PHOSPHINE-CATALYZED ADDITIONS OF NUCLEOPHILES AND ELECTROPHILES TO α,β–UNSATURATED CARBONYL COMPOUNDS

Reported by Michael Scott Bultman November 4, 2004

INTRODUCTION

Organophosphorous compounds are becoming increasingly important in organic synthesis. Phosphines serve as precursors to phosphonium ylides in the Wittig reaction,[1] and as nucleophilic triggers in the Mitsunobu[2] and Staudinger[3] reactions. In these processes, the phosphine is stoichiometrically consumed and converted into a phosphine oxide. Phosphines are also commonly used as ligands for transition metal-catalyzed reactions, to modulate reactivity and stereocontrol.[4] On the other hand, the use of phosphines as nucleophilic catalysts for organic reactions has only gained attention in the last ten years. First reported by Rauhut and Currier in 1963,[5] phosphine catalysis has since been reinvestigated after the phosphine ligands in some transition-metal-catalyzed reactions were found to be better catalysts than the metal/phosphine complexes alone![6] Phosphines are well suited for catalyzing the addition of both nucleophiles and electrophiles to electron deficient alkenes, alkynes, and allenes. Activation of these α,β-unsaturated carbonyl systems with the phosphine enables the formation of new bonds at the α-, β-, and γ-positions. This report will highlight these different modes of addition to α,β-unsaturated carbonyl systems under phosphine catalysis that allow for the formation of a wide array of products from a single class of substrates.

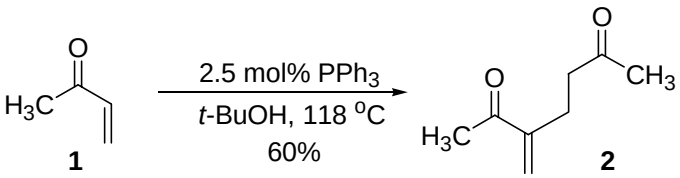
GENERAL REACTIVITY OF PHOSPHINES

Key characteristics required for successful nucleophilic catalysis lie in the balance of leaving group ability, nucleophilicity, and ease of ylid formation. Increasing leaving group ability can often be correlated with decreasing basicity. Whereas phosphines are less basic than amines (pK_a values: $HPEt_3^+$ (8.7), $HNEt_3^+$ (10.7) in H_2O), and therefore better leaving groups, they have strikingly different nucleophilic profiles. Tertiary phosphines are much stronger nucleophiles than corresponding amines. For example, the rate of the S_N2 substitution of C_2H_5I with Et_2PhP is more than 500 times faster than that of Et_2PhN.[7] Greater nucleophilicity is observed with electron-donating alkyl substituents than with aryl groups, resulting in an increased nucleophilic reactivity of trialkyl phosphines. Lastly, the ability to stabilize an adjacent carbanion to form an ylide is an important characteristic of phosphines. This unique combination of properties allows phosphines to act as strong nucleophiles for conjugate addition, stabilize high energy intermediates, and still possess the ability to serve as an efficient leaving group.

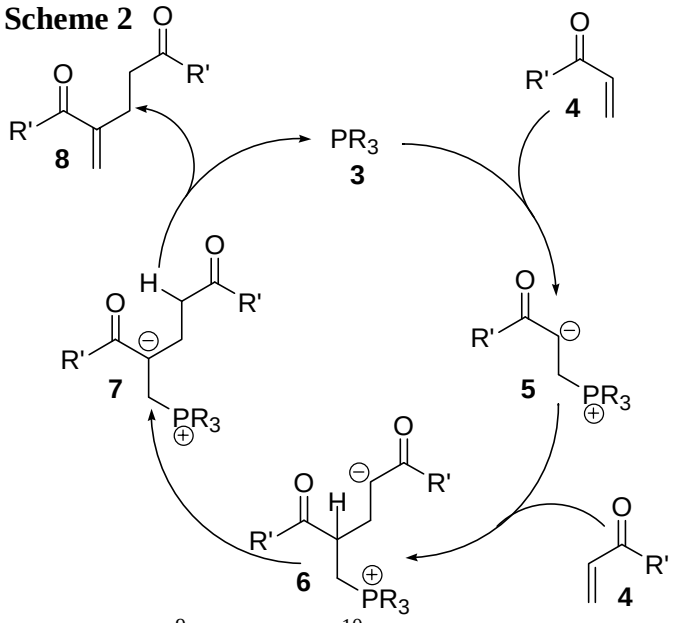
RAUHUT-CURRIER AND MORITA-BAYLIS-HILMAN REACTIONS

Formation of new bonds at the α-position of α,β-unsaturated carbonyl compounds using phosphine catalysis was first observed by Rauhut and Currier[5] during the course of their studies on the dimerization of activated olefins (Scheme 1). Later work by Morita, Baylis, and Hillman[8] expanded the scope of the reaction to include aldehydes as the electrophilic component. Unfortunately, long reaction times and limited substrate dependence precluded broad application of this method in synthesis.

Scheme 1



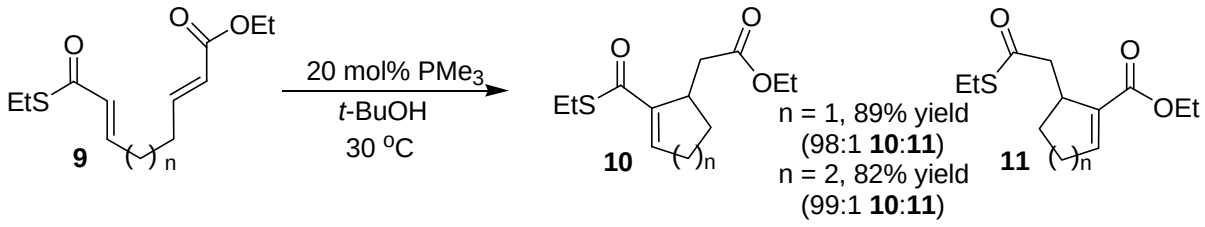
Scheme 2



As is the case with all reactions catalyzed by phosphines, the proposed catalytic cycle for the Rauhut-Currier reaction begins with the conjugate addition of phosphine **3** to enone **4** to provide β-phosphonium enolate **5** (Scheme 2). Subsequent conjugate addition of **5** to another molecule of enone **4** affords δ-phosphonium enolate **6**. Finally, a proton transfer provides β-phosphonium enolate **7**, which undergoes β-elimination to regenerate catalyst **3** and form the dimerized enone product **8**.

Krische[9] and Roush[10] have developed intramolecular variants of the Rauhut-Currier reaction, which eliminate the problem of homo-dimerization found in the coupling of different alkenes (Scheme 3). In cases where enones of similar electrophilicities are used, no selectivity is observed and mixtures are obtained. Instead, the use of enones with sufficiently different electrophilicity ensures the generation of a single constitutional isomer. As shown from the product ratio the catalyst favors addition to the (more electrophilic) α,β-unsaturated thioester. The (less electrophilic) α,β-unsaturated ester then serves as the conjugate acceptor for the ring-closing step, strongly favoring the production of **10**.[9]

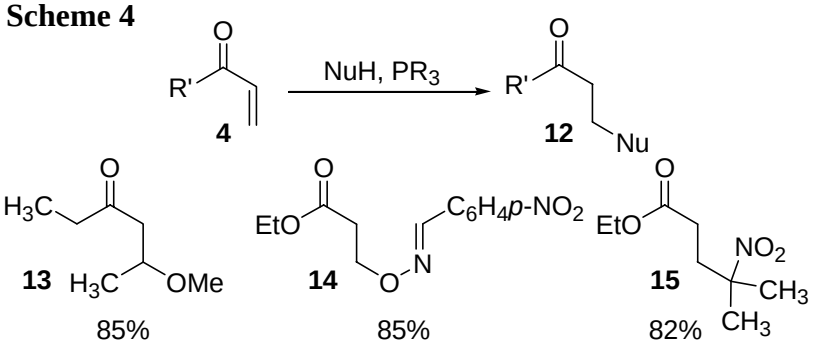
Scheme 3



CONJUGATE ADDITION TO ACTIVATED ALKENES AND ALKYNES

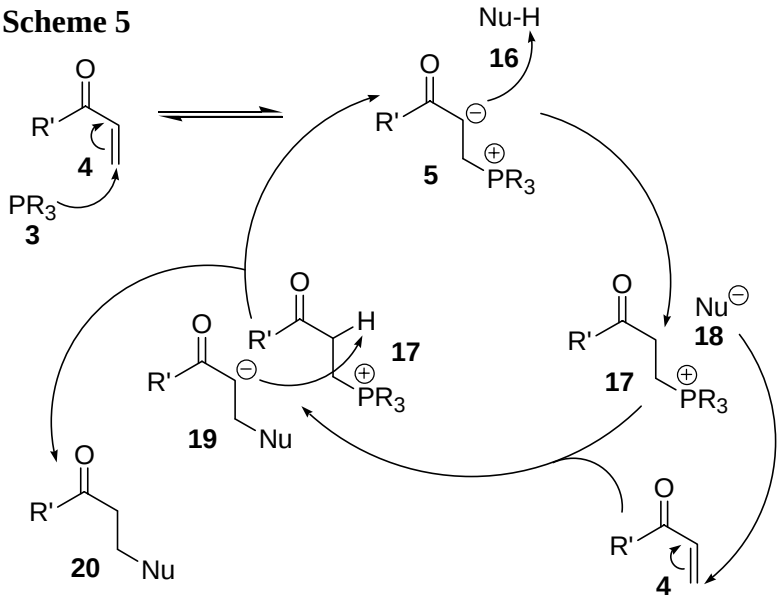
Phosphines are very effective catalysts for the addition of nucleophiles to α,β-unsaturated carbonyl compounds. Phosphines mediate the conjugate addition of nucleophiles such as alcohols,[11] oximes,[12] and carbon acids[7,13] to activated alkenes (Scheme 4). Whereas these reactions are generally catalyzed by a strong alkoxide base, the use of phosphines allows the addition to occur under much milder conditions.

Scheme 4



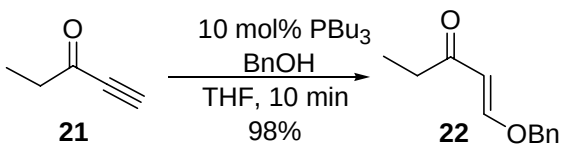
The mechanism for conjugate addition differs significantly from the Rauhut-Currier reaction in that the phosphine-generated β-phosphonium enolate **5** acts as a base to catalyze the addition of the nucleophile to enone **4** (Scheme 5). Addition of the phosphine **3** to enone **4**, generates β-phosphonium enolate **5**, which serves as the active catalyst by deprotonating pronucleophile **16** to generate β-phosphonium ketone **17**. The resulting activated nucleophile **18** then undergoes conjugate addition into another molecule of enone **4** to generate enolate **19**. Subsequent deprotonation of phosphonium ketone **17** then regenerates **5** and produces the β-substituted product **20**.

Scheme 5



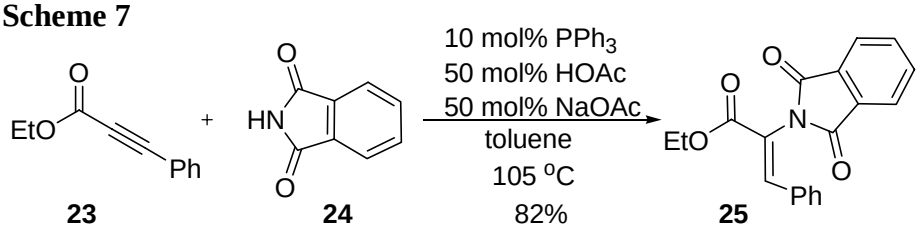
The analogous conjugate addition of alcohols activated to terminal alkynes has also been achieved. Inanaga described the addition of benzyl alcohol to ynones to form vinylogous benzyl esters in excellent yields and olefin selectivities (Scheme 6).[14] Carbon acids, saturated secondary and tertiary alcohols failed to add under similar conditions. These results indicate that nucleophiles with minimal steric hinderance are essential for successful addition. Not surprisingly, tributylphosphine is more effective than triphenylphosphine because of its increased nucleophilicity and reduced steric hindrance.

Scheme 6

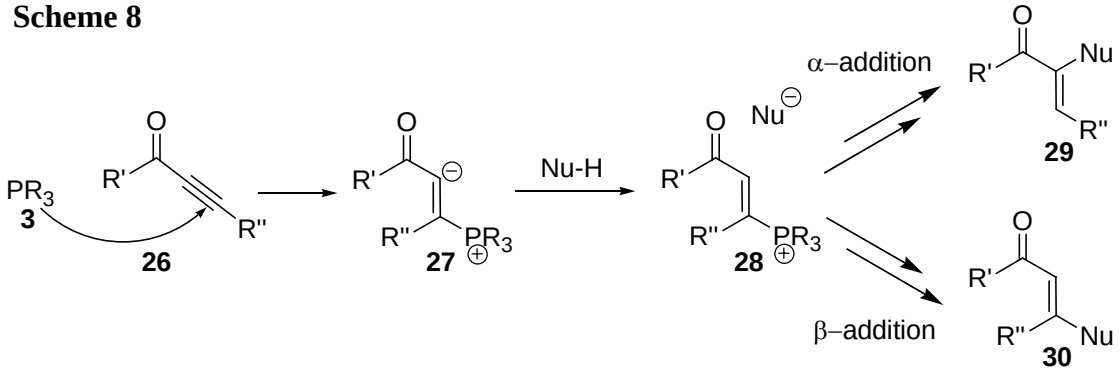


Under certain conditions with specific nucleophiles attack will take place at the *α-position* of an activated alkyne (Scheme 7).[15] The addition at both the a- and b-carbons of activated alkynes can be understood by the unified mechanism shown in Scheme 8. The conjugate addition of phosphine **3** to alkyne **26** followed by protonation with the pronucleophile (Nu-H) affords phosphonium salt **28**. This intermediate possesses two electrophilic centers; one at the β-position (from conjugation with the carbonyl group) and another at the α-position (from electrostatic activation by the phosphonium ion). Under buffered acidic conditions with weak nucleophiles, nucleophilic attack occurs at the α-position. Alternatively, attack occurs at the β-position under neutral conditions with strong alkoxide nucleophiles. Subsequent proton transfers and phosphine elimination afford the addition product **29** and **30** and regenerate the catalyst.

Scheme 7



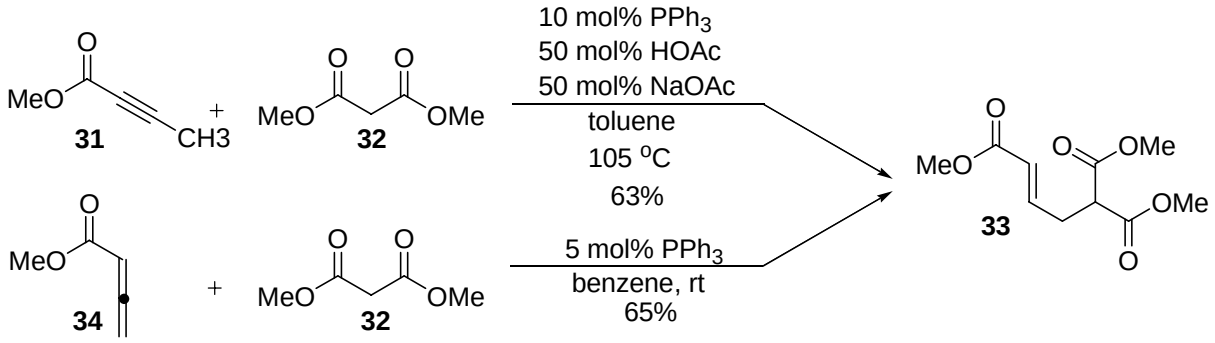
Scheme 8



γ-ADDITION AND ISOMERIZATION OF ACTIVATED ALKYNES AND ALLENES

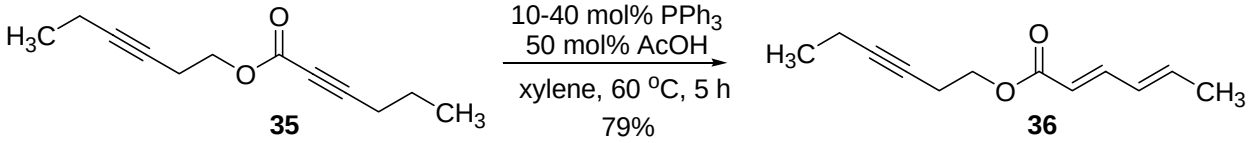
A novel mode of reactivity is available when activated alkynes bear acidic protons at the γ-position. This variant was first demonstrated by Trost[16] in the addition of carbon nucleophiles (Scheme 9). A contemporaneous report by Lu[17] employed activated allenes as the starting materials under milder conditions to create the same product **33**. This avenue is made possible by isomerization of electron deficient alkynes to allenes under the buffered acidic reaction conditions. In general, better yields are obtained with activated alkynes than with the corresponding allenes. Heteroatom nucleophiles (e.g. alcohols and imides), and intramolecular additions have also been employed.[18]

Scheme 9



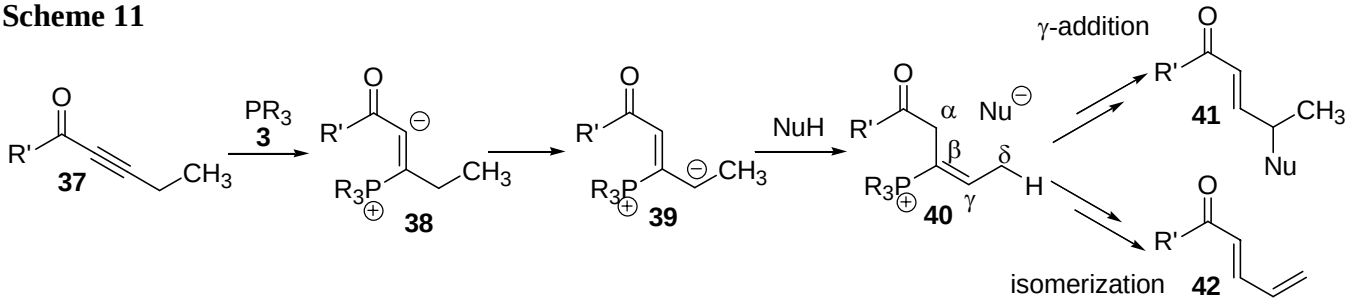
If hydrogens are present on the δ-position of the substrate, yet another mode of reactivity can be accessed. For example, in the absence of a nucleophile activated alkynoate **35** will isomerize to 2,4-dienoate **36** (Scheme 10). Trost,[6] Lu,[19a] and Rychnovsky[19b] have all used this method synthetically for the production of polyenes. As shown in Scheme 10, only electron deficient alkynes undergo isomerization under these conditions. Differentiation of activated alkynes of different electrophilicities and the use of activated allenes have also been explored under isomerization conditions.[6]

Scheme 10



A mechanism proposed for these competitive processes is shown in Scheme 11. After conjugate addition of phosphine **3** to the electron poor alkyne **37**, a proton transfer forms extended β-phosphonium enolate **39**. Protonation by the pronucleophile (Nu-H) results in phosphonium salt **40**, which is uniquely electrophilic at the γ-position. If the nucleophile is sufficiently strong and conditions allow, attack occurs at the γ-position; otherwise deprotonation at the δ-position predominates. Subsequent proton transfers and elimination of the phosphine affords the respective products **41** and **42** with regeneration of the catalyst.

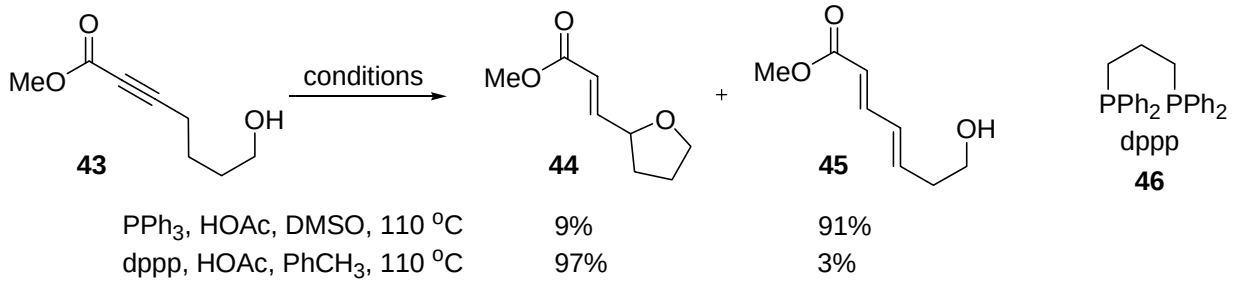
Scheme 11



In specific cases, the product distribution can be controlled to favor isomerization or the γ-addition product. For example, use of a polar coordinating solvents such as DMSO with triphenylphosphine as a catalyst strongly favors formation of the isomerized dienoate **45** (Scheme 12).[18b]

On the other hand, switching from a monodentate phosphine to the bidentate 1,3-bis-(diphenylphosphino)propane (dppp, **46**) strongly favors formation of the γ-addition product **44**. The bidentate phosphine is thought to act as a nucleophile and a general base catalyst in order to mediate formation of γ-addition product.

Scheme 12

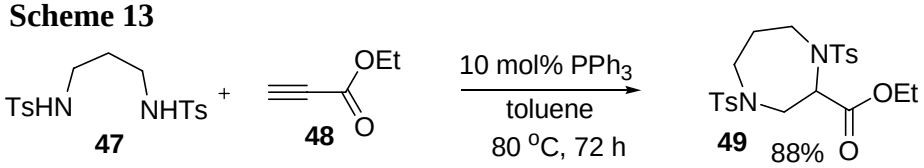


ANNULATIONS - Bifunctional Nucleophiles

The potential for addition to adjacent positions in α,β-unsaturated carbonyl compounds using phosphine catalysis allows for annulation reactions. Tethered bifunctional nucleophiles allow for nonconcerted annulations. Lu has constructed seven member rings, as well as dihydrofuran systems, with this method (Scheme 13).[20] The reaction proceeds through a phosphine-catalyzed nucleophilic addition to the α-position of the activated alkyne, followed by a separate phosphine-catalyzed conjugate addition with the second tethered nucleophile.

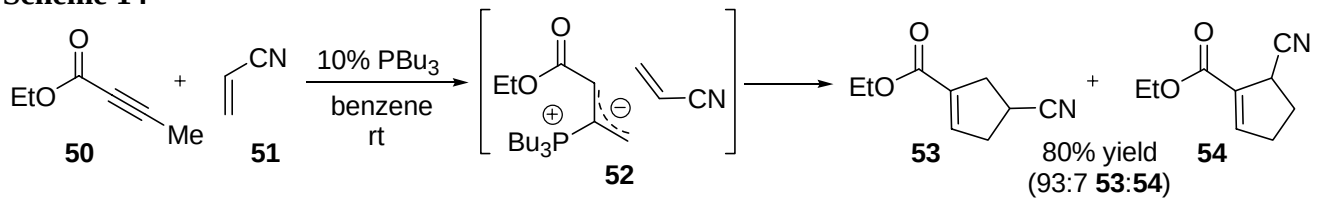
[3 + 2] Cycloadditions

Scheme 13



Electron deficient alkenes are used as dipolarophiles in phosphine-catalyzed [3+2] cycloadditions to form substituted cyclopentenes from allenes.[21] Poor regioselectivity in the cycloaddition limits the utility of this process. However, alkynes are found to give better yields and selectivities (Scheme 14). The proposed mechanism begins with conjugate addition of the phosphine to generate phosphonium enolate **52** followed by [3+2] cycloaddition with the activated alkene. Subsequent proton transfers allow for the elimination of the phosphine and formation of isomers **53** and **54**. The observation that diethyl fumarate and maleate react stereospefically to afford exclusively *trans* and *cis* cycloadducts, respectively, provides support for a concerted reaction.[21]

Scheme 14

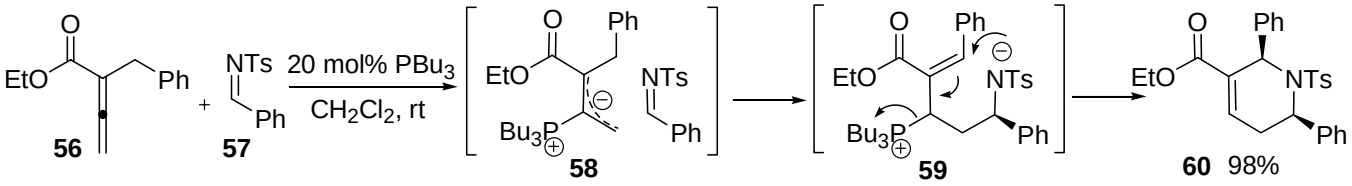


The scope of dipolarophiles has been expanded to include imines for the synthesis of pyrrole derivatives,[22a] exocyclic alkenes to form spirocycles.[22b] In addition, traditional phosphonium ylides have been explored as starting materials.[22c] Intramolecular and enantioselective variants of the [3+2] cycloaddition have also been devised.[23]

[4 + 2] Cycloadditions

Stepwise [4+2] cycloadditions of α-substituted allenoates with a wide variety of imines have been developed by Kwon.[24] This cyclization allows access to highly substituted tetrahydropyridines in excellent yields and diastereoselectivities (Scheme 15).

Scheme 15



Substitution at the α-position of 2,3-butadienoate **56** with an alkyl group blocks the α-attack and instead leads to γ-addition of the zwitterionic intermediate **58** into the dipolarophile **57**. Two proton transfers allow the new zwitterionic intermediate **59** to undergo 6-*endo* cyclization; expulsion of the catalyst generates tetrahydropyridine **60**.

CONCLUSION

Trialkyl and triaryl phosphines catalyze the formation of adducts from a variety of nucleophiles and electrophiles with α,β-unsaturated carbonyl compounds. Although some of the reactions are limited by substrate specificity and long reaction times, this class of reactions has become a useful tool in organic synthesis. This is illustrated by applications in the production of polymers[25] and the synthesis of natural products.[26] The versatility of this methodology relies in the ability to form a wide array of products from a single substrate class. Limitations result from the scope of reaction partners, and further work is needed to expand this field. Future work is also required to elucidate the factors that dictate product distribution and develop more effective enantioselective methods.

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