

PPh₃-Catalyzed (3 + 3) Annulations of 5-Acetoxy-penta-2,3-dienoate with 1C,3O-Bisnucleophiles: Facile Entry to Stable Monocyclic 2H-Pyrans

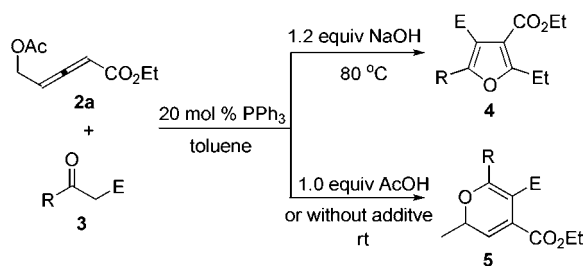
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ABSTRACT

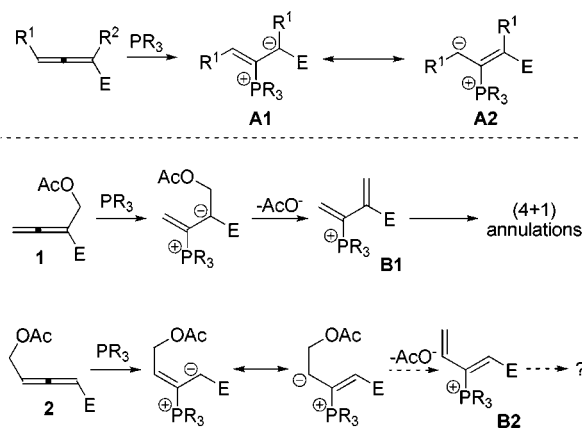


Phosphine-catalyzed (3 + 2) and (3 + 3) annulations between 5-acetoxy-penta-2,3-dienoate and 1C,3O-bisnucleophiles are presented. The former cases can be achieved with the assistance of base while the latter is dominant without any additive. A series of deuterium-labeling experiments disclosed that the divergence in annulations is likely determined by the involved proton transfer processes.

Tertiary phosphine is an important class of Lewis base catalysts,¹ which has shown great potential for the catalysis of numerous reactions, such as the Morita–Baylis–Hillman reaction,² Rauhut–Currier reaction,³ Michael addition,⁴ etc.⁵ In this regard, phosphine catalysis of activated allene has attracted extensive attention, which strongly relies on, from the point of view of reaction mechanism, the formation of zwitterionic intermediates **A1** and **A2** (Scheme 1).⁵

Recently, we have developed a novel intermediate **B1** via a two-step process: addition of a phosphine catalyst to

Scheme 1. Phosphine-Catalyzed Reactions of Activated Allene (E = activated group)



allenoate **1** and subsequent elimination of an acetate group. **B1** has been proven to be a good 1,4-biselectrophilic intermediate for (4 + 1) annulations (Scheme 1).⁶ Our continuing

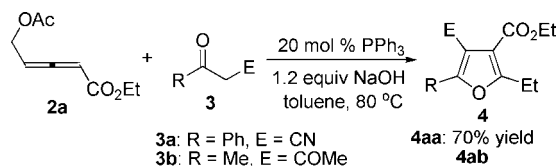
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efforts along this line allow us to focus on allenolate **2**.⁷ We envisioned that **2** would also be able to undergo a similar addition–elimination process to form intermediates **B2** which might be labile for further transformations (Scheme 1). Herein, we report the phosphine-catalyzed (3 + 3) annulations between allenolates **2a–2d** and 1C,3O-bisnucleophiles (Tables 1–3). Moreover, the (3 + 3) annulations provide a facile entry to stable monocyclic 2*H*-pyrans which are greatly challenging targets in organic synthesis⁸ since they readily undergo a reversible electrocyclic ring opening⁹ to 1-oxatrienes.

Scheme 2. PPh₃-Catalyzed (3 + 2) Annulations



We realized at the outset that the electron-withdrawing effect of phosphinium and ester groups could enable the alkene(s) of **B** being attacked by a nucleophile. Thus, we began our investigation by treating the mixture of allenolate **2a** (1.2 equiv) and PPh₃ (20 mol %) with pronucleophile **3a** (1.0 equiv) and a base (Scheme 2). After several attempts, we were pleased to find that the PPh₃-catalyzed (3 + 2) annulation between **2a** and **3a** could be achieved using NaOH (1.2 equiv) as a base in toluene at 80 °C and furan product **4aa** was isolated in 70% yield. This transformation could be extended to pentane-2,4-dione **3b**, although the corresponding product **4ab** could not be isolated in a pure form (see Supporting Information). However, other 1,3-dicarbonyl compounds failed to achieve (3 + 2) annulations under the conditions and complicated reactions were found in most cases.

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Table 1. Optimization of Reaction Conditions for (3 + 3) Annulations^a

run	3	solvent	temp (°C)	5 /yield ^b
1	3a	toluene	50	5aa /22%
2 ^c	3a	toluene	50	5aa /58%
3 ^c	3b	toluene	50	5ab /70%
4	3b	toluene	50	5ab /75%
5	3b	toluene	rt	5ab /92%
6	3b	THF	rt	5ab /90%
7	3b	acetone	rt	5ab /74%
8	3b	DCM	rt	5ab /20%
9	3b	MeCN	rt	5ab / $<$ 5%

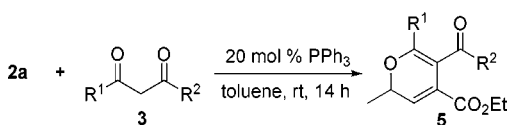
^a Reactants were conducted with 1.2 equiv of **2a** and 1.0 equiv of **3**, 16 h. ^b Isolated yield. ^c 1.0 equiv of HOAc was added.

During the course of further optimization of reaction condition for the (3 + 2) annulations, it was unexpected to find that, without any base additive, the furan product **4aa** was not detected but the (3 + 3) annulation product 2*H*-pyran **5aa** was isolated instead (Table 1, run 1). Surprisingly, addition of HOAc (1 equiv) to the reaction of **2a** and **3a** improved the yield of **5aa** from 22% to 58% under otherwise identical conditions (Table 1, run 2). However, it was found that the HOAc additive had no similar positive effect on the reaction of **2a** and **3b**; the yield of **5ab** was 70% in the presence of HOAc while the corresponding yield was 75% in the absence of HOAc (Table 2, runs 3 and 4). Without the HOAc additive, the reaction of **2a** and **3b** took place smoothly even at room temperature to afford **5ab** in 92% yield (Table 1, run 5). Further solvent screening proved that toluene was optimal and other solvents, such as THF, acetone, DCM, and MeCN, did not exhibit any superior performance in terms of reaction yield (Table 1, runs 6–9).

With these promising results in hand, we then turned our attentions toward investigating the reaction scope of (3 + 3) annulations of **2a** with various 1C,3O-bisnucleophiles, and the results are summarized in Table 2. 1,3-Dicarbonyl compounds **3c** and **3d** also smoothly underwent (3 + 3) annulations with **2a** to afford the corresponding products in high yields (Table 2, entries 1–3). It should be noted that unsymmetrical 1,3-dicarbonyl compound **3c** suffered regioselectively, affording two separable isomers **5ac-1** (49% yield) and **5ac-2** (42% yield) (Table 2, entry 2). 3-Oxo-esters **3e–3h** proved to be suitable partners for (3 + 3) annulations with **2a**, leading to the corresponding 2*H*-pyran products in high yields (Table 2, entries 4–7).

To our delight, a variety of δ -substituted allenolates, such as **2b**, **2c**, and **2d**, were also suitable substrates for this process, and the desired (3 + 3) annulation products **5ba–5de** were obtained in good to excellent yields (Table 3, entries 1–8). However, substrate **2e**, with a phenyl group at

Table 2. Reaction Scope of (3 + 3) Annulations of **2a** with 1C,3O-Bisnucleophiles^a



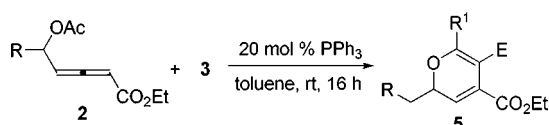
entry	3	5	yield (%) ^b
1		5ab (R ² = Me)	92
2		5ac-1 (R ² = Ph) 5ac-2 (R ² = Me)	49 42
3		5ad (R ² = Ph)	87
4		5ae (R ² = OMe)	93
5		5af (R ² = OEt)	84
6		5ag (R ² = OMe)	82
7		5ah (R ² = OEt)	91

^a Reaction conditions: for details please see the Supporting Information. ^b Isolated yield.

the δ -position, did not give the corresponding product (Table 3, entry 9). In all cases of the (3 + 3) annulations, no (3 + 2) annulation products were detected.

While the mechanisms of these two unprecedented annulations, especially the intriguing divergence in annulations, have not been firmly established, we believed that the reactions were initiated by the addition of PPh₃ to **2a**, resulting in zwitterion **A3** and **A4** formation (Scheme 3). The installation of an acetate group at the δ -position would facilitate the process of 1,2-elimination to generate intermediate **B2**, which is believed to be electrophilic due to the electron-withdrawing effect of phosphinium and ester groups. Michael addition of **3a** to **B2** and subsequent resonance would result in the formation of intermediate **D**.¹⁰ Under basic conditions, the carbanion of **D** would selectively abstract H¹ to form zwitterions **E1** and **E2**. The carbanion of **E2** might serve as a base to promote oxo-Michael addition in 5-endo fashion to generate **G** via intermediate **F**, which was followed by 1,2-elimination of the PPh₃ catalyst to release the (3 + 2) annulation product. On the other hand, under acidic conditions, the carbanion of **D** would undergo intermolecular hydrogen atom abstraction from HOAc to generate **H**. Selective deprotonation of H² of intermediate **H** would result in the formation

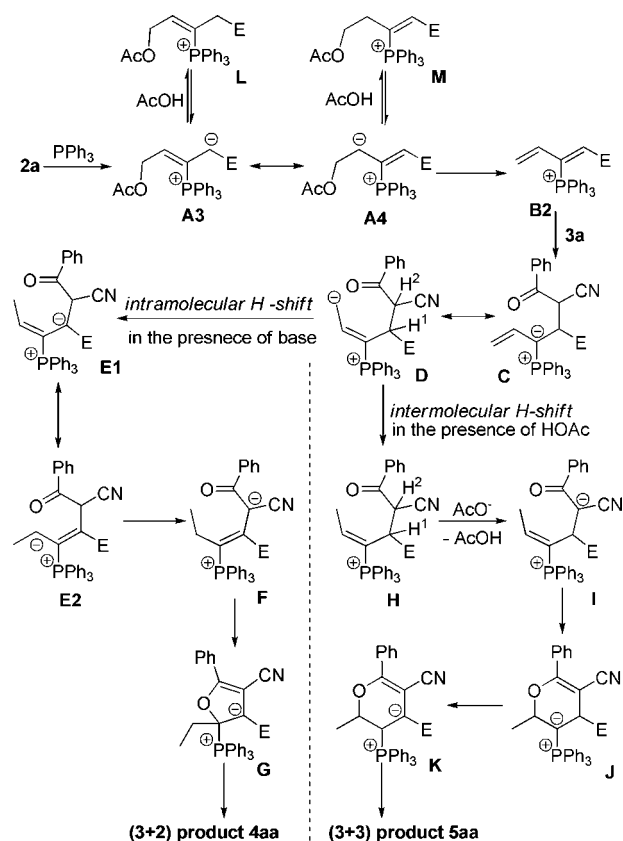
Table 3. Reaction Scope of (3 + 3) Annulations of **2b–2e** with 1C,3O-Bisnucleophiles^a



entry	2 (R)	3	5	yield (%) ^b
1 ^c	2b (<i>n</i> -Pr)	3a	5ba	48
2	2b (<i>n</i> -Pr)	3b	5bb	83
3	2b (<i>n</i> -Pr)	3d	5bd	95
4	2b (<i>n</i> -Pr)	3e	5be	96
5	2c (Bn)	3b	5cb	66
6	2c (Bn)	3d	5cd	41
7	2c (Bn)	3e	5ce	68
8	2d [(CH ₂) ₂ OTBS]	3e	5de	88
9	2e (Ph)	3e	5ee	trace

^a For reaction conditions, see the Supporting Information. ^b Isolated yield. ^c 1.0 equiv of HOAc was added, and the reaction was run at 50 °C.

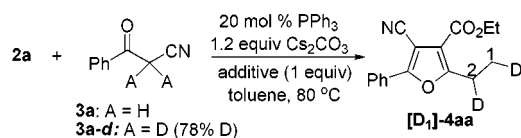
Scheme 3. Proposed Catalytic Cycles (with **2a** and **3a** as substrates)



of intermediate **I**. Then, a 6-endo oxo-Michael addition would occur to form intermediate **J**, which was followed by 1,2-proton transfer and 1,2-elimination of the phosphine catalyst to generate the (3 + 3) annulation product.

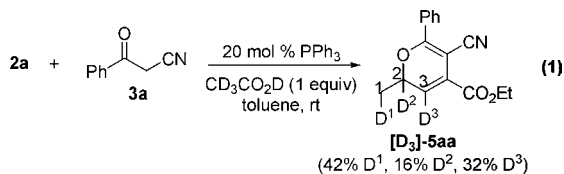
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Scheme 4. Deuterium-Labeling Studies on (3 + 2) Annulation between **2a** and **3a**



entry	3	additive	[D ₁]-4aa
1	3a-d	--	24% D ² , <5% D ¹
2	3a	D ₂ O	56% D ² , 5% D ¹

To provide more information about the reaction mechanism, a series of deuterium-labeling studies were conducted. The reaction of **2a** and deuterated **3a-d** produced partially deuterated product **[D₁]-4aa** with incorporation of deuterium at the C2 position (Scheme 4, entry 1). When D₂O (1 equiv) was added into the reaction of **2a** and **3a**, **[D₁]-4aa** with incorporation of deuterium into the C2 position was also obtained (Scheme 4, entry 2). In these two cases, no deuterium was found to be incorporated at the C1 position. These results exclude the possibility that the hydrogen atom of the C1 position stems from **3a** or the reaction medium, which are consistent with the presumption that the carbanion of **D** would selectively abstract H¹ by way of intramolecular H-transfer.¹¹



In the case of (3 + 3) annulations, the reaction of **2a** and **3a** in the presence of CD₃CO₂D (1 equiv) gave **[D₃]-5aa**

(11) For the deuterium-labeling studies as shown in Scheme 4, the following two issues should be noted: (1) Unfortunately, we failed to synthesize α -deuterated **2a** at this stage. (2) The less deuterium incorporation at C1 position might also result from the shorter lifetime of intermediate **D**.

(12) **3a-d** was also employed to probe the (3 + 3) annulation mechanism. For details, please see the Supporting Information. However, we found that **3a** was obtained instead when **3a-d** was stirred in toluene solution in the presence of AcOH (1 equiv) and NaOAc (20 mol %) for 1 h.

(13) In recent computational and experimental studies, Yu, Kwon and their co-workers found that water plays an important role on the proton transfer processes to facilitate phosphine-catalyzed [3 + 2] cycloaddition: (a) Xia, Y.; Liang, Y.; Chen, Y.; Wang, M.; Jiao, L.; Huang, F.; Liu, S.; Li, Y.; Yu, Z.-X. *J. Am. Chem. Soc.* **2007**, *129*, 3470. (b) Mercier, E.; Fonovic, B.; Henry, C.; Kwon, O.; Dudding, T. *Tetrahedron Lett.* **2007**, *48*, 3617. (c) Liang, Y.; Liu, S.; Yu, Z.-X. *Synlett* **2009**, 905.

with incorporation of deuterium at the C1, C2, and C3 positions (eq 1).¹² The presence of deuterium at the C1 position of **[D₃]-5aa** partially supported the mechanism of intermolecular proton transfer of intermediate **D** under acidic conditions. Furthermore, the presence of deuterium at the C2 position inspired us to propose that zwitterions **A3** and **A4** would be protonated by AcOH, leading to the formation of intermediates **L** and **M**, respectively (Scheme 3), which indicated that 1,2-elimination of the acetate group might be a slow step. The absence of deuterium at the C1 position of **[D₁]-4aa** implied that H₂O would not be able to promote similar protonation processes.

In the absence of AcOH, the carbanion of intermediate **D** selectively abstracted H¹ likely due to the formation of more stable zwitterions **E1** and **E2**, leading to (3 + 2) annulation. In the presence of AcOH, intermediate **D** would undergo intermolecular proton transfer preferentially to form intermediate **H** whose H² was abstracted in turn, resulting in (3 + 3) annulation. Thus, AcOH seems to serve as a switch of proton transfer processes and play essential roles in the divergence in annulations.¹³

In summary, we have developed the phosphine-catalyzed (3 + 2) and (3 + 3) annulations between allenolate **2** and 1C,3O-bisnucleophiles; the former are favored with the assistance of a base additive while the latter are achieved under acidic reaction conditions. The transformations provide facile access to two important classes of heterocycles, furan and 2H-pyran, respectively. The mechanistic investigations disclosed that the divergence in annulations might be strongly dependent on the involved proton transfer processes. Further understanding of the mechanism via computational studies and the development of an enantioselective variant are being pursued and will be reported in due course.

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Supporting Information Available. Experimental procedures and copies of NMR spectra for all new products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.