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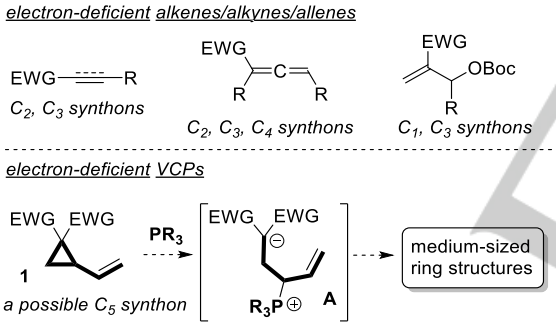
Phosphine-Catalyzed Activation of Vinylcyclopropanes: Rearrangement of Vinylcyclopropylketones to Cycloheptenones

Jun Wu, Yuhai Tang, Wen Wei, Yong Wu, Yang Li, Junjie Zhang, Yuansuo Zheng, and Silong Xu*

Abstract: We report a phosphine-catalyzed activation of electron-deficient vinylcyclopropanes (VCPs) to generate an ambident C_5 synthon that is poised to undergo consecutive reactions. The utility of the activation is demonstrated in a phosphine-catalyzed rearrangement of vinylcyclopropylketones to cycloheptenones in good yields with a broad substrate scope. Mechanistic investigations support a stepwise process comprising homoconjugate addition, water-involved hydrogen transfer, and 7-*endo*-trig S_N2' ring closure.

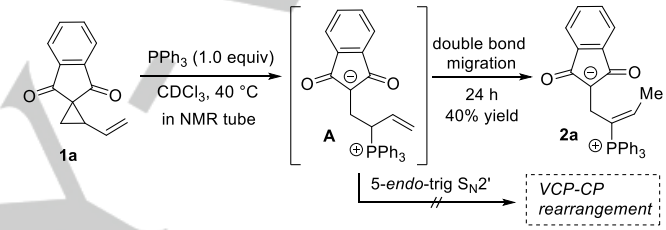
Phosphine catalysis[1] has emerged as a reliable and powerful platform for the construction of structurally diverse carbo- and heterocycles. Lu's [3 + 2],[2] Kwon's [4 + 2][3] and Tong's [4 + 1][4] annulations represent seminal paradigms in the area, which have inspired a myriad of cyclization reactions[5] including asymmetric variants.[6] To date, phosphine-catalyzed annulations typically rely on electron-deficient alkenes, alkynes, allenes, and their derivatives (Scheme 1).[1e] These precursors serve as effective C_1 to C_4 synthons for generating various cyclic structures, especially five- and six-membered ring systems. However, phosphine-catalyzed formation of seven- or eight-membered rings[7] are comparatively underdeveloped, despite their great potential in natural product synthesis.[8]



Scheme 1. Substrates of Phosphine-Catalyzed Annulations

In an effort to expand phosphine catalysis, we hypothesized that electron-deficient vinylcyclopropanes (VCPs) **1** might serve as a complementary C_5 synthon capable of producing value-added medium-sized ring structures (Scheme 1). Mechanistically, regioselective homoconjugate addition[9] of a phosphine to VCPs **1** may generate an allylic phosphonium intermediate **A**. By virtue of the leaving group ability of the phosphonium, the alkene of **A** can be rendered electrophilic for a potential S_N2' reaction, thus making it possible to be used as a C_5 surrogate under phosphine catalysis.

VCPs[10] have drawn tremendous interests in contemporary organic synthesis due to their unique and versatile reactivity. Transition-metal coordination has played a prominent role on the catalytic activation of VCPs,[10c] and complexes of rhodium, palladium, nickel, etc. have facilitated a diverse range of [3 + n][11] and [5 + n][12] cycloadditions. A thiyl radical-catalyzed activation of VCPs has also been demonstrated to effect [3 + 2] annulations.[13] To our knowledge, the organocatalytic Lewis base-triggered activation of VCPs remains thus far unexplored. Stemming from our interest in Lewis base catalysis,[14] we herein report a phosphine-catalyzed activation of electron-deficient VCPs and its utility in an efficient rearrangement of vinylcyclopropylketones to cycloheptenones in good yields with a broad scope (*vide infra*).



Scheme 2. Initial investigation.

We began by examining the reactivity of vinylcyclopropane **1a**[15] with 1.0 equiv of PPh_3 by NMR tracking (Scheme 2). Significantly, the reaction in $CDCl_3$ at 40 °C cleanly generated a zwitterion **2a** in 40% yield after 24 h. It is likely that **2a** is derived from the putative intermediate **A** via a double bond migration (see Supporting Information (SI)). We reasoned that the vinyl of **A** would lend itself easily to eventual annulation reactions.

In principle, the direct cyclization of intermediate **A** via 5-*endo*-trig S_N2' pathway would result in a vinylcyclopropane–cyclpentene (VCP–CP) rearrangement,[16] which, however, was not observed presumably disfavored by Baldwin's rules[17] (Scheme 2). Instead, when 1,1-diacetyl-2-vinylcyclopropane **1b** was employed, we were pleased to observe an unprecedented phosphine-catalyzed rearrangement of vinylcyclopropylketones to cycloheptenones (Table 1). Heating **1b** with 20 mol % of PPh_3 in toluene at 110 °C for 24 h resulted in the formation of 2-acetyl-4-cycloheptenone **2b** in 10% yield existing in keto–enol tautomers (keto/enol = 1 : 2) (entry 1). Replacing PPh_3 with electron-rich triarylphosphines or trialkylphosphines enhanced the efficiency (entries 2–6), among which P^nBu_3 stood out giving 85% yield of the product. The reaction is reminiscent of divinylcyclopropane–cycloheptene rearrangement under thermal conditions.[18] However, the lack of reactivity in the absence of phosphines suggests the crucial role of the catalyst (entries 7 and 8). Of note DABCO as the catalyst produced a small amount of **2b** (14%) together with a dihydrofuran product **2b'** in 37% yield (entry 9).[14a] Solvent screening indicated that toluene remained the best, while acetonitrile, DMSO, acetone,

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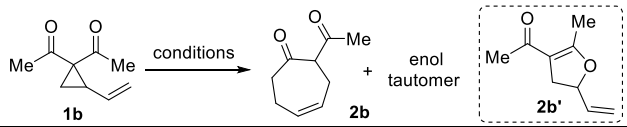
dichloromethane, and THF all provided diminished yields or trace amounts of the product (entries 10–14). A lowered temperature at 60 °C was insufficient to promote the reaction (entry 15). It was found the rearrangement could tolerate 1.0 equiv of H_2O giving a comparable 82% yield, whereas strictly anhydrous conditions led to a decreased 69% yield, suggesting that water may play a role in the reaction (*vide infra*) (entries 16 and 17). Lowering the catalyst loading to 2.5 mol % could still furnish 72% yield; however, increasing that to 50 mol % or 1.0 equiv decreased the yield to 71% or 22%, respectively, and oligomerization of **1b** was observed (entries 18–20).

Table 1. Investigation on Conditions.[a]

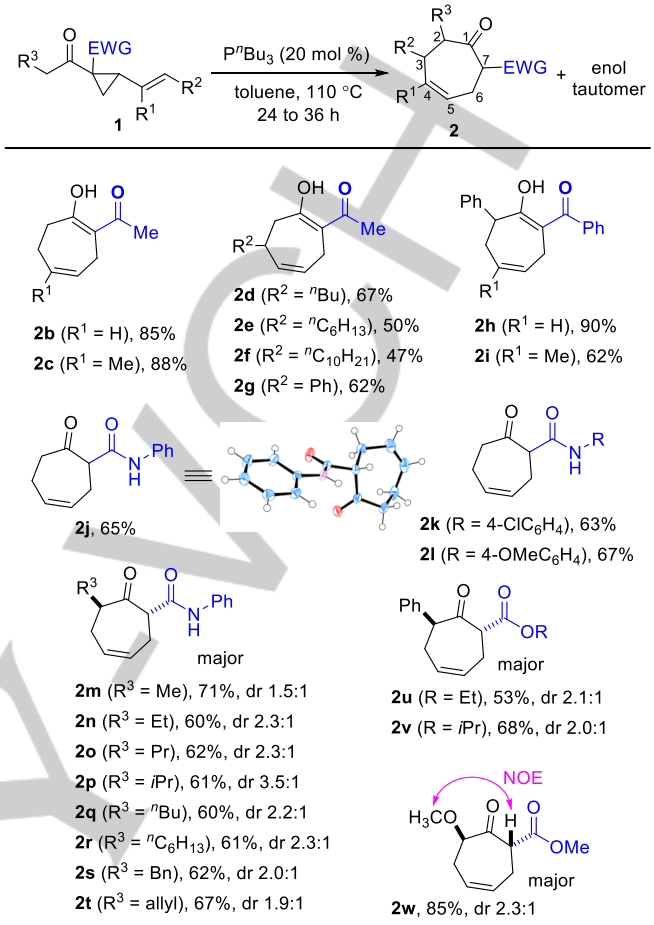


Entry	Catalyst	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	PPh_3	toluene	110	24	10
2	$P(PMP)_3$	toluene	110	24	39
3	P(*p*-tolyl)$_3$	toluene	110	24	62
4	P^{t}Bu$_3$	toluene	110	24	61
5	PCp$_3$	toluene	110	24	69
6	P^{n}Bu$_3$	toluene	110	24	85
7	none	toluene	110	48	trace
8	K_2CO_3	toluene	110	48	trace
9[c]	DABCO	toluene	110	24	14
10	P^{n}Bu$_3$	acetonitrile	reflux	24	77
11	P^{n}Bu$_3$	DMSO	110	24	30
12	P^{n}Bu$_3$	acetone	reflux	24	51
13	P^{n}Bu$_3$	CH_2Cl_2	reflux	24	trace
14	P^{n}Bu$_3$	THF	reflux	24	trace
15	P^{n}Bu$_3$	toluene	60	24	trace
16[d]	P^{n}Bu$_3$	toluene	110	24	82
17[e]	P^{n}Bu$_3$	toluene	110	24	69
18[f]	P^{n}Bu$_3$	toluene	110	24	72
19[g]	P^{n}Bu$_3$	toluene	110	24	71
20[h]	P^{n}Bu$_3$	toluene	110	36	22

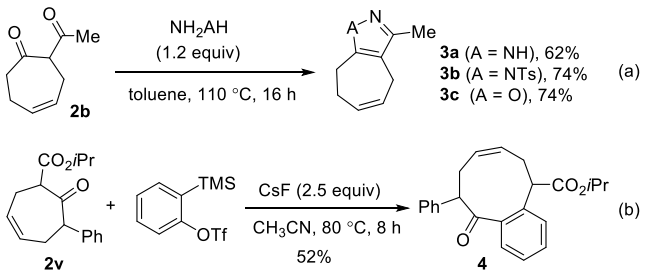
[a] Under N_2 and indicated temperature, to a solution of **1b** (0.5 mmol) in the solvent (5.0 mL) was added the catalyst (20 mol %). [b] Isolated yield. [c] Dihydrofuran **2b'** was obtained in 37% yield. [d] 1.0 equiv of H_2O was added. [e] Under strictly anhydrous conditions. [f] 2.5 mol % of catalyst was used. [g] 50 mol % catalyst loading. [h] 1.0 equiv of P^{n}Bu$_3$ was adopted.

The scope of the phosphine-catalyzed rearrangement was then probed (Table 2). Substitution at either internal or external positions (R^1 and R^2) of the vinyl group could be tolerated, affording the corresponding cycloheptenones **2c**–**g** in 47–88% yields with enol isomers as the major. Introduction of a phenyl on the acetyl fragment (R^3 = Ph), in combination with a benzoyl EWG group, led to the formation of **2h** and **2i** in 90% and 62% yields, respectively. Of note DABCO was a superior catalyst in these two cases. Substrates with an amide group (EWG = CONHAr) also worked well under similar conditions (P^{t}Bu$_3$, PhCl or DMSO, 110°C), and the corresponding products **2j**–**t**, including those bearing varied R^3 substituents, were generated in 60–71% yields. The structure of **2j** was unequivocally established by single-crystal X-ray diffraction analysis (CCDC 1816803). Finally, it was found that ketoester substrates were also competent, whose rearrangement afforded cycloheptenones **2u**–**w** in 53–85% yields. Noteworthy amide and ester functionalized products **2j**–**w** exist only in keto isomers, albeit as mixtures of diastereomers favoring *trans* configuration which is confirmed by 2D NOESY.

Table 2. Investigation on Substrate Scope.[a]



[a] Conditions: under N_2 and at 110 °C, the reaction was carried out with P^{n}Bu$_3$ (20 mol %) in toluene for 24–36 h, except that for **2h** and **2i**, DABCO (50 mol %) was used as the catalyst, and for **2j**–**t**, P^{t}Bu$_3$ (50 mol %) was employed as the catalyst and PhCl or DMSO as the solvent.



Scheme 3. Diversification of Products.

Collectively, the above results suggest a broad scope of the phosphine-catalyzed rearrangement of vinylcyclopropylketones, which allows controlled synthesis of 2-, 3-, or 4-substituted cycloheptenones. As cycloheptenones are ubiquitous, though synthetically challenging, units in natural products and biologically active molecules,[8] this reaction thus offers a mild protocol for accessing this kind of medium-sized carbocycles. In order to underline the usefulness, treatment of diketone **2b** with hydrazines or hydroxylamine led to the formation of pyrazole- or

oxazole-fused cycloheptenes **3** in good yields (Scheme 3a). Benzyne insertion into ketoester **2v** was also achieved to access a nine-membered carbocycle **4** in 52% yield (Scheme 3b).[19]

A plausible mechanism is illustrated in Figure 1. Initial regioselective attack of P^nBu_3 on vinylcyclopropane **1b**, via the well-known homoconjugate addition,[9],[14a] produces a zwitterionic intermediate **A**. Species **A** then undergoes a proton transfer to shuttle the anion to the methyl carbon leading to the formation of intermediate **B**. Finally, a favored 7-*endo*-trig S_N2' cyclization[17] furnishes the product **2b** and releases the catalyst.

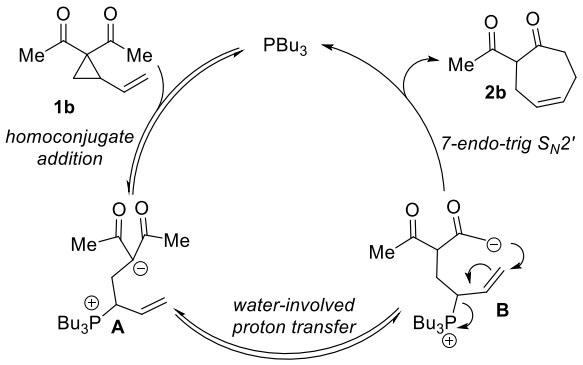
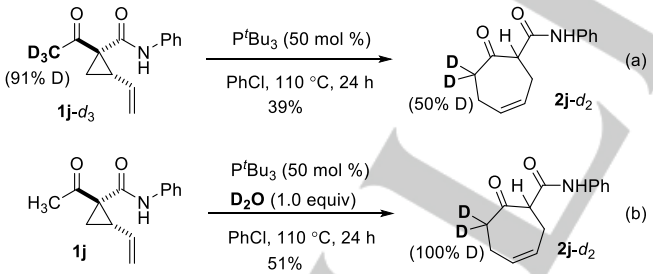


Figure 1. A Proposed Catalytic Cycle.

Although the formation of **2a** (Scheme 2) could be supportive to the mechanism, several mechanistic studies were conducted to gain more insights. To inspect the proton transfer step, a deuterated substrate **1j**-d_3 (91% D at CH_3) was subjected to the standard conditions, which produced a deuterated product **2j**-d_2 in 39% yield with significant loss of deuterium (Scheme 4a).[20] In addition, it was found that the presence of 1.0 equiv of D_2O in the rearrangement of non-deuterated **1j** led to full deuteration at the α-methylene of the product (Scheme 4b).[21] These results suggest that the proton transfer is presumably stepwise and assisted by trace amount of water in the solvent.[22],[23]



Scheme 4. Deuterium Labeling Investigations.

Furthermore, a ^{31}P NMR tracking experiment was conducted to verify the essential role of the phosphine catalyst (Figure 2). When substrate **1j** (0.05 mmol) and P^tBu_3 (0.025 mmol) in toluene-d_8 (0.6 mL) was heated at 110 °C for 20 min, two new signals at δ 62.8 and 64.1 ppm were observed apart from the peaks of P^tBu_3 (62.1 ppm) and $^tBu_3P{=}O$ (61.0 ppm).[24] This result strongly supports the involvement of the phosphine in the rearrangement. The new signals are presumably corresponding to the proposed intermediates of type **A** and **B** (Figure 1).[25]

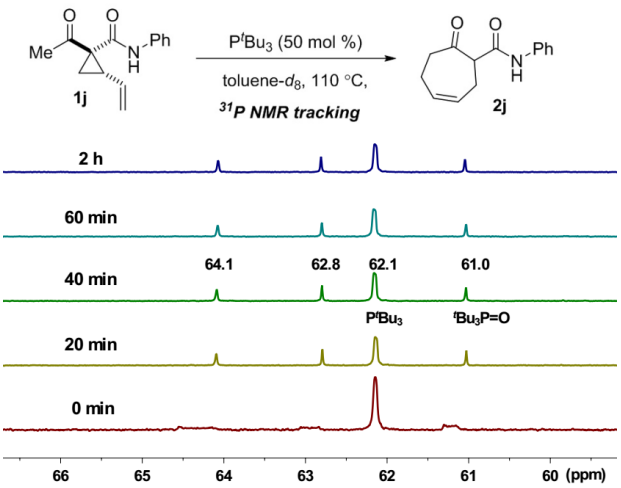


Figure 2. ^{31}P NMR Tracking on the Rearragement of **1j**.

In summary, we have expanded phosphine catalysis to encompass activation of electron-deficient VCPs. This has been utilized in an unprecedented phosphine-catalyzed rearrangement of vinylcyclopropylketones to cycloheptenones in good yields with a broad scope. Mechanistic investigations including deuterium labeling and ^{31}P NMR tracking support a stepwise mechanism comprising homoconjugate addition, water-involved proton transfer, and 7-*endo*-trig S_N2' ring closure. This organocatalytic activation not only enriches the reactivity of VCPs, but also introduces a new subset of phosphine catalysis by supplying a distinct C_5 synthon. Future efforts will focus on detailed survey on mechanism and exploring intermolecular reactivity of the phosphine-catalyzed activation of electron-deficient VCPs.

Acknowledgements

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Keywords: phosphine catalysis • vinylcyclopropanes • cycloheptenones • organocatalysis • rearrangement

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[20] When stopping the reaction at 10 h, **1j**-d_3 could be recovered in 43% yield with 59% D on the methyl. The loss of deuterium infers that the ring-opening and proton transfer steps of the mechanism are reversible.

[21] Deuterium at the methine of **2j**-d_2 was not observed probably due to rapid D/H exchange during work-up and separation. Treating **2j** under identical conditions of Scheme 4b incorporated 18% D on the α-methylene, which should not account for the full deuteration event.

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[23] Prelimiary DFT studies indicate that a concerted proton transfer is less possible for it has a activation barrier of 42.5 kcal mol^{-1}.

[24] $^{t}Bu_3P{=}O$ was confirmed by comparing ^{31}P NMR with authentic samples, which may be from oxidizing of $P^{t}Bu_3$ by residual molecular oxygen.

[25] Due to overlap and complex splitting of signals, it is difficult to discern the intermediates via ^{1}H NMR. However, quenching with acetic acid forms observable zwitterions resembling **2a**. For details, see SI.

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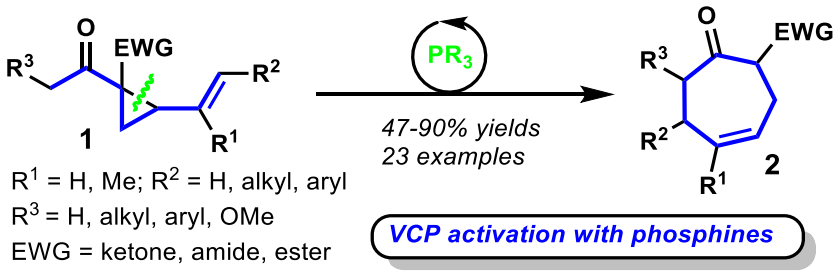

R^1 = H, Me; R^2 = H, alkyl, aryl
R^3 = H, alkyl, aryl, OMe
EWG = ketone, amide, ester

VCP activation with phosphines

Phosphine-catalyzed activation of VCPs: A phosphine-catalyzed activation of electron-deficient vinylcyclopropanes (VCPs) for the generation of an ambident C_5 synthon is presented, which effects a phosphine-catalyzed rearrangement of vinylcyclopropylketones to cycloheptenones in good yields with a broad substrate scope.

*J. Wu, Y. Tang, W. Wei, Y. Wu, Y. Li, J. Zhang, Y. Zheng, and S. Xu**

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Phosphine-Catalyzed Activation of Vinylcyclopropanes: Rearrangement of Vinylcyclopropylketones to Cycloheptenones