Catalytic C–P Ylide Reaction

A Catalytic Carbon–Phosphorus Ylide Reaction: Phosphane-Catalyzed Annulation of Allylic Compounds with Electron-Deficient Alkenes**

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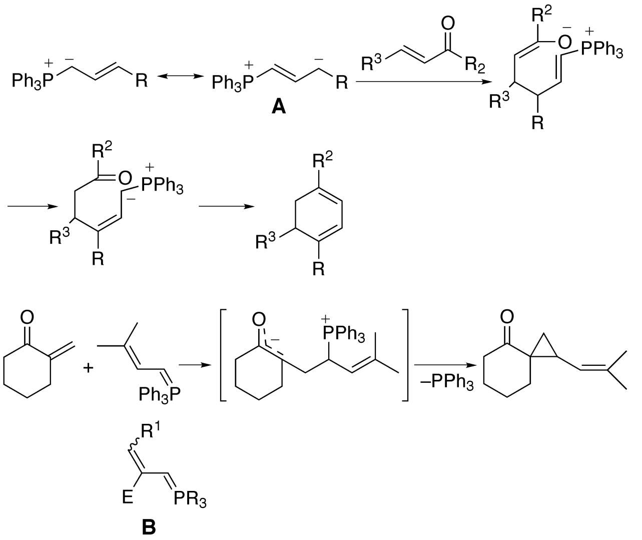
To ensure high efficiency, turning a stoichiometric reaction into a catalytic one, and developing new catalytic reactions have been long-standing goals in modern synthesis. Ylide reactions are among the most powerful tools for constructing olefins[1] and small rings,[2] but few are catalytic, in particular those involving phosphorus ylides.[3] The first example of a catalytic Wittig-type reaction of arsenic ylides, in which a stoichiometric amount of reducing agent was used to regenerate the arsane, was described by Huang's group in 1989.[4] Afterwards, catalytic olefinations, epoxidations, aziridinations, and cyclopropanations of tellurium or sulfur ylides were accomplished.[2,5] Aggarwal's group developed catalytic, asymmetric ylide reactions that afforded three-membered rings by a carbene approach, in which the ylide was formed directly from aryl diazomethane in the presence of a catalytic amount of a chiral sulfide and a transition-metal complex.[6] To our knowledge, there are no phosphane-catalyzed versions of the carbon–phosphorus ylide reaction.[7] This might be due to the fact that, compared to other elemento-organic compounds of Groups 15 and 16, phosphanes exhibit higher oxyphilicity and the phosphorus–oxygen bond in phosphine oxides have a higher bond energy. To develop a catalytic reaction with carbon–phosphorus ylides, it was thus necessary to explore a new type of reaction.

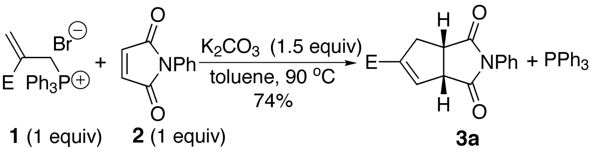


Scheme 1. Two types of reactions of allylic phosphorus ylides.

Two types of reactions of allylic phosphorus ylides **A** with electron-deficient alkenes have been reported (Scheme 1). The initial nucleophilic addition of the ylide to the olefin is followed by an intramolecular Wittig reaction to afford 1,3-cycloalkadienes[8a–f] or by intramolecular nucleophilic substitution to give cyclopropanes.[8f,g] However, both reactions are stoichiometric with regard to the phosphane and the products are obtained in low yields.

The success of the phosphane-catalyzed isomerizations, α- and γ-additions, and [3+2] cycloadditions of electron-deficient allenes or alkynes was ascribed to the presence of electron-withdrawing groups, which facilitated the nucleophilic additions and the elimination of phosphanes to complete the catalytic cycles.[9] With this in mind, we thought that phosphane-catalyzed reactions might be realized with a modified allylic phosphorus ylide **B** (see Scheme 1). Here we report a novel phosphane-catalyzed annulation reaction of modified allylic compounds with electron-deficient alkenes.

To initiate our study, phosphonium salt **1**, compound **2**, and potassium carbonate were stirred in toluene at 90 °C to afford the adduct **3a** and triphenylphosphane [Eq. (1); $E = CO_2Et$]. Since **1** was prepared from ethyl 2-bromomethyl-2-propenoate (**4a**) and PPh_3, it was expected that this reaction might take place starting from **4a** by utilizing a catalytic amount of PPh_3. Indeed, the phosphane-catalyzed annulation



(1)

1 (1 equiv) **2** (1 equiv) **3a**

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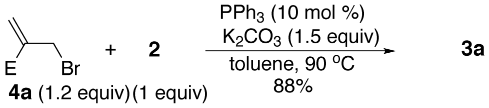
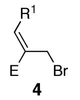
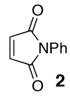
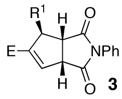
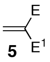
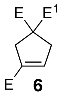
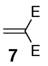
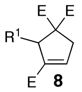
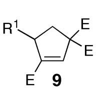
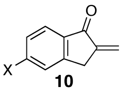
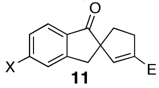
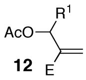
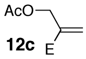
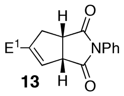
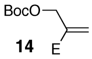


(2)

of ylides did proceed [Eq. (2); E = CO_2Et], implying that a catalytic ylide reaction is possible.

We then turned our attention to studying the scope of this reaction with respect to the C_3 component. Under similar conditions, the reaction of **4b** and **2** proceeded smoothly upon reflux, albeit in lower yields (50 %; Table 1, entry 2). The yield was improved to 68 % by the slow addition of the reactants to maintain low concentrations of **2** and **4b** in the reaction system (entry 3). Under these conditions, good yields of adducts were obtained for C_3 components containing aromatic as well as aliphatic substituents (Table 1, entries 3–7).

Table 1: Phosphane-catalyzed annulation reaction of ylides.[a]

Entry	C_3 component	C_2 component	*T* [°C]	*t* [h]	Product	Yield [%][b]
	 **4**	 **2**			 **3**	
1[c]	**4a**: R^1 = H	**2**	90	12	**3a**: R^1 = H	88
2[c]	**4b**: R^1 = Ph	**2**	110	4	**3b**: R^1 = Ph	50[d]
3	**4b**	**2**	110	4	**3b**	68[d]
4	**4c**: R^1 = *p*-MeC_6H_4	**2**	110	4	**3c**: R^1 = *p*-MeC_6H_4	66[d]
5	**4d**: R^1 = *p*-$O_2NC_6H_4$	**2**	110	4	**3d**: R^1 = *p*-$O_2NC_6H_4$	71[d]
6	**4e**: R^1 = *p*-$MeOC_6H_4$	**2**	110	4	**4e**: R^1 = *p*-$MeOC_6H_4$	74[d]
7	**4f**: R^1 = *n*Pr	**2**	110	4	**4f**: R^1 = *n*Pr	60[d]
8	**4a**	 **5**	110	20	 **6**	70[e]
		 **7**			 **8**  **9**	
9	**4a**	**7**	110	20	**8a**: R^1 = H; **9a**: R^1 = H	61[f]
10	**4d**	**7**	110	6	**8d**: R^1 = *p*-$O_2NC_6H_4$	66
		 **10**			 **11**	
11	**4a**	**10a**: X = H	110	20	**11a**: X = H	72 g]
12	**4a**	**10b**: X = MeO	110	20	**11b**: X = MeO	65
	 **12**					
13	**12a**: R^1 = H	**2**	70	4	**3a**	76
14	**12b**: R^1 = Ph	**2**	110	4	**3b**	62[d]
15	 **12c**	**2**	30	2	 **13**	64
16[h]	 **14**	**2**	110	2	**3a**	74

[a] For the typical reaction conditions, see the Experimental Section. E = CO_2Et, E^1 = COPh. [b] Yield of isolated product. [c] The reaction conditions were similar to those in [a], except without slow addition. [d] *trans*:*cis* > 97:3 (relative stereochemistry of the R^1 group and the other substituents). [e] A minor by-product was also isolated which was not fully characterized. [f] **8a**:**9a** = 90:10. [g] The regioselectivity of the reaction was higher than 97:3. [h] The reaction conditions were similar to those in [a], except without the addition of K_2CO_3. Boc = *tert*-butyloxycarbonyl.

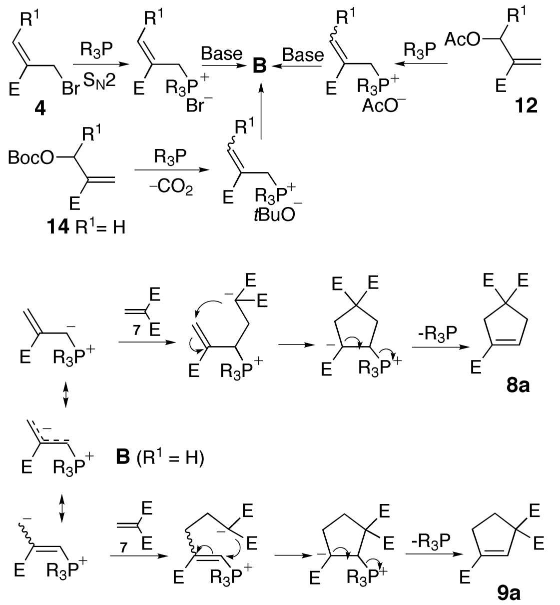
The stereochemistry of the products was assigned on the basis of the NOESY spectra of **3c**.[10] It is worth noting that, in only a single step, cyclopentenes with two or three stereogenic centers were constructed stereoselectively.

The scope of this novel ylide reaction with respect to the C_2 component was also investigated, focusing on reactions of compound **4a** with various compounds in place of **2**. Terminal olefins or unsymmetrical C_2 components reacted smoothly with **4a** to give annulation products with high selectivities (Table 1, entries 8, 9, 11, and 12).[10] While the reaction of **7** with **4a** provided the expected product with lower yield (61 %), it still showed a high regioselectivity (**8a**/**9a**: 90/10, entry 9).[10,11]

Further investigation revealed that the key intermediate (ylide **B**; see Scheme 1) of this catalytic annulation reaction could be generated not only from the corresponding bromides **4a–f** but also from the acetates **12a–c** (Table 1, entries 13–15).[12,13] We also found that the reaction could be modified from heterogeneous conditions to homogeneous conditions by using the *tert*-butyl carbonate **14,** from which the *tert*-butoxide anion was generated as a base in situ (entry 16).

Although detailed mechanistic studies have not been undertaken, a plausible mechanism for the phosphane-catalyzed annulation reaction of ylides is proposed (Scheme 2). The reaction might be initiated by the formation of the phosphonium salt from **4** by an S_N2 or addition–elimination step.[11] This salt can be deprotonated by a base such as potassium carbonate or the in situ generated *tert*-butoxide anion to afford ylide **B**. As exemplified by the annulation reaction of **7** and **4a**, subsequent nucleophilic addition of **B** to the electron-deficient olefin yields zwitterionic intermediates. Subsequent cyclization upon intramolecular conjugate addition provides betaine-like intermediates. Finally, elimination of the phosphane completes the catalytic cycle. As shown in the bottom part of Scheme 2, the formation of the two isomers **8a** and **9a** can be explained by α- or γ-attack of ylide **4a** to **7**. Of course, the possibility of migration of the double bond in cyclopentene products under the reaction conditions cannot be excluded.

In conclusion, the first phosphane-catalyzed allylic ylide reaction was developed. The appealing features of this process involve the



Scheme 2. Proposed mechanism of the phosphane-catalyzed annulation reaction of ylides.

ready availability of the starting materials—for example, the C_3 components including bromides, acetates, or *tert*-butyl carbonates could be easily obtained by further transformation of the adduct of Morita–Baylis–Hillman reactions—and its high selectivity. The synthetic utility of the active intermediate was exemplified by the facile construction of different cyclopentenes.

Experimental Section

Typical reaction conditions: Under argon a mixture of **4a** (116 mg, 0.60 mmol) and **2** (87 mg, 0.50 mmol) in toluene (2.0 mL) was added over the indicated time (see Table 1) with a syringe pump to a mixture of PPh_3 (13 mg, 0.05 mmol) and K_2CO_3 (104 mg, 0.75 mmol) in toluene (0.5 mL) at the temperature indicated (K_2CO_3 was not added for the reaction of **14**). The reaction mixture was stirred for a further 1 h. The reaction mixture was directly subjected to column chromatography (ethyl acetate/petroleum ether) on silica gel to give **3a** (125 mg, 88 %).

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[10] Experimental procedures and characterization data of new compounds as well as NOESY spectra of compound **3c** and ^1H–^1H COSY spectra of compounds **6, 8a, 9a**, and **11a** are available in the Supporting Information.

[11] The high regioselectivity of the reaction might be explained by steric factors. A similarly high regioselectivity was reported in a phosphane-catalyzed cycloaddition reaction: G. Zhu, Z. Chen, Q. Jiang, D. Xiao, P. Cao, X. Zhang, *J. Am. Chem. Soc.* **1997**, *119*, 3836.

[12] The isolation of the same product **3b** starting from **4b** and **12b** implies that the reaction of **12b** was initiated by the nucleophilic addition of PPh_3 to the electron-deficient double bond of **12b** followed by elimination of the acetate ion (compare entries 3 and 13 of Table 1). The ylide formed from the resulting phosphonium salt is the same as that generated from the reaction of **4b** with PPh_3. For a similar addition–elimination reaction, see: M. Harre, P. Raddatz, R. Walenta, E. Winterfeldt, *Angew. Chem.* **1982**, *94*, 496; *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 480; D. Seebach, M. Missbach, G. Calderari, M. Eberle, *J. Am. Chem. Soc.* **1990**, *112*, 7625.

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