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A One-Pot Palladium-Catalyzed Allylic Alkylation and Wittig Reaction of Phosphorus Ylides

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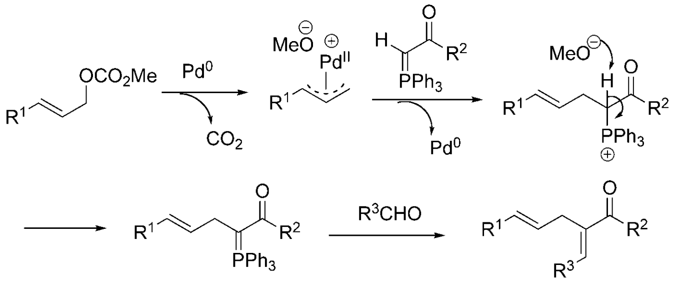
Stabilized phosphorus ylides (P-ylides) are used extensively in organic synthesis, particularly since the discovery of the Wittig reaction.[1] In addition to their reactions with carbonyl compounds,[2] P-ylides are used in Michael additions and alkylation reactions, in which they act as nucleophiles.[3] An elegant study by Chen and co-workers recently demonstrated that P-ylides can be used in an organocatalytic Mannich-type process that, following a Wittig reaction, affords aza-Morita–Baylis–Hillman products.[4] However, in general, the utilization of P-ylides as nucleophiles in alkylation reactions has been scarcely explored. To our knowledge, there are no reports of the use of P-ylides as nucleophiles in Pd-catalyzed allylic alkylation reactions (Tsuji–Trost reactions) despite these being widely recognized as one of the most important reactions in organic synthesis;[5] all previous reports on P-ylides with transition-metals have been coordination studies.[6] The strong binding ability of P-ylides with transition metals will likely impede their use in transition-metal-catalyzed reactions. However, as part of our ongoing efforts in the development of transition-metal-catalyzed allylic substitution reactions,[7] we recently found that P-ylides are suitable nucleophiles in Pd-catalyzed allylic alkylation reactions which occur via functionalized P-ylide intermediates. This intermediate then undergoes a Wittig reaction in a novel reaction pathway (Scheme 1).[8] In this paper, we report the results of such a one-pot reaction.

We began our study by carrying out the reaction of P-ylide **1a** (1.5 equiv) with allyl carbonate **2b** and Cs_2CO_3 (1.5 equiv) in THF, which was heated at reflux, utilizing the catalyst generated in situ from $[\{Pd(C_3H_5)Cl\}_2]$ (5 mol%) and 1,2-bis(diphenylphosphino)ethane (dppe; 11 mol%). After all of the starting material (**2b**) had disappeared, an excess of formalin was added and the mixture was stirred for a further 24 h. To our delight, the desired product **4ab** was obtained in 30% yield (entry 1, Table 1). Encouraged by this result, we examined a series of phosphine ligands, such as 1,3-bis(diphenylphosphino)propane (dppp), 1,1′-bis(diphenylphosphino)ferrocene (dppf), 1,4-bis(diphenylphosphino)butane (dppb), PPh_3, and $P(OPh)_3$.



Scheme 1. Possible pathway of the one-pot Tsuji–Trost/Wittig reaction.

Interestingly, the Trost ligand, **L1**, was found to provide the optimal conditions, affording **4ab** in 57% yield under otherwise identical conditions (entry 7, Table 1). Further optimization of the conditions revealed that the reaction in dioxane at reflux gives the best yield (79%, entry 8, Table 1).[9] Notably, intermediate **3** can be isolated in 33% yield prior to the quenching with formalin, which provides evidence for the reaction pathway proposed in Scheme 1.[9]

Under these optimized reaction conditions, the scope of this one-pot Tsuji–Trost/Wittig reaction was investigated with various P-ylides, allylic carbonates, and aldehydes, as summarized in Table 2. Interestingly, both cinnamyl methyl carbonate (**2a**) and methyl 1-(phenylallyl) carbonate (**2′a**) led to the same, linear, product, **4aa**, indicating that the π-allyl–palladium intermediate shown in Scheme 1 is involved in both cases (entries 1 and 2, Table 2). The reactions of allyl carbonates containing *para*-, *meta*-, or *ortho*-methoxyphenyl groups (**2b–d**) occurred smoothly and gave the desired products (**4ab–ad**) in 46–79% yields (entries 3–5,

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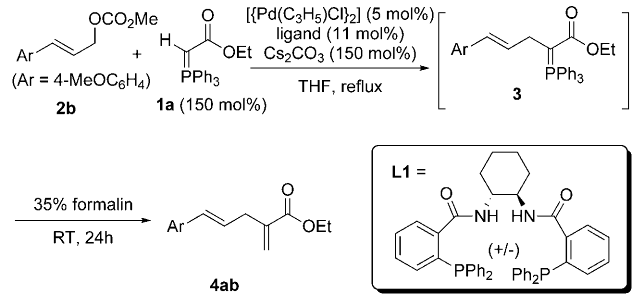
Table 1. Screening the ligands.[a]



Entry	Ligand	t [h]	Yield [%][b]
1	dppe	6	30
2	dppp	19	39
3	dppf	24	13
4	dppb	17	<5
5[c]	PPh_3	96	–[d]
6[e,f]	$P(OPh)_3$	3	50
7	**L1**	72	57
8[f]	**L1**	16	79
9[f,g]	**L1**	11	71

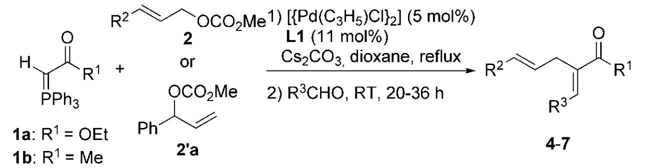
[a] $[Pd(C_3H_5)Cl]_2$ (5 mol%), ligand (11 mol%), Cs_2CO_3 (150 mol%), **1a** (150 mol%), and **2b** (100 mol%) in THF at reflux for the indicated time, then excess formalin was added (for a further 24 h). [b] Isolated yield over two steps. [c] $[Pd(PPh_3)_4]$ (10 mol%) was used. [d] Complex mixture. [e] 4Å molecular sieves were added. [f] In dioxane at reflux. [g] Performed on a 1 mmol scale.

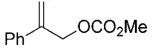
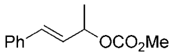
Table 2). Allylic carbonates containing aromatic electron-withdrawing groups (p-F, m-Cl, o-Cl, p-Br, p-CF_3, and p-NO_2; **2e**–**j**) all gave the products (**4ae**–**aj**) in excellent yields (82–89%). The reaction of 1-naphthyl- and 2-furyl-substituted allyl carbonates (**2k** and **l**) with P-ylide **1a** afforded products **4ak** and **4al** in 71 and 45% yields, respectively. The one-pot reaction of methyl 2-(phenylallyl) carbonate (**2m**) led to the formation of **4am** in 88% yield (entry 14, Table 2). The allyl carbonates containing aliphatic groups (**2q** and **r**) gave the desired products in low yields (entries 16 and 17, Table 2).

The P-ylide **1b**, containing an acetyl group, exhibited a lower reactivity than **1a** under the current catalytic system (entry 18, Table 2). In addition to formaldehyde, other aldehydes such as benzaldehyde, acrylaldehyde, and propionaldehyde were also well tolerated (47–66% yield; entries 19–22, Table 2), which greatly expands the range of applications of the method. Notably, the trisubstituted alkenes were exclusively formed in E configurations, as confirmed by 2D-NOESY experiments.[9] Furthermore, a 1,3-disubstituted allylic carbonate (**2n**) could also be used in this one-pot process (entry 15, Table 2), which provides a basis for further asymmetric studies into this reaction.[10]

Interestingly, this one-pot reaction can be extended to the synthesis of allenes,[11] which are important intermediates in organic synthesis, by means of the olefination of ketenes.[12] When phenylethylketene was used in place of an aldehyde, tetrasubstituted allenes **8** were obtained in 23–49% yields (Table 3).

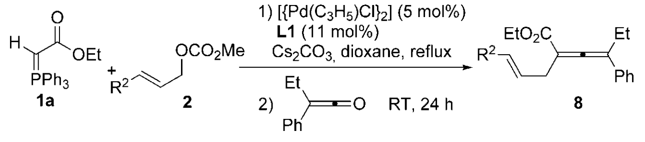
Table 2. Substrate scope of the one-pot allylic alkylation of P-ylides/Wittig reaction.[a]



Entry	R^1	R^2		R^3	t [h]	Product	Yield [%][b]
1	OEt	Ph	**2a**	H	14	**4aa**	86
2[c]	OEt	Ph	**2′a**	H	17	**4aa**	75
3	OEt	4-MeO-C_6H_4	**2b**	H	16	**4ab**	79
4	OEt	3-MeO-C_6H_4	**2c**	H	28	**4ac**	57
5	OEt	2-MeO-C_6H_4	**2d**	H	32	**4ad**	46
6	OEt	4-F-C_6H_4	**2e**	H	14	**4ae**	84
7	OEt	3-Cl-C_6H_4	**2f**	H	14	**4af**	82
8	OEt	2-Cl-C_6H_4	**2g**	H	10	**4ag**	89
9	OEt	4-Br-C_6H_4	**2h**	H	12	**4ah**	82
10	OEt	4-CF_3-C_6H_4	**2i**	H	12	**4ai**	86
11	OEt	4-NO_2-C_6H_4	**2j**	H	5	**4aj**	84
12	OEt	1-naphthyl	**2k**	H	20	**4ak**	71
13	OEt	2-furyl	**2l**	H	14	**4al**	45
14[d,e]	OEt		**2m**	H	8	**4am**	88
15[d,f]	OEt		**2n**	H	8	**4an**	27
16[d,g]	OEt	(E)-1-propenyl	**2q**	H	5	**4aq**	25
17[d,g]	OEt	n-C_4H_9	**2r**	H	3	**4ar**	18
18[h]	Me	4-MeO-C_6H_4	**2b**	H	48	**4bb**	23
19	OEt	4-MeO-C_6H_4	**2b**	Ph	16	**5ab**	50
20	OEt	4-NO_2-C_6H_4	**2j**	Ph	5	**5aj**	47
21	OEt	4-MeO-C_6H_4	**2b**	vinyl	16	**6ab**	66
22	OEt	4-Br-C_6H_4	**2h**	Et	12	**7ah**	58

[a] See the Supporting Information for details. [b] Isolated yield over two steps. [c] **2′a** was used. [d] No base was used. [e] Carbonate **2m** was used. [f] Carbonate **2n** was used. [g] 4 Å molecular sieves were added. [h] In refluxed THF.

Table 3. Synthesis of allenes by using the one-pot reaction.



Entry	R^2		Product	Yield [%][a]
1	4-MeO-C_6H_4	**2b**	**8ab**	37
2	3-MeO-C_6H_4	**2c**	**8ac**	40
3	2-MeO-C_6H_4	**2d**	**8ad**	49
4	4-NO_2-C_6H_4	**2j**	**8aj**	33
5	2-NO_2-C_6H_4	**2o**	**8ao**	23
6	6-MeO-2-naphthyl	**2p**	**8ap**	39

[a] Isolated yield over two steps.

During the optimization of the reaction conditions,[9] we found that, if no extra base was added to the reaction mixture, by-product **9** was isolated in 27% yield, possibly due to a reaction of intermediate **3** with a second molecule of substrate **2b** in the presence of the palladium catalyst [Eq. (1)]. Encouraged by this result, ylide **1c** was also tested under the base free allylic alkylation conditions. As expected, the product **10cb** was obtained in 65% yield [Eq. (2)]. Further studies into this reaction indicated that water is the proton

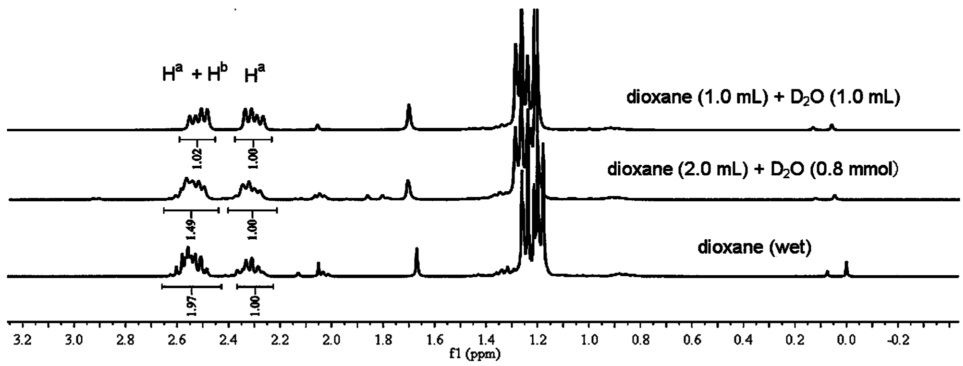
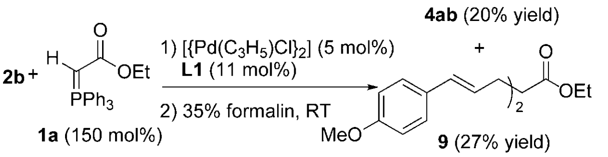
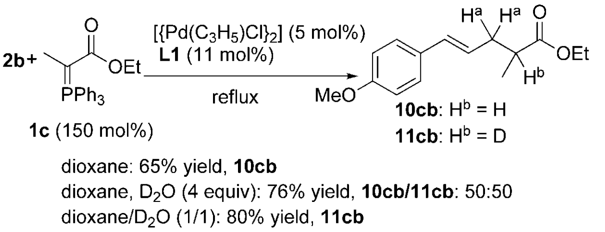


Figure 1. Pd-catalyzed allylic alkylation of P-ylide **1c**.

source. In the presence of D_2O (4 equiv), the reaction led to a 50:50 ratio of **10cb**/**11cb**, in 76 % yield, while with dioxane/D_2O (1:1) as the solvent, the reaction gave the deuterated product (**11cb**) exclusively, in 80 % yield (Figure 1). This reaction provides an alternative method for C_{sp^3}–C_{sp^3} bond formation.[13]

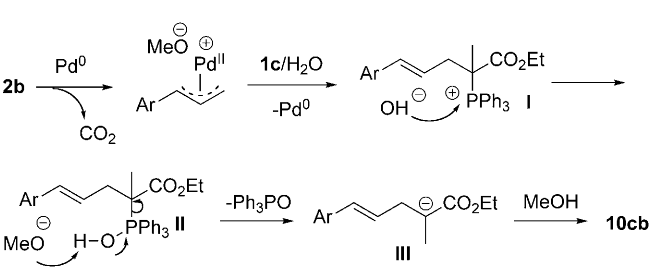


(1)



(2)

A possible mechanism for the Pd-catalyzed allylic alkylation with **1c** is depicted in Scheme 2. The P-ylide (**1c**) acts as a nucleophile and attacks the π-allyl-palladium intermediate to give intermediate **I**. The hydroxide anion, generated during this process from water, then reacts with intermediate **I** to give intermediate **II**. Upon the release of triphenylphosphine oxide from intermediate **II**, intermediate **III** is formed, which, after protonation, gives the product. This proposed reaction mechanism is supported by the formation of triphenylphosphine oxide and the acceleration of the reaction rate if water is added to the reaction mixture.



Scheme 2. A plausible mechanism for the allylation with **1c**.

In conclusion, we have demonstrated for the first time that P-ylides are suitable nucleophiles for allylic alkylation reactions in the presence of a Pd/Trost ligand system. This one-pot Tsuji–Trost/Wittig reaction with various aldehydes and ketenes was accomplished, providing skipped dienes, including trisubstituted alkenes, and tetrasubstituted allenes in moderate to good overall yields. P-ylide **1c** was also used in the allylic alkylation reaction, providing an efficient method for C_{sp^3}–C_{sp^3} bond formation.

Experimental Section

Typical procedure for the one-pot Pd-catalyzed allylic alkylation and Wittig reaction: [{Pd(C_3H_5)Cl}$_2$] (3.7 mg, 0.010 mmol) and Trost ligand **L1** (*N,N′*-(cyclohexane-1,2-diyl)bis[2-(diphenylphosphino)benzamide]; 15.3 mg, 0.022 mmol) were dissolved in dioxane (2.0 mL) in a dry Schlenk tube filled with argon and stirred for 20 min at room temperature. Then allyl carbonate **2** (0.20 mmol) was added to the mixture. After stirring for 10 min, P-ylide **1** (0.30 mmol) and cesium carbonate (97.7 mg, 0.30 mmol) were added and the mixture was heated at reflux until the allyl carbonate was fully consumed (as monitored by TLC). After cooling to room temperature, formalin (0.50 mL, 35 % in water, w/w) was added and the resulting reaction mixture was stirred for a further 24 h. Then water (5.0 mL) was added and the product was extracted with dichloromethane (5.0 mL × 3). The combined organic layers were washed with brine, separated, and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue purified by silica gel column chromatography using petroleum ether/ethyl acetate (20:1) as the eluent to give products **4**.

Full experimental details and characterization data are given in the Supporting Information.

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Keywords: allenes · alkylation · allylic compounds · one-pot reactions · palladium · ylides

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