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COMMUNICATION

Phosphine-Catalyzed Regiodivergent Annulations of γ-Substituted Allenoates with Conjugated Dienes

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A phosphine catalyzed regiodivergent annulations of γ-substituted allenoates with conjugated dienes is reported, and the highly functionalized cyclohexenes or cyclopentenes were obtained in high yields and regioselectivities. This transformation takes advantage of mild conditions, wide substrate scope and significant functional group tolerance. The high regioselectivity can be achieved by tuning the nucleophilicity of the phosphine catalyst.

Functionalized cyclohexenes are valuable intermediates in organic synthesis, and they are also widely found in natural products and pharmaceuticals (Figure 1).[1-4] Thus, the development of efficient strategies for the construction of these motifs is highly desirable in the field of synthetic chemistry and medicinal chemistry.[5]

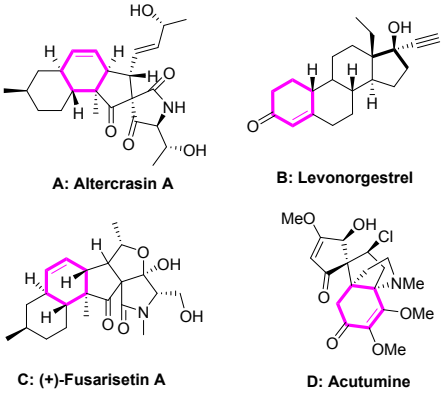
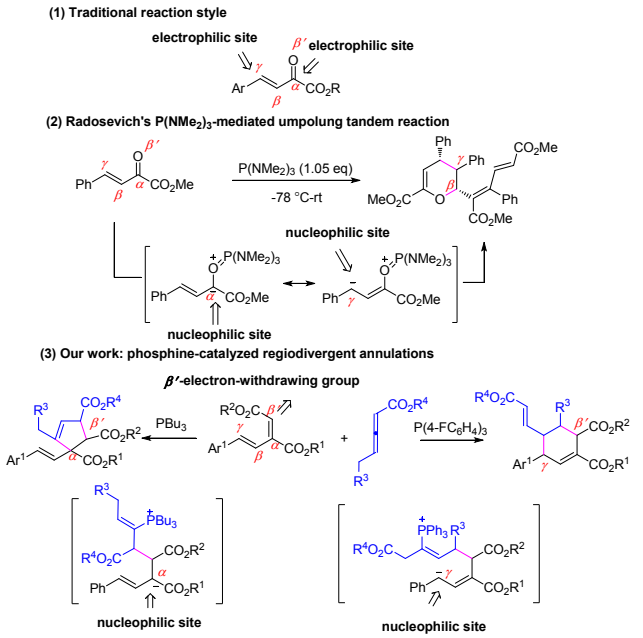


Figure 1. Selected natural products and bioactive molecules

Since Lu's (3 + 2) was reported in 1995,[6] phosphine-catalyzed annulation of allenoates has become one of the most efficient methods to construct diverse cyclic compounds.[7] However, most of these reactions occurred at α, β, γ- or β′-positions of 2, 3-butadienoates and α-substituted allenoates to form various (1 + 4),[8] (2 + 2 + 2),[9] (2 + 3),[10] (3 + 2),[11] (4 + 1)[12] and (4 + 2)[13] cyclized products. In 2009, He's group and Huang's groups reported the first phosphine-catalyzed annulation reactions at less reactive δ site of γ-methyl allenoates, respectively.[14] Series of phosphine-catalyzed domino reactions of γ-benzyl allenoates[15] and γ-acetoxymethyl substituted allenoates[16] were developed. The presence of a phenyl or acetoxy moiety improves the reactivity of δ carbon. However, Lu's (3 + 2) reaction has remained dormant due to the higher electrophilicity of allenoate's α site.[17] It is still a challenge for developing new methods involving the δ site of γ-methyl allenoate in a highly controllable manner.[18]



Scheme 1. Phosphine-catalyzed annulations of allenoates

Nucleophilic addition of β, γ-unsaturated α-ketoester usually occurs at more electrophilic α or γ site (Scheme 1, (1)).[19] In 2013, Radosevich reported a $P(NMe_2)_3$–mediated

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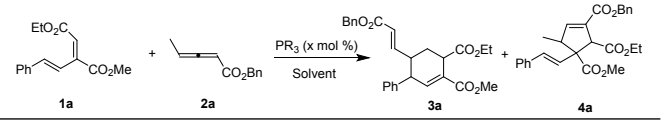
nucleophilic/electrophilic umpolung of the *γ*-site of *β*, *γ*-unsaturated *α*-ketoester (Scheme 1, (2)).[20] Inspired by this result, we developed and utilized a molecular engineering approach for a catalytic *γ*-umpolung. Herein, we report a phosphine-catalyzed regiodivergent annulation of *γ*-substituted allenoates with a new diene moiety (Scheme 1, (3)). It should be noted that the selectivity between (4 + 2) (*δ*-addition) and (3 + 2) (*α*-addition) annulations can be tuned by the Lewis basicity of the phosphine catalysts.

Initially, we investigated the reaction of conjugated diene **1a** and benzyl *γ*-methyl allenoates **2a** as model substrates under the influence of a variety of phosphines and solvents, as shown in Table 1. Both PPh_3 (Table 1, entries 1-4) and (4-$MeOC_6H_4)_3P$ (entry 7) were less effective for the model reaction, giving (4 + 2) and (3 + 2) annulations products in low selectivity. A series of other solvents, including CH_2Cl_2 (entry 2), toluene (entry 3), and THF (entry 4), were also examined, but none of these solvents performed better than $CHCl_3$ (entry 1). In contrast, when the reaction was carried out using Ph_2PMe (entry 5) or (4-$FC_6H_4)_3P$ (entry 8), (3 + 2) product **4a** (entry 5) and (4 + 2) product **3a** (entry 8) were obtained, respectively, in high yields and good selectivity. The selectivity for **4a** could be improved further by using PBu_3 as catalyst (entry 6). In the case of (4-$FC_6H_4)_3P$ catalyzed (4 + 2) cyclization, increasing the reaction temperature (entry 5) or the loading of the catalyst (entries 11, 12) resulted in higher conversions at the cost of selectivity. Running the reaction at 0 °C led to almost no formation of the desired product (entry 9). Therefore, complementary conditions (entries 6, 8) were established to access both regioisomers.

Table 1. Optimization of the reaction conditions.[a]



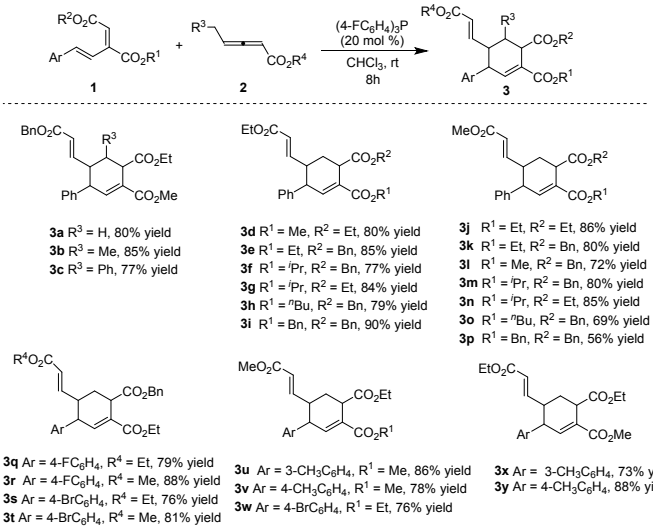
1a 2a 3a 4a

entry	catalyst	solvent	time (h)	yield (%)[b] 3a	4a
1	PPh_3 (20)	$CHCl_3$	5	43	35
2	PPh_3 (20)	CH_2Cl_2	5	27	13
3	PPh_3 (20)	Toluene	5	trace	trace
4	PPh_3 (20)	THF	5	trace	trace
5	Ph_2PMe (20)	$CHCl_3$	4	5	72
6	**PBu_3 (20)**	**$CHCl_3$**	**0.2**	**-**	**90**
7	(4-$MeOC_6H_4)_3P$ (20)	$CHCl_3$	8	19	10
8	**(4-$FC_6H_4)_3P$ (20)**	**$CHCl_3$**	**8**	**80**	**2**
9[c]	(4-$FC_6H_4)_3P$ (20)	$CHCl_3$	20	7	trace
10[d]	(4-$FC_6H_4)_3P$ (20)	$CHCl_3$	5	78	14
11	(4-$FC_6H_4)_3P$ (50)	$CHCl_3$	5	61	26
12	(4-$FC_6H_4)_3P$ (100)	$CHCl_3$	3	66	25

[a] Unless otherwise specified, all reactions were carried out using **1a** (0.3 mmol) and **2a** (0.45 mmol) at room temperature. [b] Isolated yield. [c] Reaction temperature: 0 °C. [d] Reaction temperature: 50 °C.

Subsequently, the scope of the substrates has been investigated under optimized conditions to evaluate the control of selectivity between **3** and **4**.

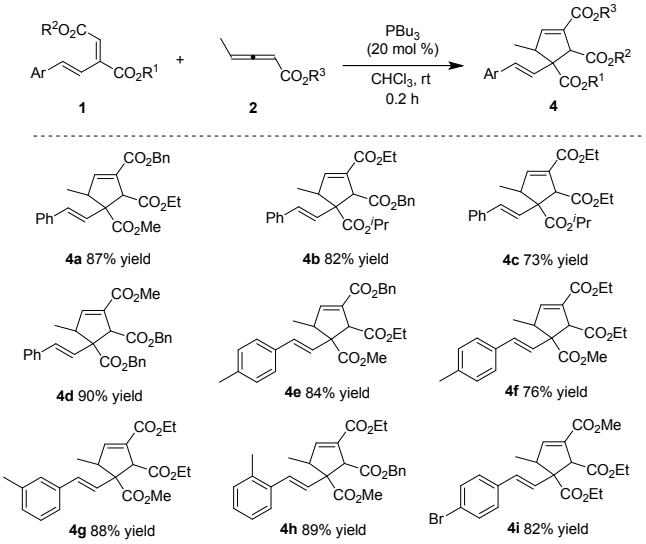
A wide range of cyclohexenes **3** have been selectively prepared with (4-$FC_6H_4)_3P$ catalyst, the results are summarized in Scheme 2. The reactions proceeded smoothly with various conjugated dienes **1** and *γ*-substituted allenoates (Scheme 2, **3a**-**3y**). The aryl moieties bearing functional groups such as *para*-F (**3q**, **3r**), *para*-Br (**3s**, **3t**, **3w**), and *meta*-Me (**3u**, **3x**) were all well-converted into the desired products in 73−88% yields. The structures of **3** were characterized by a combination of NMR, HRMS spectra, and single crystal X-ray analysis (**3w**) (*see Supporting Information*).



[a] Unless otherwise specified, all reactions were carried out using **1a** (0.3 mmol) and **2a** (0.45 mmol) at room temperature. [b] Isolated yield.

Scheme 2. Substrate scope for the synthesis of products **3**.

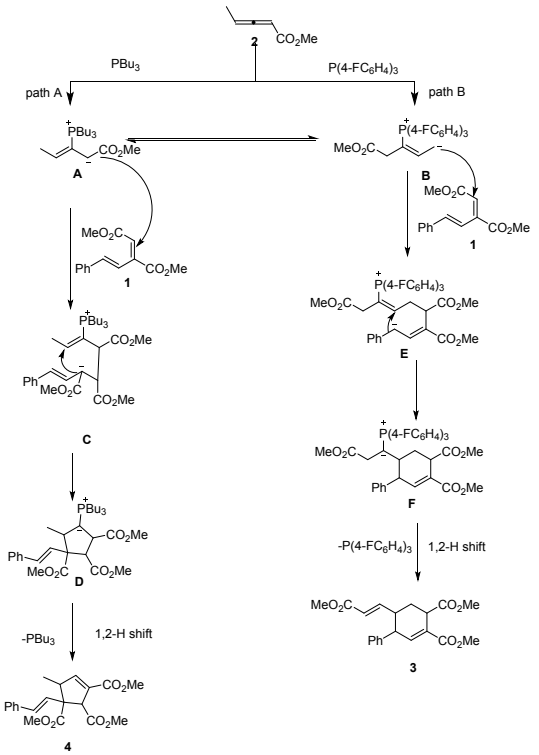
The representative results of the PBu_3-catalyzed (3 + 2) annulations are listed in Scheme 3. In all cases, the desired products were isolated in high yields and good selectivities.



[a] Unless otherwise specified, all reactions were carried out using **1a** (0.3 mmol) and **2a** (0.45 mmol) at room temperature. [b] Isolated yield.

Scheme 3. Substrate scope for the synthesis of products **4**.

On the basis of these results, [21] a plausible mechanism was proposed (Scheme 4). The reaction was initiated by the nucleophilic attack of the phosphine catalyst on the allenoates **2** to form intermediates **A** or **B**. We hypothesized that the phosphine might impose different inducing effects to achieve site selectivity, which depended on the Lewis basicity. The electron-rich PBu_3 is more prone to **A**, while **B** is preferred by the electron-deficient $(4\text{-}FC_6H_4)_3P$. Intermediates **A** and **B** undergo addition reaction with **1** to produce intermediate **C** and **E,** respectively. The following annulation reaction and proton-transfer process lead to the formation of **3** or **4** with the regeneration of the catalyst.



Scheme 4. Proposed mechanism

Conclusions

In summary, we have designed and developed a phosphine catalyzed site selective annulations of *γ*-substituted allenoates with conjugated dienes. The impact of catalyst and substrate on the final product suggest that the activity and selectivity could be tuned through appropriate molecular engineering. The method has also enabled the selective preparation of cyclohexenes and cyclopentenes in good yields. Further studies on an asymmetric version of these annulations and applications for the synthesis of biologically active molecules are underway.

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Conflicts of interest

The authors declare no competing financial interests.

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