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Synthesis of β-Aryl-α,β-Dehydroaminophosphonates by Pd-Catalyzed Fujiwara–Moritani C–C Coupling

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The treatment of diethyl α,β-dehydroaminophosphonate **1** with various arenes (ArH = toluene **2a**, benzene **2b**, anisole **2c**, bromobenzene **2d**, chlorobenzene **2e**, benzyl alcohol **2f**, *p*-xylene **2g**) in acetic acid (AcOH) at 120 °C for 8 h in the presence of $Pd(OAc)_2$ (10% mol, OAc = acetate) and AgOAc (3.4 equivalents) results in the formation of the corresponding β-aryl derivatives *E*-Ar(H)C=C(NHAc)P(O)$(OEt)_2$ **3a–3g**. The reaction proceeds through double C–H activation (arene and alkene) and subsequent C–C oxidative coupling (Fujiwara–Moritani reaction), processes catalyzed by Pd and assisted by Ag. The obtained products **3a–3g** are isosteric analogs of phenylalanine and are obtained with high selectivity. Thus, geometrical *E*-isomers have been obtained in all studied cases, however mixtures of *ortho*-/*meta*-/*para*-isomers are observed when the activated position in the starting arene **2** is considered.

Introduction

α-Aminophosphonic acids (Figure 1a), isosteric analogs of α-amino acids, constitute a family of organophosphorus compounds of high interest due to their significant biological activity.[1a–d] The presence of the phosphonate group is mainly responsible for their biological properties, a fact demonstrated by their behavior as irreversible inhibitors of serine proteases,[1e,f] as analogs of the transition state of peptidic hydrolysis,[1g] or as aminocarboxylic acid mimetics.[1b] Due to this remarkable activity, there is a growing interest in studying the synthesis and biological properties of this type of compounds with structures as diverse as possible, not only those closer to protein amino acids.[2]

Molecular scaffolds of particular interest are the α,β-dehydroaminophosphonates (Figure 1b), key intermediates in the preparation of other amino acid derivatives and present in numerous biologically active peptides.[3] Regarding their role as intermediates, derivatives of α,β-dehydroamino acids can lead to enantioenriched amino acids through stereoselective hydrogenations,[4] conjugate addition reactions of trifluoroaryl or alkenylborates,[5] or through stereoselective hydroboration followed by oxidation to obtain β-hydroxy-α-amino acids.[6] These compounds can also undergo reactions such as double bond metathesis,[7] cycloaddition,[8] or C–C cross–coupling, especially Heck, Suzuki, and Sonogashira reactions.[8f,9] On the other hand, concerning their role in peptides, interest has been growing since the structure[10] and the mode of action[11] of the dehydrophos peptide was determined, which includes a dehydroamino–phosphonate residue in its structure (Figure 1c).[3a]

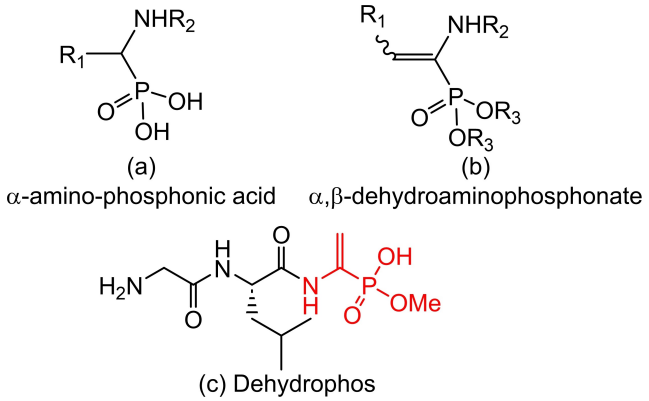

Figure 1. General structure of (a) α-aminophosphonic acids; (b) β-substituted-α,β-dehydro-aminophosphonates; (c) dehydrophos peptide, whose activity is due to the dehydro-aminophosphonate residue.

The preparation of N–, P–, and β-substituted α,β-dehydroaminophosphonate derivatives can be carried out using various synthetic procedures that have been adequately reviewed, and are summarized in Figure 2a.[12] Analysis of possible disconnections shows that in the synthesis methods of β-substituted-α,β-dehydroaminophosphonates, the R^1 or R^2 groups at the β position are always incorporated into one of the reagents. That is, up to now, no synthesis of β-substituted α,β-dehydroaminophosphonates involves the reactivity of the double C=C bond by activation of its β(C–H) bonds. In this work, the β-arylation of α,β-dehydroaminophosphonates is proposed through oxidative C–C coupling based on CH activation reactions catalyzed by Pd (Fujiwara–Moritani reaction), a process depicted in Figure 2b. While the Fujiwara–Moritani reaction has received special consideration due to its synthetic utility,[13] the examples

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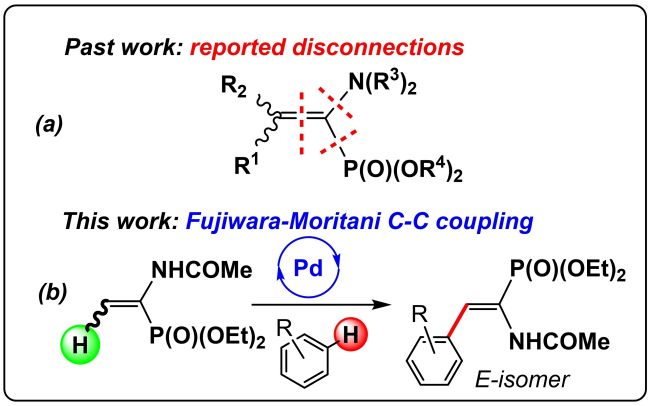


Figure 2. (a) Disconnections reported in the synthesis of β-substituted α,β-dehydroaminophosphonates; (b) Work presented here, based on vinyl C–H activation and subsequent oxidative C–C coupling (Fujiwara–Moritani coupling).

described in the literature where this strategy is applied to introduce β-aryl substituents in derivatives with a general α,β-dehydroamino acid structure are scarce,[14] and in the case of α,β-dehydroaminophosphonates, entirely unknown. In this work we present the obtained results in the Fujiwara–Moritani oxidative CH functionalization of dehydroaminophosphonates.

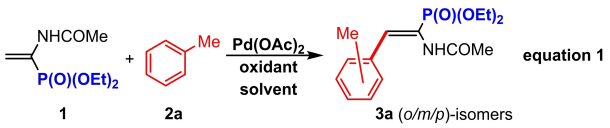
Results and Discussion

As a model substrate to optimize reaction conditions, diethyl (1-acetamidovinyl)phosphonate **1** has been chosen. The selection of protecting groups is due, on one hand, to the stability of the acetyl group against moderately acidic conditions,[15] which are common in Fujiwara–Moritani reactions. On the other hand, it relates to the compromise solution that ethyl esters represent for the phosphonate group, since they are more stable than methyl esters[16] without significantly increasing steric bulkiness. The synthesis of **1** has been carried out using methods described in the literature.[5a,8a,17] Toluene **2a** has been used as the arene due to its high boiling point and because it is an excellent NMR probe. As the starting palladium catalyst, $Pd(OAc)_2$ (OAc = acetate) has been employed due to its recognized catalytic capability in C–H bond functionalization reactions. Furthermore, the acetate ligand has shown to play a key role in such processes, assisting the release of H that is activated from the aryl C–H group and stabilizing it as acetic acid.[14d,18] Therefore, acetic acid is included as an additive in the reaction mixture. The reaction requires an oxidant, and thus, the first step of the optimization has been to determine the best oxidant. The process to be optimized is that shown in equation 1.

The treatment of **1** with $Pd(OAc)_2$ (30 % mol) in toluene **2a** and acetic acid at 120 °C in the presence of Oxone® as oxidant does not promote the transformation of **1** into its corresponding arylated derivative. Arylation is also not observed when the *N*-fluoro-2,4,6-trimethylpyridinium triflate salt [F⁺](OTf) is used (entries 1, 2, Table 1), the monitoring of the reaction by ^{31}P NMR revealing the presence of numerous decomposition products instead.

When (diacetoxiodo)benzene $PhI(OAc)_2$ is used as the oxidant, it is possible to isolate the arylated derivatives (*Z*)– and (*E*)–PhC(H)=C(NHC(O)Me)P(O)(OEt)$_2$ **3b**, albeit with a low 27 % yield (*E* 20 %; *Z* 7 %) (Figure 3). The incorporation of the Ph group into **1**, instead of the C_6H_4Me group, shows that toluene

Table 1. Optimization of the reaction conditions for the Fujiwara–Moritani coupling between toluene **2a** and aminophosphonic ester **1** shown in eq. 1.



	Pd (%)	Oxidant	Cosolvent	T (C)	t (h)	Atm	Conv. (%)	Yield (%)
1	30	Oxone®	AcOH	120	7	Ar	–	–
2	30	[F+]OTf	AcOH	120	7	Ar	–	–
3	30	$PhI(OAc)_2$	AcOH	120	7	Ar	–	27[a]
4	30	$Cu(OAc)_2$	AcOH	120	6	Ar	–	3
5	30	AgOAc[b]	AcOH	120	6	Ar	100	53
6	–	AgOAc[b]	AcOH	120	6	Ar	–	–
7	30	AgOAc[b]	AcOH	120	3	O_2	100	62
8	**10**	**AgOAc[b]**	**AcOH**	**120**	**8**	**O_2**	**100**	**62**
9	5	AgOAc[b]	AcOH	120	96	O_2	95	–[d]
10	10	AgOAc[c]	AcOH	120	8	O_2	85	–[d]
11	10	AgOAc[b]	HFIP	60	8	O_2	85	53
12	10	AgOAc[b]	–	120	8	O_2	40	–

General conditions: aminophosphonic **1** 100 mg (0.45 mmol), toluene 5.7 mL (53.6 mmol), AcOH 1.3 mL (29.7 mmol). [a] The obtained product is **3b**, see text. [b] 3.4 equivs AgOAc. [c] 1.7 equivs AgOAc. [d] Multiple side–products observed.

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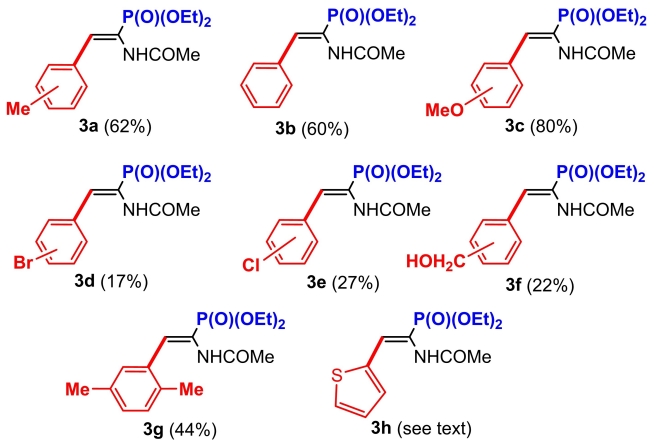

Figure 3. Scope of the Fujiwara–Moritani arylation of α,β-dehydroamino-phosphonate **1**.

does not participate in the reaction and the origin of the Ph group is the $PhI(OAc)_2$ iodonium salt used as the oxidant (entry 3). This is confirmed by conducting the reaction in the presence of acetonitrile instead of toluene, resulting again in the production of **3b** with slightly better yields than those obtained in entry 3 (*E* 33%, *Z* 5%, overall yield 38%). The behavior of $PhI(OAc)_2$ as an arylating agent is not entirely new,[19] although it is indeed uncommon. The use of $Cu(OAc)_2$ as an oxidant also did not yield the expected results (entry 4). However, treating **1** with toluene **2a** and acetic acid at 120 °C for 6 h in the presence of $Pd(OAc)_2$ (30% mol) and Ag(I) salt AgOAc (3.4 equivs) results in the complete disappearance of the starting product **1** and the isolation of the arylated derivative **3a** in a 53% yield as a mixture of *ortho*-/*meta*-/*para*-isomers (1/1.6/1.8) as deduced from the analysis of the ^{31}P NMR spectrum of the crude (entry 5). The use of AgOAc as an excellent reagent in such couplings is not only due to its role as an oxidant to close the catalytic cycle,[20a] but also because the formation of a Pd/Ag bimetallic complex is possible, which can further promote the C–H bond activation[20b] and even the formation of the new C–C bond.[20c] The control reaction in absence of Pd but in presence of Ag does not give detectable coupling products at all (entry 6), so the presence of Pd is mandatory. If the reaction is carried out in the presence of oxygen (open air) and with non-distilled solvents, the reaction time decreases to 3 h and the yield of **3a** improves to 62% of isolated product (entry 7). Taking AgOAc as the optimal oxidant in the presence of air (O_2), the rest of the parameters were optimized.

Reducing the catalyst loading to 10% is feasible. However, to keep the yield of **3a** as high as in entry 7 it is necessary to extend the reaction time to 8 h (entry 8). A further reduction in the catalyst loading to 5% (entry 9) requires excessively long reaction times (at least 96 h) and, although conversion is almost complete (95%), numerous side-products have been observed in the ^{31}P NMR of the crude. Using a 10% catalyst loading, attempts were made to reduce the amount of oxidant to 1.7 equivalents (entry 10). This produced a decrease in the conversion and the appearance of unidentified side-products as well, establishing that the optimal amount of oxidant is 3.4 equivalents. The change of cosolvent was also studied. Only in the case of hexafluoroisopropanol (HFIP) full conversions were observed (entry 11) at 60 °C, and **3a** could be obtained with an isolated yield of 53%. The remarkable properties of HFIP as an acidic solvent in catalytic processes have recently been highlighted.[21] Unfortunately, all attempts to extend the scope of this C–C coupling in HFIP to other arenes beyond toluene failed, as low or very low (even zero) conversions were observed for other arenes such as chloro- or bromobenzene, even if longer reaction times and/or temperatures higher than 60 °C were used. Therefore, acetic acid seems to be the optimal cosolvent. Finally, the control reaction for the need of the cosolvent showed that if the reaction is carried out in the absence of acetic acid (entry 12), the conversion of **1** sharply drops to 40%, confirming that an acidic medium is critical in the reaction as previously suggested. Subsequent modification of the reaction parameters did not yield further improvements, so these were the optimized conditions used in evaluating the reaction scope, which is shown in Figure 3.

As can be seen, the arylation reaction operates with moderate to good yields (up to 80%) when the arene has electron–donating substituents (**3a**, **3c**, **3g**) or when there are no substituents (**3b**). However, in the presence of electron–withdrawing substituents, the yields notably decrease (**3d**, **3e**). Nonetheless, the reduction of the yield in the case of these haloarenes is not a consequence of reduced reactivity since the conversion is 100% in both cases. Instead, it is due to the formation of **3b** through a competitive classical Heck pathway *via* the reactivity of the C-halogen bond. We have also attempted the arylation using electron–rich heterocycles such as thiophene (**3h**). However, low conversions (8%) were obtained under the optimized reaction conditions, showing that these heterocycles need further optimization. In all studied cases, the arylation products **3** are obtained exclusively as the geometric *E*-isomer, as deduced from the observation of a coupling constant $^3J_{PH}$ of around 16 Hz in **3c**, **3e**, and **3f**, and in the major isomer of **3b**.[12a] In products **3a** and **3d**, it is not possible to clearly observe this coupling due to overlap, but the trend observed in the other compounds suggests that the *E*-isomer is obtained here too. Only when the arylation is promoted by the use of $PhI(OAc)_2$ (**3b**) the *Z*-isomer is observed as a minor species. Also, in all studied cases (except, obviously, **3b** and **3g** which are obtained as single regioisomers, the arylation gives products **3** as a mixture of *ortho*-, *meta*-, and *para*–isomers, in varying ratios that do not seem to follow a clear pattern.

Conclusions

In conclusion, we have shown that the Fujiwara–Moritani reaction is a suitable tool for the synthesis of β-aryl-α,β-dehydroaminophosphonic esters through oxidative C–C coupling of different arenes **2** with diethyl α,β-dehydroamino-phosphonate **1**, process catalyzed by Pd^{2+} and assisted by Ag^+. The catalytic arylation takes place in both electron–rich and electron–poor substrates, although it proceeds more efficiently

in the former. The β-aryl-α,β-deshydroaminophosphonic esters are obtained as geometric *E*-isomers with respect to the C=C double bond, and as a mixture of *ortho*, *meta*, and *para* isomers with respect to the C–H activation position in the arene.

Experimental Section

General Methods

Solvents and reagents were obtained from commercial sources and were used without further purification. All reactions were performed without special precautions against air and moisture. IR spectra were measured in solid state on a Nicolet Avatar 360 FT-IR spectrophotometer. The ^{1}H, $^{13}C\{^{1}H\}$ and $^{31}P\{^{1}H\}$ NMR spectra of the isolated products were recorded in $CDCl_3$, CD_2Cl_2 and dmso-d_6 solutions at 25 °C (other conditions were specified) on Bruker AV300 or AV400 spectrometers (δ in ppm, *J* in Hz) at ^{1}H operating frequencies of 300.13 and 400.13 MHz, respectively. The ^{1}H and ^{13}C NMR spectra were referenced using the solvent signal as internal standard, while ^{31}P NMR spectra were referenced to H_3PO_4 (85 %). The assignment of ^{1}H NMR peaks has been performed through standard 2D ^{1}H–COSY (2 K points in t_2 using a spectral width of 10 ppm; 128 t_1 experiments were recorded and zero–filled to 1 K; for each t_1 value two scans were signal-averaged using a recycle delay of 1 s) and selective 1D ^{1}H-SELNOE experiments. Typical mixing times in the case of selective 1D-SELNOE experiments were in the range 0.5–2 s, as a function of the irradiated signal. These values of optimized mixing times were set equal to the longitudinal relaxation time T_1, determined using the inversion–recovery sequence. The ^{13}C NMR peaks were identified using standard ^{1}H–^{13}C edited–HSQC and ^{1}H–^{13}C HMBC 2D-experiments. In both cases 4 K points in t_2 using spectral widths of 10 ppm (^{1}H) and 200 ppm (^{13}C) were used, with averaged values of the coupling constants $^{1}J_{CH}$ = 145 Hz and long–range $^{n}J_{CH}$ = 10 Hz. Typically, 128 t_1 experiments were recorded and zero–filled to 2 K. For each t_1 value 8 (HSQC) or 32 (HMBC) scans were signal–averaged using a recycle delay of 1 s. High–resolution mass spectra–ESI (HRMS-ESI) were recorded using a Bruker MicroToF–Q™ system equipped with an API–ESI source and a Q–ToF mass analyzer, allowing a maximum error in the measurement of 5 ppm. Acetonitrile was used as solvent. Samples were introduced in a continuous flow of 0.2 mL/min and nitrogen served both as the nebulizer gas and the dry gas. The starting material diethyl (1-acetamidovinyl) phosphonate (**1**) was prepared following published methods.[5a,8a,17]

Catalytic Fujiwara–Moritani Oxidative Arylation of 1

All catalytic reactions between **1** and arenes **2a**–**2g** were carried out following the same experimental procedure, which is exemplified here for the synthesis of **3a**. All characterization data are collected in the Supporting Information.

Synthesis of diethyl (*E*)-(1-acetamido-2-(*o,m,p*-tolyl) vinyl) phosphonate 3a. To a suspension of **1** (100 mg, 0.45 mmol) in toluene (5.7 mL) and acetic acid (AcOH, 1.3 mL), $Pd(OAc)_2$ (10 mg, 0.043 mmol) and AgOAc (258 mg, 1.53 mmol) were added. This mixture was heated (oil bath) in a sealed tube at 120 °C for 8 h. After this time, a TLC (ethyl acetate/n-hexane = 9/1) of the reaction mixture showed complete disappearance of the starting material **1**. Then the cold reaction mixture was filtered through a Celite bed, which was washed several times with CH_2Cl_2 (3×5 mL), and the resulting solution was evaporated to dryness to give **3a** as an impure orange oil. Compound **3a** was purified by column chromatography over silica gel using the mixture ethyl acetate/toluene/isopropanol = 6/3/1 as eluent, and isolated as an orange oil. Obtained: 87 mg (62 % yield). **3a** was characterized as the mixture of *o-/m-/p*-isomers of the *E*-olefin in 1/1.9/2.7 molar ratio.

Synthesis of diethyl (*E,Z*)-(1-acetamido-2-phenylvinyl) phosphonate 3b. *(A) From benzene*: compound **3b** was obtained following the same experimental procedure than that described for **3a**, but starting from benzene. Therefore, **1** (100 mg, 0.45 mmol) was reacted with $Pd(OAc)_2$ (10 mg, 0.043 mmol) and AgOAc (258 mg, 1.53 mmol) in benzene (5.7 mL) and acetic acid (1.3 mL) for 8 h at 120 °C to give **3b** as an orange oil after chromatographic purification in silica (ethyl acetate/toluene/ isopropanol = 6/3/1 as eluent). Obtained: 81 mg (yield 60 %). *(B) From $PhI(OAc)_2$* (entry 3, Table 1). To a suspension of **1** (100 mg, 0.45 mmol) in toluene (5.7 mL) and acetic acid (1.3 mL), $Pd(OAc)_2$ (30 mg, 0.13 mmol) and $PhI(OAc)_2$ (194 mg, 0.60 mmol) were added under argon atmosphere. This mixture was heated (oil bath) in a sealed tube at 120 °C for 6 h. After this time, a TLC (ethyl acetate/n-hexane = 9/1) of the reaction mixture showed complete disappearance of the starting material **1**. The cold reaction mixture was filtered through a Celite bed, which was washed several times with CH_2Cl_2 (3×5 mL), and the resulting solution was evaporated to dryness to give **3b** as an impure orange oil. The (*E*)– and (*Z*)– isomers of **3b** were separated and purified by column chromatography over silica gel using the mixture ethyl acetate/toluene/isopropanol = 6/3/1 as eluent. They were isolated as orange oils. Obtained: Isomer *E*: 27.05 mg (20 % yield); Isomer *Z*: 9.73 mg (7 % yield). *(C) From $PhI(OAc)_2$ and acetonitrile.* If the reaction (B) is carried out exactly under the same conditions but using NCMe (3 mL) instead of toluene, (*E*)– and (*Z*)– isomers can be obtained in 33 % yield (48 mg) and 5 % yield (7.3 mg) respectively.

Synthesis of (*E*)-diethyl (1-acetamido-2-(*o,m,p*–methoxy-phenyl)-vinyl) phosphonate 3c. Compound **3c** was obtained following the same experimental procedure than that described for **3a**, but starting from anisol. Therefore, **1** (100 mg, 0.45 mmol) was reacted with $Pd(OAc)_2$ (10 mg, 0.043 mmol) and AgOAc (258 mg, 1.53 mmol) in anisol (5.7 mL) and acetic acid (1.3 mL) for 8 h at 120 °C to give **3c** as an orange oil after chromatographic purification in silica (ethyl acetate/toluene/isopropanol = 6/3/1 as eluent). Obtained: 119 mg (yield 80 %). Compound **3c** was characterized as the mixture of *o-/m-/p*-isomers in 1/2.4/7.1 molar ratio.

Synthesis of (*E*)-diethyl (1-acetamido-2-(*o,m,p*-bromo phenyl)-vinyl) phosphonate 3d. Compound **3d** was obtained following the experimental procedure described for **3a**, but starting from bromobenzene. Therefore, **1** (100 mg, 0.45 mmol) was reacted with $Pd(OAc)_2$ (10 mg, 0.043 mmol) and AgOAc (258 mg, 1.53 mmol) in bromobenzene (5.7 mL) and HOAc (1.3 mL) for 8 h at 120 °C to give **3d** as an orange oil after chromatographic purification in silica (ethyl acetate/toluene/isopropanol = 6/3/1 as eluent). Obtained: 29 mg (yield 17 %). Compound **3d** was characterized as the mixture of *o-/m-/p*-isomers in 2.9/1/3.4 molar ratio.

Synthesis of (*E*)-diethyl (1-acetamido-2-(*o,m,p*-chloro phenyl)-vinyl) phosphonate 3e. Compound **3e** was obtained following the same experimental procedure than that described for **3a**, but starting from chlorobenzene. Therefore, **1** (100 mg, 0.45 mmol) was reacted with $Pd(OAc)_2$ (10 mg, 0.043 mmol) and AgOAc (258 mg, 1.53 mmol) in chlorobenzene (5.7 mL) and AcOH (1.3 mL) for 8 h at 120 °C to give **3e** as an orange oil after chromatographic purification in silica (ethyl acetate/toluene/isopropanol = 6/3/1 as eluent). Obtained: 46 mg (yield 27 %). Compound **3e** was characterized as the mixture of *o-/m-/p*-isomers in 5.94/2.7/1 molar ratio.

Synthesis of (*E*)-diethyl (1-acetamido-2-(*o,m,p*-hydroxymethylphenyl)vinyl) phosphonate 3f. Compound **3f** was obtained following the same experimental procedure than that

described for **3 a**, but starting from benzyl alcohol. Therefore, **1** (100 mg, 0.45 mmol) was reacted with $Pd(OAc)_2$ (10 mg, 0.043 mmol) and AgOAc (258 mg, 1.53 mmol) in benzyl alcohol (5.7 mL) and AcOH (1.3 mL) for 8 h at 120 °C to give **3 f** as an orange oil after chromatographic purification in silica (ethyl acetate/ toluene/ isopropanol = 6/3/1 as eluent). Obtained: 33 mg (yield 22 %). Compound **3 f** was characterized as the mixture of *o-/m-/p*-isomers in 0/1/1.58 molar ratio.

Synthesis of (*E*)-diethyl (1-acetamido-2-(2,5-dimethylphenyl)vinyl) phosphonate 3 g. Compound **3 g** was obtained following the same experimental procedure than that described for **3 a**, but starting from *p*-xylene. Therefore, **1** (100 mg, 0.45 mmol) was reacted with $Pd(OAc)_2$ (10 mg, 0.043 mmol) and AgOAc (258 mg, 1.53 mmol) in *p*-xylene (5.7 mL) and AcOH (1.3 mL) for 8 h at 120 °C to give **3 g** as an orange oil after chromatographic purification in silica (ethyl acetate/toluene/isopropanol = 6/3/1 as eluent). Obtained: 65 mg (yield 44 %).

Supporting Information

The following information is provided in the on-line Supporting Information: characterization data of all prepared compounds, copies of ^{1}H, ^{13}C NMR and ^{31}P NMR spectra of compounds **1** and **3 a**–**3 g**.

Acknowledgements

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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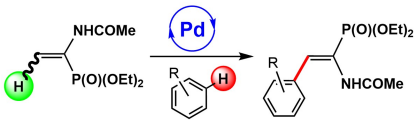
RESEARCH ARTICLE

β-aryl-N-acetyl-α,β-dehydroamino-phosphonic esters can be synthesized through oxidative Fujiwara–Moritani C–C coupling of different arenes with diethyl α,β-dehydroaminophospho-nate **1**, process catalyzed by Pd^{2+} and assisted by Ag^{+}. The reaction is regio-selective to the *E*-isomer and tolerates the presence of both electrodonating and electronwithdrawing substituents.arylationC–H functionali-zationdehydroaminophosphonic acid-sFujiwara–Moritanipalladium catalysis



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