Nucleophilic Phosphine Organocatalysis

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Abstract: Phosphines have recently become popular choices as nucleophilic catalysts in organic synthesis. The unique reactivity of phosphines compared to amines has allowed the discovery of new nucleophilic addition reactions at the α- and γ-positions of unsaturated carbonyl compounds, as well as novel [3+2] and [4+2] cycloaddition reactions of activated alkynes and alkenes. The accessibility of chiral phosphines has rendered several of these transformations enantioselective and has made possible the kinetic resolution of racemic secondary alcohols by phosphine-catalyzed acylation. This mini-review presents recent advances in nucleophilic phosphine organocatalysis for carbon-carbon bond formation.

Keywords: catalysis; cycloaddition; Morita–Baylis–Hillman; phosphine; resolution; umpolung

1 Introduction

Organophosphorus compounds are widely used in synthetic organic chemistry. Some of the more common applications include the use of phosphonium ylides in the Wittig reaction, the use of phosphines in the Staudinger and Mitsunobu reactions, and the use of phosphines as ligands in transition metal-mediated processes.[1] During the 1960s, 70s, and 80s, phosphines behaving as nucleophilic catalysts were reported sporadically. However in the last ten or so years, reports of phosphines as nucleophilic catalysts have grown significantly. The purpose of this mini-review is to convey the scope of these applications of phosphines in nucleophilic catalysis.

Phosphines participate readily in Michael-type additions to activated alkenes and alkynes and will also undergo 1,2-addition to carbonyl groups. While triphenylphosphine and its derivatives have historically been most often used due to their low cost and air-stability, they are outperformed by the more air-sensitive trialkylphosphines in cases where greater nucleophilicity is required.

As is also the case with amines, the chemistry of the phosphines is centered on the non-bonded lone pair of electrons that may be used to form new bonds between phosphorus and a variety of electrophilic species. Both tertiary phosphines and amines are pyramidal, although the inversion is rapid in amines at room temperature whereas phosphines are configurationally stable above room temperature. Thus, acyclic phosphines retain chirality at phosphorus at room temperature. Phosphines are generally less basic and more nucleophilic than similarly substituted amines. Nucleophilicity is strongest in trialkylphosphines and decreases with aryl substitution.

The nucleophilicity of phosphines in their reaction with alkyl halides has been studied extensively and their rates measured by Henderson and Buckler.[2] Pearson calculated relative reactivity parameters (or Swain–Scott parameters; termed n) to provide a nucleophilicity scale.[3] When the rate of the reaction of nucleophiles with methyl iodide in methanol at 25 °C was used for comparison, n_{MeI} values were calculated. Thus $n_{MeI} = \log (k_Y/k_{MeOH})$ where k_Y is the rate of reaction of Y with MeI in methanol. Methyl iodide was chosen as it has a soft electrophilic center that reacts rapidly with soft polarizable nucleophiles. Table 1.1 lists n_{MeI} and pK_a (H_2O) values for various nucleophiles.

The data presented in Table 1.1 indicate that there is only slight correlation between the strength of the nucleophile in the reaction with MeI and its basicity. While triphenylphosphine was among the weakest nucleophiles examined, the trialkylphosphines exhibit strong nucleophilicity, being about 100-fold more nucleophilic than triethylamine. Yet triethylamine is 100-fold more basic

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Table 1.1. Nucleophilicity and basicity properties of some nucleophiles.

Nucleophile	n_{MeI}	pK_a (H_2O)	Nucelophile	n_{MeI}	pK_a (H_2O)
PhS^-	9.9	2.9	SEt_2	5.3	−5.3
PEt_3	8.7	8.7	pyridine	5.2	5.2
PBu_3	8.7	8.4	$P(OMe)_3$	5.2	2.6
I^-	7.4	−10.7	imidazole	5.0	7.1
$AsEt_3$	6.9	<2.6	$AsPh_3$	4.8	–
CN^-	6.7	9.3	BzO^-	4.5	4.2
NEt_3	6.7	10.7	Cl^-	4.4	−5.7
MeO^-	6.3	15.7	AcO^-	4.3	4.8
Br^-	5.8	−7.7	F^-	2.7	3.5
PhSH	5.7	–	PPh_3	1.3	2.7
NH_3	5.5	9.3	MeOH	0.0	1.7

than the trialkylphosphines; this non-linear relationship is likely due to the greater polarizability of phosphines.[4] However, it is important that nucleophilic scales be considered only in the context of how they were generated; use of electrophiles other than methyl iodide, such as hard electrophiles, may give different relationships.[5]

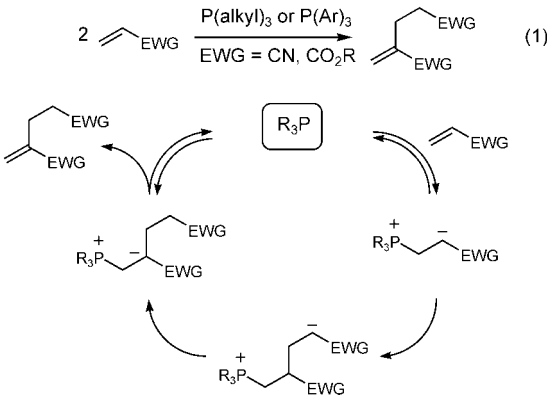
Finally, asymmetric organocatalysis promises to be a powerful tool in organic synthesis.[6] Chiral phosphines are expected to play a significant role in this emerging field in that the phosphorus center is capable of behaving as a nucleophile as well as a source stereochemical information.

2 The Rauhut–Currier and Morita–Baylis–Hillman Reactions

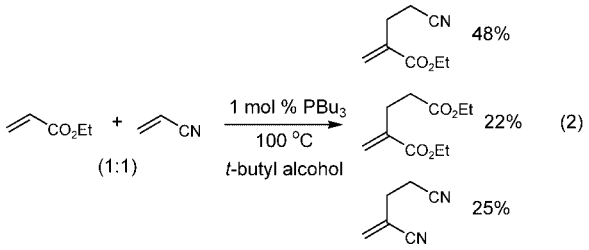
In 1963 Rauhut and Currier disclosed a patent describing a phosphine-catalyzed dimerization of activated alkenes [Eq. (1), Scheme 2.1].[7] This transformation was independently investigated by McClure[8] and Baizer and Anderson,[9] and is believed to involve a reversible phosphine conjugate addition to the activated alkene, followed by a Michael reaction of the enolate with the second activated alkene. A prototropic shift followed by an elimination process forms the dimer and releases the phosphine. Subsequently, in 1970, McClure reported[10] the first cross-coupling reaction between ethyl acrylate and acrylonitrile (Scheme 2.2). Only a single cross-coupled product, 2-ethoxycarbonyl-4-cyano-1-butene, was isolated in 48% yield; products of dimerization of both reactants were formed in 22–25% yield.

A number of years passed with little activity reported on the phosphine-catalyzed Rauhut–Currier reaction.[11] Several authors did report a tertiary amine-catalyzed variant of the homocoupling process,[12] however the lack of control in the cross-coupling reaction remained a problem. Recently, the groups of Krische and Roush addressed this through an *intramolecular* process, in which the activated alkenes are tethered by a 2- or 3-atom connecting chain (Scheme 2.3).[13] Symmetric bis(enones) cyclized efficiently in the presence of a phosphine catalyst [Eq. (3)], and certain unsymmetric electronically differentiated bis(enones) [Eqs. (4) and (5)] underwent chemoselective addition of the more electrophilic alkene onto the less electrophilic alkene. The available data suggest that the kinetic phosphine Michael adducts were efficiently trapped *via* cyclization to cyclopentene derivatives. Enone-enoate [Eq. (6)] and enal-enoate [Eq. (7)] combinations cyclized with high chemoselectivity, with the more electrophilic α,β-unsaturated system serving as the "initiator" of the cyclization.

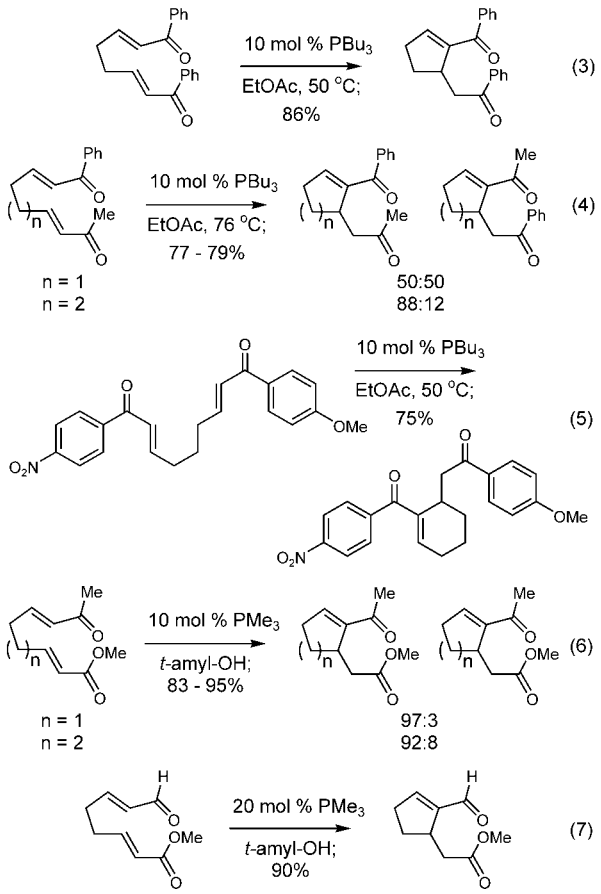
It is noteworthy that phosphines have been far superior to amine nucleophiles such as DABCO, DBU, Et_2NH and DMAP in the intramolecular Rauhut–Currier reaction, perhaps due to their softer character being better



Scheme 2.1. The Rauhut–Currier dimerization of activated alkenes.



Scheme 2.2. Crossed Rauhut–Currier reaction.



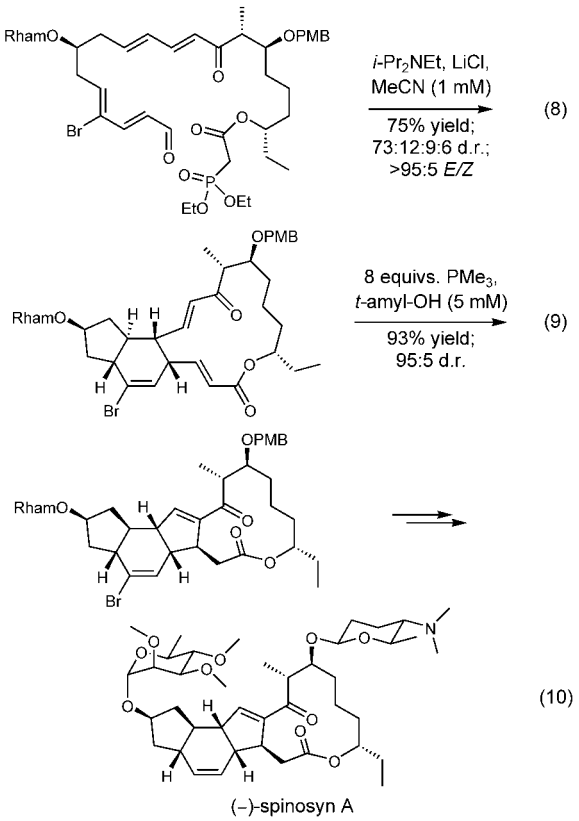
Scheme 2.3. Intramolecular Rauhut–Currier reactions.

suited for the soft activated alkene substrate. In addition, triphenylphosphine was ineffective, while tricyclohexylphosphine generally gave low conversion. The smaller phosphines, tributylphosphine and particularly trimethylphosphine have proven to be optimal. Self-condensation of reactive enal-enoate substrates could be suppressed by lowering the concentration from 0.1 M to 0.01 M, and reactions performed in protic solvents were faster than those in polar aprotic solvents.

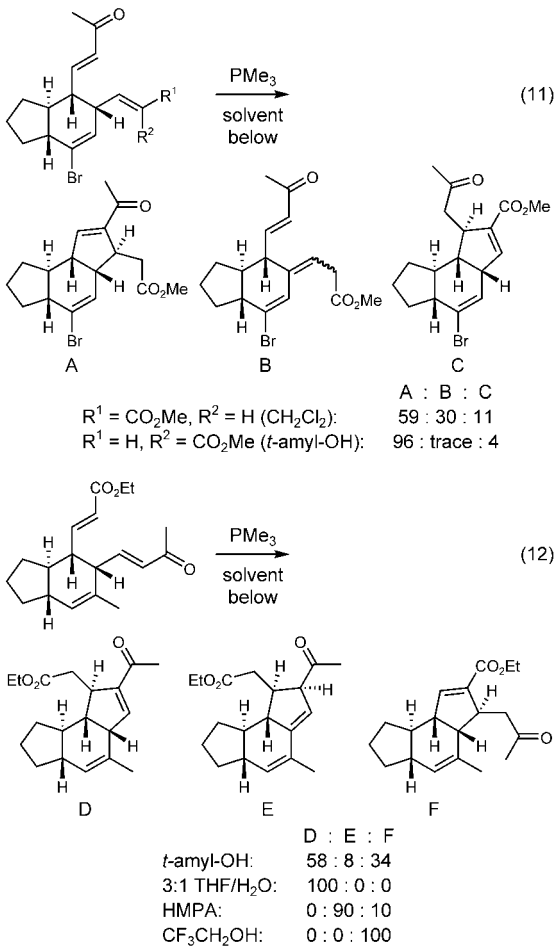
Recently a transannular Rauhut–Currier reaction was employed by Roush, Mergott and Frank in their total synthesis of (−)-spinosyn A (Scheme 2.4).[14] An intramolecular Horner–Wadsworth–Emmons reaction [Eq. (8)] of the indicated phosphonate ester was followed by a spontaneous transannular Diels–Alder reaction which favored the desired *endo* cyclization product with 76:12:9:6 diastereoselectivity. Ring contraction *via* transannular Rauhut–Currier cyclization using PMe_3 in *tert*-amyl alcohol proceeded with excellent 95:5 diastereoselectivity at the newly formed stereocenter [Eq. (9)].

Roush and coworkers also reported several noteworthy observations with trimethylphosphine-mediated intramolecular Rauhut–Currier reactions toward various *as*-indacene ring systems (Scheme 2.5).[15] Attempted cyclization of a bicyclic enone-enoate precursor with an (*E*)-enoate olefin geometry [Eq. (11)] gave a 2:1 mixture of the desired cyclization product (A) along with substantial quantities of an olefin migration product (B). However use of a substrate with a (*Z*)-enoate olefin geometry virtually shut down the olefin migration. It was suggested that the (*Z*)-olefin experiences greater allylic strain with the bicycle, restricting orbital alignment between the enoate and the γ-hydrogen; thereby suppressing γ-deprotonation which led to the migration product. Cyclization of another bicyclic enone-enoate precursor [Eq. (12)] was found to be highly solvent-dependent. Using 3:1 THF/H_2O as the reaction solvent an efficient enone cyclization onto enoate (D) was observed, while in CF_3CH_2OH the opposite mode of cyclization was observed. Then in HMPA, an olefin migration product (E) was isolated as the major product.

The zwitterionic phosphonium Michael adducts can be trapped with other electrophiles such as aldehydes. The Morita–Baylis–Hillman reaction is an atom economical coupling of an activated alkene and an aldehyde in the presence of a nucleophilic catalyst (Scheme 2.6). The reaction was first reported by Morita and coworkers[16] in 1968 and by Baylis and Hillman in 1972.[17] The nucleophilic catalyst employed by Morita was tricyclohexylphosphine, while Baylis and Hillman used tertiary amines such as DABCO. Activated alkenes include acrylic esters, acrylonitrile, vinyl ketones, phenyl vinyl



Scheme 2.4. Application to a total synthesis of spinosyn A.



Scheme 2.5. Synthesis of *as*-indacene ring systems.

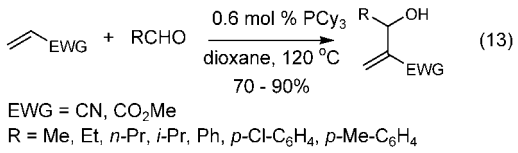
sulfone, phenyl vinyl sulfonate ester, vinyl phosphonate and acrolein. β-Substituted alkenes required more forcing conditions due to the slow addition of the phosphine catalyst. A variety of coupling partners such as aliphatic, aromatic and α,β-unsaturated aldehydes have been successfully employed.

Unfortunately, applications of the Morita–Baylis–Hillman reaction in complex synthetic problems have been limited by low rates and conversions as well as by highly substrate-dependent yields. The rate-determining step is typically the bimolecular coupling of the zwitterionic intermediate and the aldehyde.[18] Because of this the Morita–Baylis–Hillman reaction remained relatively undeveloped for many years, despite its obvious synthetic potential. In the 1980s research on the tertiary amine-catalyzed variant escalated.[19] Although tertiary amines are cheaper and less toxic than phosphines, the latter sometimes give higher yields in shorter reaction times. The phosphine-catalyzed variant was explored only sporadically, with an improvement in reaction efficiency reported by Kawanisi using the cocatalysts tributylphosphine and triethylaluminum in dichloromethane.[20]

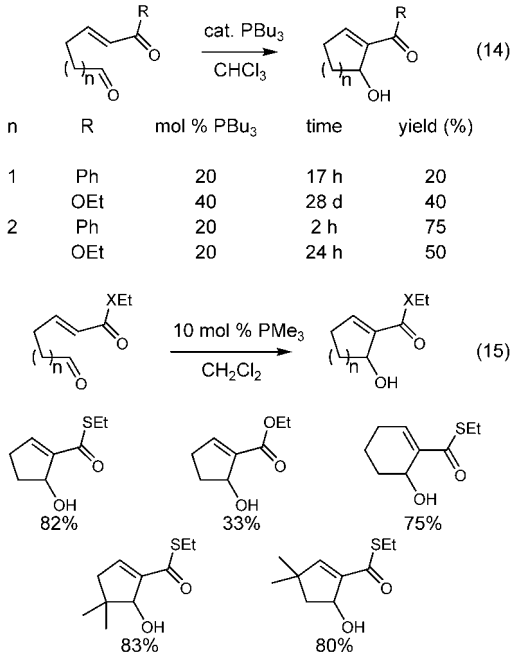
The intramolecular variant of the Morita–Baylis–Hillman reaction was reported first by Frater in 1992[21] and investigated further by Murphy[22] who reported enone cyclization onto an aldehyde to give five- and six-membered rings [Eq. (14), Scheme 2.7]. While tributylphosphine proved to be the optimal catalyst for six-membered ring formation, only low yields could be obtained for five-membered ring formation. Keck[23] observed slow cyclization of unsaturated esters using trimethylphospine [Eq. (15)], however unsaturated thiol esters cyclized efficiently giving both cyclopentene and cyclohexene derivatives. Enolizable aldehydes were more prone to side reactions, such as bimolecular condensation, and cyclizations are sensitive to small variations in experimental conditions.

Several asymmetric versions of the Morita–Baylis–Hillman reaction have recently emerged.[24] The first intermolecular application of a chiral phosphine catalyst was reported by Soai in 1998, using 20 mol % BINAP to catalyze the coupling of pyrimidine-5-carboxaldehyde and methyl acrylate with 44% ee obtained in chloroform as the solvent.[25] Zhang prepared a chiral phospholane from D-mannitol which catalyzed the coupling of 4-pyridinecarboxaldehyde and methyl acrylate, although in low (17%) enantioselectivity.[26]

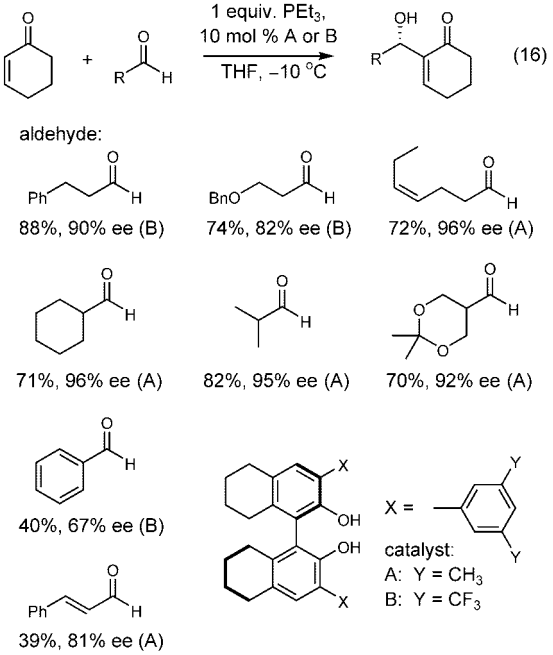
In 2000, Ikegami reported that phenol or BINOL (20 mol %) serve as co-catalysts with tributylphosphine



Scheme 2.6. Discovery of the Morita–Baylis–Hillman reaction, Morita (1968).



Scheme 2.7. Intramolecular Morita–Baylis–Hillman reaction.



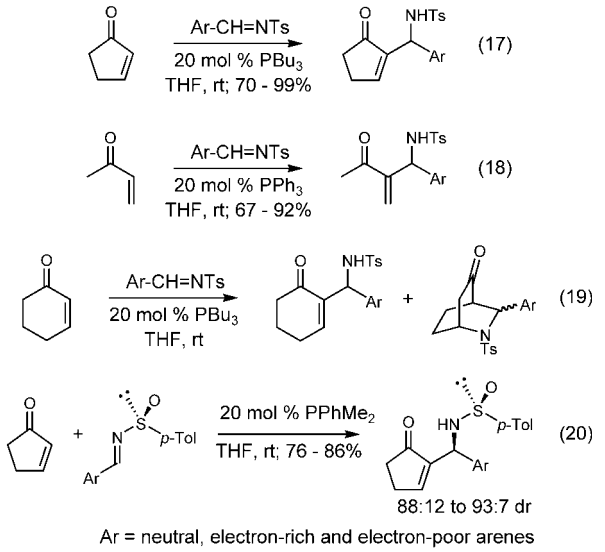
Scheme 2.8. A catalytic asymmetric Morita–Baylis–Hillman reaction.

(20 mol %) in the coupling of cyclic enones and aliphatic aldehydes using THF as the solvent.[27] The mild Brønsted acid additive improved yields from 23% to near quantitative. While optically active (*R*)-BINOL failed to induce enantioselectivity in the reaction of hydrocinnamaldehyde and 2-cyclopentenone, a calcium Lewis acid cocatalyst [Ca^{+2}-(*R*)-BINOL, 16 mol %] with PBu_3 (10 mol %) gave the desired Morita–Baylis–Hillman adduct in 62% yield and 56% ee.

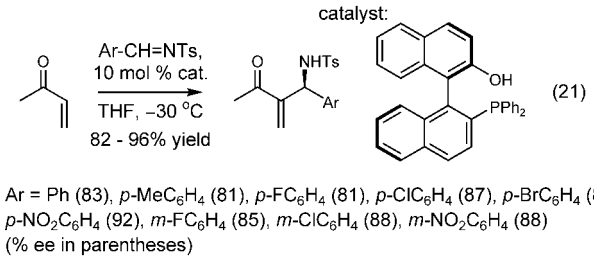
Recently Schaus and coworkers reported the application of partially saturated BINOL derivatives substituted at the 3/3′ positions as cocatalysts in the coupling of 2-cyclohexenone and various aldehydes in the presence of triethylphosphine [Eq. (16), Scheme 2.8].[28] Good yields and good to excellent enantioselectivities (67–96% ee) were obtained with several aldehydes, with aliphatic aldehydes giving higher selectivity than unsaturated or aromatic aldehydes. Presumably the Brønsted acid stabilizes the enolate formed from the Michael addition of the phosphine and then remains hydrogen-bound for the subsequent enantio-determining addition to the aldehyde. Catalysts with two hydrogen bonding partners are necessary as the mono-*O*-methylated catalysts gave low conversion and $<4\%$ ee.

A modification to the traditional Morita–Baylis–Hillman reaction was developed by Shi and coworkers wherein aldehydes are replaced by more reactive *N*-arylidene-4-methylbenzenesulfonamides, giving α-alkylidene-β-amino carbonyl compounds (Scheme 2.9).[29] 2-Cyclopentenone [Eq. (17)] or methyl vinyl ketone [Eq. (18)] reacted in the presence of a phosphine catalyst and activated imines deriving from a variety of electronically-rich and electronically-deficient aromatic aldehydes to give the coupling products in good yield. Phosphine catalysts were generally superior to tertiary amine catalysts for these reactions. However similar reaction with 2-cyclohexenone [Eq. (19)] gave a mixture of products, the Morita–Baylis–Hillman product, and two diastereomeric bicyclic products resulting from initial aldol reaction at C-6 followed by intramolecular Michael addition of the sulfonamide. Morita–Baylis–Hillman reactions with chiral non-racemic *N*-sulfinimines [Eq. (20)] gave a *ca.* 9:1 diastereomeric ratio of allylic amines using dimethylphenylphosphine as the catalyst. Use of PBu_3 gave only a 3:1 diastereomeric ratio, while PPh_2Me or DABCO did not catalyze the reaction.[30]

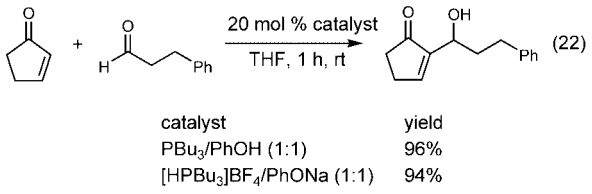
Following the discovery that the aza-Morita–Baylis–Hillman reaction of methyl vinyl ketone with *N*-tosylbenzaldimines can be catalyzed by triphenylphosphine, Shi and coworkers sought a chiral phosphine for an asymmetric version of this reaction. They found that the 2′-diphenylphosphanyl-[1,1′]binaphthalenyl-2-ol catalyst shown in Scheme 2.10 catalyzed the reaction with a variety of *N*-tosylbenzaldimines at $-30\,^{\circ}C$ with good to excellent enantiomeric excess (81–92% ee).[31] The reaction was much slower with acrylate esters, requiring a reaction temperature of 40 °C in CH_2Cl_2 to af-



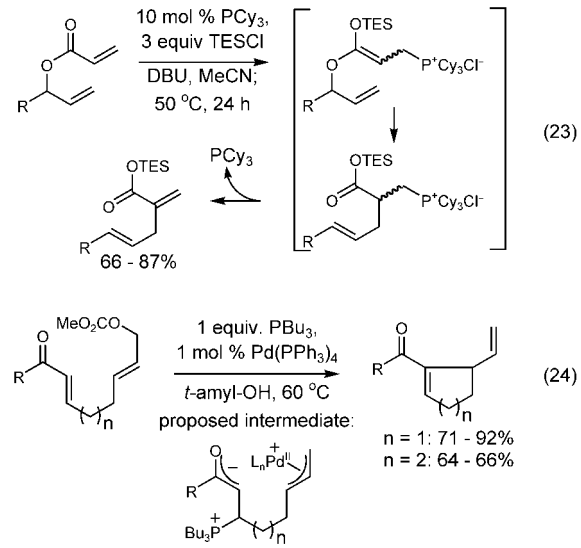
Scheme 2.9. Morita–Baylis–Hillman reactions with *N*-sulfinimines.



Scheme 2.10. Catalytic asymmetric aza-Morita–Baylis–Hillman reaction.



Scheme 2.11. Morita–Baylis–Hillman reaction with an air-stable trialkylphosphonium salt.



Scheme 2.12. Related transformations.

ford the aza-Morita–Baylis–Hillman products in moderate enantiomeric excess (52–77% ee). The authors speculate that the catalyst is bifunctional with the phosphine behaving as a nucleophilic Lewis base and the phenol behaving as a Brønsted acid, with intramolecular hydrogen bonding between the phenol and the imine nitrogen in the Mannich-type transition state.

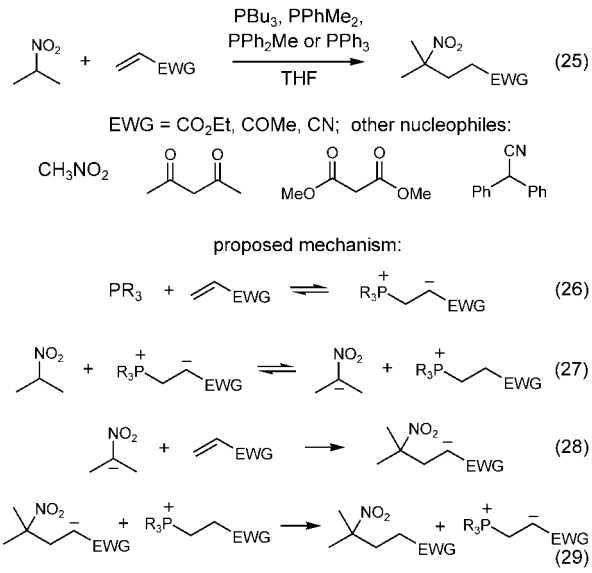
The growing interest in trialkylphosphines as nucleophilic catalysts is evidence of their utility and the enhanced reactivity they possess *versus* their triarylphosphine or trialkylamine counterparts. Yet trialkylphosphines are air-sensitive reagents that must be handled with care. Fu and coworkers suggest protecting these phosphines as their conjugate acids, rendering them air-stable, and then releasing them *in situ* by treatment with an appropriate base. Fu reports that $[HPBu_3]BF_4$ is stable and can be stored in air for several months without any detectable deterioration.[32] Furthermore, it was shown to be equally effective as the free phosphine in catalyzing the Morita–Baylis–Hillman reaction (Scheme 2.11).

Several variants of the Rahut–Currier and Morita–Baylis–Hillman reactions warrant inclusion in this section. In 1978, Evans and coworkers reported the phosphoniosilylation of α,β-unsaturated carbonyl compounds by treatment with triphenylphosphine in the presence of silylating agents.[33] Based on this precedent, Inanga proposed the generation of a phosphonium silyl ketene acetal from allylic acrylates which could then undergo an Ireland rearrangement after deprotonation by a base [Eq. (23), Scheme 2.12]. The process proceeded efficiently and was catalytic in tricyclohexylphosphine, giving α-methylene-γ,δ-unsaturated carboxylic acids.[34] Note that silylation of the intermediate phosphonium enolate is necessary.

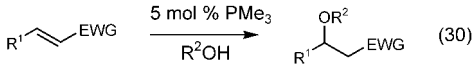
Another interesting variant recently reported by Krische involves an allylic carbonate employed as a latent electrophile which was activated by palladium-π-allyl formation in a two-component catalyst system [Eq. (24), Scheme 2.12].[35] The π-allyl complex underwent intramolecular nucleophilic attack by a zwitterionic phosphonium enolate to form five or six-membered rings, followed by elimination of the phosphine to regenerate the enone. Enoates were unreactive in this system. This remarkable transformation combines the nucleophilic features of the Morita–Baylis–Hillman reaction and the electrophilic features of the Trost–Tsuji π-allyl-palladium intermediates.

3 Michael Addition Reactions of Activated Alkenes and Alkynes

The Michael addition of carbon acids to activated alkenes is usually catalyzed by strong bases such as hydroxide or alkoxide ions.[36] The mechanism generally entails deprotonation of the carbon acid by the base, followed by addition of the stabilized carbanion to the activated alkene. In 1973 White and Baizer of Monsanto Co. reported a phosphine-catalyzed Michael addition of 2-nitropropane to ethyl acrylate, acetonitrile and methyl vinyl ketone [Eq. (25), Scheme 3.1).[37] The weak basicity of the catalysts, PBu_3, PPh_3, $PPhMe_2$ and PPh_2Me, suggests a mechanism in which the phosphines behave as nucleophiles rather than as bases. It is reasonable that the zwitterionic phosphine-alkene adduct [Eq. (26)] behaves as the general base, deprotonating the carbon acid [Eq. (27)] which then undergoes Michael addition to another activated alkene [Eq. (28)]. Similar reactions were reported with other carbon acids as well [e.g., CH_3NO_2, $CH_2(CO_2Me)_2$, $CH_2(COMe)_2$, Ph_2CHCN]. Echavarren and coworkers observed related phosphine catalysis in studies using $RuH_2(PPh_3)_4$ as a catalyst in the Michael addition of carbon nucleophiles such as malonates, cyanoacetates and β-ketoesters to α,β-unsaturated aldehydes, ketones and esters.[38]



Scheme 3.1. Phosphine-catalyzed Michael addition of carbon acids.



EWG	R^1	R^2OH	yield (%)
COEt	Me	H_2O	77
		MeOH	85
COMe	H	PhOH	59
		MeOH	56
CO_2Me	Me	MeOH	71
CN	H	MeOH	79

Scheme 3.2. Phosphine-catalyzed Michael addition of alcohols to activated alkenes.

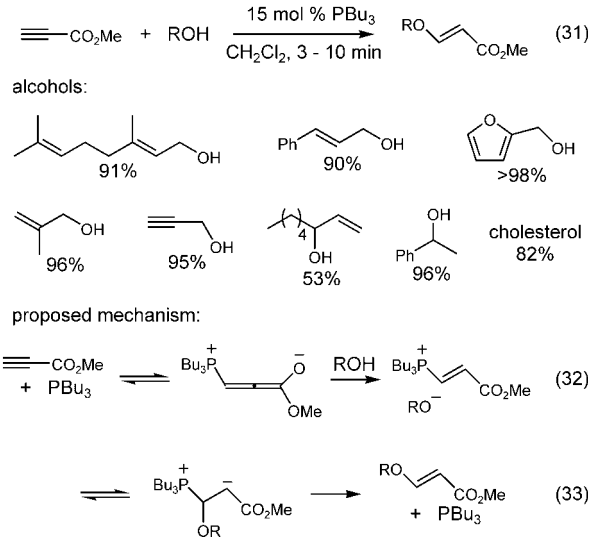
Recently, Toste and Bergman reported a phosphine-catalyzed Michael addition of alcohols and water to activated alkenes [Eq. (30)].[39] The mechanism likely involves again the zwitterionic phosphonium Michael adduct of Eq. (26) behaving as a general base to deprotonate the alcohol or water; the alkoxide or hydroxide then undergoes Michael addition to the activated alkene. Investigation of the reaction by ^{31}P NMR spectroscopy revealed that the resting state of the catalyst is in fact the β-phosphonium ketone alkoxide ion pair. It is noteworthy that trialkylphosphines catalyze the transformation while tertiary amines such as DABCO and triethylamine did not; this is consistent with the phosphine behaving as a nucleophile and not as a base.

Phosphines also catalyze the Michael addition of alcohols to activated alkynes, but through a different mechanism. In 1993 Inanaga and coworkers reported that tributylphosphine catalyzes the addition of primary and secondary alcohols to α,β-unsaturated alkynoates in good to excellent yield [Eq. (31), Scheme 3.3].[40] Again the phosphine adds to the alkynoate and the intermediate zwitterion deprotonates the alcohol [Eq. (32)], however the alkoxide then adds in a Michael fashion into the same phosphonium salt [Eq. (33)] and the phosphine is then regenerated. Tributylphosphine generally rendered exclusive (*E*)-stereoselectivity, while with triphenylphosphine the (*E*)/(*Z*)-selectivity was only 5:1.

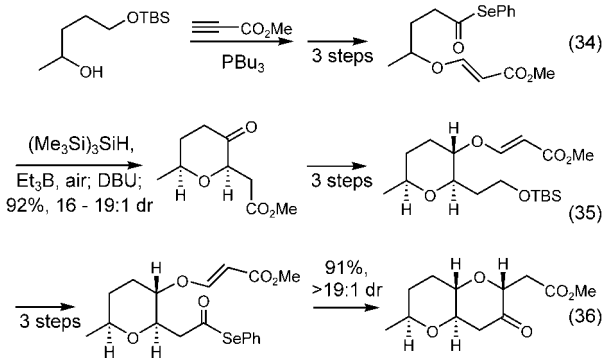
This process has become quite valuable in synthetic studies toward the polycyclic ether family of natural products. For example, in 1996, Evans reported a diastereoselective iterative acyl radical cyclization sequence to prepare fused pyran structures (Scheme 3.4).[41] Treatment of the secondary alcohols with methyl propiolate and PBu_3 gave vinylogous carbonates [Eq. (34)]. Further manipulation led to the acyl selenide substrates for the radical cyclization. Later Evans used a similar strategy to synthesize (−)-kumausallene.[42]

When alkynoates are treated with thiols in the presence of a phosphine catalyst, two Michael additions occur to give dithioacetals [Eq. (37), Scheme 3.5].[43] Studies indicate that the second intermolecular thiol Michael addition occurs about 1000-fold slower than the first. When 1,3-propanedithiol is used, cyclic dithioacetals are isolated [Eq. (38)]. Another application is the tributylphosphine-catalyzed reaction of diols with bis(ynones), reported by Endo and coworkers for the synthesis of certain polymers.[44]

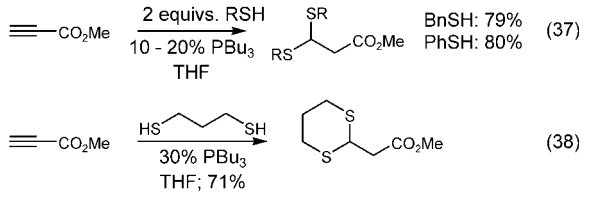
Recently, Yavari reported a new and efficient synthesis of coumarins *via* the triphenylphosphine-mediated reaction of phenols and dimethyl acetylenedicarboxylate [Eq. (39), Scheme 3.6].[45] The phenol likely proto-



Scheme 3.3. Conjugate addition of alcohols to methyl propiolate.

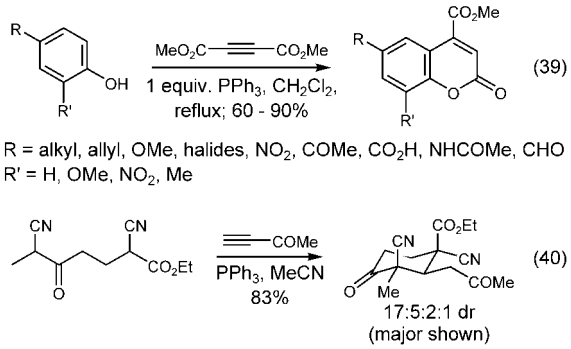


Scheme 3.4. Radical acyl cyclization reaction.



Scheme 3.5. Synthesis of dithioacetals from propiolate esters.

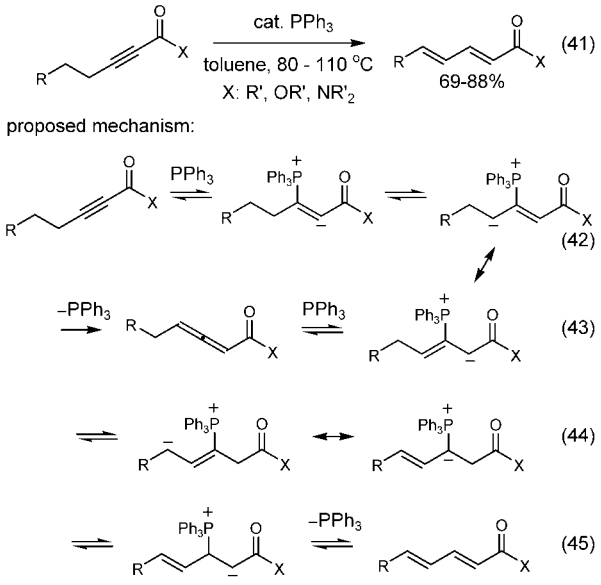
nates the zwitterionic phosphonium-alkyne adduct, and the phenoxide then undergoes electrophilic aromatic Michael addition at the *ortho*-position. Similarly, Grossman reported two carbon acids connected by a tether undergoing two successive phosphine-catalyzed Michael reactions to 3-butyn-2-one [Eq. (40)].[46] Initial attempts employing NaH, Et_3N, Cs_2CO_3, *i*-Pr_2NEt and pyridine all failed, but with 10 mol % PPh_3 in MeCN the double Michael reaction occurred smoothly.



Scheme 3.6. Additional phosphine-catalyzed Michael additions of carbon nucleophiles.

4 Isomerization of Conjugated Alkynes to Conjugated Dienes

In 1988, Lu, Trost and Inoue independently reported the isomerization of alkynones to dienones by ruthenium and palladium complexes.[47] Further study showed that addition of excess phosphine as the ligand improved the reaction efficiency. In fact, Trost reported in 1992 that triphenylphosphine alone catalyzes the transformation when warmed to 80–110 °C in toluene [Eq. (41), Scheme 4.1]![48] Unactivated alkynes were unreactive and the reaction does not proceed under tertiary amine catalysis. The relative rate of the isomerization coincides with the electron-deficiency of the alkyne, i.e., acetylenic ketones react faster than esters, which in turn isomerize faster then amides. Acetic acid can be added as a cocatalyst to accelerate slow-reacting substrates. Alternatively, Rychnovsky and coworkers suggest the use of phenol as a cocatalyst for sensitive substrates.[49]



Scheme 4.1. Isomerization of conjugated alkynes to conjugate dienes.

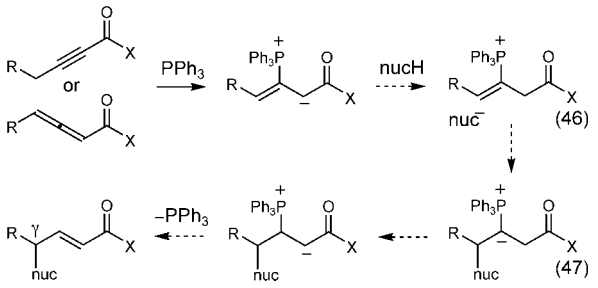
Trost suggests that the internal redox reaction proceeds through a series of prototropic shifts *via* an allenic intermediate. Attempts to detect the intermediates in Eqs. (42) – (45) were unsuccessful, however Trost did demonstrate that allenic esters do indeed isomerize to the corresponding dienoate at a much faster rate than alkynyl esters, and so are viable reaction intermediates. The general mechanism[50] outlined in Scheme 4.1 details the formation of an allene intermediate which then undergoes nucleophilic addition of triphenylphosphine [eq. (43)]. Two prototropic shifts [Eq. (44)] allow for an elimination to give the diene. The high selectivity of this simple procedure makes it a practical approach for the synthesis of conjugated diene systems.

5 Nucleophilic Addition to the α- and γ-Positions of Activated Alkynes and Allenes

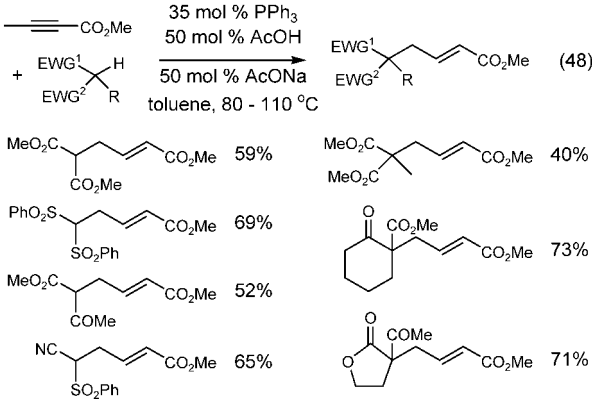
The proposed mechanism for the isomerization of conjugated alkynes to conjugated dienes outlined in Scheme 4.1 suggests the potential for the interception of vinylphosphonium intermediates with appropriate nucleophiles. For example, Scheme 5.1 details a γ-addition sequence which formally constitutes an umpolung process; normally the γ-position of an enone when deprotonated reacts with electrophiles. Phosphine addition to an alkynyl or allenyl carbonyl compound generates a vinylphosphonium salt, which may then deprotonate a pronucleophile (nucH) [Eq. (46)]. Subsequent nucleophilic addition of the conjugate base occurs at the γ-position to give an ylide. A prototropic shift allows for elimination and recycling of the phosphine [Eq. (47)].

In 1994, Trost demonstrated this concept by using alkynyl substrates that are incapable of isomerization to the diene.[51] A variety of carbon acids with $pK_a < 16$ were treated with alkynyl ketones, esters and amides using triphenylphosphine as the catalyst to give γ-alkylated products (Scheme 5.2). An acetic acid-sodium acetate buffer assists with the proton shuffling while maintaining a pH range in which the carbon acids can behave as nucleophiles.

Oxygen nucleophiles have also been utilized in the γ-addition reaction. Generally alcohols are much poorer Michael donors than carbon nucleophiles, however in this phosphine-catalyzed isomerization-addition reaction they are in fact superior [Eq. (49), Scheme 5.3]. Primary alcohols react faster than secondary alcohols.[52] This led Trost and coworkers to consider if an intramolecular γ-addition of an alcohol tethered to the phosphonium intermediate deriving from an alkynoate would proceed faster than isomerization to the diene [Eq. (50)]. An encouraging 1 : 1 ratio of γ-addition to diene formation was obtained using methyl 7-hydroxy-2-heptynoate as a substrate. Switching from toluene to



Scheme 5.1. Nucleophilic interception of a phosphonium intermediate.

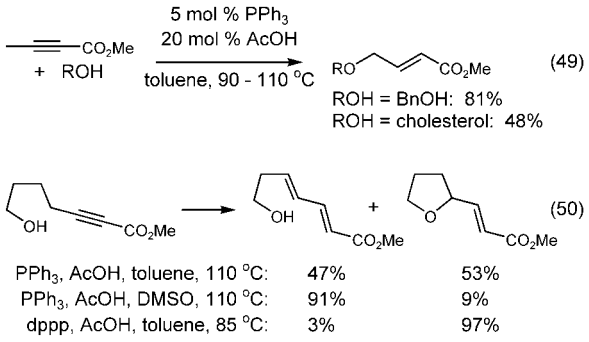


Scheme 5.2. Umpolung γ-alkylation of an ynoate by pronucleophiles.

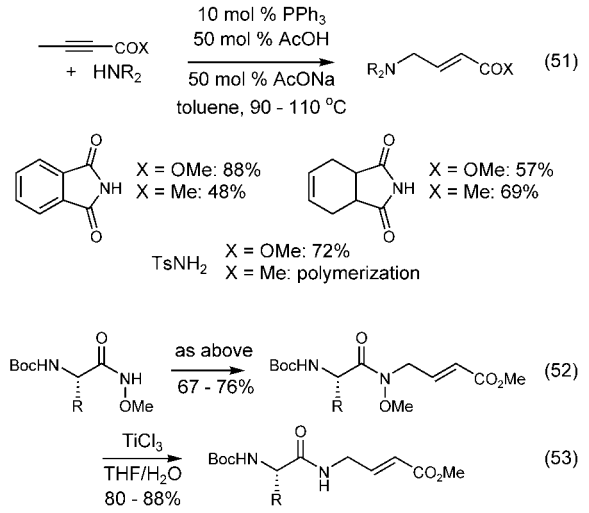
the more polar DMSO strongly favored diene formation, while catalysis with 1,3-bis(diphenylphosphine)-propane (dppp) strongly favored isomerization-addition! The advantage of a bidentate phosphine may stem from the ability of the second phosphine to function as a general base catalyst.

With the successful use of oxygen nucleophiles, attention turned to use of acidic nitrogen nucleophiles such as *p*-toluenesulfonamide, phthalimide and tetrahydrophthalimide.[53] γ-Addition of these nucleophiles proceeded in good yield with alkynyl esters, however the more reactive alkynyl ketones gave lower yields or polymerization [Eq. (51), Scheme 5.4]. Alanine, valine and tryptophan-derived hydroxamic acids also underwent smooth reaction with methyl 2-butynoate [Eq. (52)], and subsequent cleavage of the N–O bond by $TiCl_3$ provided an entry into vinylogous amino acid derivatives [Eq. (53)]. Alvarez-Ibarra reported carboxylates as pronucleophiles in a similar phosphine-catalyzed γ-addition to both alkynyl esters and ketones, with both aliphatic and aromatic carboxylic acids (Scheme 5.5).[54]

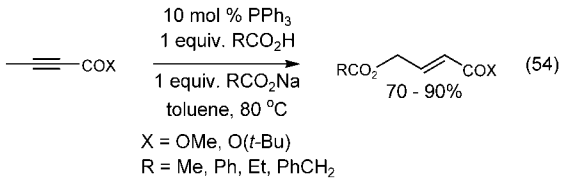
Potential exists for asymmetric synthesis using chiral phosphines in the γ-addition reaction. Recently Zhang and coworkers reported the application of their phosphabicyclo[2.2.1]heptane catalysts to this problem (Scheme 5.6).[55] Treatment of a toluene solution of ethyl



Scheme 5.3. Isomerization-addition of oxygen nucleophiles.



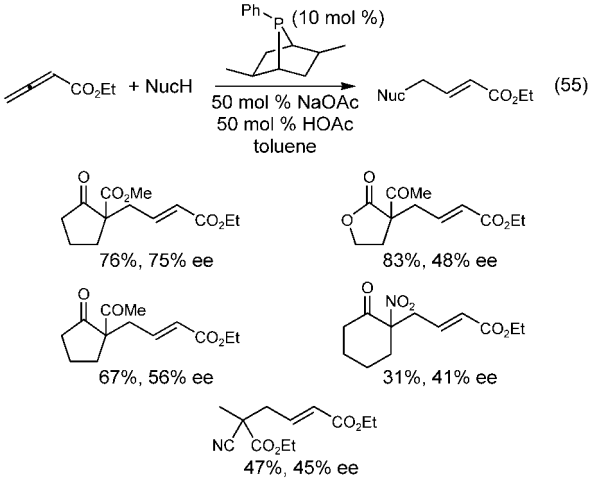
Scheme 5.4. Nitrogen pronucleophiles in γ-addition to activated alkynes



Scheme 5.5. Carboxylates as pronucleophiles in γ-addition to activated alkynes.

2,3-butadienoate and a variety of carbon acids with 10 mol % of the *P*-chiral phosphine and a sodium acetate-acetic acid buffer gave γ-addition products in 41–75% ee. Although the NaOAc/HOAc buffer slows the reaction rate, it was found that these additives enhance enantioselectivity considerably. Several other salts examined (e.g., Li^+, K^+, Cs^+, NH_4^+) gave comparable results.

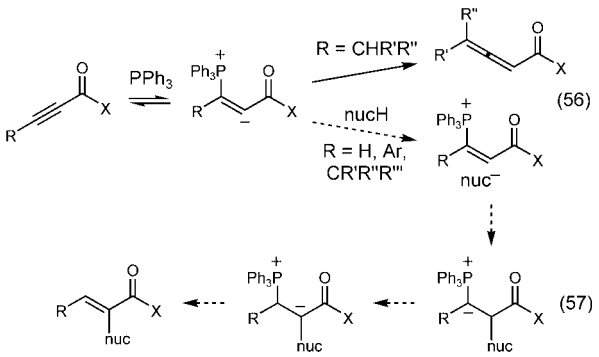
When an acidic hydrogen is present at the γ-position of an activated alkyne, treatment with a phosphine at elevated temperatures leads to allene formation



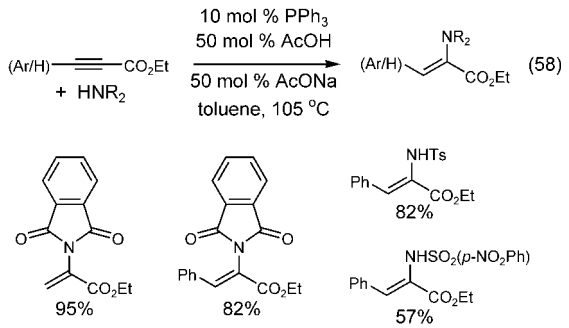
Scheme 5.6. Asymmetric quaternary center synthesis through γ-addition.

(Scheme 4.1). However in the absence of this methine, the intermediate phosphonium ion could in principle be trapped by a nucleophile at the α-position (Scheme 5.7). Consider a case in which the zwitterionic adduct deprotonates a weak acid [Eq. (56)], and the conjugate base then can behave as a nucleophile [Eq. (57)]. Trost and coworkers discovered that the addition of nitrogen pronucleophiles does indeed occur at the α-position of propiolate esters (Scheme 5.8).[56] Related experiments with methyl 2-heptynoate gave the expected products of α-addition, γ-addition and isomerization to the corresponding diene. The ability to redirect the selectivity from the classical β-addition to an α-addition through the influence of phosphine catalysis is quite remarkable.

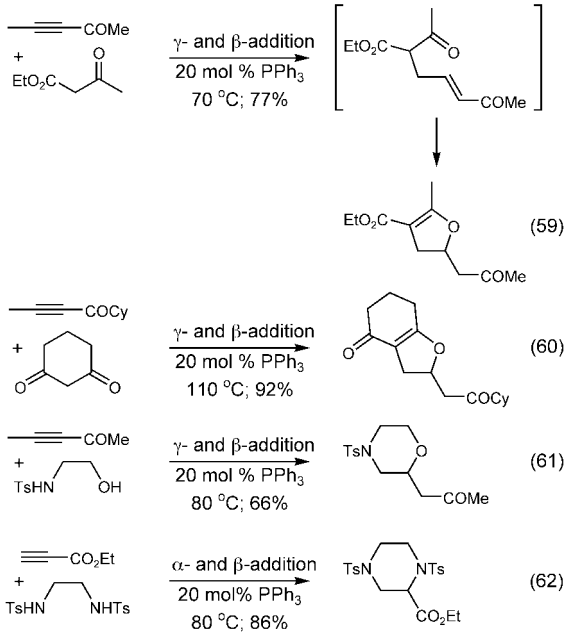
In Section 3, phosphine-catalyzed β-additions of carbon and oxygen pronucleophiles to activated alkenes and alkynes were discussed. In this section, phosphine-catalyzed γ-additions of carbon, oxygen and nitrogen pronucleophiles as well as α-addition of nitrogen pronucleophiles to activated alkynes have been summarized. A bifunctional nucleophile can be envisioned to combine these processes. The first γ- or α-addition to an activated alkyne or allene would afford an intermediate product with a nucleophilic center and an activated alkene for a second intramolecular β-addition reaction (Scheme 5.9). Lu and Lu demonstrated this tandem reaction to construct various oxygen and nitrogen-containing heterocycles.[57] A number of 1,3-dicarbonyl compounds gave dihydrofuran derivatives in good yield [Eqs. (59) and (60)], while *N*-tosyl-2-aminoethanol [Eq. (61)] and bis(*N*-tosyl)ethylenediamine [Eq. (62)] provided morpholine and piperazine derivatives, respectively. Available data suggest that the second β-addition is phosphine-catalyzed, as lower catalyst loadings (e.g., 5 mol % PPh_3) afforded substantial quantities of the intermediate acyclic monoaddition products.



Scheme 5.7. Nucleophilic interception at the α-position.



Scheme 5.8. Nucleophilic α-addition into propiolates.



Scheme 5.9. Tandem α- or γ-addition and Michael addition.

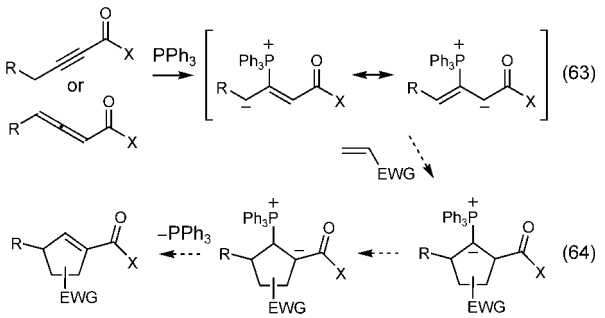
6 Cycloaddition Reactions of Activated Alkynes and Allenes

The proposition of a four-electron, three-carbon zwitterionic intermediate along the reaction pathway for phosphine-catalyzed isomerization of activated alkynes and allenes (Scheme 4.1) suggests the possibility that this intermediate can be intercepted in a [3+2] cycloaddition reaction (Scheme 6.1). After the bond construction event, a prototropic shift [Eq. (64)] would allow for elimination of the phosphine to give cyclopentene products.

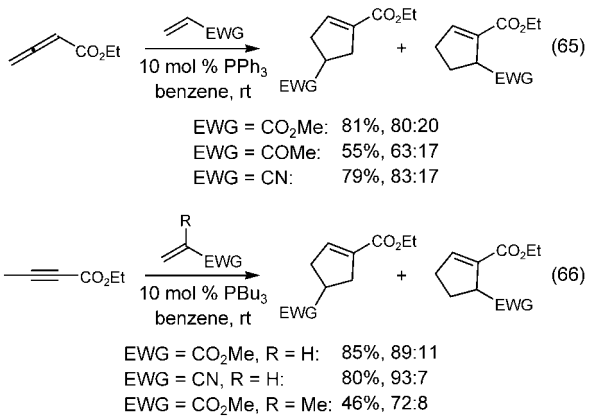
In 1995 Lu and coworkers reported that these allylic anions [see Eq. (63)] can be trapped with ethyl acrylate, methyl vinyl ketone and acrylonitrile (Scheme 6.2).[58] Treatment of allenyl esters [Eq. (65)] with triphenylphosphine or tributylphosphine in the presence of the activated olefin gave the [3+2] cycloadducts at room temperature with good (~4:1) regioselectivity, with the former catalyst providing higher yields. Attempted cycloaddition with less active alkenes such as methyl (*E* or *Z*)-crotonate or methyl methacrylate failed due to competing homodimerization of the allenyl ester. In addition, with alkynyl esters as the precursor, the reaction failed with triphenylphosphine even at 135 °C. Fortuitously, tributylphosphine provided [3+2] adducts in good yield at room temperature [Eq. (66)]. No reaction occurred when triethylamine was used instead of a phosphine with either allenyl or alkynyl esters, thus supporting the nucleophilic catalysis mechanism.

With Lu's finding that phosphines catalyze the [3+2] annulation reaction, Zhang and coworkers investigated an asymmetric variant with chiral mono- and bisphosphines.[59] A screen of multiple chiral phosphines revealed that the phosphabicyclo[2.2.1]heptane catalyst shown in Eq. (67) (Scheme 6.3) gave the best enantioselectivity (93% ee) in the [3+2] reaction of ethyl 2,3-butadienoate with isobutyl acrylate, giving a single regioisomer in 88% yield.

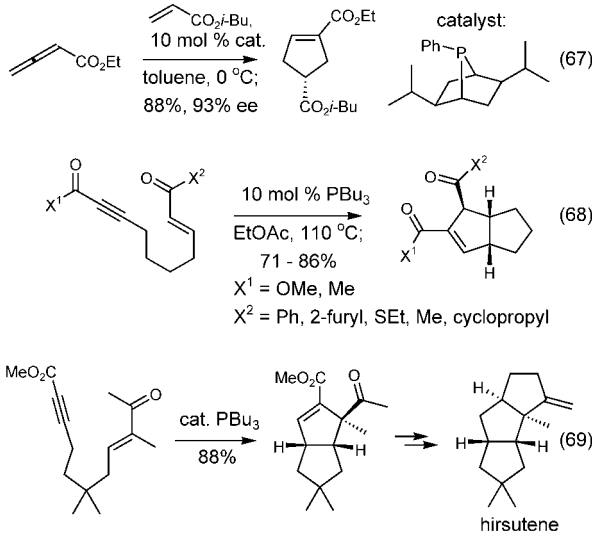
Intramolecular cycloadditions enable expeditious entry into complex polycyclic ring systems from simple acyclic starting materials. They can be more diastereoselective and regioselective than intermolecular cycloadditions. A concern in the development of an intramolecular variant of the phosphine-catalyzed [3+2] reaction is the potential for isomerization of 2-alkynoates and alkynones to conjugated dienes. Recently Krische reported the tributylphosphine-catalyzed cycloisomerization of



Scheme 6.1. Interception of the phosphonium adduct *via* [3+2] reaction.



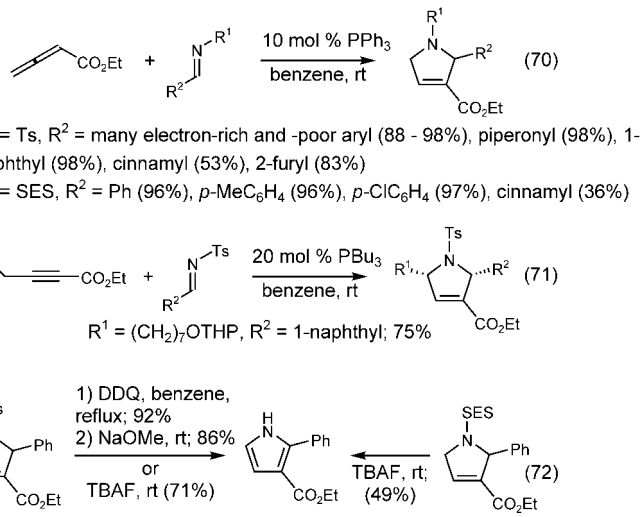
Scheme 6.2. [3+2] Cycloaddition of allenyl and alkynyl esters.



Scheme 6.3. Asymmetric and intramolecular [3+2] reactions.

electron-deficient 1,7-enynes giving access to diquinane structures in >95:5 de [Eq. (68), Scheme 6.3].[60] Included in an array of substrates examined are cyclopropyl enones, which are generally incompatible with transition metal catalysis but which react smoothly under nucleophilic organocatalysis. Krische has applied the intramolecular [3+2] reaction to the total synthesis of hirsutene [Eq. (69)], in which a quarternary center is generated as a single diastereomer.[61]

The success of the phosphine-catalyzed [3+2] reaction with activated olefins led Lu and coworkers to consider other dipolarophiles such as *N*-tosylimines. At room temperature, triphenylphosphine catalyzed a highly regioselective cycloaddition of 2,3-butadienoates with a variety of *N*-tosylimines to afford pyrrolines in good to excellent yield [Eq. (70), Scheme 6.4].[62] Unfortunately aliphatic imines failed limiting the scope of the reaction. Similarly, DABCO or DMAP failed to catalyze the cycloaddition. The observed regioselectivity indicates that the zwitterionic phosphonium intermediate undergoes electrophilic addition to the imine at the α-position.

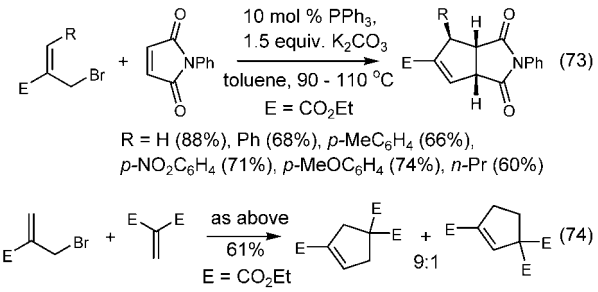


Scheme 6.4. [3+2] Cycloaddition of activated alkynes and allenes with imines.

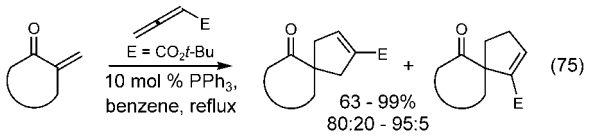
Lu also investigated *N*-(β-trimethylsilylethanesulfonyl)imines to afford products with a β-trimethylsilylethanesulfonyl (SES) protective group as it is more easily removed after the reaction. Conveniently ethyl 2-heptynoate and *N*-tosylbenzaldimine combine in the presence of tributylphosphine to give a single *syn* diastereomeric pyrroline cycloadduct [Eq. (71)].[63] *N*-Tosylpyrrolines can be oxidized to *N*-tosylpyrroles upon treatment with DDQ in hot benzene [Eq. (72)], and the tosyl group subsequently removed under mild sodium methoxide/methanol conditions. Both the SES- and *N*-tosylpyrrolines can be converted directly into deprotected pyrroles with TBAF/THF at room temperature.

Recently, Lu et al. reported a novel [3+2] annulation of allylic bromides and activated alkenes catalyzed by triphenylphosphine in the presence of stoichiometric K_2CO_3 (Scheme 6.5).[64] Presumably, the phosphine triggers the reaction through salt formation with the allylic bromide. The inorganic base then generates the allylic anion setting up for the cycloaddition reaction. This is the first reported phosphine-catalyzed allylic ylide reaction.

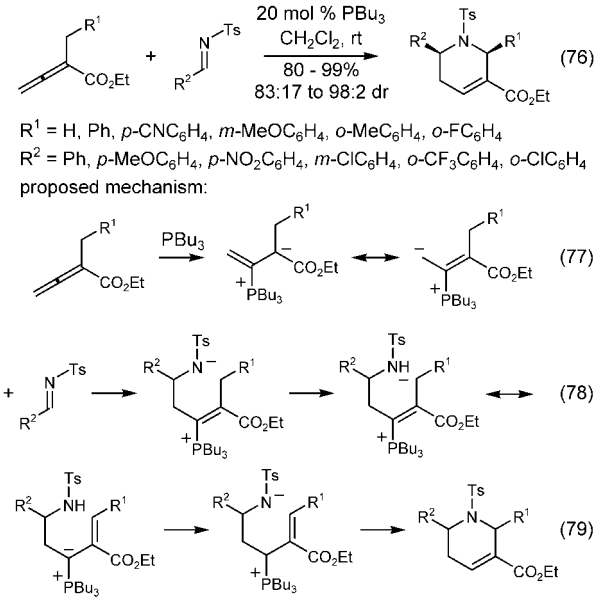
The selective synthesis of quaternary centers remains a challenge in organic synthesis. Lu and coworkers also reported a highly regioselective construction of spirocycles *via* triphenylphosphine-catalyzed [3+2] cycloaddition of α-methylene cyclic ketones with alkynyl and allenyl esters (Scheme 6.6).[65] The bulky *tert*-butyl 2,3-butadienoate gave marked improvement in regioselectivity over smaller esters, supporting a steric argument for the observed regioselectivity.



Scheme 6.5. Catalytic carbon-phosphorus ylide [3+2] annulation.



Scheme 6.6. Synthesis of spirocyclic quaternary centers.



Scheme 6.7. A phosphine-catalyzed [4+2] annulation.

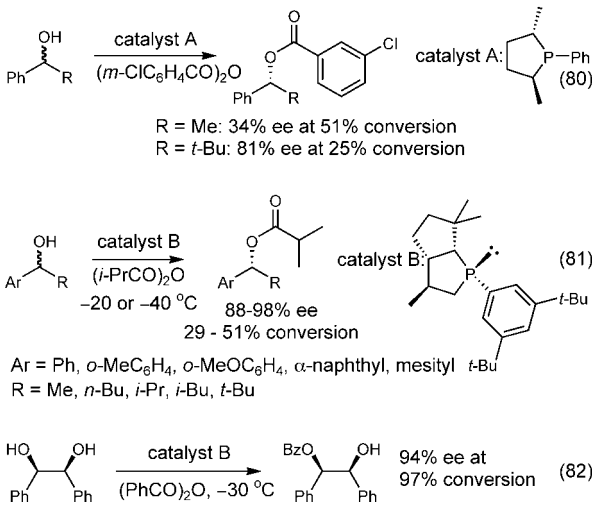
The [3+2] cycloaddition of imines with 2-allyl substituted 2,3-butadienoates in the presence of a phosphine catalyst is triggered by α-addition of the zwitterionic intermediate to the imine leading to pyrroline formation (Scheme 6.4).[66] Kwon and coworkers envisioned that substitution of the hydrogen at the α-position of the 2,3-butadienoate with an alkyl group might block α-attack of the phosphonium intermediate and lead to a reaction manifold initiated by γ-addition. Remarkably, mixing 2-alkyl-2,3-butadienoate derivatives with *N*-tosylbenzaldimines in the presence of 20 mol % PBu_3 [Eq. (76)] resulted in the diastereoselective formation of tetrahydropyridine derivatives instead of pyrrolines (Scheme 6.7).[67] Apparently, 2-alkyl-2,3-butadienoates act as 1,4-dipole synthons and not 1,3-dipole synthons, giving products of a [4+2] cycloaddition reaction in good to excellent yields with a variety of aromatic imines. Again, alkyl and vinyl *N*-tosylimines failed to give the desired cycloadducts. The mechanism has not yet been established, but one reasonable pathway is outlined in Scheme 6.7. A γ-addition to the imine by the zwitterionic phosphonium adduct [Eq. (78)] followed by two consecutive proton-transfer steps sets up for an *N*-tosyl Michael addition [Eq. (79)] to close the tetrahydropyridine ring. Preliminary experiments with a chiral phosphine, (*S,S*)-DIPAMP, gave an encouraging 34% ee confirming phosphine involvement in the carbon-carbon bond forming event.

7 Alcohol Acylation and Kinetic Resolution

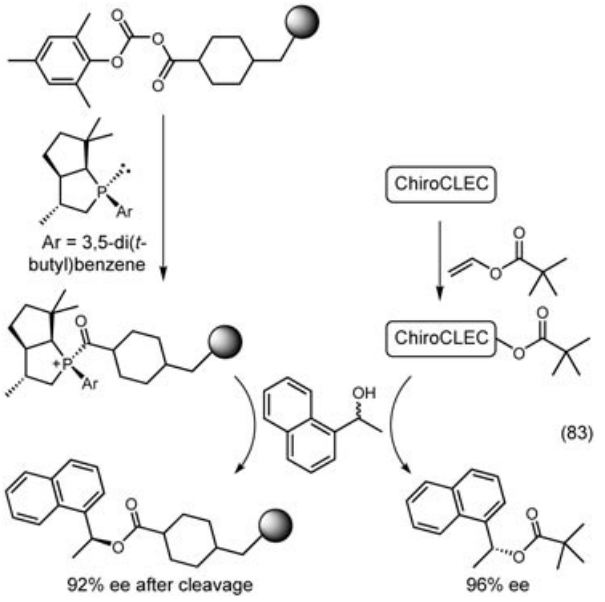
While the bulk of nucleophilic phosphine literature involves addition to activated alkenes, phosphines undergo 1,2-addition to carbonyl compounds as well. In 1993, Vedejs and coworkers reported that tributylphosphine is an effective catalyst for the acylation of alcohols with carboxylic acid anhydrides,[68] with reactivity similar to that of 4-dimethylaminopyridine (DMAP).[69] The reagents Ac_2O/PBu_3 and Bz_2O/PBu_3 acylated typical alcohol substrates including menthol, hindered phenols and tertiary alcohols. A likely mechanistic pathway involves nucleophilic activation of the anhydride via an ion pair $[Bu_3P^+COR][RCO_2^-]$. Acylation rates decreased in the following order as expected: $PBu_3 > PPhEt_2 > PPh_2Et$, while $Bu_3P{=}O$ and $P(MeO)_3$ are unreactive. Tributylphosphine can be easily removed from the reaction mixture by dilute mineral acid extraction or filtration chromatography.

Even more intriguing is the kinetic resolution of racemic alcohols with chiral phosphines through chiral acylphosphonium salts. Phosphines may be advantageous compared to chiral tertiary amines in asymmetric catalysis as they are in general configurationally stable at phosphorus, while the latter require built-in geometric constraints to prevent racemization through pyramidal inversion. In 1996, Vedejs reported that *trans*-2,5-dimethyl-1-phenylphospholane resolved secondary alcohols [Eq. (80)] and desymmetrized *meso*-diols giving acylated products in moderate enantiomeric excess (Scheme 7.1).[70] These results were encouraging; however, the steric crowding about the phosphorus center rendered acylation with this catalyst slow.

In 1999, Vedejs reported a more reactive second generation 2-phosphabicyclo[3.3.0]octane catalyst (Scheme 7.1).[71] For most aryl alkyl carbinols, acylation with $(i\text{-PrCO})_2O$ and 3–5 mol % chiral phosphine in heptane at −40 °C gave optimal results, with enantiomeric purity of the isopropyl ester product ranging from 88% to 98% ee [Eq. (81)]. Certain allylic alcohols,



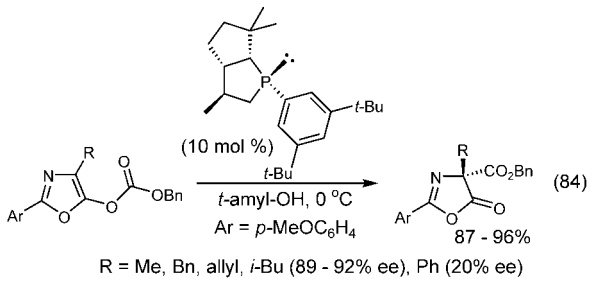
Scheme 7.1. Chiral phosphines as enantioselective acylating agents.



Scheme 7.2. Doubly catalytic parallel kinetic resolution.

especially those with the olefin embedded within a carbocycle, gave modest to good enantioselectivity with this catalyst.[72] The desymmetrization of *meso*-hydrobenzoin with benzoic anhydride [Eq. (82)] gave a remarkable 94% ee at 97% conversion.[73]

A classical problem in kinetic resolution is how to obtain high enantiomeric purity in both the product and the unreacted starting material when the selectivity is not exceedingly high. As the reaction progresses, the relative concentration of the faster reacting enantiomer *versus* the slower reacting enantiomer decreases, resulting in a drop in the relative rates of the intrinsically faster *versus* the intrinsically slower acylation reactions. One way to avoid this change in the relative concentrations



Scheme 7.3. Application to quaternary carbon synthesis.

of the enantiomers is to run two simultaneous derivatization reactions, a method termed parallel kinetic resolution. Vedejs first reported this technique in 1997 using a chiral DMAP catalyst.[74] If the rates and enantioselectivities are similar and complementary, the enantiomer ratio of the substrate remains 1:1 throughout the reaction. Vedejs and coworkers[75] selected an insoluble cross-linked lipase (ChiroCLEC-PC) as an acyl transfer catalyst to complement the nucleophilic chiral phosphine catalyst (Scheme 7.2). The anhydride intended for phosphine activation was attached to an insoluble resin as a mixed anhydride such that phosphine activation at the less-hindered carbonyl would generate a *P*-acylphosphonium attached to the solid support. In this manner the (*S*)-enantiomer of the alcohol became resin-bound as an ester, while the (*R*)-enantiomer remained in solution as an ester. From racemic 1-naphthyl methyl carbinol, excellent (92–96% ee) resolution was achieved with both reactions benefiting in terms of product ee versus simple resolution to 50% conversion.

Recently Vedejs and coworkers also reported an application of their bicyclic chiral phosphine catalyst for the synthesis of quaternary carbon centers by an acyl transfer reaction of an oxazole enol carbonate giving an azlactone (Scheme 7.3) in good enantioselectivity.[76]

8 Conclusions

The rich organic chemistry exhibited by phosphines over the past decade is remarkable. The unique reactivity compared to their amine cousins has led to the discovery of novel reactions of activated alkenes and alkynes such as the nucleophilic addition to α,β-unsaturated carbonyl compounds at the α- or γ-position and the generation of a three- or four-carbon synthons useful for [3+2] or [4+2] cycloaddition reactions. A full appreciation of the chemistry nucleophilic phosphines provides the organic chemist with an expanded toolbox for organocatalysis.

The physical and chemical properties of triaryl- and trialkylphosphines are often complementary, allowing considerable latitude in designing and executing organic reactions. Their non-basic character provides compatibility with base-sensitive substrates and allows the use

of Lewis or Brønsted cocatalysis. One drawback to the use of trialkylphosphines is their inherent air-sensitivity. Protection of the phosphine as a salt with a weak acid, as suggested by Fu and coworkers (Scheme 2.8), is a practical solution that will likely witness further development. Creative new applications of the basic transformations described herein undoubtedly will further expand the scope and utility of nucleophilic phosphines as catalysts in organic synthesis.

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