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A sidearm-assisted phosphine for catalytic ylide intramolecular cyclopropanation†

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The first phosphine-catalyzed cyclopropanation reaction *via* covalent ylide catalysis has been realized with high efficiency in the presence of sidearm-assisted phosphine catalysts. An ether sidearm group is found critical to turn on the catalytic activity. Crystal structures of the catalyst-derived phosphonium salts indicated a significant O···P+ interaction between the pendant ether oxygen and the phosphonium center, which is believed to favor the catalyst regeneration. DFT calculations rationalize the insight of the sidearm effects.

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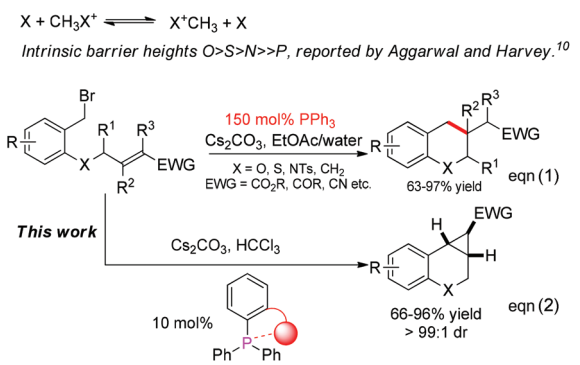
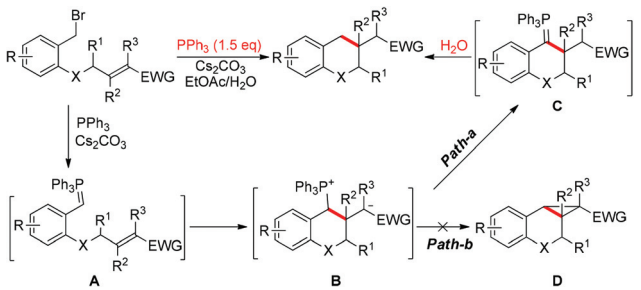
Ylide cyclopropanation provides a convenient and attractive method for the synthesis of cyclopropanes, an important motif that frequently occurs in natural products as well as in synthetically useful intermediates.[1,2] Although both phosphorus ylide reactions and phosphine-catalyzed reactions have been intensively studied in the past few decades,[3,4] phosphine-catalyzed cyclopropanation remains elusive.[5–9] Rational theoretical studies by Aggarwal and Harvey on the leaving group ability of onium ylides show that compared with other ylides, such as ammonium, oxonium, sulfonium ylides, the phosphonium ylide needs to overcome a much higher energy barrier to act as a leaving group in a S_N2 substitution reaction (Scheme 1).[10] Accordingly, the key step is to regenerate phosphine in the ylide cyclopropanation to complete the catalytic cycle.[5] As the leaving group ability depends on the nature of phosphine, it could be envisioned that a rational design of phosphine would provide a solution for the catalyst turnover in such a reaction. Based on this idea, recently, we found that the introduction of a sidearm, an ether group at the *ortho*-position of triphenylphosphine (Ph_3P), could substantially alter the phosphine reactivity to enable its regeneration *via* a S_N2 substitution, allowing the realization of the first phosphine-catalyzed cyclopropanation reaction (eqn (2) in Scheme 1). In this communication, we wish to report our efforts on this subject.



Scheme 1 Leaving group ability of phosphine and phosphine-mediated annulation reactions.

Recently, we reported an intramolecular conjugation for the synthesis of chromans and their relevant analogues in the presence of 150 mol% PPh_3.[11] The mechanism of this reaction is proposed as shown in Scheme 2. According to this mechanism, two factors are crucial to change the pathway to the cyclopropane: reducing the hydrolysis rate and/or improving the leaving ability of phosphine. We envisioned that tuning the steric hindrance around the phosphorus in the phosphine might balance the nucleophilicity and leaving group ability,



Scheme 2 Reaction pathway to the conjugation product.

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switching ylide hydrolysis into S_N2 substitution and giving cyclopropanes as the desired products.

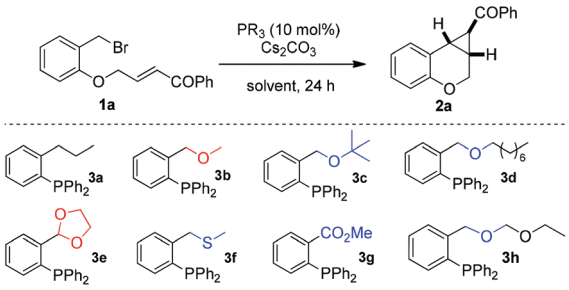
As PPh_3 is inert to this reaction (entry 1, Table 1), initially, we synthesized bulky phosphines **3a** and **3b** with an *ortho*-propyl group and an *ortho*-methoxymethyl group. With 10 mol% of **3a**, no cyclopropanation product was obtained at room temperature; however, with 10 mol% of **3b** as a catalyst, we found that the desired cyclopropane was afforded with 33% yield (entries 2 & 3). In contrast, several other common phosphines with varied electronic nature were also tested in this reaction, but no product could be isolated in all these cases (entries 4–6). Then we employed **3b** as the catalyst for further study. In the presence of 10 mol% **3b**, optimization of the reaction parameters (temperature, solvent, and base) increased the yield to 64% (entries 7–13). As the activity was improved by the replacement of an *ortho*-propyl group in **3a** with the *ortho* ether group in **3b** (sidearm effect), it intrigued us to prepare several phosphine catalysts that also have this ether functional group for enhancing the efficiency. Though decreased yields were obtained with **3c** and **3d** (entries 14 & 15), possibly caused by the steric hindrance of the ether group, to our delight, the less hindered acetal phosphine **3e** was found very effective for this cyclopropanation, improving the yield to 90% (entries 20 & 21). In contrast, thioether **3f** gave lower yield, and ester **3g** was even inactive (entries 17 & 18). With **3h** as a catalyst, 53% yield was obtained. Noticeably, neither a sulfide nor an amine catalyst afforded the desired cyclopropanation product even under the optimal literature conditions, although tetrahydrothiophene is very efficient for the phenol derived α,β-unsaturated ester (entries 22 and 23).[6c,7a]

The scope of this cyclopropanation reaction was investigated under the optimized reaction conditions, and the results are tabulated in Table 2. Various α,β-unsaturated carbonyl compounds with different structures worked well, giving the desired [n.1.0] bicycloalkanes **2a**–**w** in good to high yields. Notably, in all examples, only a single diastereoisomer was observed. The electronic nature of the substituent on the phenol ring slightly influences the yields (83–93%, entries 1–6). The substituent effect is more obvious on the benzoyl part, in which the electron-donating groups gave in general higher yields (entries 8–14), probably because the electron-donating group would increase the nucleophilicity of the enolate in the key intramolecular S_N2-substitution step to regenerate the catalyst. Remarkably, aliphatic enone is also suitable for this reaction (94%, entry 17). And the all carbon [n.1.0] bicycles can also be obtained in even higher yields (91–95%, entries 18–21). It is worth mentioning that the enal substrate **1v** was also compatible with the current reaction conditions; and the product **2v** is a key intermediate for the synthesis of a potential antidepressant.[12] The α,β-unsaturated ester **1w** was also examined as a substrate, using 20 mol% of **3e**, after 45 hours, 71% yield was obtained in toluene at 110 °C (entry 23).

To further understand the role of the sidearm effect, we developed the single crystals of phosphonium salts **4a**, **4b** and **4e**, which are derived from phosphines **3a**, **3b** and **3e**.[13] Interestingly, the approaching of the oxygen atom to the phosphonium was observed, with an O···P distance of 3.22 Å and 3.38 Å respectively, which are quite close to the sum of the van der Waals radii (3.32 Å) (Fig. 1). In a stark contrast, the C atom is apart from the P atom in the *ortho*-propyl group substituted phosphine. This interesting phenomenon indicated that interactions between the O atom and the P atom might account for the positive effect of the ether sidearm. A similar interaction of Te^+···O was also observed in the crystal structure of a telluronium salt containing an ether group.[15]

To rationalize the sidearm effect, density functional theory (DFT)[16] studies have been performed with the GAUSSIAN09 program[17] using the M06[18] method. For the Cs atom the SDD basis set with an effective core potential (ECP)[19] was used; for the rest of the atoms, the 6-31+G** basis set was used. Geometry optimization was performed in chloroform (ε = 4.711) using the SMD[20] method. Harmonic vibration frequency calculations were carried out at 338.15 K, the optimized structures are all shown to be either minima (with no imaginary frequency) or transition states (with one imaginary frequency).

Table 1 Reaction optimization[a]



Entry	PR_3	Solvent	T (°C)	t (h)	Yield[b] (%)
1	PPh_3	DCE	rt	21	—
2	**3a**	DCE	rt	21	—
3	**3b**	DCE	rt	21	33
4	PCy_3	DCE	rt	21	—
5	$(4\text{-}ClC_6H_4)_3P$	DCE	rt	21	—
6	$(4\text{-}MeOC_6H_4)_3P$	DCE	rt	21	—
7	**3b**	DCE	80	20	52
8	**3b**	DME	80	16	15
9	**3b**	$PhCH_3$	80	16	7
10	**3b**	CH_3CN	80	14	24
11	**3b**	$CHCl_3$	65	24	64
12	**3b**/Na_2CO_3	$CHCl_3$	65	24	—
13	**3b**/K_2CO_3	$CHCl_3$	65	24	54
14	**3c**	$CHCl_3$	65	24	46
15	**3d**	$CHCl_3$	65	24	41
16	**3e**	$CHCl_3$	65	24	77
17	**3f**	$CHCl_3$	65	24	25
18	**3g**	$CHCl_3$	65	24	—
19	**3h**	$CHCl_3$	65	24	53
20	**3e**	$CHCl_3$	65	48	80
21[c]	**3e**	$CHCl_3$	65	48	90
22	Tetrahydrothiophene	DCE	80	34	—
23	DABCO/Na_2CO_3	CH_3CN	80	24	—

[a] Reaction conditions: **1a** (0.3 mmol), catalyst (10 mol%), base (0.6 mmol), solvent (4 mL). DABCO = 1,4-diazobicyclo[2.2.2]octane. [b] Isolated yield. [c] With 20 mol% catalyst.

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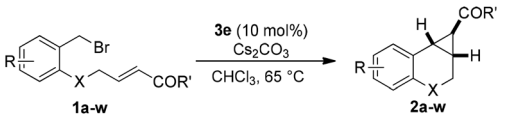
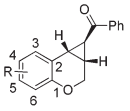
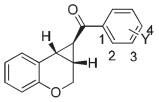
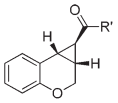
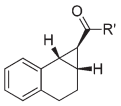
Table 2 Reaction scope[a]



Entry	Product		t (h)	Yield[b] (%)
				
1[c]	R = H	**2a**	25	90
2	4-Me	**2b**	46	92
3	4-OMe	**2c**	37	84
4[c]	4-Br	**2d**	26	83
5	6-Me	**2e**	37	93[14]
6	6-F	**2f**	40	86
7	5,6-Benzo	**2g**	40	91
				
8[c]	Y = 2-OMe	**2h**	40	96
9[c]	3-OMe	**2i**	21	94
10[c]	4-OMe	**2j**	26	91
11[c]	4-F	**2k**	26	80
12[c]	4-Br	**2l**	25	66
13[c]	4-Ph	**2m**	40	84
14[c]	2,3-Benzo	**2n**	63	80
				
15[c]	R′ = 2-furyl	**2o**	18	72
16[c]	2-Thienyl	**2p**	18	84
17[c]	Cy	**2q**	24	94
				
18	R′ = 2-furyl	**2r**	45	92
19[c]	2-Thienyl	**2s**	45	91
20	Ph	**2t**	68	95
21[c]	4-BrC_6H_4	**2u**	63	93
22[c]	H	**2v**	18	81
23[d]	OCH_2CF_3	**2w**	45	71

[a] Reaction conditions: **1a** (0.3 mmol), **3e** (10 mol%), base (0.6 mmol), $CHCl_3$ (4 mL). [b] Isolated yield. [c] With 20 mol% **3e**. [d] With 20 mol% **3e**, in toluene, at 110 °C.

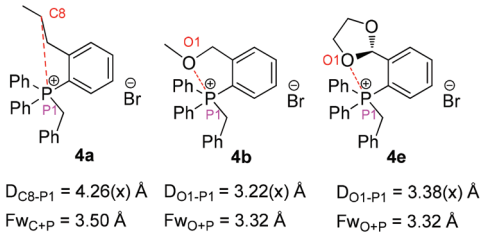


Fig. 1 X-ray crystal structure data of the phosphonium salts.

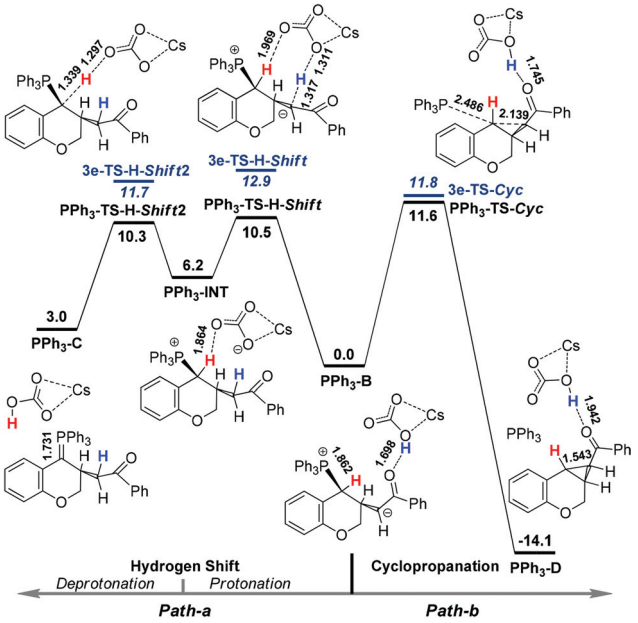


Fig. 2 The calculated reaction pathways for phosphine PPh_3. The energy barriers for phosphine **3e** are also given (in italics). The selected bond lengths are in angstrom, and the relative free energies in chloroform (G_{sol}) are in kcal mol^{-1}. Calculated at the M06/6-31+G**/SDD level.

Both the poor and the optimal phosphines, PPh_3 and **3e**, were used to explore the reaction pathways Path-a and Path-b starting from the intermediate **B**. As shown in Fig. 2, for PPh_3, the hydrogen shift pathway (10.5 kcal mol^{-1}) is more favorable than the cyclopropanation pathway (11.6 kcal mol^{-1}), which is well consistent with the experimental observations that only a trace amount of the cyclopropanation product was obtained. For the optimal phosphine **3e**, the barrier of cyclopropanation (11.8 kcal mol^{-1}) is almost the same as that of PPh_3. However, the barriers of the hydrogen shift pathways increase to 12.9 kcal mol^{-1} (**3e-TS-H-*Shift***) and 11.7 kcal mol^{-1} (**3e-TS-H-*Shift2***), respectively. Thus, the cyclopropanation pathway becomes favorable for **3e**.

These results indicate that the sidearm on the phosphine changes the selectivity of the reaction mainly by suppressing the hydrogen shift process. A detailed structural analysis[21] shows that in **3e-B**, the acetal group increases the repulsion among the three phenyl rings on the P atom, leading to a more flat "umbrella", which is more sensitive to the steric effect. Compared with **PPh_3-TS-H-*Shift***, the attacking of $CsHCO_3$ on the phosphonium group in **3e-TS-H-*Shift*** causes larger repulsion, resulting in a more rigid structure with an entropy loss of 4.759 cal mol^{-1} K^{-1}, which is equivalent to a barrier increase of 1.6 kcal mol^{-1}. Based on these understandings, it is natural that the phosphonium group has a much less effect on the "backside-attack" cyclopropanation transition state than the "side-attack" protonation transition state. For phosphines **3a**, **3b** and **3f**, the rate determining steps of Path-a and Path-b were also calculated, and the results are in good agreement with the experiments.[21]

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Conclusions

In summary, a phosphine-catalyzed cyclopropanation reaction has been successfully realized for the first time with an ether sidearm-assisted phosphine catalyst. X-ray crystal analysis indicated an interaction between the ether oxygen and the phosphonium atom, which was believed to be crucial for switching the phosphine reactivity from a typical ylide route to an unprecedented catalytic cyclopropanation path. DFT calculations rationalize the insight of the sidearm effects. This beneficial effect of a sidearm group would provide a brightening idea for the design and modification of phosphines and other sulfide and amine catalysts. Further investigation on the mechanism and the development of an asymmetric version are in progress in our laboratory.

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14 When the *Z*-isomer of **1e** was employed as a substrate in the catalytic ylide intramolecular cyclopropanation, the desired product **2e** was produced in 21% yield with the same diastereoselectivity of the *E*-configuration substrate **1e**, and 51% of the *Z*-isomer was recovered.

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