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Phosphine-Catalyzed (3 + 2) Annulation of δ-Acetoxy Allenoates with 2-Sulfonamidomalonate: Synthesis of Highly Substituted 3-Pyrrolines and Mechanistic Insight

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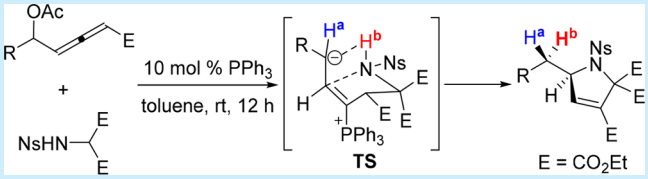
Supporting Information

ABSTRACT: A mild and efficient synthetic protocol for 3-pyrrolines via the phosphine-catalyzed (3 + 2) annulation of δ-acetoxy allenoates with 2-sulfonamidomalonate is reported. The asymmetric version (up to 83% ee) is also achieved by using phosphine (*R*)-SITCP as the catalyst. Mechanistic experiments disclose that the involved deprotonation of amide N−H and aza-addition to vinyl phosphonium might proceed in a concerted manner.



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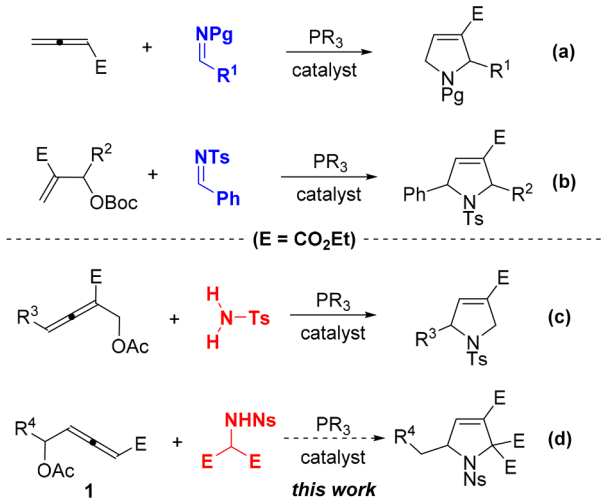
3-Pyrrolines present an important type of heterocycle due to their presence in a wide array of natural products and bioactive synthetic compounds.[1] Highly substituted 3-pyrrolines are also useful intermediates for the construction of structurally complex pyrrolidines and pyrroles.[2]

These distinct features have stimulated the development of various synthetic strategies.[3] In this context, phosphine catalysis has emerged as one of the most straightforward convergent approaches toward 3-pyrrolines with structural diversity (Scheme 1).[4] A milestone of this field is Lu's phosphine-catalyzed (3 + 2) annulation of allenoates and imines (Scheme 1a).[5] Since its first report, this methodology has been extensively investigated to extend the reaction scope and to realize an asymmetric variant.[6] The Lu group developed another elegant phosphine-catalyzed (3 + 2) annulation starting from Morita−Baylis−Hillman carbonates and imines, which provides rapid access to 2,5-disubstituted 3-pyrrolines with excellent stereoselectivity (Scheme 1b).[7] Interestingly, a phosphine catalyst is able to promote the reaction of vinylpyridines with imines to afford triarylsubstituted 3-pyrrolines.[8]

In contrast to the aforementioned cases with the use of imine electrophiles as a reaction partner, sulfonamide nucleophiles as a one-atom component can engage in phosphine-catalyzed (4 + 1) annulation of β′-acetoxy allenoates, accessing a complementary set of 3-pyrrolines that cannot be generated by the classic Lu (3 + 2) annulation (Scheme 1c).[9] The introduction of an acetate group into allenoate helps to establish the feasibility for formation of the electrophilic phosphonium diene intermediate. This chemistry has been successfully extended to δ-acetoxy allenoates **1**, which is exemplified by the annulation with several bisnucleophiles.[10] Given the intrinsic C,N-bisnucleophilicity and ready availability of 2-amidomalonates, they are undoubtedly valuable for the development of phosphine-catalyzed annulation with acetoxy allenoates. Herein, we wish to report a phosphine-catalyzed (3 + 2) annulation of 2-sulfonamidomalonate with δ-acetoxy allenoates **1** under mild reaction conditions, affording highly substituted 3-pyrrolines in good to excellent yields (Scheme 1d).

Recently, the Lewis base catalyzed transformations of δ-acetoxy allenoates **1** have been actively investigated, which disclosed that their reactivity is strongly dependent on the nature of the Lewis base catalyst and nucleophile partner.[10,11] For instance, allenoates **1** serve as a 1,3-biselectrophilic component in the amine-catalyzed (3 + 3) annulation with 1C,3O-bisnucleophiles[11a] while they are able to undergo either (2 + 3) annulation or (3 + 3) annulation with the specified 1,3-bisnucleophiles under phosphine catalysis.[10]

Scheme 1. Access to 3-Pyrrolines via Phosphine Catalysis



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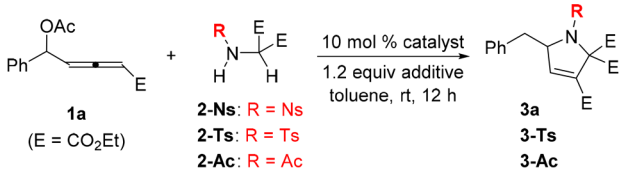
In view of the potential 1C,2N-bisnucleophilicity of 2-amidomalonate derivatives, the 1,3-biselectrophilic reactivity of allenoates **1** should be aroused to furnish (3 + 2) annulation. Thus, the reaction of allenoate **1a** and 2-sulfonamido-malonate **2-Ns** was conducted with the help of DABCO (10 mol %) and Na_2CO_3 (1.2 equiv) in toluene solvent at room temperature (Table 1, entry 1). To our disappointment, no reaction was

Table 1. Effect of Reaction Parameters[a]



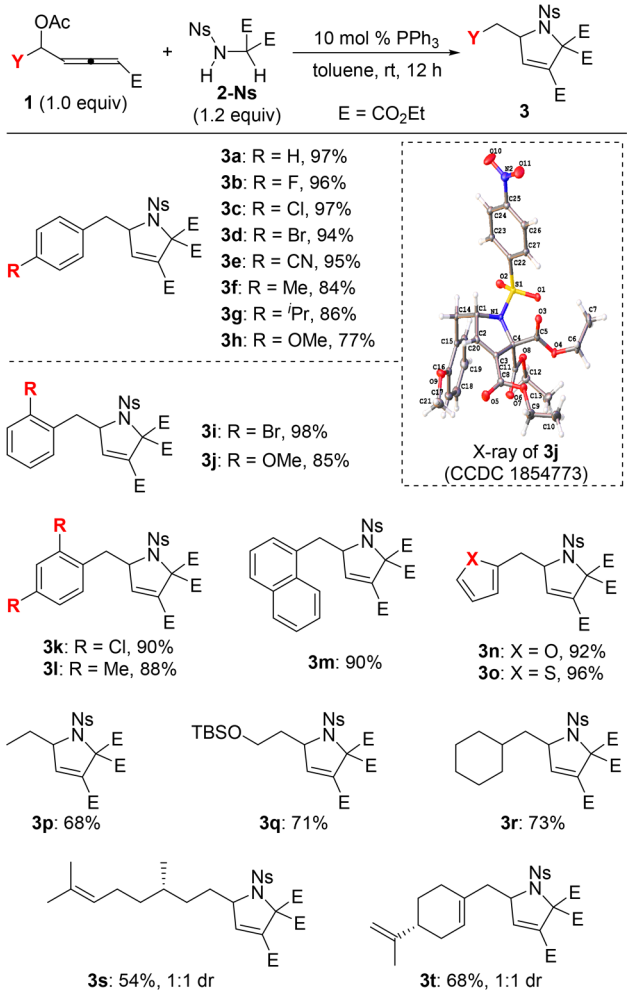
entry	2	catalyst	additive	3, yield (%)[b]
1	**2-Ns**	DABCO	Na_2CO_3	**3a**, NR[c]
2	**2-Ns**	PPh_3	Na_2CO_3	**3a**, 41
3	**2-Ns**	PPh_3	Cs_2CO_3	**3a**, 29
4	**2-Ns**	PPh_3	$NaHCO_3$	**3a**, 58
5	**2-Ns**	PPh_3	–[d]	**3a**, 97
6	**2-Ns**	PPh_3	HOAc	**3a**, 90
7	**2-Ns**	$P(^nBu)_3$	–[d]	**3a**, 32
8	**2-Ns**	$PPhMe_2$	–[d]	**3a**, 68
9	**2-Ns**	PPh_2Me	–[d]	**3a**, 60
10	**2-Ns**	$P(4\text{-F-}C_6H_4)_3$	–[d]	**3a**, 95
11	**2-Ts**	PPh_3	–[d]	**3-Ts**, 36
12	**2-Ac**	PPh_3	–[d]	**3-Ac**, NR[c]

[a]Reaction conditions: **1a** (0.12 mmol, 1.2 equiv), **2** (0.1 mmol), additive (0.24 mmol, 1.2 equiv), catalyst (10 mol %), toluene (2 mL). [b]Isolated yield. [c]NR = no reaction. [d]No additive was added. Ns = 4-nitrophenylsulfonyl, Ts = 4-methylphenylsulfonyl.

detected and the starting materials were recovered in >90% yields. However, 3-pyrroline **3a** could be obtained in 41% yield when the DABCO catalyst was replaced by PPh_3 (Table 1, entry 2). Then, a base additive was further evaluated. Cs_2CO_3 was found to be deleterious to reaction yield (Table 1, entry 3). On the other hand, $NaHCO_3$ was capable of improving the yield to 58% (Table 1, entry 4). These results indicate that the reaction efficiency might correlate negatively with the basicity of the base additive. Therefore, the PPh_3-catalyzed reaction of **1a** and **2-Ns** was carried out without any additive, which afforded compound **3a** in almost quantitative yield (Table 1, entry 5). Under this set of reaction conditions, HOAc was simultaneously generated, implying that the reaction was insensitive to acid. Indeed, a 90% yield of **3a** was still obtained even in the presence of additional HOAc (Table 1, entry 6). The stronger nucleophilic phosphines, such as $P(^nBu)_3$, $PPhMe_2$, and PPh_2Me, were proven to be somewhat less efficient while $P(4\text{-F-}C_6H_4)_3$ showed the same catalytic activity as PPh_3 (Table 1, entries 7–10). Amidomalonates **2-Ts** and **2-Ac** were also tested (Table 1, entries 11 and 12). The corresponding product **3-Ts** was isolated only in 36% yield, and product **3-Ac** was not detected at all. The strong electron-withdrawing effect of the Ns group would significantly activate the methenyl group of **2-Ns**, thus facilitating its nucleophilic addition.

With the optimal reaction conditions in hand, the substrate scope of this PPh_3-catalyzed (3 + 2) annulation was explored with a variety of allenoates **1** (Scheme 2). In general, this procedure serves as a practical and efficient approach to various polysubstituted 3-pyrrolines. As shown in Scheme 2, a wide

Scheme 2. Reaction Scope



range of phenyl substituents at the δC position of allenoates **1** [4-F-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-CN-C_6H_4, 4-Me-C_6H_4, 4-^{i}Pr-C_6H_4, 4-MeO-C_6H_4, 2-Br-C_6H_4, 2-MeO-C_6H_4, 2,4-Cl_2-C_6H_3, 2,4-Me_2-C_6H_3] were tolerated and products **3a**–**3j** were isolated in good to excellent yields. Among them, the crystal of compound **3j** was found to be suitable for X-ray diffraction analysis and its structure was thus solidly established. Compared with substrate **1a**, allenoates **1b**–**1e** with an electron-poor phenyl group also afforded the corresponding products **3b**–**3e** in excellent yields, whereas **1f**–**1h** with an electron-rich phenyl group performed relatively worse. In particular, the yield of **3h** bearing a 4-methoxyphenyl group sharply dropped to 77%. In contrast to this evident electronic effect, the steric hindrance did not affect the reaction performances, which was exemplified by the cases of **3i**–**3l**. It was found that the 1-naphthyl-substituted substrate **1m** reacted well with **2-Ns** to deliver product **3m** in 90% yield. Moreover, allenoates **1n** and **1o** bearing a heteroaryl group were also tolerated, affording **3n** and **3o** in excellent yields. While the reaction scope could be extended to allenoates **1p**–**1t** bearing an alkyl group, these reactions were somewhat less efficient and moderate yields were obtained. Interestingly, when the reaction of allenoate **1a** with ketoester analogue **4** was conducted under the optimal conditions, the desired (3 + 2) annulation product was not detected and an unexpected product **5** as a single isomer was instead isolated in 70% yield (eq 1).

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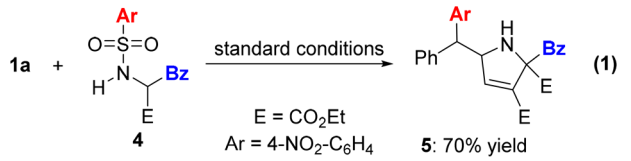
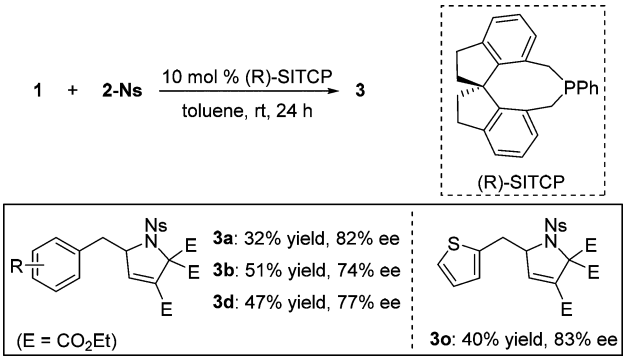


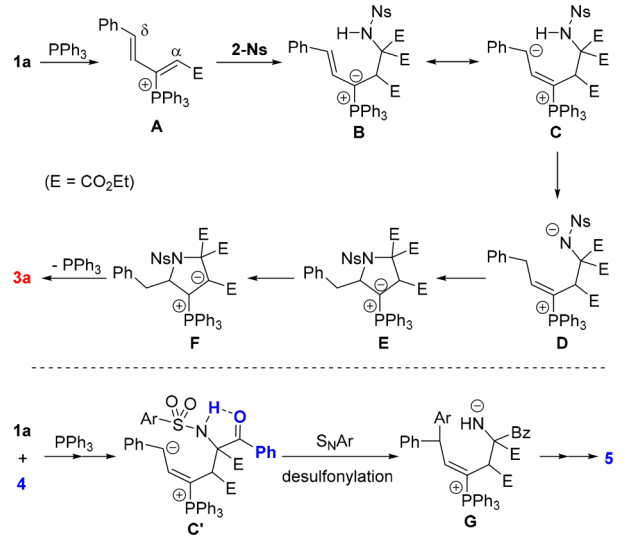
In a preliminary attempt, the asymmetric (3 + 2) annulation of **1a** and **2-Ns** was evaluated with several chiral phosphine catalysts.[12] Among them, (*R*)-SITCP[13] was found to be optimal, which gave product **3a** with 82% ee albeit only in 32% yield (Scheme 3). While the yields increased to ca. 50% for the cases of **3b** and **3d**, the enantioselectivity dropped to 74% and 77%, respectively.

Scheme 3. Preliminary Attempt at Asymmetric Variant



On the basis of these results and our previous reports, a plausible reaction mechanism for the reaction of **1a** and **2-Ns** was proposed in Scheme 4. Initially, addition of PPh_3 to

Scheme 4. Plausible Mechanisms

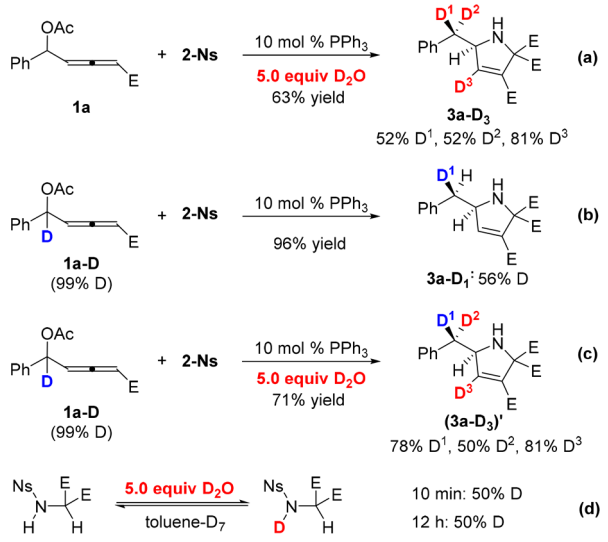


allenoate **1a** and subsequent elimination of acetate lead to 3-phosphonium-2,4-dienoate intermediate **A**. Although both αC- and δC-positions of **A** are available for nucleophilic addition, compound **2-Ns** selectively attacks αC atom to give intermediate **B** which coexists with its resonance **C**. Then, a proton shift process results in the formation of intermediate **D**, which eventually allows for intramolecular addition of the nitrogen anion to vinyl phosphonium to form ylide **E**. Finally, the sequence of proton shift and 1,2-elimination leads to product **3a** and regenerates the PPh_3 catalyst.

To account for the reaction of **1a** and **4**, we speculated that an intramolecular H-bond in the corresponding intermediate **C′** may be responsible for such unexpected behavior, which in turn enables intramolecular nucleophilic aromatic substitution (S_NAr) and concomitant desulfonylation. A similar phenomenon was also observed in the phosphine-promoted [3 + 3] annulations of aziridines with allenoates.[14] As a result, intermediate **G** is generated, which is followed by aza-addition and elimination of PPh_3 to give product **5** (Scheme 4).

In order to gain more insight into the reaction mechanism, several control experiments were carried out (Scheme 5). As

Scheme 5. Mechanistic Experiments



expected, the reaction of **1a** and **2-Ns** in the presence of additional D_2O (5.0 equiv) generated product **3a-D$_3$** with incorporation of deuterium at the βC and δC (Scheme 5a), which is consistent with the involvement of carbanion intermediates **C** and **E**. To our surprise, the reaction of allenoate **1a-D** with **2-Ns** under the standard conditions afforded product **3a-D$_1$** with excellent diastereoselectivity albeit with partial deuterium loss and no deuterium scrambling was observed (Scheme 5b). When allenoate **1a-D** was subjected to the standard conditions with addition of D_2O (5.0 equiv), product **(3a-D$_3$)′** was isolated (Scheme 5c). Compared with product **3a-D$_3$**, the deuterium content of D^1 in **(3a-D$_3$)′** increased from 52% to 78% while those of D^2 and D^3 maintained the same level. These interesting results inspired us to conclude that a fast equilibrium between intermediate **C** and H_2O should establish (Scheme 6). Afterward, the amide N−H of **C** would be intramolecularly deprotonated by its carbanion, which indicated the source of D^2 atom in either **3a-D$_3$** or **(3a-D$_3$)′** directly from the amide N−D rather than D_2O. This indication received support from the fast equilibrium between **2-Ns** and D_2O as depicted in Scheme 5d. More importantly, the observed stereochemical outcome[15] of compounds **3a-D$_1$** and **(3a-D$_3$)′** implied that this deprotonation of amide N−H and aza-addition to vinyl phosphonium might proceed in a concerted manner via transition state **TS** (Scheme 6).[12]

In summary, we have developed a phosphine-catalyzed (3 + 2) annulation of δ-acetoxy allenoates and 2-sulfonamidomalonate under mild reaction conditions, which provides practical

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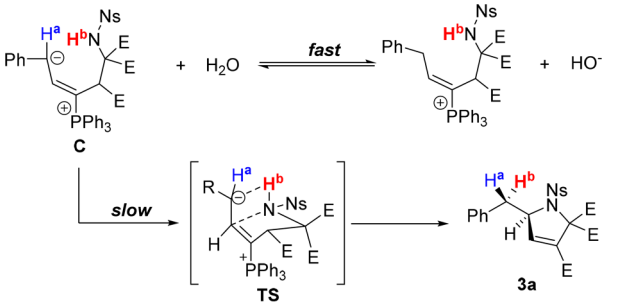
Scheme 6. Rationale for the Proton Shift Processes



and efficient access to highly substituted 3-pyrrolines. Several mechanistic experiments disclosed the underlying proton shift processes, which may be helpful to understand the importance of the proton shift process in phosphine catalysis.[16] Moreover, the reaction could easily be performed on a gram scale, and further chemical transformations of products **3** provided some compounds with interesting structures.[12]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02156.

Experimental details, data, and spectra (PDF)

Accession Codes

CCDC 1854773 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(12) For more details, see the Supporting Information.

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(15) The stereochemistry of compounds **3a-D$_1$** and (**3a-D$_3$**)′ was determined by the coupling constants: J_{H^a-H} = 9.6 Hz, J_{H^b-H} = 3.6 Hz.

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