
Bench reported a tandem preparation of cyclohexadiene enaminonitriles from aryl methyl ketones and diethyl cyanomethylphosphonate [133] (Scheme **80**). This methodology resembles a previously developed LDA promoted dimerization of α,β–unsaturated



Scheme 80.



Scheme 81.



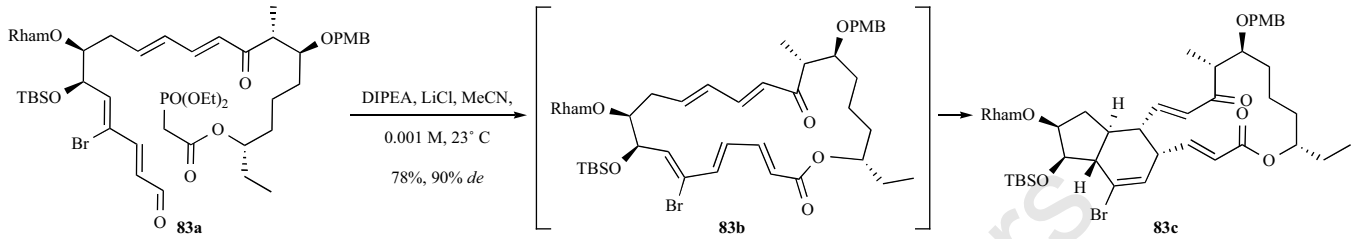
Scheme 82.

nitriles [134] but includes *in situ* generation of such reagents. Addition of arylmethylketones **80a** to a preformed solution of cyanomethylphosphonate (**80b**) ylide leads first to the HWE reaction product **80c**, which undergoes a dimerization/cyclization/tautomerization tandem sequence to afford **80g**.

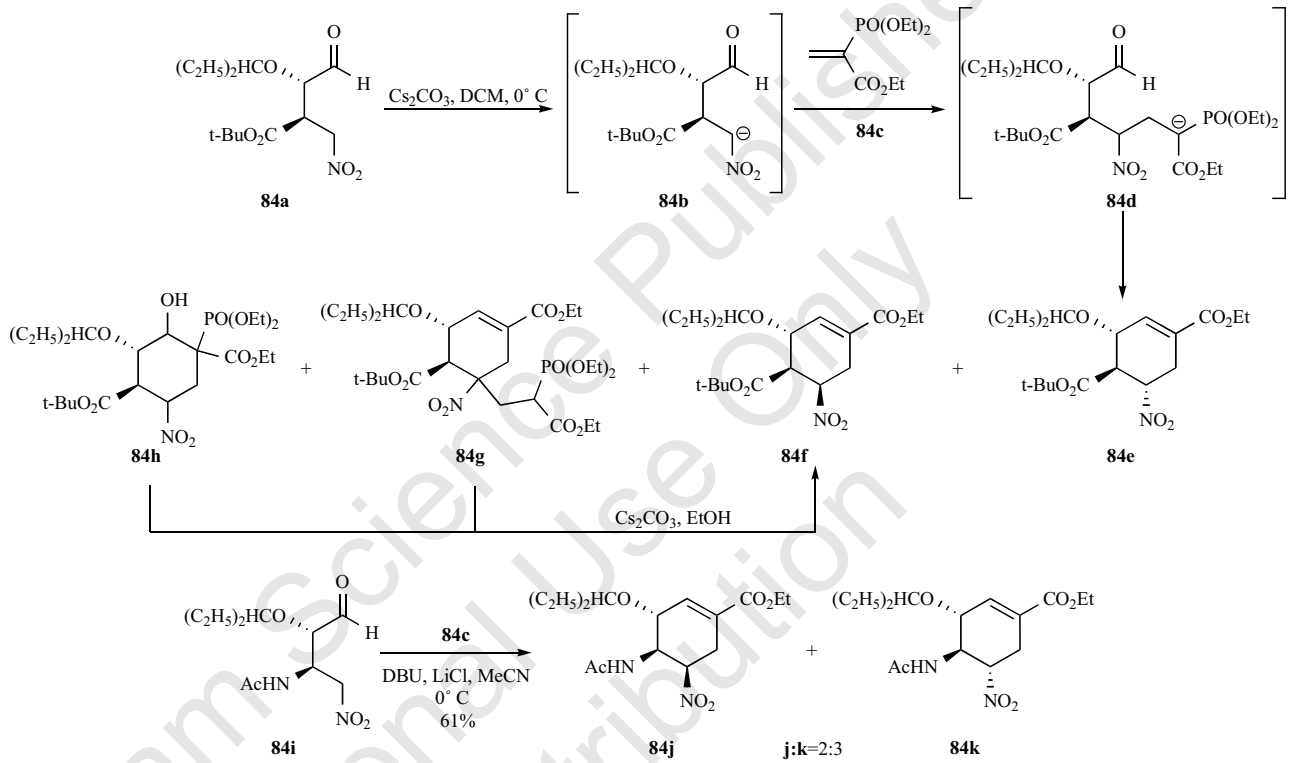
In 2005, Kawasaki reported a straightforward method for the preparation of 3a-allyl-substituted derivatives of hexahydropyrrolo[2,3-b]indole (**81f**), a tricyclic core present in many bioactive alkaloids [135]. 2-Allyloxyindolin-3-ones **81a** were reacted with diethyl cyanomethylphosphonate as the C_2N building block, yielding 3,3-disubstituted indolinones **81d** through a HWE-isomerization-Claisen rearrangement sequence (Scheme **81**), together with some oxi-Claisen rearrangement product (**81e**).

HWE reaction is also useful in generating polyene systems which are prone to pericyclic reactions. An example of this is Maier´s synthesis of (+)-Neosymbioimine, where the HWE generated diene **82b** engages in a intramolecular Diels-Alder reaction, leading to dehydrodecalin **82c** [136] (Scheme **82**).

The newly generated double bond can not only be involved in the subsequent [4+2] cycloaddition, but its formation induces a



Scheme 83.



Scheme 84.

favorable conformation for reaction to take place. Roush investigated the stereoselectivity of a key TADA leading to (-)-Spinosyn A. In this case, the macrolactonization product **83b**, arising from a high dilution intramolecular HWE reaction of **83a**, undergoes cycloaddition to yield **83c** with excellent diasteroselectivity [137] (Scheme **83**).

As shown previously (Scheme **49**), intramolecular HWE reaction is an evident disconnection to access the cyclic core of osaltamivir. In 2009, Ishikawa reported a three one-pot operations synthesis of this antiviral agent [138], one of them involving a tandem nitro-Michael/HWE reaction (Scheme **84**). The requisite nitroaldehyde **84a**, prepared in the same one-pot operation by means of an organocatalyzed Michael addition [139], was treated with cesium carbonate and vinylphosphonate **84c**. The nitronate anion **84b** initiates the domino sequence, behaving as Michael donor and the anionic product **84d** engages in the subsequent HWE reaction. This efficient approach is hampered by the fact that the reaction favours the formation of unwanted diastereomer **84f** over **84e** and that by-products are also formed (**84g**, as a consequence of a double Michael reaction and **84h** because of an *anti* disposition of the hydroxyl and phosphonate groups). Recycling of **84g** and **84h** back to the reaction sequence is possible, but at the expense of an additional operation [140].

More recently, Weng refined this approach, using **84i** as the Michael donor [141]. The reaction carried out on this substrate under Masamune-Roush conditions led to a more advantageous diastereomer distribution, favouring the desired epimer **84k**. The unwanted diastereomer was isomerized to the desired product by the procedure developed by Ishikawa. This last example shows how HWE reaction versatility can be useful to further improve the efficiency of an already powerful transformation.

4. CONCLUDING REMARKS

After more than 50 years, the HWE reaction has evolved as one of the most powerful methods for stereocontrolled C=C bond formation. Features like robustness of the reaction, wide functional group tolerance, availability of a large variety of phosphonate reagents, ease of introduction of the phosphonate moiety in advanced synthetic precursors and predictable stereochemical outcome have established the HWE reaction as a ubiquitous carbonyl olefination method.

Recent innovation in this field includes the development and applications of novel functionalized phosphonates and the inclusion of the HWE reaction as a step within sequential reactions. The former considerably expand, enrich and diversify the product scope of

the original method. The latter exploits the reliability and versatility of this much studied reaction, and has led to one-pot, MCR and tandem reactions many of which now constitute well established synthetic protocols. All these recent advances significantly broaden the scope of the original method beyond the classical C_2 building block paradigm and allow for an increasing number of applications of the reaction to challenging or complex synthetic targets, relevant organic compounds, synthetic intermediates and natural products.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

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ABBREVIATIONS

Boc	=	*tert*-butytloxycarbonyl
Cbz	=	benzyloxycarbonyl
DBU	=	1,8-Diazabicycloundec-7-ene
DBAD	=	dibenzyl azodicarboxylate
DCM	=	methylene chloride
DMP	=	Dess-Martin periodinane (1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one)
Dppf	=	1,1'-Bis(diphenylphosphino)ferrocene
EDC	=	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EWG	=	electron withdrawing group
F-TEPA	=	triethyl α–fluorophosphonoacetate.
KDA	=	Potassium diisopropylamide
KHMDS	=	potassium hexamethyldisilylamide
LHMDS	=	lithium hexamethyldisilylamide
NHMDS	=	sodium hexamethyldisilylamide
NHS	=	*N*-hydroxy succinimide
NPSP	=	*N*-(phenylseleno)phthalimide
Mes	=	mesitoate (2,4,6-trimethylbenzoate)
MTM	=	monomethoxytrityl
NMO	=	*N*-methylmorpholine-*N*-oxide
OBO	=	4-methyl-2,6,7-trioxa-bicyclo[2.2.2]octan-1-yl
PG	=	protecting group
PMB	=	4-methoxybenzyl
PMP	=	4-methoxyphenyl
POM	=	pivaloyloxymethyl
rt	=	room temperature
Selectfluor ™	=	1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane tetrafluoroborate
TBS	=	*tert*-butyldimethylsilyl
TEPA	=	triethylphosphonoacetate
TFE	=	2,2,2-Trifluoroethanol
TPAP	=	tetra-*n*-propylammonium perrhuthenate.
TMG	=	*N-N-N'-N'*-tetramethylguanidine

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