Article

Efficient Synthesis of Novel Phostone and Phostam Derivatives *via* Regioselective Intramolecular Heck Cyclizations of (2-Iodobenzyl)buta-1,3-dienylphosphonates, (2-Iodophenyl)buta-1,3-dienylphosphonates, and *N*-(2-Iodophenyl)-*P*-buta-1,3-dienylphosphonamidates

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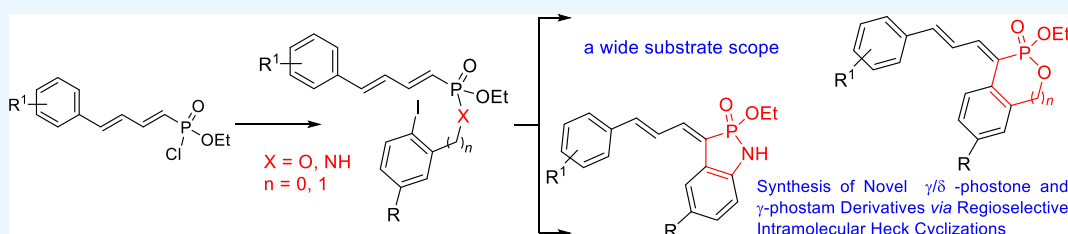Cite This: *ACS Omega* 2024, 9, 44542−44548

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a wide substrate scope

X = O, NH
n = 0, 1

Synthesis of Novel γ/δ -phostone and γ-phostam Derivatives *via* Regioselective Intramolecular Heck Cyclizations

ABSTRACT: Here, we report the intramolecular Heck cross-coupling of 1,3-dienylphosphonates, affording unique and regioselective access to unprecedented benzofused phostone and phostam derivatives. The reactions proceeded under operationally simple and mild conditions with a wide substrate scope.

1. INTRODUCTION

Phosphorus heterocycles continue to receive widespread attention due to their wide range of applications in the agrochemical, pharmaceutical, and material industries.[1,2] Phostones, phostines, and phostams, which formally consist of 1,2-oxaphosphaheterocycle and 1,2-azaphosphaheterocycle 2-oxide derivatives, are the phosphorus analogues of lactones and lactams and thus constitute an important subclass of phosphorus-containing heterocyclic compounds with widespread applications in both medicinal and material science.[3,4] The sizes of these O,P- and N,P-heterocycles extend generally from four to nine members. However, five-membered 1,2-azaphosphaheterocycles (γ-phostams) and oxaphosphaheterocycles, such as 1,2-oxaphospholanes and 1,2-oxaphospholes, also called γ-phostones and γ-phostines,[5,6] as well as their analogous six-membered δ-phostones[7] and δ-phostines,[8] are the most studied due to their biological interest. Indeed, they are crucial structural motifs of many biologically active compounds serving as antagonists of lysophosphatidic acid receptors,[9] inhibitors of autotaxin and tumor cell metastasis,[10] antibiotics,[11] anti-inflammatory agents,[12] and antitumor agents against human tumor cell lines such as glioblastoma, melanoma and pancreatic cancer,[13] antioxidant,[14] and inhibitors of acetylcholinesterase, protein tyrosine phosphatase, and pancreatic cholesterol esterase[15] (Figure 1). Of particular interest are carbohydrate-based phostones and phostines, known as phosphonosugars, which exhibit interesting biological activities

due to their potential to serve as carbohydrate mimics[16] (Figure 1, phostine PST3.1a).

Numerous methodologies for the synthesis of phostones, phostines, and phostams have been developed over the past two decades. Among the most commonly applied strategies are those involving cyclization and annulation reactions *via* ring-closing olefin metathesis (RCM) and transition metal-catalyzed oxidative cyclizations, which are the most reported in the literature.[3,4,5,6,7,13d,14,17] Despite the diversity of these synthetic methods, there is an ongoing search for new and efficient approaches to other varieties of these valuable heterocyclic scaffolds through alternative modern synthetic processes.
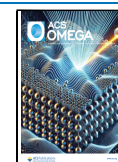
With this in mind, and motivated by the aforementioned biological importance of these 1,2-aza/oxaphospha heterocycles, and in continuation of our interest in developing efficient protocols for the synthesis of novel heterocyclic systems,[18] we now report the first intramolecular Heck cross-coupling on 1,3-dienylphosphonates, affording unique and
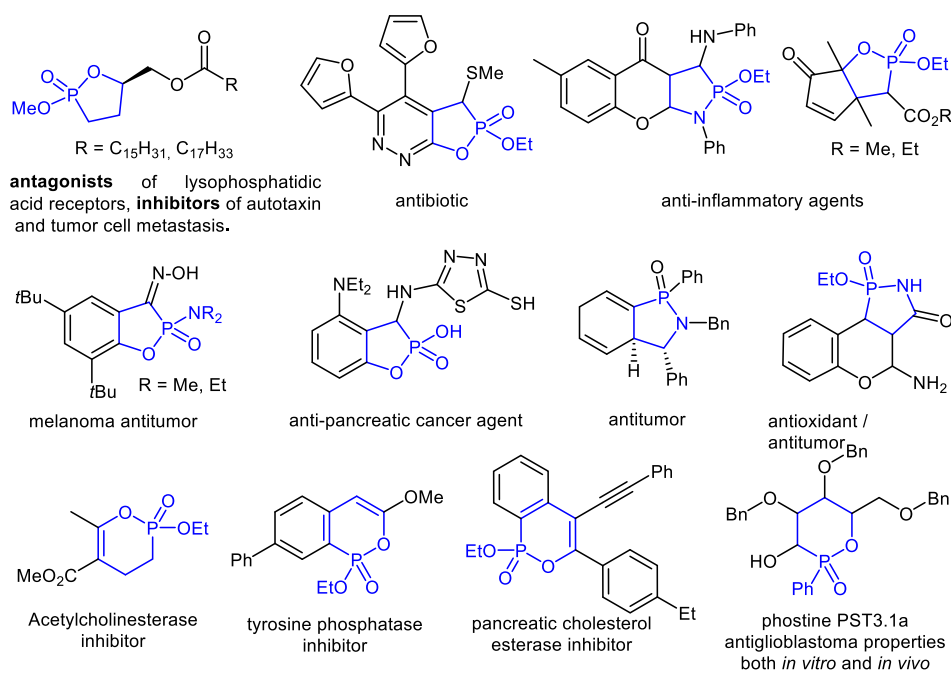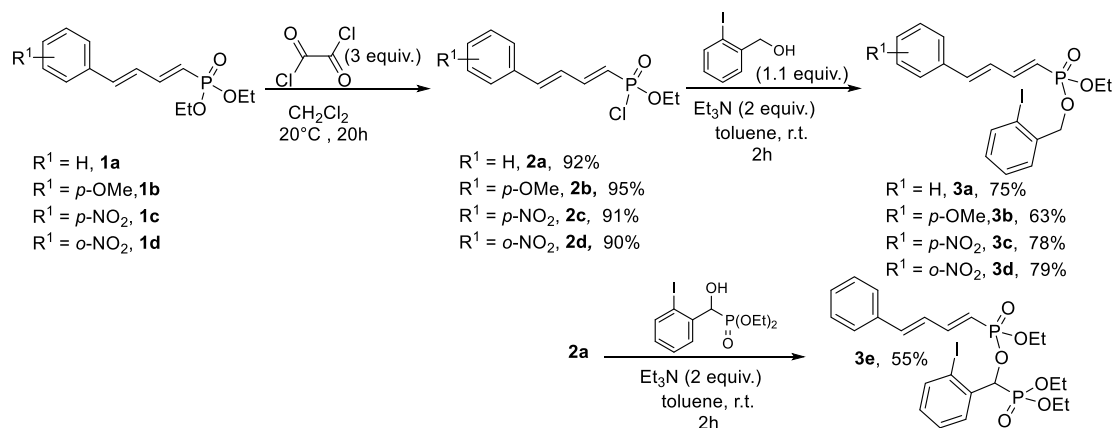
Figure 1. Examples of biollogically active molecules containing 1,2-oxaphospholane 2-oxide, 1,2-azaphospholine 2-oxide, 1,2-oxaphosphinine, and 1,2-oxaphosphinine units.

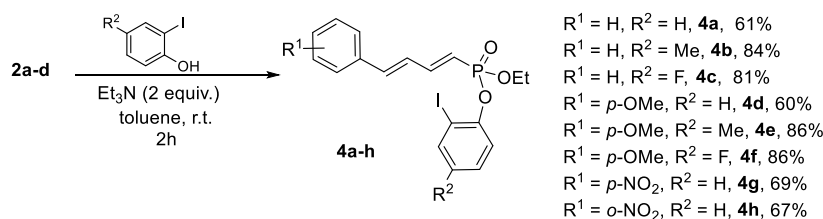**Scheme 1. Synthesis of Ethyl(2-Iodobenzyl)Buta-1,3-Dienylphosphonate Derivatives 3a-e**

regioselective access to unprecedented benzofused phostone and phostam derivatives.

2. RESULTS AND DISCUSSION

We recently reported a two-step protocol for the substitution reactions at the phosphorus atom of 1,3-dienylphosphonates through chlorination of the phosphonate group, followed by amination or thiolation of the phosphonochloridate intermediates.[19] We reasoned that it would be interesting to apply this methodology to 2-iodobenzyl alcohol, 2-iodophenols, and 2-iodoanilines as nucleophiles to access the corresponding (2-iodobenzyl)buta-1,3-dienylphosphonates, (2-iodophenyl)buta-1,3-dienylphosphonates, and N-(2-iodophenyl)-P-buta-1,3-dienylphosphonamidates, which could undergo cyclization via an intramolecular Heck coupling reaction to access the target benzofused phostone and phostam derivatives. While the Heck reaction has long been known in its intermolecular version,[20] the extension to the intramolecular process is less widespread but it allows the formation of useful heterocycles,[21] and for our part, we have already developed a base-free intramolecular

Heck-type coupling catalyzed by a nickel complex, enabling us to obtain benzofurans or indole-type cores. This process has been extended to trisubstituted olefins to construct an ACE ring system of morphine with an all-carbon quaternary center at a ring junction.[22] Based on this expertise, we decided to evaluate this coupling process with dienylphosphonates. We first started with the synthesis of phosphonochloridate intermediates **2**, which were prepared from 1E,3E-dienylphosphonates **1**, in excellent yields, using oxalyl chloride as the chlorinating agent.[19] Subsequent selective substitution at the phosphorus atom of 1,3-dienylphosphonochloridates **2** by 2-iodobenzyl alcohol was carried out under mild conditions in the presence of triethylamine in toluene as solvent, providing the corresponding ethyl(2-iodobenzyl)buta-1,3-dienylphosphonate derivatives **3a−d** in good yields. Gratifyingly, this process can also convert the sterically crowded diethyl-(hydroxy(2-iodophenyl)methyl)-phosphonate and ethyl(4-phenylbutadienyl)phosphonochloridate **2a** to the desired product **3e** in moderate yield (Scheme 1).
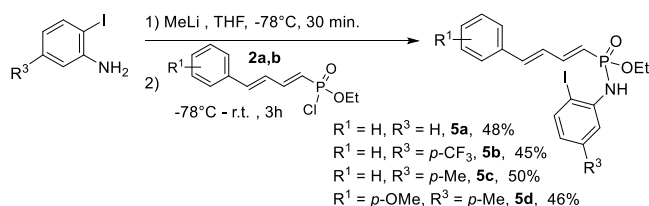
Scheme 2. Synthesis of Ethyl(2-Iodophenyl)Buta-1,3-Dienylphosphonate Derivatives 4a−h

R^1 = H, R^2 = H, **4a**, 61%
R^1 = H, R^2 = Me, **4b**, 84%
R^1 = H, R^2 = F, **4c**, 81%
R^1 = p-OMe, R^2 = H, **4d**, 60%
R^1 = p-OMe, R^2 = Me, **4e**, 86%
R^1 = p-OMe, R^2 = F, **4f**, 86%
R^1 = p-NO$_2$, R^2 = H, **4g**, 69%
R^1 = o-NO$_2$, R^2 = H, **4h**, 67%

To expand the scope of the process, the reaction of 2-iodophenol derivatives as nucleophiles with phosphonochloridates **2** was examined. We found that 2-iodophenol derivatives react smoothly with phosphonochloridates **2**, in the same conditions, to afford the expected ethyl(2-iodophenyl)buta-1,3-dienylphosphonate derivatives **4a−h** in good yields (Scheme 2).

When we examined the reactivity of 2-iodoanilines, the formation of the corresponding phosphoramides **5** was incomplete when using Et$_3$N (2 equiv) in toluene at room temperature. However, switching the base to MeLi afforded the target N-(2-iodophenyl)-P-buta-1,3-dienylphosphonami-dates **5a−d** in satisfactory yields (Scheme 3).

Scheme 3. Synthesis of 1,3-Dienylphosphonamidate Derivatives 5a-d

R^1 = H, R^3 = H, **5a**, 48%
R^1 = H, R^3 = p-CF$_3$, **5b**, 45%
R^1 = H, R^3 = p-Me, **5c**, 50%
R^1 = p-OMe, R^3 = p-Me, **5d**, 46%

In the second part of this work, we focused our efforts on using precursors **3**, **4**, and **5** as building blocks for the construction of the target benzofused phostone and phostam derivatives through intramolecular Heck cross-coupling, which is well recognized as a powerful tool for Csp^2-Csp^2 bond formation, particularly, in its intermolecular variant, which has

found widespread application for the assembly of natural products and other molecules containing complex ring systems.[21,23] To this end, we took precursor **3a** as a model substrate for optimization of the reaction conditions. The major challenge in such intramolecular Heck reactions is the lack of regioselectivity.[17f,23] In fact, in our case, the cyclization may thus generate either the expected six-membered oxaphosphinine **6a** resulting from a 6-exo-trig process or the seven-membered oxaphosphepine **6a'** regioisomer obtained according to a 7-endo-trig ring closure, despite its rarity.[23,24] The reactions were studied under different conditions, such as the palladium source, temperature, reaction time, and various bases and solvents. The results of these comparative experiments are summarized in Table 1. First, the reaction was experimented without PPh$_3$ ligand using 10 mol % of Pd(PPh$_3$)$_4$ in the presence of potassium carbonate as the base in toluene at 100 °C for 12 h. In this case, the starting dienylphosphonate **3a** remained unchanged (Table 1, entry 1). When palladium trifluoroacetate (Pd(TFA)$_2$ 10 mol %) was used with triphenylphosphine ligand (20 mol %) in the presence of K$_2$CO$_3$ in toluene at 80 °C for 12 h, low conversion of **3a** to the expected oxaphosphinine **6a** was observed, accompanied by the seven-membered regioisomer **6a'**, while the major amount of the starting material remained unconsumed (Table 1, entry 2). Increasing the temperature to 100 °C with a longer reaction time led to a higher conversion of dienylphosphonate **3a** but, unfortunately, to less regiose-lectivity (Table 1, entry 3). In order to improve the regioselectivity of the process, we then tested PdCl$_2$ (10 mol %) as a palladium source in the presence of PPh$_3$ and K$_2$CO$_3$

Table 1. Optimization of the Reaction Conditions[a]

Entry	Palladium source (mol %)	PPh$_3$ (mol %)	Base	Solvent	T°C/Time	Ratio(%)[b] 3a/6a/6a'
1	Pd(PPh$_3$)$_4$ (10 mol %)	None	K$_2$CO$_3$	toluene	100 °C/12 h	100/0/0
2	Pd(TFA)$_2$(10 mol %)	20 mol %	K$_2$CO$_3$	toluene	80 °C/12 h	40/35/25
3	Pd(TFA)$_2$(10 mol %)	20 mol %	K$_2$CO$_3$	toluene	100 °C/16 h	10/45/45
4	PdCl$_2$(10 mol %)	20 mol %	K$_2$CO$_3$	toluene	100 °C/12 h	10/60/30
5	Pd(OAc)$_2$ (10 mol %)	20 mol %	K$_2$CO$_3$	toluene	100 °C/12 h	0/100(82)[c]/0
6	Pd(OAc)$_2$ (5 mol %)	10 mol %	K$_2$CO$_3$	toluene	100 °C/12 h	70/30/0
7	Pd(OAc)$_2$ (10 mol %)	20 mol %	Et$_3$N	toluene	100 °C/12 h	0/100/0
8	Pd(OAc)$_2$ (10 mol %)	20 mol %	iPr$_2$NH	toluene	100 °C/12 h	0/100/0
9	Pd(OAc)$_2$ (10 mol %)	20 mol %	Ag$_2$CO$_3$	toluene	100 °C/12 h	0/100/0
10	Pd(OAc)$_2$ (10 mol %)	20 mol %	K$_2$CO$_3$	MeCN	100 °C/12 h	0/100/0[d]
11	Pd(OAc)$_2$ (10 mol %)	20 mol %	K$_2$CO$_3$	DMF	100 °C/12 h	0/100/0

[a]Reaction conditions: **3a** (0.2 mmol), [Pd] (0.02 mmol), PPh$_3$ (0.04 mml), base (0.4 mmol), solvent (3 mL). [b]Determined by ^{31}P NMR on the crude. [c]Isolated yield. [d]Reaction performed in sealed tube.

Scheme 4. Synthesis of 1,4-Dihydrobenzo[d][1,2]Oxaphosphninine 3-Oxide Derivatives 6a–e
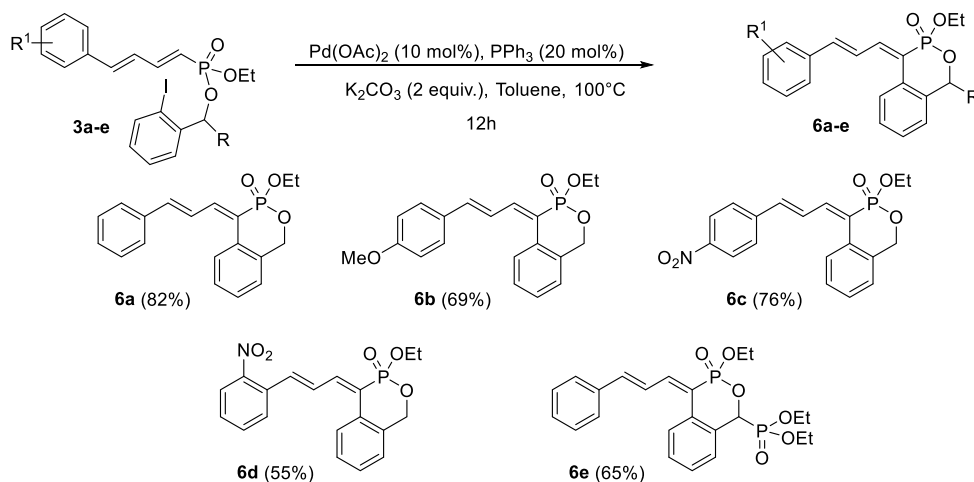
Scheme 5. Synthesis of Benzo[d][1,2]Oxaphosphole 2-Oxide Derivatives 7a–h
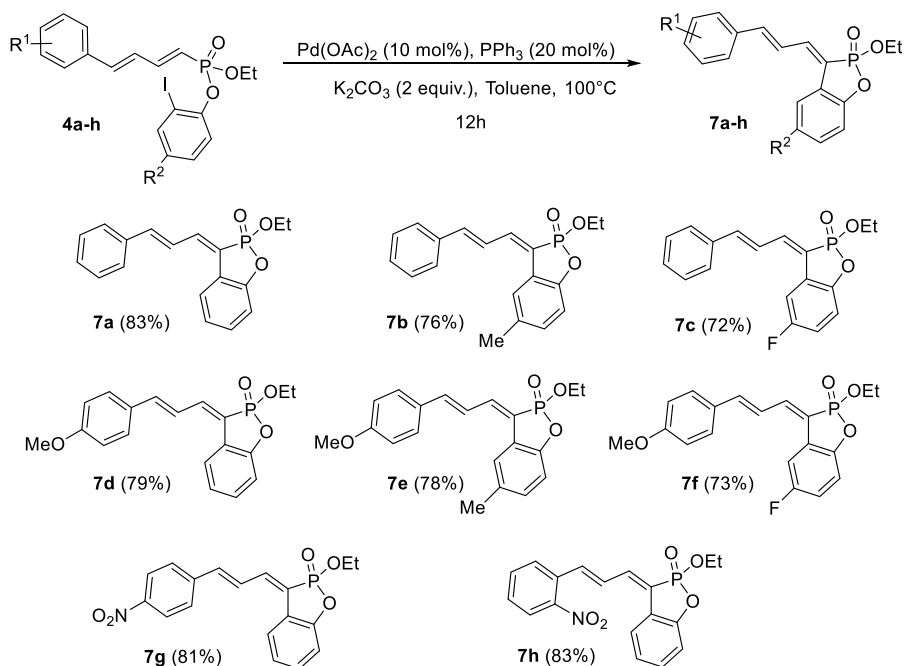

in toluene at 100 °C for 12 h. Although complete conversion could not be reached, we slightly improved the regioselectivity of the reaction with a better **6a/6a'** ratio of 2/1 (Table 1, entry 4). Gratifyingly, upon switching to Pd(OAc)$_2$ (10 mol %) as the catalyst, in the presence of 20 mol % of PPh$_3$, the conversion of **3a** to 100% with total regioselectivity dramatically improved in favor the oxaphosphinine 3-oxide derivative **6a** (82% isolated yield), and no trace of the competitive seven-membered regioisomer **6a'** could be observed (Table 1, entry 5). However, by decreasing the amount of Pd(OAc)$_2$ to 5 mol % only the expected benzofused oxaphosphinine 3-oxide derivative **6a** was produced during the cyclization process, but lower conversion was observed (Table 1, entry 6).

It should be noted that the reaction also showed complete stereoselectivity with the exclusive formation of the *E,E*-**6a** isomer. The *E* configuration of the newly generated C=C double bond, after intramolecular Heck coupling, was unambiguously established from the NMR data based on the

$^3J_{HP}$ and $^3J_{CP}$ coupling constants values (14.4 and 21.3 Hz, respectively), which indicate, according to some literature data,[25] that the vinylic proton is *cis* to the phosphorus atom and that the benzylidene group is *trans*.

Furthermore, to test the effect of the base on the cyclization process, we conducted the reaction under the same catalytic conditions [Pd(OAc)$_2$ 10 mol %, PPh$_3$ 20 mol %] in the presence of various bases, such as triethylamine, diisopropylamine, and silver carbonate. As a result, the reactions proceeded with total conversion and regioselectivity, leading to benzofused phostone **6a**, but along with traces of some degradation products that could not be identified (Table 1, entries 7–9). Moreover, the solvent's effect was also investigated through the use of polar and aprotic solvents, such as acetonitrile or DMF, under the same conditions, but an increase in the quantity of side products was observed in those cases (Table 1, entries 10 and 11).

The optimized reaction conditions involving the use of Pd(OAc)$_2$ (10 mol %), PPh$_3$ (20 mol %), and K$_2$CO$_3$ (2

Scheme 6. Synthesis of 1,3-Dihydrobenzo[d][1,2]Azaphosphole 2-Oxide Dervatives 8a-d
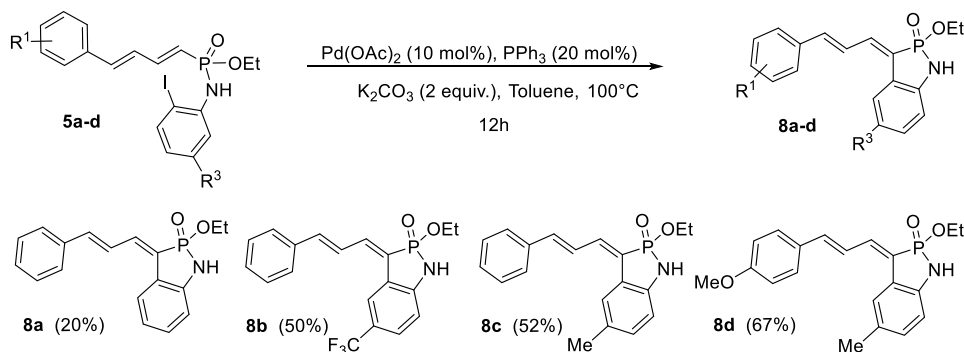
equiv) in toluene at 100 °C (Table 1, entry 5) were also successfully applied to ethyl(2-iodobenzyl)buta-1,3-dienylphosphonates 3b−e. In analogy, the corresponding benzofused phostones 6b−e were obtained in good yields with complete regio- and stereoselectivity through a *6-exo-trig* cyclization process. An exception was made for compound 6d, where the corresponding seven-membered ring regioisomer 6d' was also present, with a 6d/6d' ratio of 70/30 in the crude. It should also be mentioned that phostone 6e was obtained as a mixture of two inseparable diastereomers in an approximate 55:45 ratio, as evidenced by its NMR spectral data (Scheme 4).

To further extend the scope of this methodology, we examined the behavior of (2-iodophenyl)buta-1,3-dienylphosphonates 4a−h. The reactions proceeded efficiently under the predefined optimized conditions, allowing total conversion of the starting materials and affording the γ-photone derivatives 7a−h in good yields as unique products arising from complete regioselective *5-exo-trig* cyclization, even with the nitro compounds 7g−h in this case (Scheme 5). It is noteworthy to mention that both electron-donating and electron-withdrawing substituents at the *para* position of the 2-iodophenyle moiety were well tolerated during the reactions, as well substituents on the phenylallylidene side chain, and no significant electronic effects were observed for the aryl substituents on the regio- and stereoselectivity of the process. Indeed, the *E,E* stereochemistry of 7a−h was determined from the coupling constants obtained from the NMR data, where both the coupling constants of the vinylic proton $^3J_{HP}$ (~15 Hz) and $^3J_{CP}$ (~20 Hz) indicate an *E* configuration[25] of the newly generated double bond.

The promising results obtained with (2-iodobenzyl)- and (2-iodophenyl)-buta-1,3-dienylphosphonates 3 and 4 prompted us to further investigate the behavior of *N*-(2-iodophenyl)-*P*-buta-1,3-dienylphosphonamidates 5a−d in this Heck-type cyclization process, allowing a straightforward approach to unprecedented benzofused phostam derivatives. To our delight, the reactions proceeded efficiently under the same optimized conditions affording the target γ-phostams 8a−d, resulting from *5-exo-trig* cyclization, in moderate to good yields, although 8a showed incomplete conversion of the starting material (Scheme 6). As in the previous case, the reactions showed full regioselectivity except for compound 8d, which was obtained as a mixture with a trace of the *6-endo-trig* regioisomer product.

3. CONCLUSION

We successfully developed an efficient and straightforward approach to unprecedented benzofuzed phostone and phostam

derivatives *via* fully regioselective intramolecular Heck cyclizations of (2-iodobenzyl)buta-1,3-dienylphosphonates, (2-iodophenyl)buta-1,3-dienylphosphonates, and *N*-(2-iodophenyl)-*P*-buta-1,3-dienylphosphonamidates. Given the presence of the synthetically very flexible dienyl functionality on the heterocyclic ring, the synthesized compounds may serve as branching points for accessing a wide variety of phostone and phostam derivatives for the evaluation of their pharmacological profiles. Further work aims at biological evaluation of the synthesized compounds and the application of the methodology for the synthesis of libraries with high molecular diversity.

■ ASSOCIATED CONTENT

ⓈI Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.4c06616.

Spectroscopic characterization and NMR spectra of the synthesized compounds (PDF)

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Notes

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