DOI: 10.1002/ejoc.201101293

P–C Cross-Coupling Onto Enamides: Versatile Synthesis of α-Enamido Phosphane Derivatives

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Keywords: Cross-coupling / Phosphaalkenes / Enols / Phosphanes / Boranes

We report herein the Pd-catalyzed P–C cross-coupling reaction between enol phosphates and secondary phosphane–borane complexes or phosphane oxides. The reaction was performed under mild conditions, owing to Pd activation of the P–H bonds of the phosphane–boranes (or phosphane oxides) and to the powerful enol phosphate coupling reagents. New useful chiral and achiral α-β-alkenylphosphane derivatives bearing an amido group in the α-position to the P center were obtained in yields up to 70 %.

Introduction

To date, a great deal of attention has been paid to the development of new functionalized phosphane derivatives as a result of their use in catalysis[1] or organocatalysis.[2] However, methods available for their preparation that are both easy and modular are still scarce, thus hindering the design of hybrid ligands or organocatalysts and, consequently, their applications. This is particularly true for the synthesis of P-stereogenic phosphorus compounds bearing a functional group.[1,3,4] Thus, the demand for innovative synthetic routes to functionalized phosphorus compounds led us to investigate a versatile P–C bond-forming reaction starting from secondary phosphane derivatives by using a Pd-catalyzed cross-coupling reaction.[5] Although hydrophosphination of alkynes provides an economical and tolerant method to produce α,β-unsaturated phosphorus compounds, this methodology is not applicable to the preparation of cycloalkenylphosphorus compounds because of the absence of small ring alkynes.[6] To overcome this problem, a metal-catalyzed coupling procedure from vinyl halides or triflates has been recently described.[7] However, as the synthesis of functionalized phosphanes by a heterocyclic substituent remains challenging, the use of a heterocyclic precursor reagent such as **2** has been investigated in the present study for the Pd-catalyzed coupling with phosphane derivatives.

In this communication, we wish to report the use of α-amido enol phosphate **2**, which is easily accessible from amides, lactams, or imides,[8] in Pd-catalyzed coupling reactions with chiral or achiral secondary phosphane–boranes (or phosphane oxides) to afford their enamido derivatives. These compounds are potentially interesting to yield hybrid heterocyclic phosphane derivatives.[8]

Results and Discussion

Access to alkenylphosphane–borane complexes by Pd-catalyzed P–C cross-coupling of vinyl halides or triflates with secondary phosphane–borane complexes or phosphane oxides has already been disclosed.[7] However to the best of our knowledge, there are no literature examples of this coupling with non-aromatic heterocyclic scaffolds. The major advantage of our strategy lies in the fact that a direct precursor of the free phosphane function (such as a borane complex or phosphane oxide) can be easily introduced at the α position to the nitrogen-containing heterocycle. This method would allow the synthesis of a range of original α-enamido phosphane derivatives (Scheme 1).

To this end, the synthesis of requisite starting enol phosphates **2a**–**e** was achieved in accordance with our previously reported results.[8] The use of α-amido enol phosphate **2** presents several advantages over triflate reagents, particularly because of its easy preparation and stability. Preliminary studies to focus the reaction were performed by using seven-membered α-amido enol phosphate **2c** and secondary diphenylphosphane–borane complex **3a** (Scheme 2). The use of secondary phosphane–boranes has led to significant progress in P–C bond formation,[9] and their products can

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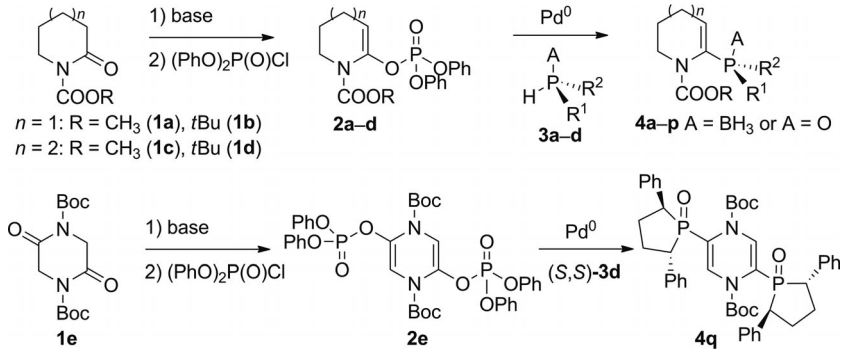
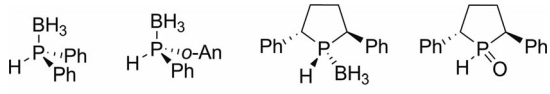
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201101293.



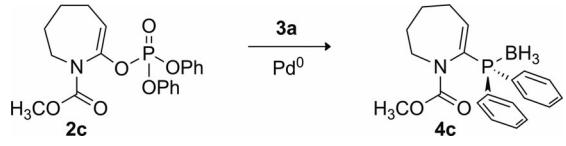
Scheme 1. P–C cross-coupling of secondary phosphane–boranes or phosphane oxides **3a**–**d** with enol phosphates **2a**–**e**.

be directly used in organic synthesis or in coordination chemistry for the preparation of derivatives that cannot be easily prepared by alternative approaches or obtained in their trivalent form.[1f,4] The results are reported in Table 1.



Scheme 2. Starting secondary phosphane–boranes **3a**–**c** and phosphane oxide **3d**.

Table 1. Optimization of the P–C coupling reaction between enol phosphate **2c** and $Ph_2PH{\cdot}BH_3$ (**3a**).[a]



Entry	Base	Solvent	Catalyst	Time [h]	Yield [%][b]
1	K_2CO_3	DMSO	$dppfPdCl_2$	3	38
2[c]	K_2CO_3	DMSO	$dppfPdCl_2$	0.25	11
3[c]	K_2CO_3	DMSO	$dppfPdCl_2$	0.5	0
4	Cs_2CO_3	DMSO	$dppfPdCl_2$	24	60
5	K_2CO_3	CH_3CN	$dppfPdCl_2$	24	51
6	Cs_2CO_3	CH_3CN	$dppfPdCl_2$	2	95
7	Cs_2CO_3	CH_3CN	(IMes)Pd(η3-2-methylallyl)Cl[10]	1	90

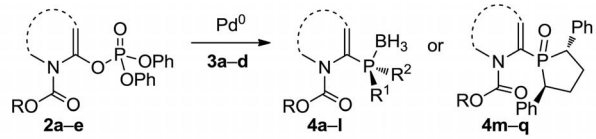
[a] Conditions: $Ph_2PH(BH_3)$ (**3a**, 2 equiv.), base (2 equiv.), and Pd catalyst (5 mol-%) at 60 °C. [b] Isolated yield after purification by column chromatography in air. [c] Reaction performed under microwave irradiation.

Using conditions similar to those reported for triflate reagents,[7a] the P–C Pd-catalyzed cross-coupling reaction was best performed by mixing phosphane **3a** (2 equiv.) and enol phosphate **2c** (1 equiv.) in acetonitrile at 60 °C for 2 h in the presence of a weak base (2 equiv. of Cs_2CO_3), and $(dppf)PdCl_2$ (5 mol-%) as catalyst (Table 1, Entry 6). Expected *N*-acetamido tetrahydroazepinylphosphane **4c** was thus isolated in 95% yield after purification by chromatography on silica gel. The ^{31}P NMR spectrum of phosphane–borane **4c** displays a significant signal at δ = +24.1 ppm. An excess amount of phosphane substrate **3a** was required for complete conversion of the starting enol phosphate. Using (IMes)Pd(η-3–2-methylallyl)Cl, developed by Nolan's group,[10] as a coupling catalyst was also successful and afforded expected phosphane–borane **4c** in similar yield (Table 1, Entry 7). It is noteworthy that lower yields were observed in the presence of K_2CO_3 as a base (Table 1, Entries 1 and 5). Performing the reaction in a polar coordinating solvent such as DMSO (Table 1, Entries 1–4) and/or under microwave irradiation (MWI) to ensure a shorter reaction time (Table 1, Entries 2 and 3) was ineffective due to significant decomposition.

In light of the optimized conditions (Table 1, Entry 6), we envisaged performing the P–C cross-coupling reaction of enol phosphates **2a**–**e** with secondary phosphane derivatives **3a**–**d** (Scheme 2, diphenylphosphane–borane **3a**, chiral enantiopure phosphane–boranes **3b**[11] and **3c**,[12a] and chiral phosphane oxide **3d**).[12b] The results are summarized in Table 2. The Pd-catalyzed coupling of enol phosphates **2a**, **2c**, and **2d** with diphenylphosphane–borane **3a** allowed us to isolate desired tetrahydropyridinyl- and azepinylphosphane derivatives **4a**, **4c**, and **4d** in low to good yields (Table 2, Entries 1, 3, and 4). A noticeable exception was observed with *N*-Boc six-membered enol phosphate **2b** (Table 2, Entry 2), from which expected phosphane **4b** could not be isolated, presumably because of its weak stability arising from internal steric hindrance.[13] Unfortunately, only starting material was recovered. Increasing the reaction temperature or using microwave activation was ineffective, as an increase in the amount of decomposition products was observed. Moreover, as borane decomplexation could occur during the coupling reaction,[6b] an additional amount of $BH_3{\cdot}Me_2S$ was also added at the end of each previous experiment in an attempt to increase the amount of phosphane–boranes **4a**–**d**. Unfortunately, in these cases, only unsubstituted enecarbamates resulting from the reduction of the enol phosphate moiety and degradation products were recovered.

The investigation was then conducted with enantiomerically pure (*S*)-(*o*-anisyl)phenylphosphane–borane **3b** prepared by metal–halide exchange starting from the corresponding chlorophosphane–borane (Table 2, Entries 5–8).[4,11,14] We anticipated that the borane protecting group

Table 2. Pd-catalyzed P–C bond formation from enol phosphates **2a**–**e**.



Entry	Enol phosphate	Product	Temperature [°C]	Time [h]	Yield[f,g] [%]	*ee*[h] [%]
1[a]	**2a**	**4a** (R = Me)	60	2	28	–
2[a]	**2b**	**4b** (R = tBu)	60	2	0	–
3[a]	**2c**	**4c** (R = Me)	60	2	95	–
4[a]	**2d**	**4d** (R = tBu)	60	2	75	–
5[b]	**2a**	**4e** (R = Me)	60	2	42	0
6[b]	**2b**	**4f** (R = tBu)	60	2	0	0
7[b]	**2c**	**4g** (R = Me)	60	2	58	0
8[b]	**2d**	**4h** (R = tBu)	60	2	42	0
9[c]	**2a**	**4i** (R = Me)	40	3	30	>99.5
10[c]	**2b**	**4j** (R = tBu)	40	3	0	–
11[c]	**2c**	**4k** (R = Me)	40	3	46	>99.5
12[c]	**2d**	**4l** (R = tBu)	40	3	35	>99.5
13[d]	**2a**	**4m** (R = Me)	100	2	64	99.4
14[d]	**2b**	**4n** (R = tBu)	100	2	28	99.4
15[d]	**2c**	**4o** (R = Me)	100	2	70	99.7
16[d]	**2d**	**4p** (R = tBu)	100	2	70	>99.5
17[e]	**2e**	**4q**	100	2	75	>99.5

[a] Conducted with **3a** (2 equiv.), Cs_2CO_3 (2 equiv.), and (dppf)$PdCl_2$ (5 mol-%) in CH_3CN. [b] Conducted with (*S*)-**3b** (2 equiv.), Cs_2CO_3 (2 equiv.), and (dppf)$PdCl_2$ (5 mol-%) in CH_3CN. [c] Conducted with (*S*,*S*)-**3c** (2 equiv.), Cs_2CO_3 (2 equiv.), and (dppf)$PdCl_2$ (10 mol-%) in CH_3CN. [d] Conducted with (*S*,*S*)-**3d** (2 equiv.), DIPEA (4 equiv.), and (dppf)$PdCl_2$ (10 mol-%) in DMSO. [e] Conducted with (*S*,*S*)-**3d** (4 equiv.), DIPEA (8 equiv.), and (dppf)$PdCl_2$ (10 mol-%) in DMSO. [f] Isolated yield after purification by column chromatography in air. [g] Compounds were characterized by ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR spectroscopy. [h] Determined by using chiral SFC-DAD.[15]

of **3b** would prevent undesirable inversion at the phosphorus atom. Notably, the yields recorded for **4e**–**h** were significantly lower than those previously obtained (see Table 2, Entries 1–4) probably due to the lower reactivity of phosphane **3b** as a result of the inductive donor effect of the methoxy group. Degradation products were also ob-

served and no starting material was recovered. However, it should be pointed out that, unfortunately, complete racemization of products **4e**–**h** occurred during the P–C cross-coupling reactions with **3b**. Racemization at the P center was established by chiral supercritical fluid chromatography (SFC);[15] it may be explained by an inversion, under basic conditions, of the phosphide–borane anion before ligand exchange in the coordination sphere of the Pd.[3a,16] No improvement in the stereoselectivity of the reaction was observed by changing the nature of the solvent (DMF, CH_3CN) or the temperature (40–60 °C). Nevertheless, the stereoselective synthesis of chiral tetrahydropyridinyl- or azepinylphosphane derivatives was alternatively achieved by a Pd-catalyzed P–C bond-forming reaction by using enantiomerically pure (*S*,*S*)-2,5-diphenylphospholane-borane (**3c**).[5a] As chirality is borne by the phospholane skeleton, no racemization was observed. Expected phosphanes **4i**–**l** (Table 2, Entries 9–12) were thus isolated enantiomerically pure (>99.5%*ee*) in moderate yields. As reported by Toffano et al.,[5] the observed low yield could be explained by a lack of reactivity of secondary phosphane **3c** and the possible decomplexation of the borane group. Enantiomeric excesses were determined by chiral SFC analysis: diode-array detection ensured identification of the minor enantiomer. In most cases, its concentration was so small that it was not detected.[15] For the six-membered ring (Table 2, Entry 10), we assume that the steric hindrance of the Boc group is accountable for the failure to obtain derivative **4j**.

Nevertheless, encouraged by these promising results, we then turned our attention toward the use of enantiomerically pure (*S*,*S*)-2,5-diphenylphospholane oxide (**3d**).[12] Applying conditions previously reported,[5] the reaction was carried out in the presence of (dppf)$PdCl_2$ (10 mol-%) as a catalyst and *i*Pr_2NEt as a base in DMSO. Desired phosphane oxides **4m**–**p** were thus isolated in fair to good yields in an enantiomerically pure form (Table 2, Entry 13–16). In light of prior studies,[5] we were also pleased to observe that the higher reactivity of phospholane oxide **3d** ensured the accomplishment of the P–C coupling with hindered six-membered ring **2b**, albeit in low yield (Table 2, Entry 14). The good solubility of the base (*i*Pr_2NEt) in the reaction solvent also appeared to be a positive factor for this P–C coupling. The structures of **4h** and **4o** were unambiguously determined by X-ray analyses (Figure 1, see also the Supporting Information).[17] In the case of compound **4o**, X-ray diffraction analysis revealed that no epimerization at the benzylic carbon atoms of the phospholane ring, which would have led to diastereomeric or enantiomeric compounds, was observed.

To study the scope of our methodology, we then focused on the double P–C cross-coupling reaction. Given our previously reported results that describe the easy functionalization of the dihydropyrazine ring and its possible aromatization into pyrazine,[8c] we anticipated obtaining a diphosphane with a dihydropyrazine moiety as a bridge. Pyrazines are widely used intermediates in medicinal chemistry and for functional transformations.[8c,18] Furthermore, the incorporation of phosphorus into organic molecules could increase their biological activity.[19] To date, only a few papers have reported the synthesis of pyrazinylphosphane derivatives.[20] We therefore investigated the Pd-catalyzed P–C bond construction between symmetrical bis-enol phosphate **2e**[8c] and enantiopure phosphane oxide **3d** (Table 2, Entry 17). Dihydropyraninyl derivative **4q** bearing two phosphane oxide groups in the 2- and 5-positions was isolated in good yield in an enantiomerically pure form. Extensive exploration to exploit the usefulness of the P–C cross-coupling reaction and to obtain more mechanistic details will be reported in due course.

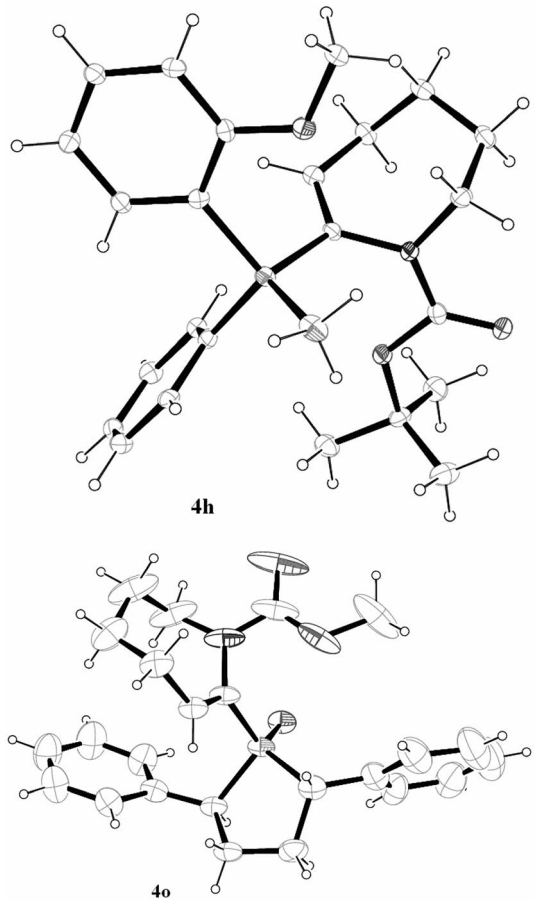


Figure 1. X-ray structures of α-enamido phosphane derivatives **4h** and **4o**.

Conclusions

In summary, we have described a useful Pd-catalyzed P–C cross-coupling reaction that has been successfully applied to a range of chiral or achiral secondary phosphane–boranes (or phosphane oxides) and α-amido enol phosphate reagents. This coupling was achieved under rather mild conditions and in a very short time, leading stereoselectively to hindered tertiary α-enamido phosphane derivatives with up to 99.4%*ee* when the chirality is borne by the phospholane ring. A large variety of phosphane derivatives as well as different enol phosphates were coupled, showing the efficiency of this cross-coupling reaction. It is worth noting

that this methodology makes it possible, for the first time, to synthesize a range of α-enamido phosphane derivatives from widely available ketones. This strategy may thus efficiently provide access to phosphanyl heterocyclic compounds based on privileged substructures with potential biological interest. Further experiments by using chiral catalysts are also currently under investigation.

Experimental Section

General Procedure for the Pd-Catalyzed P–C Cross-Coupling: Under an atmosphere of argon, enol phosphate **2** (120 mg, 0.30 mmol) was dissolved in distilled acetonitrile (2.5 mL) and secondary phosphane–borane **3a**, **3b**, or **3c** (0.60 mmol) was added. Then, the contents of the flask were evacuated and backfilled with argon three times. After that, $dppfPdCl_2$ (0.014 mmol) and Cs_2CO_3 (0.60 mmol) were introduced, and the degassing procedure was repeated. The reaction was carried out in an oil bath (65–70 °C) for the appropriate time. The reaction mixture was filtered through Celite, and the filtrate was evaporated. The crude product was purified by flash column chromatography to yield expected alkenylphosphanes **4a**–**l**.

Supporting Information (see footnote on the first page of this article): Experimental procedures and crystallographic data.

Acknowledgments

This work and the postdoctoral grant for A. B. were funded by the Agence Nationale de la Recherche (grant ANR-07-blan-0292–04), which is gratefully acknowledged. The French Embassy in Poland is acknowledged for providing a cotutelle PhD grant to M. C.

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Received: September 5, 2011
Published Online: January 13, 2012

