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# Phosphine-Promoted [3 + 3] Annulations of Aziridines With Allenoates: Facile Entry Into Highly Functionalized Tetrahydropyridines

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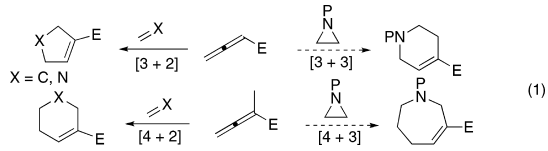
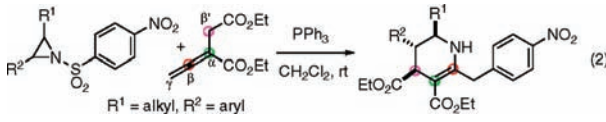
Intermolecular cycloadditions are powerful reactions for synthesizing carbo- and heterocycles from simpler starting materials.[1] The development of many transition metal- and organomolecule-promoted cycloadditions has expanded the scope of starting materials that can be engaged in such transformations.[2] Nucleophilic phosphine catalysis is now established as a reliable platform for cycloadditions employing activated allenes as one of the reaction partners.[3] In phosphine-promoted processes, allenes typically react as three- and four-carbon synthons in [3 + 2] and [4 + 2] additions, respectively, with alkenes or imines.[4] On the basis of this behavior, we pondered the possibility of employing aziridines as a three-atom components in [4 + 3] and [3 + 3] annulations with allenoates (eq 1).




(1)

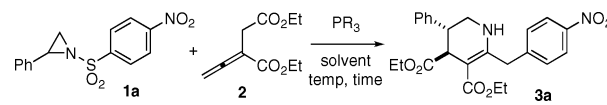
While [4 + 2] and [3 + 2] cycloadditions are widely used in organic synthesis, only a limited number of [3 + 3] additions have been reported to date.[5] Aziridines contain one of the most valuable three-membered ring systems in modern synthetic chemistry; they are extremely versatile synthetic building blocks.[6] Although formal [3 + 3] cycloadditions of aziridines with Pd−trimethylenemethane (TMM) species have been used to furnish piperidines,[5b] the phosphonium enolate zwitterionic intermediate[7] has not been employed previously for coupling with aziridines. Herein, we describe the development of a new phosphine-promoted [3 + 3] annulation of aziridines with allenoates to afford highly functionalized tetrahydropyridines under simple and mild conditions (eq 2).




(2)

Initially, we examined the reaction of *N*-nosylaziridine **1a** and diethyl 2-vinylidenesuccinate (**2**) with $PBu_3$ (20 mol %) at room temperature (Table 1, entry 1).[8] Although the aziridine was consumed completely within 24 h, we obtained no product from its coupling with the allenoate. Since the aziridine ring can be opened directly through nucleophilic attack,[9] we employed the weaker nucleophile $PPh_3$ to take advantage of its more discerning reactivity.[10] To our delight, we isolated the [3 + 3] adduct **3a** in modest yield and excellent diastereoselectivity (10:1 trans/cis; entry 2).[11] Surprisingly, the three carbon atoms constituting the tetrahydropyridine **3a** were the α, $\beta$, and $\beta'$ carbon atoms of the starting allenoate rather than the α, $\beta$, and $\gamma$ carbon atoms encountered in well-established phosphine-mediated [3 + 2] annulations.[4] Moreover, the *p*-nitrobenzene ring was attached to the $\gamma$ carbon atom of the starting allenoate, with an apparent loss of $SO_2$ (see below). The reaction yield improved significantly, without erosion of the diastereoselectivity, after an increase in the amount of $PPh_3$ (entry 3). Although NMR spectroscopy revealed that some free phosphine remained after the reaction, we added 1 equiv of phosphine to expedite the reaction (entry 4); more than 1 equiv of $PPh_3$ did not improve the reaction efficiency (entry 5). The reaction was best run in $CH_2Cl_2$ (entry 6) and at room temperature; the product decomposed at elevated temperatures (entry 7). Other tertiary phosphines did not facilitate the reaction as well as $PPh_3$ did (entries 8−11).

***Table 1.*** Phosphine-Mediated [3 + 3] Aziridine/Allene Annulation[a]




| entry | $PR_3$ | mol % | yield (%)[b] | dr (trans/cis)[c] |
|---|---|---|---|---|
| 1 | $PBu_3$ | 20 | 0 | N/A |
| 2 | $PPh_3$ | 20 | 15 | 10:1 |
| 3 | $PPh_3$ | 50 | 37 | 9:1 |
| 4 | $PPh_3$ | 100 | 73 | 9:1 |
| 5 | $PPh_3$ | 200 | 61 | 9:1 |
| 6[d] | $PPh_3$ | 100 | 63 | 9:1 |
| 7[e] | $PPh_3$ | 100 | 48 | 9:1 |
| 8 | $EtPPh_2$ | 100 | 2 | − |
| 9 | $Et_2PPh$ | 100 | 0 | N/A |
| 10 | $P(NMe_2)_3$ | 100 | 0 | N/A |
| 11 | $P(OEt)_3$ | 100 | 0 | N/A |

[a] All of the reactions were performed using 0.1 mmol of **1a** and 4.8 equiv of **2** in $CH_2Cl_2$ at room temperature for 72 h, unless otherwise specified. [b] Isolated yield. [c] Diastereoisomeric ratio determined through HPLC (internal standard: 2-bromopyridine). [d] 1,2-Dichloroethane was used as the solvent. [e] Performed at 40 °C for 48 h.

We examined a range of aziridine derivatives for their [3 + 3] annulations under the optimized reaction conditions (Table 2). Aryl-substituted aziridines underwent the reaction in good to excellent yield with good 1,2-trans diastereoselectivity; phenyl groups featuring electron-withdrawing or -donating substituents at the ortho, meta, and para positions worked well (entries 1−11), as did a naphthyl group (entry 12). Interestingly, the alkyl-substituted aziridine **1n** provided a different regioisomeric tetrahydropyridine with diminished diastereoselectivity, favoring the formation of the 1,3-cis product **3n** (entry 13).[11] Whereas aryl-substituted C−N bonds of aziridines are polarized for nucleophilic fission, alkyl-substituted carbon atoms block direct nucleophilic attack. The unsubstituted aziridine substrate provided a poorer yield (entry 14), presumably because it is more susceptible to phosphine-mediated direct ring opening, leading to undesired side products.[9]

To better understand the mechanisms of these intriguing processes, we subjected the deuterium-labeled allenoate **2D** (92% D) to [3 + 3] annulations with the aziridines **1a** and **1b** (Scheme 1). We obtained the tetrahydropyridines **3p** and **3q** in yields comparable to those of the nondeuterated allenoate **2** but with 19 and 25% D at the $\gamma$ carbon atoms of **3p** and **3q**, respectively, and 27% D at their $\beta'$ carbon atoms. The loss of deuterium content at the $\gamma$ carbon atom and its incorpora-



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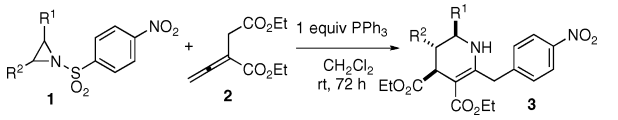
tion at the $\beta'$ carbon atom suggests the formation of intermediates featuring carbanions located at both carbon atom centers. The decrease in the overall deuterium content was due to the presence of adventitious water, which facilitated the intermolecular proton transfer processes.[12]

***Table 2.*** Syntheses of Tetrahydropyridines[a]

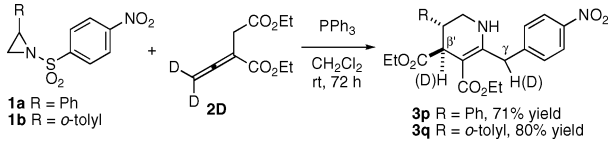



| entry | $R^1$ | $R^2$ | product | yield (%)[b] | dr (trans/cis)[c] |
|---|---|---|---|---|---|
| 1 | H (**1b**) | 2-Me$C_6H_4$ | **3b** | 88 | 90:10 |
| 2 | H (**1c**) | 3-Me$C_6H_4$ | **3c** | 82 | 86:14 |
| 3 | H (**1d**) | 4-Me$C_6H_4$ | **3d** | 64 | 89:11 |
| 4 | H (**1e**) | 2,4-$Me_2C_6H_3$ | **3e** | 82 | 81:19 |
| 5 | H (**1f**) | 2,5-$Me_2C_6H_3$ | **3f** | 98 | 92:8 |
| 6 | H (**1g**) | 4-F$C_6H_4$ | **3g** | 76 | 88:12 |
| 7 | H (**1h**) | 2-Cl$C_6H_4$ | **3h** | 46 | 97:3 |
| 8 | H (**1i**) | 3-Cl$C_6H_4$ | **3i** | 86 | 83:17 |
| 9 | H (**1j**) | 4-Cl$C_6H_4$ | **3j** | 84 | 90:10 |
| 10 | H (**1k**) | 3-Br$C_6H_4$ | **3k** | 58 | 85:15 |
| 11 | H (**1l**) | 4-Br$C_6H_4$ | **3l** | 75 | 88:12 |
| 12 | H (**1m**) | 2-naphthyl | **3m** | 58 | 85:15 |
| 13 | Me (**1n**) | H | **3n** | 66 | 41:59 |
| 14 | H (**1o**) | H | **3o** | 37 | N/A |

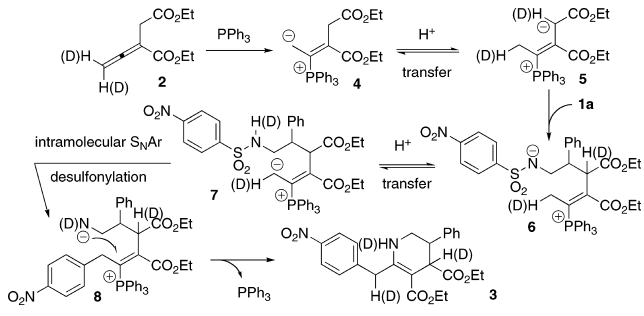
[a] All of the reactions were performed using 0.1 mmol of the aziridine and 4.8 equiv of the allenoate. [b] Isolated yield. [c] Diastereoisomeric ratio determined using HPLC (internal standard: 2-bromopyridine).

On the basis of these observations, our suggested reaction mechanism is presented in Scheme 2. Addition of $PPh_3$ to the allenoate forms the intermediate **4**, which undergoes proton transfer to give the vinylogous ylide **5**. Aziridine ring opening occurs at the $\beta'$ carbon atom to furnish the intermediate **6**.[13] Sulfonamide/dienolate equilibrium[4i] provides the intermediate **7**, which undergoes intramolecular[14] nucleophilic aromatic substitution and concomitant desulfonylation.[15] Subsequent conjugate addition and $\beta$-elimination of $PPh_3$ generates the tetrahydropyridine product **3**.[16]

***Scheme 1.*** Deuterium Labeling Experiments




***Scheme 2.*** Suggested Mechanism for the [3 + 3] Annulation




In summary, we have developed a phosphine-mediated [3 + 3] cycloaddition annulation manifold for allenes, incorporating, for the first time, aziridine derivatives as reaction partners. The reaction is operationally simple and produces highly functionalized tetrahydropyridines in good to excellent yield with high levels of diastereoselectivity. The allenoate provides its $\alpha$, $\beta$, and $\beta'$ carbon atoms in the [3 + 3] cycloaddition, thereby exhibiting a new mode of reactivity for this versatile class of molecules. The mechanism includes apparent intramolecular nucleophilic aromatic substitution and extrusion of $SO_2$; this unprecedented behavior expands the reaction repertoire of nucleophilic phosphine catalysis. We are currently exploring further applications of azidirines in nucleophilic phosphine catalysis.

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**Supporting Information Available:** Representative experimental procedures, spectral data for all new compounds, and crystallographic data for **3a** and **3n** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Employment of an enantiomerically pure aziridine provided an optically pure tetrahydropyridine. See the Supporting Information for details.
(14) We obtained no crossover product when we reacted the allenaote **2** with a 1:1 mixture of a doubly (deuterium) labeled aziridine and a regular aziridine. See the Supporting Information for details.
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(16) We suspect that the deuterium atom on the enamine nitrogen atom is exchanged for a hydrogen atom from the solvent used for NMR spectroscopy; see the Supporting Information for details.

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