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

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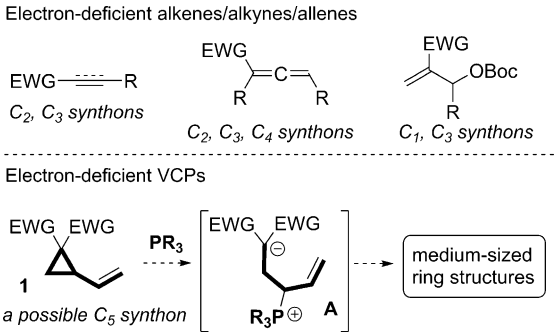
Abstract: *We report a phosphine-catalyzed activation of electron-deficient vinylcyclopropanes (VCPs) to generate an ambident C_5 synthon that is poised to undergo consecutive reactions. The utility of the activation is demonstrated in a phosphine-catalyzed rearrangement of vinylcyclopropylketones to cycloheptenones in good yields with a broad substrate scope. Mechanistic investigations support a stepwise process comprising homoconjugate addition, water-assisted proton 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 advances 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]



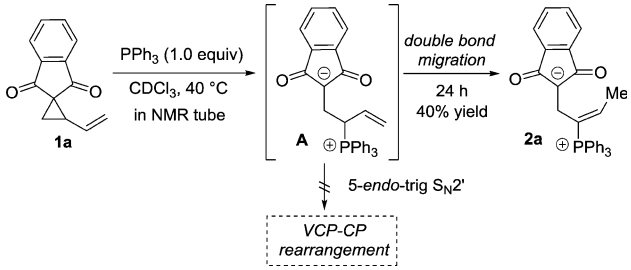
Scheme 1. Substrates of phosphine-catalyzed annulations.

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 use it as a C_5 surrogate under phosphine catalysis.

VCPs[10] have drawn tremendous interest in contemporary organic synthesis due to their unique and versatile reactivity. Transition-metal coordination has played a prominent role in the catalytic activation of VCPs,[10c] and complexes of rhodium, palladium, nickel, and others 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 (see below).

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 zwitterion **2a** in 40 % yield after 24 h. It is likely that **2a** is derived from the putative intermediate **A** through a double-bond migration (see the Supporting Information). We reasoned that the vinyl of **A** would lend itself easily to eventual annulation reactions.

In principle, the direct cyclization of intermediate **A** through a 5-*endo*-trig S_N2' pathway would result in a vinylcyclopropane–cyclpentene (VCP–CP) rearrangement,[16] which was not observed, however, presumably because it is disfavored by Baldwin's rules[17] (Scheme 2). Instead, when



Scheme 2. Initial investigation.

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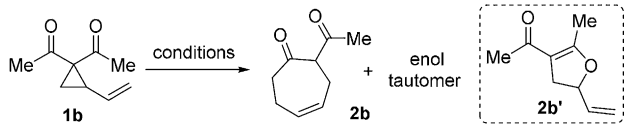
1,1-diacetyl-2-vinylcyclopropane **1b** was employed, we were pleased to observe an unprecedented phosphine-catalyzed rearrangement of vinylcyclopropylketones to cycloheptenones (Table 1). Heating **1b** with 20 mol % of PPh_3 in toluene at 110 °C for 24 h resulted in the formation of 2-acetyl-4-cycloheptenone **2b** in 10 % yield as 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 dihydrofuran product **2b′** in 37 % yield (entry 9).[14a] Solvent screening indicated that toluene was the best, while acetonitrile, DMSO, acetone, dichloromethane, and THF all provided diminished yields or trace amounts of the product (entries 10–14). A lowered temperature of 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, thus suggesting that water may play a role in the reaction (see below; 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 of the conditions.[a]

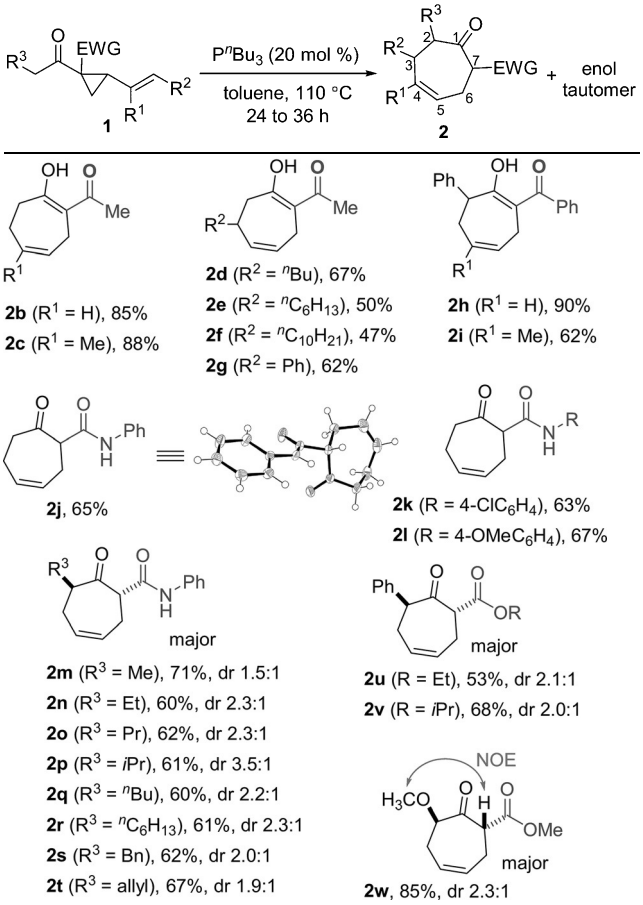


Entry	Catalyst	Solvent	*T* [°C]	*t* [h]	Yield [%][b]
1	PPh_3	toluene	110	24	10
2	$P(PMP)_3$	toluene	110	24	39
3	$P(p\text{-tolyl})_3$	toluene	110	24	62
4	P^tBu_3	toluene	110	24	61
5	PCp_3	toluene	110	24	69
6	P^nBu_3	toluene	110	24	85
7	none	toluene	110	48	trace
8	K_2CO_3	toluene	110	48	trace
9[c]	DABCO	toluene	110	24	14
10	P^nBu_3	acetonitrile	reflux	24	77
11	P^nBu_3	DMSO	110	24	30
12	P^nBu_3	acetone	reflux	24	51
13	P^nBu_3	CH_2Cl_2	reflux	24	trace
14	P^nBu_3	THF	reflux	24	trace
15	P^nBu_3	toluene	60	24	trace
16[d]	P^nBu_3	toluene	110	24	82
17[e]	P^nBu_3	toluene	110	24	69
18[f]	P^nBu_3	toluene	110	24	72
19[g]	P^nBu_3	toluene	110	24	71
20[h]	P^nBu_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^nBu_3 was adopted.

The scope of the phosphine-catalyzed rearrangement was then investigated (Table 2). Substitution at either internal or external positions (R^1 and R^2) of the vinyl group were tolerated, affording the corresponding cycloheptenones **2c–g** in 47–88 % yields with enol isomers as the major product. Introduction of a phenyl on the acetyl fragment (R^3 = Ph), in combination with a benzoyl electron-withdrawing group (EWG), 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^tBu_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 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge

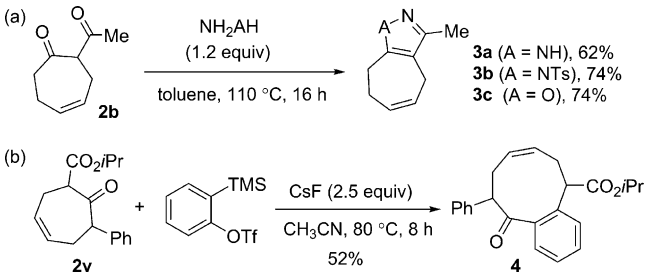
Table 2: Investigation on substrate scope.



[a] Conditions: under N_2 and at 110 °C, the reaction was carried out with P^nBu_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^tBu_3 (50 mol %) was employed as the catalyst and PhCl or DMSO as the solvent.

from The Cambridge Crystallographic Data Centre.). Finally, it was found that ketoester substrates were also competent, the rearrangement of which afforded cycloheptenones **2u–w** in 53–85% yields. Notably, amide- and ester-functionalized products **2j–w** exist only as keto isomers, albeit as mixtures of diastereomers favoring *trans* configuration, which was confirmed by 2D NOESY.

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. Since cycloheptenones are ubiquitous, though synthetically challenging, units in natural products and biologically active molecules,[8] this reaction thus offers a mild method for accessing this kind of medium-sized carbocycles. In order to underline the usefulness of this method, 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]



Scheme 3. Diversification of products.

A plausible mechanism is illustrated in Figure 1. Initial regioselective attack of P^nBu_3 on vinylcyclopropane **1b** through the well-known homoconjugate addition[9,14a] produces 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.

Although the formation of **2a** (Scheme 2) could be supportive to the mechanism, several mechanistic studies were conducted to gain further insight. 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]

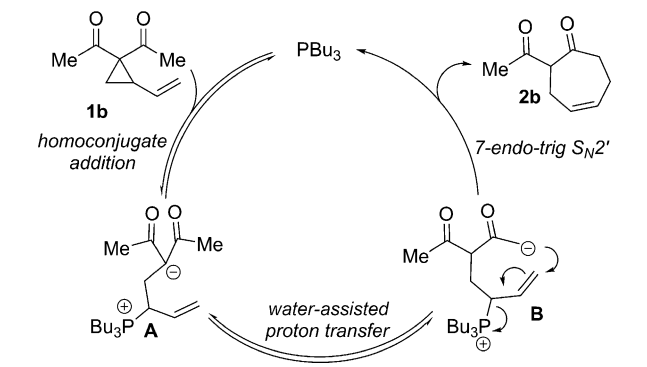
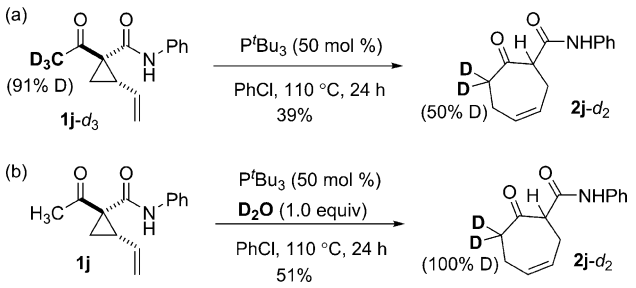


Figure 1. A proposed catalytic cycle.



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 [D_8]toluene (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 presumably correspond to the proposed intermediates of type **A** and **B** (Figure 1).[25]

In summary, we have expanded phosphine catalysis to encompass the 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

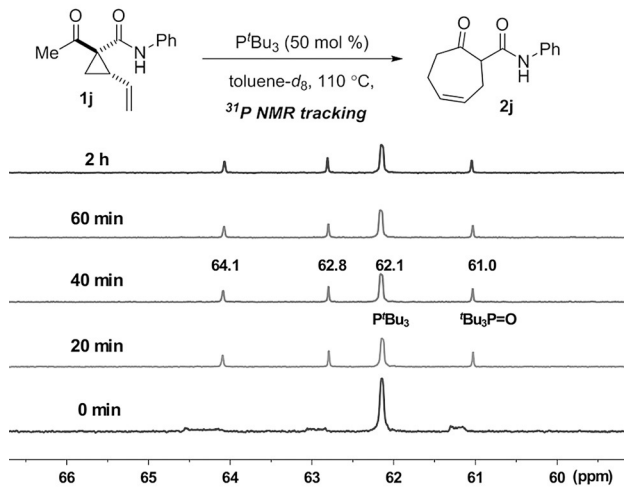


Figure 2. ^{31}P NMR tracking on the rearrangement of **1j**.

tracking support a stepwise mechanism comprising homoconjugate addition, water-assisted 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 a detailed survey of mechanism and exploring intermolecular reactivity of the phosphine-catalyzed activation of electron-deficient VCPs.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

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

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