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Nucleophilic phosphine-catalyzed [3+2] cycloaddition of allenes with *N*-(thio)phosphoryl imines and acidic methanolysis of adducts *N*-(thio)phosphoryl 3-pyrrolines: a facile synthesis of free amine 3-pyrrolines

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Dedicated to Professor Chuchi Tang on the occasion of his 70th birthday

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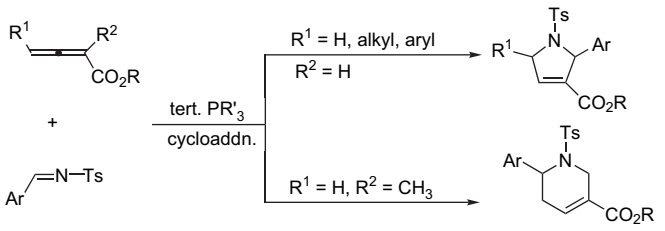
ABSTRACT

In this report, the dipolarophile imines with easily removable activating group *O*,*O*-diethyl(thio)-phosphoryl have been investigated in the nucleophilic phosphine-catalyzed [3+2] cycloaddition reaction of electron-deficient allenes. Under the catalysis of a tertiary phosphine, *N*-(thio)phosphorylimines readily undergo the [3+2] cycloaddition reaction with ethyl 2,3-butadienoate or ethyl 2,3-pentadienoate, affording the corresponding *N*-(thio)phosphoryl 3-pyrrolines in moderate to high yields with good diastereoselectivity. Removal of the (thio)phosphoryl group from the adducts has been successfully achieved via the acidic methanolysis of the P–N bond, giving the free amine 3-pyrrolines in fair to good yields without severe aromatization. Thus, a facile synthesis of *N*-unsubstituted 3-pyrrolines is established from the phosphine-catalyzed [3+2] cycloaddition reaction of allenes with imines.

1. Introduction

In recent years, the nucleophilic catalysis by tertiary phosphines has attracted much attention within the chemistry community. Many new phosphine-catalyzed reactions with highly synthetic potentials have been discovered.[1] The nucleophilic phosphine-catalyzed cycloaddition reactions of allenes with imines are the typical and important examples in this realm, which conveniently construct five- or six-membered *N*-heterocycles (Scheme 1). Due to the importance of such *N*-heterocyclic substructures in the biologically active substances, particularly pharmaceuticals,[2] those reactions have been extensively studied with regard to their synthetic potentials.[3] In those reactions, aryl substituted *N*-tosyl imines are most often used for their better reactivity, giving *N*-tosyl heterocycle products generally in high yields. Since tosyl group is not easy to be removed under mild conditions, in most cases products have been reported as *N*-tosylated ones.[3] Particularly, direct deprotection of the sulfonyl group from a fragile [3+2] cycloaddition adduct 3-pyrroline usually results in an aromatization of the pyrroline heterocycle, delivering the corresponding pyrrole product even if much easier-removed sulfonyl groups like nosyl and 2-trimethylsilylethanesulfonyl are used.[3b,c] This situation intrigued us exploring some effective and easy-deprotected activating groups for the substrate imine so that the synthetic values of the phosphine-catalyzed cycloaddition reactions of allenes with imines could be extended to those *N*-unsubstituted heterocycles.



Scheme 1. *N*-Heterocycles from tertiary phosphine-catalyzed cycloadditions of allenes with imines.

As part of our ongoing research efforts on nucleophilic phosphine-catalyzed carbon–carbon bond forming reactions,[4] we

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herein report the results on the [3+2] cycloaddition reaction of allenes with *N*-(thio)phosphoryl imines. The cycloaddition reaction, catalyzed by either Ph_3P or air-stable and highly nucleophilic PTA (1,3,5-triaza-7-phosphaadmantane), readily afforded the [3+2] cycloaddition products *N*-(thio)phosphoryl 3-pyrrolines **1** in fair to good yields. Also, the *N*-(thio)phosphoryl 3-pyrrolines **1** were successfully deprotected through a HCl-mediated acidic methanolysis, affording the corresponding free amine 3-pyrrolines **2** in moderate isolated yields. Thus, a facile synthesis for free amine 3-pyrrolines is established via the phosphine-catalyzed [3+2] cycloaddition reaction of allenes with *N*-(thio)phosphoryl imines.

2. Results and discussion

Most recently, *O*,*O*-diethylthiophosphoryl has been successfully used as an activating group for the imine substrate in the phosphine-catalyzed aza-Morita–Baylis–Hillman reaction in our laboratories.[5] Due to its better stability on storage than its oxo-analogue *N*-phosphoryl imine, *N*-thiophosphoryl imine was first chosen as the substrate in the phosphine-promoted [3+2] cycloaddition with activated allenes, although *N*-phosphoryl analogue has a similar reactivity in this reaction (vide infra).

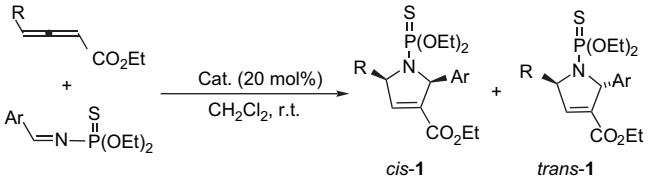
To date, nucleophilic phosphines are only found to be effective catalysts for the [3+2] cycloaddition of electron-deficient allenes with imines; nitrogen nucleophiles are ineffective in this reaction.[1a,b] The efficiency of the cycloaddition highly depends on the nucleophilicity of the employed catalyst phosphine and the reactivity of the allene; for a more reactive allene, e.g., 2,3-butadienoate, a relatively weaker nucleophile Ph_3P can readily mediate its cycloaddition with various imines, giving the adducts 3-pyrrolines in high yields;[3b] for a less reactive γ-substituted allenoate, a stronger nucleophilic catalyst like tributylphosphine is then required to secure the efficiency of its cycloaddition with imines.[3c]

In this study, two activated allenes, e.g., ethyl 2,3-butadienoate and ethyl 2,3-pentadienoate (γ-methyl allenoate), were selected to investigate their annulation with *N*-thiophosphoryl imines [Eqs. 1 and 2]. The initial survey of optimal reaction conditions was conducted on the [3+2] cycloadditions of *N*-(*O*,*O*-diethyl)thiophosphoryl phenylimine with both the allenes. It was found that methylene chloride delivered better product yields than other solvents (THF, ether, acetonitrile, benzene, toluene, and DMSO). The tertiary phosphine catalyst loading (20 mol %, compared to the substrate imine) was chosen because reduced loadings (5 mol % or 10 mol %) resulted in either substantially prolonged reaction time or much lower product yield.

Screening of the phosphine catalysts revealed that the nucleophilicity of the catalyst significantly affected its efficiency in the [3+2] cycloaddition of the allenes with *N*-thiophosphoryl imine. For the reactive ethyl 2,3-butadienoate, Ph_3P (20 mol %) delivered better results in the reaction of this allene with *N*-thiophosphoryl imine; in contrast, more nucleophilic phosphines such as Bu_3P, PTA, and $PhPMe_2$ caused severe side reactions, giving the normal cycloaddition product in lower yields. Thus, Ph_3P was chosen as the preferred catalyst for the allene ethyl 2,3-butadienoate. Under the catalysis of Ph_3P (20 mol %), various aromatic *N*-thiophosphoryl imines readily afforded the normal [3+2] cycloaddition adducts **1** in fair to good isolated yields (Table 1, entries 1–6). The substrate imines, bearing either electron-donating or electron-withdrawing groups in the benzene ring, both worked well in the cycloaddition.

For the relatively less reactive allene ethyl 2,3-pentadienoate, a more nucleophilic phosphine catalyst was expectedly needed in its cycloaddition with *N*-thiophosphoryl imine. Five selected

Table 1
Phosphine-catalyzed [3+2] cycloaddition reaction of allenes with *N*-thiophosphoryl imines[a]



cis-**1** *trans*-**1**

Entry	Ar	R	Reaction time (h)	Yield of **1**[b] (%)	Ratio of *cis*-**1**/*trans*-**1**[c]
1	C_6H_5	H	20	**1a**, 49	
2	*p*-$CH_3C_6H_4$	H	24	**1b**, 60	
3	*p*-$CH_3OC_6H_4$	H	40	**1c**, 62	
4	*p*-ClC_6H_4	H	7	**1d**, 68	
5	*o*-ClC_6H_4	H	8	**1e**, 41	
6	*p*-$NO_2C_6H_4$	H	6	**1f**, 76	
7	C_6H_5	CH_3	48	**1g**, 77	25:1
8	*p*-$CH_3C_6H_4$	CH_3	48	**1h**, 53	46:1
9	*p*-ClC_6H_4	CH_3	48	**1i**, 76	11:1
10	*o*-ClC_6H_4	CH_3	48	**1j**, 70	7:1
11	*p*-$NO_2C_6H_4$	CH_3	48	**1k**, 99	6:1

[a] For entries 1–6, the catalyst is PPh_3; for entries 7–11, PTA is used as the catalyst.
[b] Isolated yield based on the substrate imine.
[c] Determined by ^{31}P NMR.

phosphines (Ph_3P, Ph_2PMe, $PhPMe_2$, PTA, and Bu_3P) were screened in the model reaction with *N*-thiophosphoryl phenylimine under the same conditions (see Section 4, general procedure for ethyl 2,3-pentadienoate), and the result is shown as follows: isolated yield of the normal adduct/ratio of cis- and trans-isomers/catalyst: 0/Ph_3P; 57%/18:1/Ph_2PMe; 42%/11:1/$PhPMe_2$; 77%/25:1/PTA; 27%/5:1/PBu_3. This result clearly showed that the catalyst PTA was the best in terms of the product yield and diastereoselectivity. However, the catalysis of PBu_3 with the strongest nucleophilicity only produced the normal adduct in a low yield (27%) due to the complexity of the reaction. In our previous reports,[4,5] the air-stable phosphine PTA was found to be a convenient and versatile organocatalyst, with its nucleophilicity comparable to those of pure trialkylphosphines, in the phosphine-catalyzed Morita–Baylis–Hillman reaction and the [3+2] cycloaddition reaction of allenes with *N*-tosyl imines. Thus, in this study PTA was preferably chosen as a stronger nucleophilic phosphine catalyst. The experimental results (Table 1, entries 7–11) revealed that the annulation of ethyl 2,3-pentadienoate with *N*-thiophosphoryl imines smoothly proceeded under the catalysis

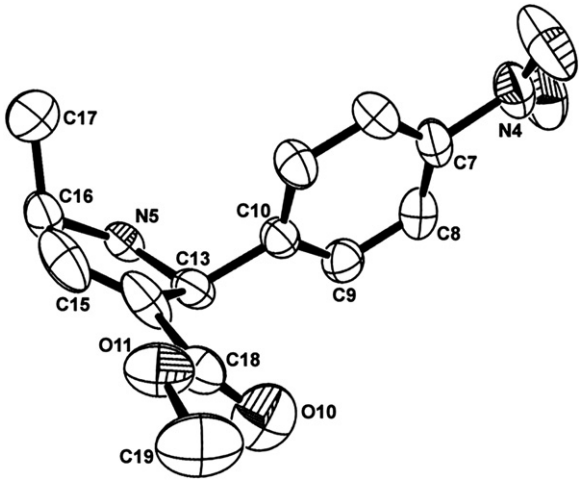
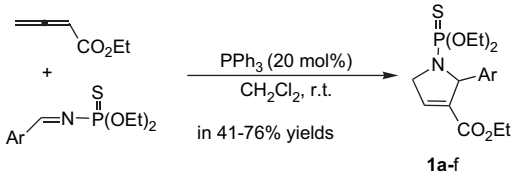
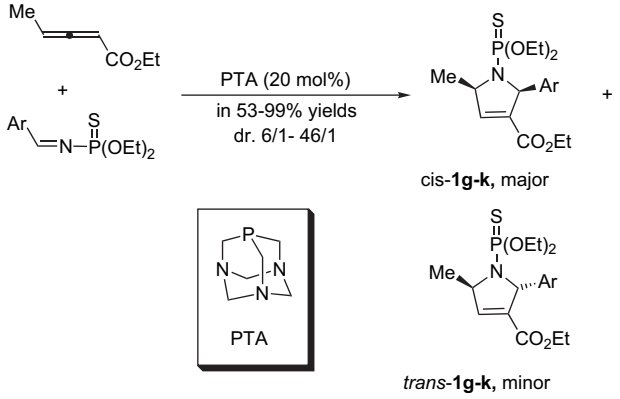


Figure 1. The crystal structure of **2k** picrate (for clarity, the picrate anion is omitted).

of PTA (20 mol %), giving the normal adducts **1** in good to excellent yields with high diastereoselectivities. In the reported phosphine-catalyzed [3+2] cycloaddition of γ-substituted allenoates or alkynoates with *N*-tosyl imines, the cis-adduct (the substituents at 2- and 5-positions locating on the same side of the pyrroline ring) is always predominant over the trans in the products.[1a,b,3c] In the case of *N*-thiophosphoryl imine, the diastereoselectivity in its PTA-mediated [3+2] cycloaddition with ethyl 2,3-pentadienoate is similar with the cis-isomer being major in **1**. The ratio of *cis*-**1** and *trans*-**1** was conveniently determined by integrating their respective ^{31}P NMR signals, which provided a good resolution of about 4 ppm chemical shift separation (see Supplementary data). The cis-configuration assignment of **1** was also secured by the X-ray crystallography (CCDC 684846) of the free amine 3-pyrroline **2k** conjugate with picric acid (Fig. 1).[6]



(1)

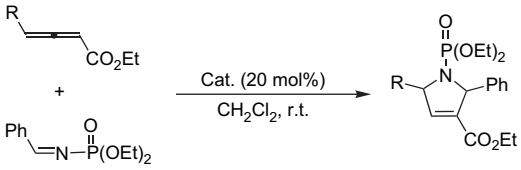


(2)

The structural assignments of **1** are in good agreement with their NMR data (^1H, ^{13}C, and ^{31}P) and elemental analyses. The presence of the phosphorus atom in **1** provides extra help in the assignment of NMR signals. It is also noteworthy that the existence of the chiral center at 2-position of the pyrroline ring in **1** results in the differentiation of two ethoxy groups at phosphorus in the NMR (^1H and ^{13}C) spectra (see Supplementary data).

On the basis of data in Table 1 and those reported in the literatures,[3b,c,4b] however, the *N*-thiophosphoryl imine is generally less reactive than the corresponding *N*-tosyl imine in terms of the catalyst loading and the product yield, in the phosphine-catalyzed [3+2] cycloaddition with activated allenes, although its overall efficiency in this reaction is still acceptable.

For the purpose of comparison, a representative *N*-phosphoryl imine analogue was also investigated in the above cycloaddition with the allenes. Thus, it was found that, under the similar conditions with the *N*-thiophosphoryl imine, *N*-(*O*,*O*-diethylphosphoryl) phenylimine readily gave normal cycloaddition products (**1a**′ and **1g**′) in moderate isolated yields with ethyl 2,3-butadienoate and ethyl 2,3-pentadienoate, respectively [Eq. 3]. Apparently, the *N*-phosphoryl imine has a similar



(3)

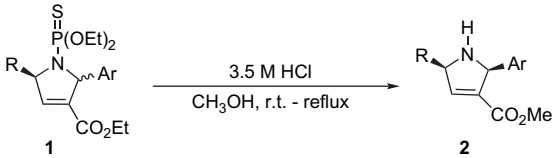
R	Cat.	Adduct	Yield	dr.
H	PPh_3	**1a'**	40%	
Me	PTA	**1g'**	54%	9/1

reactivity to its thio-analogue in the [3+2] cycloaddition with activated allenes.

The ease extent of the P–N bond cleavage is highly dependent on the specific structure of the substrate phosphorus amide,[7] although the P–N bond is generally considered to be pretty susceptible to the acidic alcoholysis or hydrolysis, and has already found its value in organic synthesis, for instance, in the synthesis of some polyamines.[8] The P–N bond cleavages via the HCl-mediated methanolysis in both *O*,*S*-dialkyl thiophosphoramidate[9] and diphenylthiophosphinic amide[10] were achieved under mild conditions by Tang and Haake et al. Following the Tang's procedure, deprotection of thiophosphoryl group from **1** was first attempted. Under mild conditions (room temperature to gentle reflux in 3.5 M HCl methanol solution), adducts **1** readily decomposed, giving the corresponding free amine 3-pyrroline-3-carboxylic methyl esters **2** in fair to good isolated yields (Table 2). Obviously, the trans-esterification with the methanol solvent occurred at the carboxylate group in **1** under above conditions. Thus, a facile synthesis of free amine 3-pyrrolines is realized from the phosphine-catalyzed [3+2] cycloaddition of activated allenes with *N*-thiophosphoryl imines.

In the cases of **1a**–**f**, a small amount (less than 5% of the theoretical yield) of the aromatization by-product *N*-thiophosphoryl pyrrole **3** was detected from the crude product [Eq. 4]. In the case of **1d**, pure **3d** (Ar=*p*-chlorophenyl) was isolated in 5% yield and identified by their NMR data (see Supplementary data). In all methanolysis cases of **1**, no deprotected free amine pyrroles from the corresponding **3** were observed. Apparently, the aromatization by-product **3** possesses a better stability against the

Table 2
The free amine 3-pyrrolines **2** prepared via the acidic methanolysis of the adducts **1**[a]

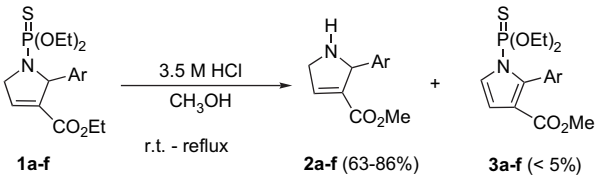


1 2

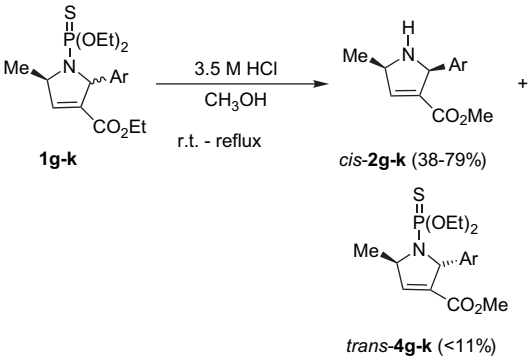
Entry	Ar	R	Yield of **2**[b] (%)
1	C_6H_5	H	**2a**, 69
2	*p*-$CH_3C_6H_4$	H	**2b**, 76
3	*p*-$CH_3OC_6H_4$	H	**2c**, 64
4	*p*-ClC_6H_4	H	**2d**, 86
5	*o*-ClC_6H_4	H	**2e**, 63
6	*p*-$NO_2C_6H_4$	H	**2f**, 71
7	C_6H_5	CH_3	*cis*-**2g**, 71
8	*p*-$CH_3C_6H_4$	CH_3	*cis*-**2h**, 38
9	*p*-ClC_6H_4	CH_3	*cis*-**2i**, 49
10	*o*-ClC_6H_4	CH_3	*cis*-**2j**, 55
11	*p*-$NO_2C_6H_4$	CH_3	*cis*-**2k**, 79

[a] Reaction time: at room temperature (12 h) and under reflux (24 h).
[b] Isolated yield based on **1**.

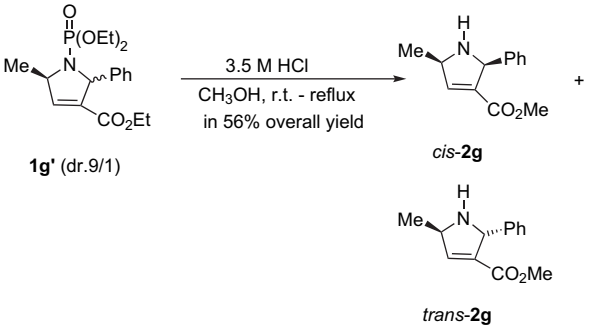
P–N bond cleavage than its parent **1** under the conditions in this study.



1a-f **2a-f** (63-86%) **3a-f** (< 5%) (4)



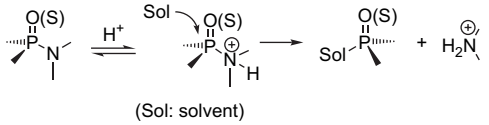
1g-k *cis*-**2g-k** (38-79%) *trans*-**4g-k** (<11%) (5)



1g' (dr.9/1) *cis*-**2g** *trans*-**2g** (6)

For the substrates **1g–k**, to our surprise, their P–N bond methanolysis had a distinct preference over the substrate's configuration: the dominant component in the substrate **1**, *cis*-**1**, was readily deprotected to its corresponding free amine *cis*-**2**; the minor component *trans*-**1** in the substrate stood inert except that its carboxylate group was changed by the transesterification, as observed by ^{31}P and ^{1}H NMR measures [Eq. 5]. In the case of **1k**, which contained relatively more trans-isomer, a pure transesterification product *trans*-**4k** (Ar=*p*-nitrophenyl), supposedly derived from *trans*-**1k**, was successfully isolated in 11% yield from the acidic methanolysis crude product by the column chromatography, and was identified by its NMR data. However, for the *N*-phosphoryl adduct **1g′**, its methanolysis under similar conditions gave the corresponding free amine 3-pyrrolines **2g′** from both cis- and trans-isomers [Eq. 6].

Extensive work by Haake et al.[10,11] on the acidic solvolytic cleavage of the P–N bond in (thio)phosphoramidates has disclosed that the amide substrate, after initial activation via the N-protonation, undergoes a bimolecular $S_N2(P)$ displacement by solvent molecule (Scheme 2); in a given solvent, the basicity of the amide N atom and the electrophilicity of the (thio)phosphoryl center are therefore two important structural factors that significantly affect the acidic solvolysis of (thio)phosphoramidates.



(Sol: solvent)

Scheme 2. The acidic solvolysis of P–N bond: $S_N2(P)$ mechanism.

In this work, the acidic methanolysis of **1** is believed to follow the general rule mentioned above with regard to its mechanism, although little mechanistic work has yet been intentionally done. The departure of the (thio)phosphoryl group from **1** is initiated with the protonation of the pyrroline ring N atom, and completed by the following nucleophilic attack of the solvent methanol at the (thio)phosphoryl center of the protonated **1**. It is known that the protonation on nitrogen is a potent labilizing force in the nucleophilic cleavage of the P–N bond.[10] The basicity of the N atom in the (thio)phosphoramidates certainly determines its effective protonation, and in turn affects the reactivity of the (thio)phosphoramidates in the acidic methanolysis. In terms of the basicity of the N atom, the inertness of the aromatization by-product **3** in the acidic methanolysis may be accordingly interpreted: compared to that of its precursor **1**, the basicity of the N atom in **3** is weakened due to the delocalization of its lone pair electrons to the whole pyrrole ring; this weakened basicity subsequently results in the deficiency or loss of activation (catalysis) via protonation.

Besides its activation for the P–N bond in the acidic methanolysis, the protonation on nitrogen is also believed to play a critical role in inhibiting the 3-pyrroline cycle from aromatization into the pyrrole ring; protonation prevents the lone pair electrons of the N atom from making any contribution to aromatization via delocalization. This assertion may get some helpful support from recent reports[3b,c,12] on the deprotection of *N*-(2-trimethylsilylethanesulfonyl) 3-pyrrolines by fluoride: under the mediation of *n*-Bu_4NF and in a neutral media, the given 3-pyrrolines only gave the corresponding deprotected aromatization products pyrroles in moderate yields;[3b,c,12a] in sharp contrast, upon the treatment of excessive HF, the corresponding free amine pyrrolines were obtained in excellent yields.[12b]

For cis- and trans-isomers of **1g–k**, the remarkable difference in their reactivity on the acidic methanolysis most likely results from the different steric hindrance, imposed by the substituted pyrroline moiety on the $S_N2(P)$ step. The difference in the basicity of the N atoms for *cis*- and *trans*-**1** should be negligibly small; compared to that in *cis*-**1**, the trans-substituted pyrroline moiety in *trans*-**1** apparently imposes more steric hindrance for the approach of the nucleophile methanol molecule to the thiophosphoryl center from the direction opposite to that of the P–N bond in the protonated **1**. It is known that the $S_N2(P)$ step is the rate-determining step in the acidic fission of the phosphinic(oric) amides.[10,11] On the other hand, the ease of the P–N bond cleavage for both cis- and trans-isomers of the *N*-phosphoryl adduct **1g′** is attributable to the better reactivity than their thio-analogues in the acidic methanolysis, for the phosphoryl group is more electrophilic in comparison with its thio-analogue in the bimolecular nucleophilic substitution at the phosphoryl center.

3. Conclusions

In conclusion, *N*-(thio)phosphoryl imines have proven to be effective dipolarophiles in the phosphine-catalyzed [3+2] cycloaddition with activated allenes, despite they are, in general, inferior to *N*-tosyl imines with regard to their efficiencies in the reaction. The ease with the deprotection of (thio)phosphoryl groups from the cycloaddition products **1** via the acidic methanolysis, and the protonation of the N atom in **1** lead to a facile synthesis of free amine 3-pyrrolines through the phosphine-mediated [3+2] cycloaddition

of allenes with imines. Most recently, an enantioselective version of the [3+2] cycloaddition of ethyl 2,3-butadienoate with *N*-diphenylphosphinoyl imines is already realized under the catalysis of chiral phosphinothiourea.[13] Diphenylphosphinoyl has also been used as an activating group for the imine substrate in the aza-Baylis–Hillman reaction.[14] Our results in this report indicate that both phosphoryl and thiophosphoryl are convenient, cost-saving, and easily removable activating groups for the imine dipolarophile. It is therefore anticipated that *N*-(thio)phosphoryl imines could be the right dipolarophiles for the phosphine-catalyzed enantioselective [3+2] cycloaddition with activated allenes, which could further lead to an effective synthesis of enantiomer-enriched free amine 3-pyrrolines and their hydrogenation products pyrrolidines. These projected conversions are currently being explored in our laboratory.

4. Experimental section

4.1. General remarks

Unless otherwise noted, all catalytic reactions were carried out in an ambient atmosphere. Commercially available chemicals were used as received. PTA was prepared from tetrahydroxymethylphosphonium sulfate according to a previous procedure.[15] 4-Substituted 2,3-butadienoates[16] and *N*-(thio)phosphoryl imines[17] were also prepared as described in the literatures.

4.2. General procedure for the PPh_3-catalyzed [3+2] cycloaddition of ethyl 2,3-butadienoate with *N*-(*O*,*O*-diethylthiophosphoryl) imines

To a solution of the substrate imine (1 mmol) and PPh_3 (52 mg, 0.2 mmol) in anhydrous CH_2Cl_2 (5 mL), a solution of ethyl 2,3-butadienoate (224 mg, 2 mmol) in CH_2Cl_2 (3 mL) was dropwise added over 1 h with stirring at room temperature. The solution was stirred till the imine was completely consumed (monitored by TLC). The solvent and volatile components were removed on a rotary evaporator, and the resulting residue was subjected to silica gel column chromatography eluted with a mixture of petroleum ether–ethyl acetate (35:1, v/v) to give the corresponding pure adduct **1**.

*4.2.1. Ethyl 1-(O,O-diethylthiophosphoryl)-2-phenyl-3-pyrroline-3-carboxylate (**1a**)*

The cycloaddition with *N*-thiophosphoryl phenylimine was completed after stirred for 20 h. The pure title compound (180 mg, yield 49%) was obtained as colorless viscous oil after work-up and purification as described in the above general procedure. ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 7.24 (m, 5H), 6.86 (s, 1H), 5.60 (pseudo t, $J_{P-N-C-H}$=6.0 Hz, 1H), 4.45 (dq, J_{AB}=17.2 Hz, $J_{P-N-C-H}$=6.0 Hz, 2H), 4.10–3.78 (m, 5H), 3.34 (m, 1H), 1.21 (t, J=7.2 Hz, 3H), 1.12 (t, J=7.0 Hz, 3H), 0.91 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 162.2, 142.0, 136.7 (d, J=9.3 Hz), 136.5 (d, J=8.8 Hz), 127.9, 127.7, 127.5, 68.0 (d, J=4.5 Hz), 62.7 (d, J=4.5 Hz, P–O–CH_2), 62.6 (d, J=4.5 Hz, P–O–CH_2), 60.5, 56.3 (d, J=7.4 Hz), 15.7 (d, J=7.8 Hz), 15.3 (d, J=9.1 Hz), 13.9; ^{31}P NMR ($CDCl_3$, 160 MHz, 85% H_3PO_4) δ 71.0 ppm. Anal. Calcd for $C_{17}H_{24}NO_4PS$: C, 55.27; H, 6.55; N, 3.79. Found: C, 54.91; H, 6.55; N, 3.58.

*4.2.2. Ethyl 1-(O,O-diethylthiophosphoryl)-2-(p-methylphenyl)-3-pyrroline-3-carboxylate (**1b**)*

The cycloaddition with *N*-thiophosphoryl *p*-tolylimine was completed after stirred for 24 h. The title compound (230 mg, yield 60%) was obtained as colorless viscous oil after work-up and purification as described in the above general procedure. ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 7.18 (d, J=8.0 Hz, 2H), 7.07 (d, J=19.0 Hz, 2H), 6.85 (s, 1H), 5.59 (pseudo t, $J_{P-N-C-H}$=6.0 Hz, 1H), 4.45 (dq, J_{AB}=17.2 Hz, $J_{P-N-C-H}$=6.0 Hz, 2H), 4.10–3.78 (m, 5H), 3.37 (m, 1H), 2.30 (s, 3H), 1.23 (t, J=7.0 Hz, 3H), 1.14 (t, J=7.2 Hz, 3H), 0.94 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 162.3, 139.1, 137.1, 136.8 (d, J=9.0 Hz), 136.3 (d, J=8.7 Hz), 128.6, 127.5, 67.8 (d, J=4.5 Hz), 62.6 (d, J=4.8 Hz, P–O–CH_2), 62.6 (d, J=4.7 Hz, P–O–CH_2), 60.5, 56.1 (d, J=7.4 Hz), 21.1, 15.8 (d, J=8.2 Hz), 15.3 (d, J=8.9 Hz), 13.9; ^{31}P NMR ($CDCl_3$, 160 MHz, 85% H_3PO_4) δ 71.0 ppm. Anal. Calcd for $C_{18}H_{26}NO_4PS$: C, 56.38; H, 6.83; N, 3.65. Found: C, 56.21; H, 6.90; N, 3.53.

*4.2.3. Ethyl 1-(O,O-diethylthiophosphoryl)-2-(p-methoxyphenyl)-3-pyrroline-3-carboxylate (**1c**)*

The cycloaddition with *N*-thiophosphoryl *p*-anisylimine was completed after stirred for 40 h. The title compound (250 mg, yield 62%) was obtained as colorless viscous oil after work-up and purification as described in the above general procedure. ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 7.21 (d, J=8.0 Hz, 2H), 6.83 (s, 1H), 6.80 (d, J=8.0 Hz, 2H), 5.57 (pseudo t, $J_{P-N-C-H}$=5.6 Hz, 1H), 4.42 (dq, J_{AB}=17.2 Hz, $J_{P-N-C-H}$=6.2 Hz, 2H), 4.10–3.78 (m, 5H), 3.76 (s, 3H), 3.39 (m, 1H), 1.21 (t, J=7.2 Hz, 3H), 1.13 (t, J=7.2 Hz, 3H), 0.96 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 162.2, 158.9, 136.7 (d, J=9.0 Hz), 136.1 (d, J=8.8 Hz), 134.2, 128.7, 113.3, 67.4 (d, J=4.6 Hz), 62.5 (d, J=4.8 Hz, P–O–CH_2), 60.4, 55.9 (d, J=7.1 Hz), 55.1, 15.7 (d, J=7.8 Hz), 15.3 (d, J=8.5 Hz), 13.9; ^{31}P NMR ($CDCl_3$, 160 MHz, 85% H_3PO_4) δ 71.0 ppm. Anal. Calcd for $C_{18}H_{26}NO_5PS$: C, 54.12; H, 6.56; N, 3.51. Found: C, 54.35; H, 6.77; N, 3.45.

*4.2.4. Ethyl 1-(O,O-diethylthiophosphoryl)-2-(p-chlorophenyl)-3-pyrroline-3-carboxylate (**1d**)*

The cycloaddition with *N*-thiophosphoryl *p*-chlorophenylimine was completed after stirred for 7 h. The title compound (274 mg, yield 68%) was obtained as colorless viscous oil after work-up and purification as described in the above general procedure. ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 7.25 (m, 4H), 6.86 (s, 1H), 5.60 (pseudo t, $J_{P-N-C-H}$=5.6 Hz, 1H), 4.42 (dq, J_{AB}=17.2 Hz, $J_{P-N-C-H}$=5.6 Hz, 2H), 4.10–3.78 (m, 5H), 3.46 (m, 1H), 1.21 (t, J=7.2 Hz, 3H), 1.15 (t, J=7.0 Hz, 3H), 1.00 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 162.1, 140.8, 136.8 (d, J=8.4 Hz), 136.3 (d, J=7.7 Hz), 133.2, 129.1, 128.1, 67.5 (d, J=4.8 Hz), 62.8 (d, J=4.7 Hz, P–O–CH_2), 60.7, 56.0 (d, J=6.6 Hz), 15.7 (d, J=8.2 Hz), 15.4 (d, J=8.7 Hz), 13.9; ^{31}P NMR ($CDCl_3$, 160 MHz, 85% H_3PO_4) δ 70.9 ppm. Anal. Calcd for $C_{17}H_{23}ClNO_4PS$: C, 50.56; H, 5.74; N, 3.47. Found: C, 50.30; H, 6.00; N, 3.34.

*4.2.5. Ethyl 1-(O,O-diethylthiophosphoryl)-2-(o-chlorophenyl)-3-pyrroline-3-carboxylate (**1e**)*

The cycloaddition with *N*-thiophosphoryl *o*-chlorophenylimine was completed after stirred for 8 h. The title compound (165 mg, yield 41%) was obtained as colorless viscous oil after work-up and purification as described in the above general procedure. ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 7.32–7.14 (m, 4H), 6.93 (s, 1H), 6.14 (pseudo t, $J_{P-N-C-H}$=6.4 Hz, 1H), 4.45 (dq, J_{AB}=17.6 Hz, $J_{P-N-C-H}$=6.4 Hz, 2H), 4.10–3.78 (m, 5H), 3.29 (m, 1H), 1.28 (t, J=7.2 Hz, 3H), 1.12 (t, J=7.2 Hz, 3H), 0.90 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 162.1, 140.6, 139.5 (d, J=7.8 Hz), 137.6 (d, J=9.1 Hz), 133.5, 129.7, 129.4, 128.6, 126.7, 64.0 (d, J=4.5 Hz), 62.9 (d, J=5.6 Hz, P–O–CH_2), 62.7 (d, J=5.6 Hz, P–O–CH_2), 60.6, 56.9 (d, J=8.3 Hz), 15.8 (d, J=8.0 Hz), 15.3 (d, J=8.5 Hz), 13.8; ^{31}P NMR ($CDCl_3$, 160 MHz, 85% H_3PO_4) δ 70.7 ppm. Anal. Calcd for $C_{17}H_{23}ClNO_4PS$: C, 50.56; H, 5.74; N, 3.47. Found: C, 50.55; H, 5.96; N, 3.45.

*4.2.6. Ethyl 1-(O,O-diethylthiophosphoryl)-2-(p-nitrophenyl)-3-pyrroline-3-carboxylate (**1f**)*

The cycloaddition with *N*-thiophosphoryl *p*-nitrophenylimine was completed after stirred for 6 h. The title compound (315 mg, yield 76%) was obtained as yellow viscous oil after work-up and

purification as described in the above general procedure. ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 8.15 (d, J=7.6 Hz, 2H), 7.50 (d, J=7.6 Hz, 2H), 6.92 (s, 1H), 5.73 (pseudo t, $J_{P-N-C-H}$=6.0 Hz, 1H), 4.46 (dq, J_{AB}=17.6 Hz, $J_{P-N-C-H}$=6.0 Hz, 2H), 4.10–3.78 (m, 5H), 3.58 (m, 1H), 1.20 (t, J=6.8 Hz, 3H), 1.15 (t, J=6.8 Hz, 3H), 1.04 (t, J=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 161.8, 149.7, 147.2, 137.6 (d, J=8.0 Hz), 135.9 (d, J=9.9 Hz), 128.7, 123.2, 67.8 (d, J=6.1 Hz), 62.9 (d, J=4.9 Hz, P–O–CH_2), 60.9, 55.8 (d, J=6.1 Hz), 15.8 (d, J=7.6 Hz), 15.5 (d, J=8.5 Hz), 13.9; ^{31}P NMR ($CDCl_3$, 160 MHz, 85% H_3PO_4) δ 70.8 ppm. Anal. Calcd for $C_{17}H_{23}N_2O_6PS$: C, 49.27; H, 5.59; N, 6.76. Found: C, 49.25; H, 5.55; N, 6.64.

4.3. The PPh_3-catalyzed [3+2] cycloaddition of ethyl 2,3-butadienoate with *N*-(*O*,*O*-diethylphosphoryl) phenylimine

According to the general procedure for *N*-thiophosphoryl imines, instead of its thio-analogue, *N*-(*O*,*O*-diethylphosphoryl) phenylimine (242 mg, 1 mmol) was similarly reacted with ethyl 2,3-butadienoate (224 mg, 2 mmol) under the mediation of PPh_3 (52 mg, 0.2 mmol). After a similar work-up, the crude product was isolated by silica gel column chromatography (petroleum ether–ethyl acetate, 10:1), giving the corresponding normal adduct **1a′** (142 mg, yield 40%) as colorless viscous oil.

*4.3.1. Ethyl 1-(O,O-diethylphosphoryl)-2-phenyl-3-pyrroline-3-carboxylate (**1a′**)*

^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 7.65–7.18 (m, 5H), 6.87 (br s, 1H), 5.47 (m, 1H), 4.38 (m, 2H), 4.06–3.74 (m, 5H), 3.32 (m, 1H), 1.20 (t, J=6.8 Hz, 3H), 1.08 (t, J=7.2 Hz, 3H), 0.90 (t, J=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 162.3, 142.0, 137.0 (d, J=8.9 Hz), 132.1 (d, J=9.9 Hz), 128.1, 127.7, 127.6, 68.2 (d, J=5.8 Hz), 62.2 (d, J=5.4 Hz, P–O–CH_2), 62.1 (d, J=4.8 Hz, P–O–CH_2), 60.6, 55.2 (d, J=6.4 Hz), 16.1 (d, J=6.8 Hz), 15.6 (d, J=7.6 Hz), 13.9; ^{31}P NMR ($CDCl_3$, 160 MHz, 85% H_3PO_4) δ 6.9 ppm. Anal. Calcd for $C_{17}H_{24}NO_5P$: C, 57.78; H, 6.85; N, 3.96. Found: C, 57.56; H, 7.03; N, 3.87.

4.4. General procedure for the PTA-catalyzed [3+2] cycloaddition of ethyl 2,3-pentadienoate with *N*-(*O*,*O*-diethylthiophosphoryl) imines

To a stirred solution of the substrate imine (1 mmol) and PTA (32 mg, 0.2 mmol) in anhydrous CH_2Cl_2 (10 mL), neat ethyl 2,3-pentadienoate (315 mg, 2.5 mmol) was dropwise added by the means of microsyringe over 10 min at room temperature. The solution was further stirred for 48 h. After evaporation of the solvent and volatile components, the crude product was purified by silica gel column chromatography (petroleum ether–ethyl acetate, 35:1), affording the corresponding adduct **1**, which contained a pair of diastereomers with the cis-isomer being predominant. The ratio of cis- and trans-isomers in **1** was determined by ^{31}P NMR.

*4.4.1. Ethyl 1-(O,O-diethylthiophosphoryl)-5-methyl-2-phenyl-3-pyrroline-3-carboxylate (**1g**)*

By once column chromatographic purification, the normal cycloaddition product **1g** (295 mg, yield 77%) from *N*-thiophosphoryl phenylimine was obtained as colorless viscous oil with a ratio of cis- and trans-isomers of 25:1. It was then characterized as pure *cis*-**1g** without further purification. For *cis*-**1g**, ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 7.37–7.10 (m, 5H), 6.78 (br s, 1H), 5.65 (d, $J_{P-N-C-H}$=8.4 Hz, 1H), 4.82 (m, 1H), 4.10–3.75 (m, 5H), 3.29 (m, 1H), 1.55 (d, J=6.4 Hz, 3H), 1.24 (t, J=7.2 Hz, 3H), 1.11 (t, J=7.2 Hz, 3H), 0.89 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 162.6, 142.0 (d, J=8.9 Hz), 141.7, 134.2 (d, J=8.5 Hz), 128.2, 128.0, 127.5, 68.8 (d, J=4.0 Hz), 63.2 (d, J=7.3 Hz), 62.7 (d, J=5.5 Hz, P–O–CH_2), 62.4 (d, J=4.7 Hz, P–O–CH_2), 60.5, 23.3, 15.8 (d, J=7.8 Hz), 15.2 (d, J=9.3 Hz), 13.9; ^{31}P NMR ($CDCl_3$, 160 MHz, 85% H_3PO_4) δ 72.4 ppm. Anal. Calcd for $C_{18}H_{26}NO_4PS$: C, 56.38; H, 6.83; N, 3.65. Found: C, 56.45; H, 6.75; N, 3.63.

*4.4.2. Ethyl 1-(O,O-diethylthiophosphoryl)-5-methyl-2-(p-methylphenyl)-3-pyrroline-3-carboxylate (**1h**)*

By column chromatographic purification, the title compound **1h** (211 mg, yield 53%) from *N*-thiophosphoryl *p*-tolylimine was isolated as colorless viscous oil with a ratio of cis- and trans-isomers of 46:1. It was then characterized as pure *cis*-**1h** without further purification. For *cis*-**1h**, ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 7.23 (d, J=8.0 Hz, 2H), 7.08 (d, J=8.0 Hz, 2H), 6.75 (m, 1H), 5.62 (m, 1H), 4.80 (m, 1H), 4.10–3.75 (m, 5H), 3.32 (m, 1H), 2.29 (s, 3H), 1.52 (d, J=6.8 Hz, 3H), 1.23 (t, J=7.2 Hz, 3H), 1.12 (t, J=7.2 Hz, 3H), 0.90 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 162.5, 141.6 (d, J=9.1 Hz), 138.6, 137.0, 134.1 (d, J=8.6 Hz), 128.6, 128.0, 68.5 (d, J=4.0 Hz), 63.0 (d, J=7.3 Hz), 62.5 (d, J=5.3 Hz, P–O–CH_2), 62.2 (d, J=4.5 Hz, P–O–CH_2), 60.4, 23.2, 21.0, 15.7 (d, J=7.9 Hz), 15.1 (d, J=9.1 Hz), 13.8; ^{31}P NMR ($CDCl_3$, 160 MHz, 85% H_3PO_4) δ 72.4 ppm. Anal. Calcd for $C_{19}H_{28}NO_4PS$: C, 57.41; H, 7.10; N, 3.52. Found: C, 57.35; H, 7.12; N, 3.49.

*4.4.3. Ethyl 1-(O,O-diethylthiophosphoryl)-2-(p-chlorophenyl)-5-methyl-3-pyrroline-3-carboxylate (**1i**)*

By once column chromatographic purification, the normal cycloaddition product **1i** (380 mg, yield 76%) from *N*-thiophosphoryl *p*-chlorophenylimine was obtained as colorless viscous oil with a ratio of cis- and trans-isomer of 11:1. It was not further purified before identified as pure *cis*-**1i** by NMR. For *cis*-**1i**, ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 7.32 (d, J=8.4 Hz, 2H), 7.28 (d, J=8.4 Hz, 2H), 6.80 (s, 1H), 5.66 (d, $J_{P-N-C-H}$=8.8 Hz, 1H), 4.83 (m, 1H), 4.10–3.75 (m, 5H), 3.46 (m, 1H), 1.55 (d, J=6.4 Hz, 3H), 1.25 (t, J=7.2 Hz, 3H), 1.15 (t, J=7.2 Hz, 3H), 1.00 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 162.3, 142.2 (d, J=9.0 Hz), 140.4, 133.8 (d, J=8.9 Hz), 133.2, 129.6, 128.1, 68.3 (d, J=4.5 Hz), 63.0 (d, J=6.7 Hz), 62.7 (d, J=4.8 Hz, P–O–CH_2), 62.5 (d, J=4.6 Hz, P–O–CH_2), 60.6, 23.2, 15.7 (d, J=7.8 Hz), 15.3 (d, J=8.9 Hz), 13.9; ^{31}P NMR ($CDCl_3$, 160 MHz, 85% H_3PO_4) δ 72.5 ppm. Anal. Calcd for $C_{18}H_{25}ClNO_4PS$: C, 51.73; H, 6.03; N, 3.35. Found: C, 51.91; H, 6.25; N, 3.30.

*4.4.4. Ethyl 1-(O,O-diethylthiophosphoryl)-2-(o-chlorophenyl)-5-methyl-3-pyrroline-3-carboxylate (**1j**)*

By once column chromatographic purification as described in the above general procedure, the normal cycloaddition product **1j** (290 mg, yield 70%) from *N*-thiophosphoryl *o*-chlorophenylimine was obtained as colorless viscous oil with a ratio of cis- and trans-isomers of 7:1. This diastereomeric mixture was further isolated by careful column chromatography (petroleum ether as eluant), affording a small amount of pure *cis*-**1j** associated with a major fraction of cis- and trans-isomer mixture. For *cis*-**1j**, ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ 7.34–7.13 (m, 4H), 6.82 (m, 1H), 6.29 (m, 1H), 4.86 (m, 1H), 4.02 (m, 4H), 3.78 (m, 1H), 3.20 (m, 1H), 1.61 (d, J=6.6 Hz, 3H), 1.29 (t, J=6.9 Hz, 3H), 1.09 (t, J=6.9 Hz, 3H), 0.84 (t, J=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 162.0, 142.4 (d, J=9.7 Hz), 139.4, 134.2, 133.8 (d, J=8.5 Hz), 129.2, 129.1, 128.4, 126.6, 64.0, 63.3 (d, J=8.1 Hz), 62.7 (d, J=5.8 Hz, P–O–CH_2), 62.2 (d, J=4.7 Hz, P–O–CH_2), 60.4, 23.4, 15.7 (d, J=7.7 Hz), 14.9 (d, J=10.0 Hz), 13.7; ^{31}P NMR ($CDCl_3$, 120 MHz, 85% H_3PO_4) δ 71.1 ppm. Anal. Calcd for $C_{18}H_{25}ClNO_4PS$: C, 51.73; H, 6.03; N, 3.35. Found: C, 51.84; H, 6.17; N, 3.32.

*4.4.5. Ethyl 1-(O,O-diethylthiophosphoryl)-5-methyl-2-(p-nitrophenyl)-3-pyrroline-3-carboxylate (**1k**)*

By once column chromatographic purification as described in the above general procedure, the normal cycloaddition product **1k** (424 mg, yield 99%) from *N*-thiophosphoryl *p*-nitrophenylimine was obtained as colorless viscous oil with a ratio of cis- and

trans-isomers of 6:1. This diastereomeric mixture was further isolated by careful column chromatography (petroleum ether as eluant), affording a small amount of pure *cis*-**1k** associated with a major fraction of cis- and trans-isomer mixture. For *cis*-**1k**, ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ 8.18 (d, J=7.8 Hz, 2H), 7.57 (d, J=7.8 Hz, 2H), 6.82 (br s, 1H), 5.78 (d, $J_{P-N-C-H}$=9.0 Hz, 1H), 4.84 (m, 1H), 4.10–3.85 (m, 5H), 3.59 (m, 1H), 1.56 (d, J=6.6 Hz, 3H), 1.21 (t, J=6.9 Hz, 3H), 1.14 (t, J=6.9 Hz, 3H), 1.02 (t, J=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 162.1, 149.3, 147.2, 142.9 (d, J=9.1 Hz), 133.4 (d, J=9.0 Hz), 129.2, 123.2, 68.5 (d, J=5.0 Hz), 63.0 (d, J=6.1 Hz), 62.9 (d, J=5.1 Hz, P–O–*CH*$_2$), 62.8 (d, J=5.1 Hz, P–O–*CH*$_2$), 60.9, 23.1, 15.7 (d, J=7.9 Hz), 15.4 (d, J=8.7 Hz), 13.9; ^{31}P NMR ($CDCl_3$, 120 MHz, 85% H_3PO_4) δ 71.7 ppm. Anal. Calcd for $C_{18}H_{25}N_2O_6PS$: C, 50.46; H, 5.88; N, 6.54. Found: C, 50.51; H, 6.02; N, 6.38.

4.5. The PTA-catalyzed [3+2] cycloaddition of ethyl 2,3-pentadienoate with *N*-(*O*,*O*-diethylphosphoryl) phenylimine

By the procedure for its thio-analogue, *N*-(*O*,*O*-diethylphosphoryl) phenylimine (242 mg, 1 mmol) was similarly reacted with ethyl 2,3-pentadienoate (315 mg, 2.5 mmol) under the mediation of PTA (32 mg, 0.2 mmol) for 24 h. After a similar work-up, the crude product was isolated by silica gel column chromatography (petroleum ether–ethyl acetate, 10:1), giving the corresponding adduct **1g′** (198 mg, yield 54%) as colorless viscous oil. The product **1g′**, with a ratio (9:1) of cis- and trans-isomer, was identified as *cis*-**1g′** by NMR without further isolation.

4.5.1. Ethyl 1-(O,O-diethylphosphoryl)-5-methyl-2-phenyl-3-pyrroline-3-carboxylate (*1g′*)

For *cis*-**1g′**, ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 7.43–7.21 (m, 5H), 6.79 (br s, 1H), 5.48 (m, 1H), 4.75 (m, 1H), 4.10–3.90 (m, 5H), 3.73 (m, 1H), 3.23 (m, 1H), 1.52 (d, J=6.4 Hz, 3H), 1.28 (t, J=7.2 Hz, 3H), 1.10 (t, J=7.2 Hz, 3H), 0.86 (t, J=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 162.5, 142.0 (d, J=9.3 Hz), 141.8, 134.5 (d, J=9.9 Hz), 128.0, 127.9, 127.5, 68.8 (d, J=4.4 Hz), 62.3 (d, J=5.9 Hz, P–O–*CH*$_2$), 62.1 (d, J=5.9 Hz, P–O–*CH*$_2$), 61.7 (d, J=5.5 Hz), 60.4, 22.9, 16.1 (d, J=7.0 Hz), 15.4 (d, J=7.7 Hz), 13.8; ^{31}P NMR ($CDCl_3$, 160 MHz, 85% H_3PO_4) δ 7.6 ppm. Anal. Calcd for $C_{18}H_{26}NO_5P$: C, 58.85; H, 7.13; N, 3.81. Found: C, 58.79; H, 7.25; N, 3.73.

4.6. General procedure for the HCl-catalyzed methanolysis of adducts 1 and the synthesis of free amine 3-pyrrolines 2

A solution of **1** (0.5 mmol) in anhydrous hydrochloric methanol (3.5 M, 20 mL) was stirred at room temperature for 12 h, followed by gentle reflux (ca. 60 °C) for additional 24 h. The solution was then concentrated to about one tenth of its original volume under reduced pressure. The residue, after being taken into CH_2Cl_2 (20 mL), was basified with Et_3N (1 mL, in excess) and stirred at room temperature for 1 h. Removal of solvents and other volatile components on a rotary evaporator gave a syrupy stuff, which was mixed with ether (20 mL) and thoroughly stirred to precipitate the by-product hydrochloric Et_3N salt. The amine salt was filtered off and rinsed with ether (5 mL×2). The combined ethereal filtrate was evaporated to afford the crude deprotected 3-pyrroline **2**, which was subsequently purified by silica gel column chromatography via gradient elution with petroleum ether–ethyl acetate (30:1, then 10:1, finally ethyl acetate only).

4.6.1. Methyl 2-phenyl-3-pyrroline-3-carboxylate (*2a*)

From the substrate **1a** (185 mg, 0.5 mmol), the pure title compound (70 mg, yield 69%) was obtained as pale yellow liquid after work-up and purification as described in the above general procedure. ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 7.24 (m, 5H), 6.98 (br s, 1H), 5.12 (br s, 1H), 4.12 (dd, J=17.2, 5.0 Hz, 1H), 4.10 (d, J=17.2 Hz, 1H), 3.58 (s, 3H), 2.23 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 163.6, 143.4, 141.2, 137.2, 128.4, 127.4, 126.8, 68.0, 53.8, 51.3 ppm; HRMS (ESI) calcd for $C_{12}H_{14}NO_2$ [$(M+H)^+$] 204.1024, found 204.1023.

4.6.2. Methyl 2-(p-methylphenyl)-3-pyrroline-3-carboxylate (*2b*)

From **1b** (192 mg, 0.5 mmol), the title compound (83 mg, yield 76%) was obtained as pale yellow liquid after silica gel chromatography. ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 7.16 (d, J=8.0 Hz, 2H), 7.10 (d, J=8.0 Hz, 2H), 6.96 (br s, 1H), 5.16 (br s, 1H), 4.12 (m, 1H), 3.90 (m, 1H), 3.60 (s, 3H), 2.35 (br s, 1H), 2.30 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 163.6, 141.0, 140.4, 137.2, 136.9, 129.1, 126.7, 67.7, 53.7, 51.2, 20.9 ppm; HRMS (ESI) calcd for $C_{13}H_{16}NO_2$ [$(M+H)^+$] 218.1180, found 218.1170.

4.6.3. Methyl 2-(p-methoxyphenyl)-3-pyrroline-3-carboxylate (*2c*)

From **1c** (198 mg, 0.5 mmol), the title compound (75 mg, yield 64%) was obtained as pale yellow liquid after work-up and purification as described in the above general procedure. ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 7.17 (d, J=8.4 Hz, 2H), 6.94 (br s, 1H), 6.80 (d, J=8.4 Hz, 2H), 5.13 (br s, 1H), 4.12 (dd, J=17.2, 5.0 Hz, 1H), 3.88 (d, J=17.2 Hz, 1H), 3.73 (s, 3H), 3.58 (s, 3H), 2.15 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 163.6, 158.8, 140.9, 137.2, 135.6, 127.9, 113.7, 67.4, 55.0, 53.6, 51.2 ppm; HRMS (ESI) calcd for $C_{13}H_{16}NO_3$ [$(M+H)^+$] 234.1130, found 234.1123.

4.6.4. Methyl 2-(p-chlorophenyl)-3-pyrroline-3-carboxylate (*2d*)

Methanolysis of **1d** (202 mg, 0.5 mmol) yielded the title compound (102 mg, yield 86%) as pale yellow liquid after work-up and purification as described in the above general procedure. Also, a small amount of aromatization by-product **3d** (9 mg, 5%) was isolated as the first fraction from the crude product. For **2d**, ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 7.25 (d, J=8.4 Hz, 2H), 7.20 (d, J=8.4 Hz, 2H), 6.96 (br s, 1H), 5.17 (br s, 1H), 4.10 (ddd, J=17.6, 5.6, 2.0 Hz, 1H), 3.92 (m, 1H), 3.59 (s, 3H), 2.13 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 163.5, 142.2, 141.4, 137.0, 133.0, 128.5, 128.4, 67.3, 53.9, 51.4 ppm; HRMS (ESI) calcd for $C_{12}H_{13}ClNO_2$ [$(M+H)^+$] 238.0634, found 238.0627 (100) and 240.0597 (33).

4.6.5. Methyl 1-(O,O-diethylthiophosphoryl)-2-(p-chlorophenyl)-1H-pyrrole-3-carboxylate (*3d*)

Colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 7.33 (m, 5H), 6.67 (m, 1H), 4.02 (m, 2H), 3.88 (m, 2H), 3.63 (s, 3H), 1.16 (t, J=6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 164.2, 140.6, 138.7, 134.6, 132.5, 130.6, 127.3, 125.4 (d, J=9.6 Hz), 111.3 (d, J=10.2 Hz), 64.7 (d, J=4.8 Hz), 51.1, 15.5 (d, J=8.1 Hz); ^{31}P NMR ($CDCl_3$, 160 MHz, 85% H_3PO_4) δ 63.9 ppm.

4.6.6. Methyl 2-(o-chlorophenyl)-3-pyrroline-3-carboxylate (*2e*)

The title compound (75 mg, yield 63%) as pale yellow liquid was obtained from the methanolysis of **1e** (202 mg, 0.5 mmol), after work-up and purification as described in the above general procedure. ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 7.34–7.12 (m, 4H), 7.08 (br s, 1H), 5.72 (m, 1H), 3.99 (m, 2H), 3.61 (s, 3H), 2.29 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 163.5, 142.7, 140.3, 136.0, 133.4, 129.6, 128.5, 127.8, 127.0, 64.0, 53.5, 51.4 ppm; HRMS (ESI) calcd for $C_{12}H_{13}ClNO_2$ [$(M+H)^+$] 238.0634, found 238.0631 (100) and 240.0602 (33).

4.6.7. Methyl 2-(p-nitrophenyl)-3-pyrroline-3-carboxylate (*2f*)

The title compound (88 mg, yield 71%) as pale yellow liquid was obtained from the methanolysis of **1f** (207 mg, 0.5 mmol), after work-up and purification as described in the above general procedure. Also, a small amount of aromatization by-product **3f** (7 mg, 4%) was isolated as the first fraction in the column chromatography. For **2f**, ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 8.13 (d, J=8.4 Hz, 2H), 7.48

(d, J=8.4 Hz, 2H), 7.02 (br s, 1H), 5.34 (br s, 1H), 4.16 (dd, J=17.6, 5.2 Hz, 1H), 4.06 (d, J=17.6 Hz, 1H), 3.61 (s, 3H), 2.24 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 163.3, 151.2, 142.0, 140.6, 136.6, 128.1, 123.6, 67.2, 54.2, 51.6 ppm; HRMS (ESI) calcd for $C_{12}H_{13}N_2O_4$ [(M+H)$^+$] 249.0875, found 249.0876.

4.6.8. Methyl 1-(O,O-diethylthiophosphoryl)-2-(p-nitrophenyl)-1H-pyrrole-3-carboxylate (**3f**)

Colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 8.24 (d, J=8.8 Hz, 2H), 7.57 (d, J=8.8 Hz, 2H), 7.38 (m, 1H), 6.71 (m, 1H), 4.10–3.88 (m, 4H), 3.64 (s, 3H), 1.16 (t, J=6.8 Hz, 6H); ^{31}P NMR ($CDCl_3$, 160 MHz, 85% H_3PO_4) δ 63.6 ppm.

4.6.9. Methyl 5-methyl-2-phenyl-3-pyrroline-3-carboxylate (**2g**)

From **1g** (192 mg, 0.5 mmol, cis/trans 25:1), the cis-isomer (*cis*-**2g**) of the title compound (77 mg, yield 71%) was only obtained as pale yellow liquid after work-up and purification in the above general procedure. For *cis*-**2g**, ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 7.30–7.10 (m, 5H), 6.77 (br s, 1H), 5.10 (br s, 1H), 4.16 (m, 1H), 3.49 (s, 3H), 2.34 (br s, 1H), 1.25 (d, J=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 163.8, 145.9, 143.4, 136.2, 128.2, 127.2, 127.1, 68.3, 60.2, 51.2, 22.0 ppm; HRMS (ESI) calcd for $C_{13}H_{16}NO_2$ [(M+H)$^+$] 218.1180, found 218.1174.

4.6.10. Methyl 5-methyl-2-(p-methylphenyl)-3-pyrroline-3-carboxylate (**2h**)

From the methanolysis of **1h** (200 mg, 0.5 mmol, cis/trans 46:1), the cis isomer of the title compound (44 mg, yield 38%) was isolated as pale yellow liquid. For *cis*-**2h**, ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 7.18 (d, J=7.6 Hz, 2H), 7.10 (d, J=7.6 Hz, 2H), 6.83 (br s, 1H), 5.13 (br s, 1H), 4.20 (br s, 1H), 3.56 (s, 3H), 2.30 (s, 3H), 2.01 (br s, 1H), 1.31 (d, J=6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 163.8, 145.8, 140.3, 136.8, 136.2, 129.0, 127.1, 68.0, 60.2, 51.1, 21.9, 20.9 ppm; HRMS (ESI) calcd for $C_{14}H_{18}NO_2$ [(M+H)$^+$] 232.1337, found 232.1333.

4.6.11. Methyl 2-(p-chlorophenyl)-5-methyl-3-pyrroline-3-carboxylate (**2i**)

The cis-isomer of the title compound (62 mg, yield 49%) was obtained as pale yellow liquid from the methanolysis of **1i** (210 mg, 0.5 mmol, cis/trans 11:1) after work-up and purification in the above general procedure. For *cis*-**2i**, ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 7.19 (m, 4H), 6.77 (br s, 1H), 5.11 (br s, 1H), 4.20 (m, 1H), 3.52 (s, 3H), 2.16 (br s, 1H), 1.26 (d, J=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 163.8, 146.2, 142.1, 135.8, 133.0, 128.8, 128.5, 67.5, 60.2, 51.4, 22.2 ppm; HRMS (ESI) calcd for $C_{13}H_{15}ClNO_2$ [(M+H)$^+$] 252.0791, found 252.0788 (100) and 254.0758 (33).

4.6.12. Methyl 2-(o-chlorophenyl)-5-methyl-3-pyrroline-3-carboxylate (**2j**)

The cis-isomer of the title compound (69 mg, yield 55%) was isolated as pale yellow liquid from the methanolysis of **1j** (210 mg, 0.5 mmol, cis/trans 7:1). For *cis*-**2j**, ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 7.35–7.10 (m, 4H), 6.92 (br s, 1H), 5.72 (m, 1H), 4.30 (m, 1H), 3.60 (s, 3H), 2.13 (br s, 1H), 1.28 (d, J=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 163.8, 147.0, 141.0, 135.4, 133.7, 129.5, 128.4, 128.3, 127.1, 64.0, 60.2, 51.5, 22.2 ppm; HRMS (ESI) calcd for $C_{13}H_{15}ClNO_2$ [(M+H)$^+$] 252.0791, found 252.0788 (100) and 254.0758 (33).

4.6.13. Methyl 5-methyl-2-(p-nitrophenyl)-3-pyrroline-3-carboxylate (**2k**)

From the methanolysis of **1k** (214 mg, 0.5 mmol, cis/trans 6:1), the cis-isomer of the title compound *cis*-**2k** (103 mg, yield 79%) as a yellow semi-solid was isolated after work-up and purification as described in the above general procedure. Also, a small amount of transesterification product *trans*-**4k** (22 mg, 11%) was obtained as the first fraction in the column chromatography. Slow evaporation of a solution of *cis*-**2k** and equivalent picric acid in CH_2Cl_2–ethanol (50:50) yielded yellow crystals of the *cis*-**2k** picrate salt (mp 166–168 °C), which were used for the X-ray diffraction. For *cis*-**2k**, ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 8.17 (d, J=8.8 Hz, 2H), 7.53 (d, J=8.8 Hz, 2H), 6.87 (br s, 1H), 5.35 (m, 1H), 4.39 (m, 1H), 3.60 (s, 3H), 2.27 (br s, 1H), 1.37 (d, J=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 163.4, 151.2, 147.0, 146.6, 135.0, 128.5, 123.4, 67.2, 60.2, 51.4, 22.4 ppm; HRMS (ESI) calcd for $C_{13}H_{15}N_2O_4$ [(M+H)$^+$] 263.1031, found 263.1029.

4.6.14. Methyl trans-1-(O,O-diethylthiophosphoryl)-5-methyl-2-(p-nitrophenyl)-3-pyrroline-3-carboxylate (trans-**4k**)

Yellow viscous oil; ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 8.14 (d, J=8.8 Hz, 2H), 7.49 (d, J=8.8 Hz, 2H), 6.74 (br s, 1H), 5.73 (m, 1H), 4.98 (m, 1H), 3.90 (m, 3H), 3.60 (s, 3H), 3.35 (m, 1H), 1.56 (d, J=6.4 Hz, 3H), 1.22 (t, J=6.8 Hz, 3H), 0.97 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 162.4, 149.9, 147.1, 143.3 (d, J=10.4 Hz), 133.9 (d, J=11.3 Hz), 128.8, 123.1, 69.0 (d, J=6.6 Hz), 63.3 (d, J=6.6 Hz), 63.0 (d, J=4.5 Hz, P–O–CH_2), 62.7 (d, J=5.5 Hz, P–O–CH_2), 51.8, 21.5, 15.8 (d, J=7.8 Hz), 15.6 (d, J=8.2 Hz); ^{31}P NMR ($CDCl_3$, 160 MHz, 85% H_3PO_4) δ 68.5 ppm.

4.7. The HCl-catalyzed methanolysis of *N*-(*O*,*O*-diethylphosphoryl) cycloaddition product 1g′

By the above general procedure, the methanolysis of ethyl 1-(*O*,*O*-diethylphosphoryl)-5-methyl-2-phenyl-3-pyrroline-3-carboxylate (**1g′**) (184 mg, 0.5 mmol, cis/trans 9:1) yielded a mixture of the corresponding cis and trans free amines **2g** (61 mg, overall yield 56%) as pale yellow oil. Further careful column chromatographic isolation gave a small amount of pure *cis*-**2g**, which was identical to the sample from the methanolysis of **1g** by their NMR spectra.

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Supplementary data

General experimental remarks; a general procedure for the preparation of *N*-(*O*,*O*-diethyl(thio)phosphoryl)imines and their ^{1}H NMR spectra; NMR (^{1}H, ^{13}C, ^{31}P) spectra for **1**, **2**, **3**, and **4** are provided. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.07.075.

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6. Selected crystal data for **2k** conjugate with picric acid (CCDC 684846): empirical formula: $C_{19}H_{17}N_5O_{11}$. Formula weight: 491.38. Crystal space group: triclinic, *P*-1. Unit cell dimensions: a=8.250(2) Å, b=10.100(3) Å, c=13.805(4) Å, α=87.412(5)°, β=80.926(5)°, γ=74.698(4)°. F_{000}=508, Z=2, D_{calcd}=1.490 g cm^{-3}, U=1095.5(5) Å^3, T=294(2) K, λ(Mo Kα)=0.7107 Å. 5715 reflections collected in the range of $1.49 \leq \theta \leq 25.02°$, R_{int}=0.0229. Refinement method: full-matrix least-squares on F^2 to R_1=0.0507, wR_2=0.1314. The supplementary crystallographic data for this compound can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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