Article

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Tandem addition of phosphite nucleophiles across unsaturated nitrogen-containing systems: mechanistic insights on regioselectivity

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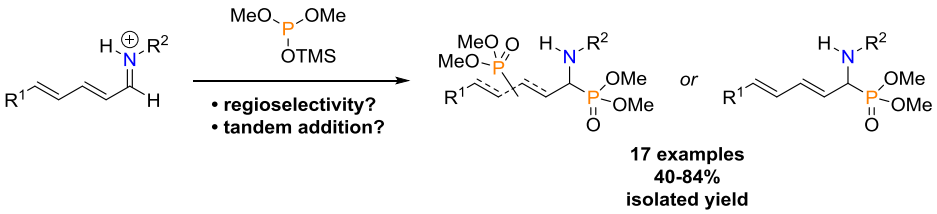


Abstract

The addition of phosphite nucleophiles across linear unsaturated imines is a powerful and atom-economical methodology for the synthesis of aminophosphonates. These products are of interest from both a biological and a synthetic point of view: they act as amino acid transition state analogs and Horner-Wadsworth-Emmons reagents,

respectively. In this work the reaction between dialkyl trimethylsilyl phosphites and *α,β,γ,δ*-diunsaturated imines was evaluated, as a continuation of our previous efforts in the field. As such, the first conjugate 1,6-addition of a phosphite nucleophile across a linear unsaturated *N*-containing system is reported herein. Theoretical calculations were performed to rationalize the observed regioselectivites and to shed light on the proposed mechanism.

Introduction

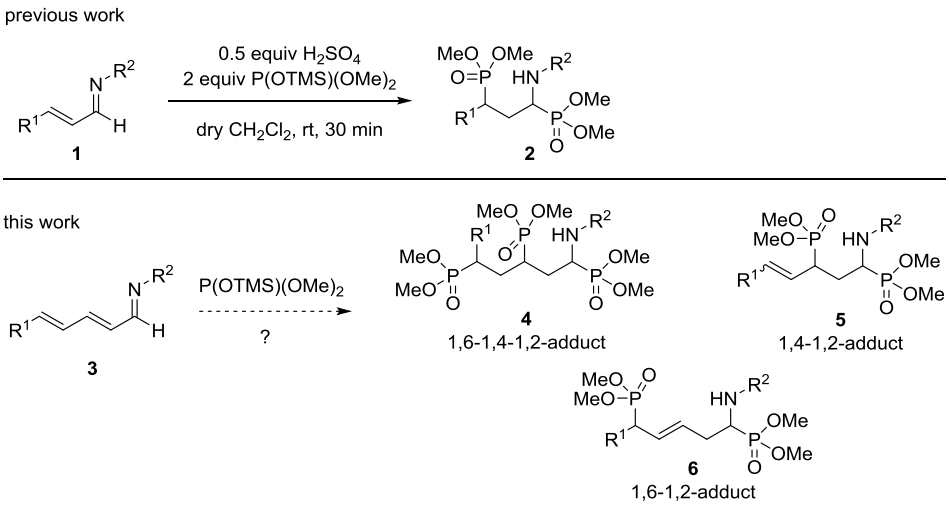
The addition of phosphorus nucleophiles across unsaturated systems is a conceptually simple yet powerful and atom-economical tool for the construction of C-P bonds.[1-7] Michael-type additions of phosphorus nucleophiles are known,[8-19] but conjugate 1,6-additions of phosphorus nucleophiles are unprecedented to the best of our knowledge. Conjugate 1,6-additions (vinylogous Michael reactions) are known for carbon nucleophiles under transition-metal catalysis or organocatalysis, and enantioselective variants have also been reported.[20]

Numerous transition metals have been used, of which Cu(I) has received the most attention. Cu-salts readily transmetalate other organometallic reagents such as trialkylaluminiums, Grignard reagents, diethyl zinc and organolithiums.[21-24] After initial formation of a π-complex, the organocuprate undergoes addition to the unsaturated system. 1,3-Migration, or the lack of it, dictates the regioselectivity of the conjugate addition and is influenced by electronic and steric factors.[22] Pd, Ir and other metals have been reported to mediate 1,6-conjugate additions as well,[25-28] and Yamamoto and coworkers even succeeded in a conjugate 1,8-addition using Pd-catalysts.[26]

The approach in organocatalytic 1,6-conjugate addition relies on lowering the LUMO of the substrate, often by formation of an intermediate iminium ion (‘vinylogous

iminium ion catalysis').[29] A pending nucleophile, activated (elevated HOMO) or not, then attacks the conjugated system and is directed to the δ-position by both steric and electronic factors.[30] Application of chiral organocatalysts, *e.g.* prolinol and cinchona derivatives, has resulted in excellent remote stereocontrol.[30-34] Ooi and coworkers used triaminoiminophosphoranes, a type of phosphazene, as organocatalysts which resulted in the regio-, stereo- and diastereoselective formation of 1,6- and 1,8-adducts.[29]

Selective uncatalyzed conjugate 1,6-addition has been reported in only two cases.[35-37] In continuation of our work on tandem 1,4-1,2-phosphite additions across *α,β*-unsaturated imines 1,[8, 38-42] the feasibility of a tandem 1,6-1,4-1,2-addition to suitable α,β,γ,δ-diunsaturated imines **3** was assessed (Scheme 1). In addition to their synthetic relevance, triadducts **4** are of potential biological interest as their tricarboxylic analogs display micromolar activity as agonists of ionotropic glutamate receptors (iGluRs).[43] Anticipated side products were 1,4-1,2-adducts **5** or 1,6-1,2-adducts **6**.



Scheme 1. Envisaged transformation of **3** to **4** based on previous work.

Results and Discussion

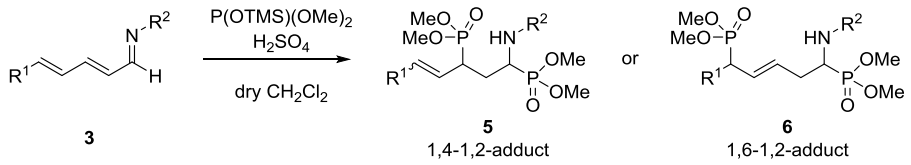
Phosphite addition: results and regioselectivity

The required α,β,γ,δ-diunsaturated imines **3** were prepared from their respective lower aldehyde homologues by Wittig reaction,[44] followed by imination (see SI for details). They were then treated with dimethyl trimethylsilyl phosphite (DMPTMS), a reactive phosphite nucleophile,[45-48] and sulfuric acid in order to activate the conjugated system for nucleophilic attack. The benzyl imine of **3a** was selected as model substrate, as tandem addition to its lower homologue proceeded readily.[8] Upon application of our previously optimized conditions (2 equiv DMPTMS, 0.5 equiv H_2SO_4, 30 minutes at room temperature),[8] the imine **3a** was completely consumed but only a trace of double addition product was detected (Table 1, entry 1). The major product was the corresponding α-aminophosphonate, resulting from 1,2-attack across the imine. Prolonging the reaction time to 24 h resulted in merely 40% conversion to a double addition product (entry 2). In order to assess whether a triple tandem addition was feasible and to drive the reaction to completion, a large excess of DMPTMS was added (entry 3). This resulted in 57% conversion to diastereomeric double addition compounds. After careful separation, it became clear that two diastereomers of the tandem 1,4-1,2-addition product **5** had been formed. Interestingly, no products **4** or **6** resulting from 1,6-phosphite addition were present in the crude reaction mixture. As reaction at room temperature failed to engender complete conversion to a double addition product, it was performed at reflux temperature (entry 4).

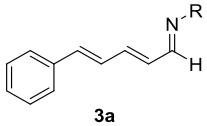
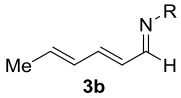
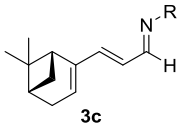
Gratifyingly, these conditions resulted in full transformation of the doubly unsaturated imine to 1,4-1,2-adducts **5** after 8 hours in a good isolated yield (77%). The tandem

addition is diastereoselective (dr 7/3, according to ^{31}P-NMR integration) in favor of the diastereomers which display ^{31}P-^{31}P coupling in ^{31}P-NMR ($^{4}J_{PP}$ = ca. 10 Hz). On account of the flexibility of the linear chain, the relative configuration of the products could not be determined.

Table 1. Tandem phosphite addition to α,β,γ,δ-diunsaturated imines.



3 **5** 1,4-1,2-adduct **6** 1,6-1,2-adduct

substrate	entry	R^2	DMPTMS (equiv)	H_2SO_4 (equiv)	Time (h)	Temp (°C)	Tandem Addition[a] (isolated yield, %)	Ratio **5**/**6**	dr
 **3a**	1	Bn (**3a1**)	2	0.5	0.5	rt	10 (-)	1/0	-
	2	Bn (**3a1**)	2	0.5	24	rt	40 (-)	1/0	-
	3	Bn (**3a1**)	10	0.5	24	rt	57 (-)	1/0	-
	4	Bn (**3a1**)	2	0.5	8	Δ	100 (77)	1/0	7/3
	5	*n*-Pr (**3a2**)	2	0.5	24	rt	60 (-)	1/0	-
	6	*n*-Pr (**3a2**)	2	0.5	7	Δ	100 (71)	1/0	7/3
	7	*i*-Pr (**3a3**)	2	0.5	24	rt	65 (-)	1/0	-
	8	*i*-Pr (**3a3**)	2	0.5	6	Δ	100 (82)	1/0	7/3
	9	*t*-Bu (**3a4**)	10	0.5	24	rt	92 (-)	1/0	-
	10	*t*-Bu (**3a4**)	2	0.5	3	Δ	100 (73)	1/0	1/1
	11	*t*-Bu (**3a4**)	5	0.5	3	Δ	100 (-)	1/0	-
 **3b**	12	Bn (**3b1**)	2	0.5	16	rt	100 (75)	1/1	[b]
	13	Bn (**3b1**)	5	0.5	24	rt	100 (69)	1/1	-
	14	Bn (**3b1**)	5	0.5	24	Δ	100 (-)	1/1	-
	15	*n*-Pr (**3b2**)	2	0.5	5	rt	100 (50)	7/3	[b]
	16	*i*-Pr (**3b3**)	2	0.5	8	rt	100 (43)	6/4	[b]
	17	*i*-Pr (**3b3**)	5	0.5	3	rt	100 (40)	1/1	-
	18	*i*-Pr (**3b3**)	2	0.5	3	Δ	100 (-)	6/4	-
	19	*i*-Pr (**3b3**)	5	0.5	3	Δ	100 (-)	1/1	-
	20	*t*-Bu (**3b4**)	2	0.5	3	rt	100 (60)	6/4	[b]
 **3c**	21	*i*-Pr (**3c**)	2	0.5	24	rt	78 (-)	1/0	-
	22	*i*-Pr (**3c**)	2	0.5	1	Δ	100 (84)	1/0	-

[a] the remainder is 1,2-addition product. [b] SeeTable 2.

Other derivatives of **3a** with various R-groups were prepared and subjected to the same reaction conditions (entries 5-11). The *n*-Pr and *i*-Pr derivatives displayed very similar behavior: reflux temperature was required to drive the reactions to completion and good yields were obtained. Again, only tandem 1,4-1,2-adducts were formed and

the diastereomeric ratios were very similar to those of the Bn-derivative. For the *t*-Bu derivative not even a large excess of DMPTMS could drive the reaction to completion at room temperature (entry 9). Again, at reflux temperature full conversion to the tandem 1,4-1,2-adduct was attained (entry 10). It is noteworthy that an excess of phosphite did not result in any 1,6-addition whatsoever, even at reflux temperature (entry 11). This implies a certain regioselectivity in case of substrates **3a**, possibly due to the conservation of a conjugated stryrenyl moiety. Any 1,6-addition would result in disruption of the conjugated system to the phenyl ring, an energetically unfavorable event. With regard to the diastereoselectivity for the *t*-Bu derivative an approximate 1/1 ratio is obtained. This is somewhat different than for the other derivatives (entries 4, 6, 8), possibly due to the sterically demanding *t*-Bu substituent.

Imines **3b** derived from *E*,*E*-hexadienal were also evaluated as substrates. In this case, the benzyl imine was completely converted into diastereomeric diphosphonylated compounds at room temperature (entry 12), contrary to the cinnamaldehyde derivatives. Interestingly, the crude ^{31}P-NMR spectrum displayed a number of novel peaks. Purification followed by careful spectral analysis demonstrated that the 1,6-1,2-adduct had also been formed in this case. A 1/1 crude of 1,6-1,2-adduct and 1,4-1,2-adduct was obtained in 75% yield. The 1,4-1,2-adducts were obtained as E/Z isomers, as was apparent from the ^{13}C-shifts of the vinylic methyl group (see experimental part for details). Similar to entry 9, augmenting the nucleophile loading had no influence on the regioselectivity, nor did performing the reaction at reflux temperature (entries 13-14). It is noteworthy that in the 1,6-1,2-adducts the double bond has shifted as compared to the starting material (for an elaborate mechanistic discussion, *vide infra*). The *n*-Pr derivative displayed a larger regioselectivity in favor of the 1,4-1,2-adducts, possibly on account of steric reasons

(entry 15). For R = *i*-Pr the nucleophile loading as well as the reaction temperature did not seem to influence the outcome of the reaction. There was a small shift towards more 1,6-1,2-adduct when an excess of nucleophile was employed (entries 16 and 18 vs. 17 and 19). From these results it is apparent that the products derived from **3b** are much more polar than their **3a** analogues, as reflected in the isolated yields.

Table 2 shows the regioselectivities of the phosphite additions as well as the diastereomeric ratios obtained. Similar to the Bn, *n*-Pr and *i*-Pr derivatives in entries 4, 6 and 8 (Table 1), the dr for the 1,4-1,2-adducts is *ca.* 7/3, except for more sterically hindered substrates (*i*-Pr and *t*-Bu). With respect to the 1,6-1,2-adducts, the dr is approximately 1/1 for all derivatives (Table 2). Finally, a diunsaturated imine derived from (1*R*)-(−)-myrtenal **3c** was subjected to the developed reaction conditions (Table 1, entries 21-22). Similar to **3a**, reflux temperature was required to obtain full conversion to diphosphonylated compounds. Furthermore, no 1,6-1,2-adduct was observed, suggesting that aside from conjugation, regioselectivity of phosphite addition is governed by steric factors at the distal end of the unsaturated system as well.

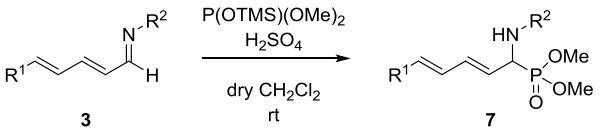
Table 2. Diastereomeric ratios for isolated 1,4-1,2- and 1,6-1,-2 adducts of **3b**.

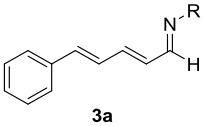
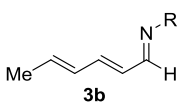
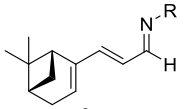
entry	Isolated yield (%)	Ratio **5**/**6**	dr **5**	dr **6**
12	75	1/1	7/3	1/1
15	50	7/3	7/3	6/4
16	43	6/4	6/4	6/4
20	60	6/4	1/1	1/1

Besides tandem addition the regioselectivity could be steered to 1,2-addition as well, furnishing the classical Kabachnik-Fields products.[49] For most derivatives it was

sufficient to simply lower the amount of DMPTMS to one equivalent and perform the reaction at room temperature (Table 3, entry 1), as compared to the conditions that result in tandem addition. For other derivatives, one equivalent of DMPTMS was inadequate to result in full conversion (entry 2-3). Upon augmenting the amount of DMPTMS, more H_2SO_4 was required in order to prevent any tandem addition (entry 4, mechanistic discussion *vide infra*). However, as DMPTMS is labile in the presence of large amounts of H_2SO_4, a larger excess of nucleophile was a prerequisite to obtain full conversion (entry 5). In this manner, all substrates were converted into the corresponding 1,2-adducts in moderate to excellent isolated yields (Table 3). As such, by adjusting the loading of both the nucleophile and acid, the regioselectivity of the phosphite addition can easily by governed.

Table 3. 1,2-addition of DMPTMS to dinusaturated imines.



substrate	entry	R^2	DMPTMS (equiv)	H_2SO_4 (equiv)	time	Conversion to **7** (%)	Isolated Yield (%)
 **3a**	1	Bn (**7a1**)	1	0.5	5 min	100	82
	2	n-Pr (**7a2**)	1	0.5	1.5 h	53	-
	3	n-Pr (**7a2**)	1	0.5	24 h	63	-
	4	n-Pr (**7a2**)	2	2	24 h	90	-
	5	n-Pr (**7a2**)	5	2	15 min	100	83
	6	i-Pr (**7a3**)	1	0.5	24 h	47	-
	7	i-Pr (**7a3**)	5	2	15 min	100	97
	8	t-Bu (**7a4**)	1	0.5	48 h	63	-
	9	t-Bu (**7a4**)	5	2	3 h	95	-
	10	t-Bu (**7a4**)	5	2	6 h	95	86
 **3b**	11	Bn (**7b1**)	1	0.5	5 min	100	87
	12	n-Pr (**7b2**)	1	0.5	5 min	80	-
	13	n-Pr (**7b2**)	1	0.5	30 min	100	71
	14	i-Pr (**7b3**)	1	0.5	30 min	57	-
	15	i-Pr (**7b3**)	1	0.5	3 h	100	68
	16	t-Bu (**7b4**)	1	0.5	48 h	85	-
	17	t-Bu (**7b4**)	5	2	1 h	87	43
 **3c**	18	i-Pr (**7c**)	1	0.5	24 h	80	-
	19	i-Pr (**7c**)	5	2	15 min	100	83

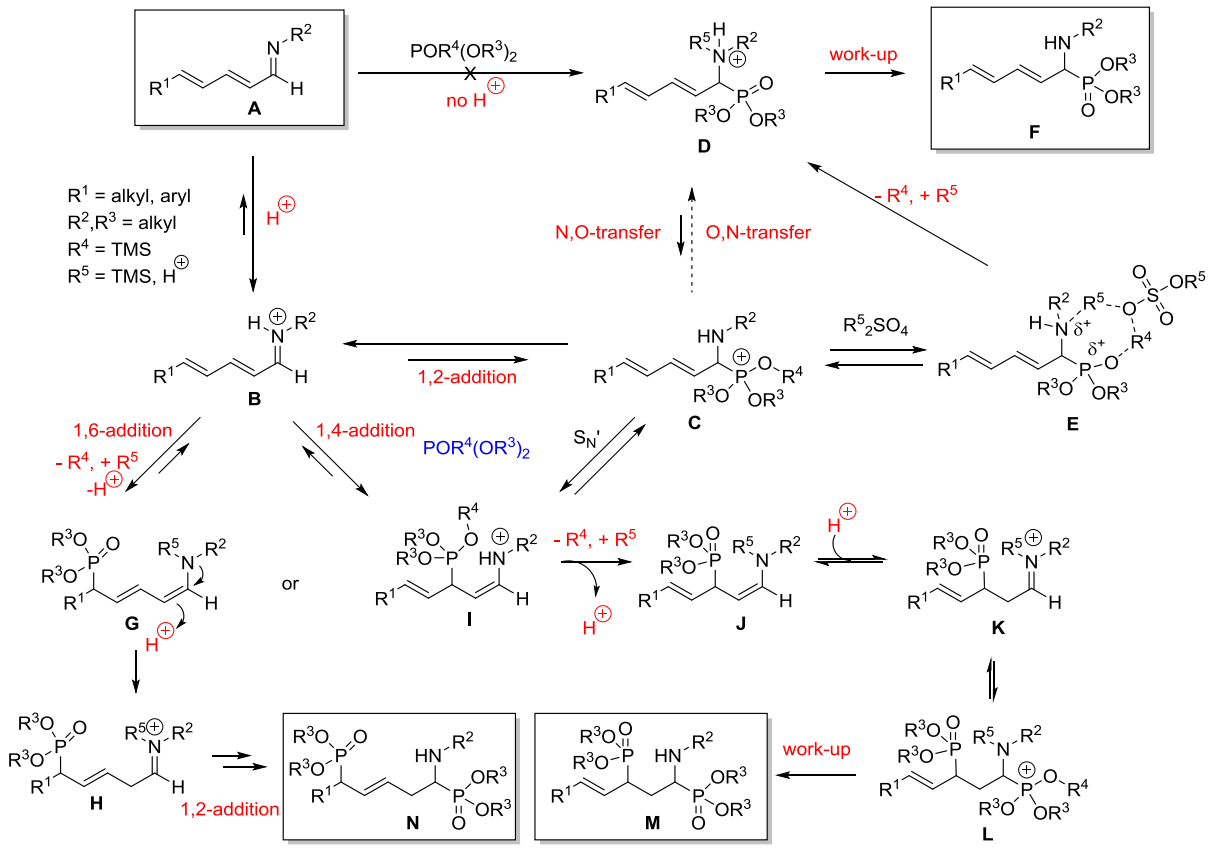
Mechanistic considerations

In our previous communications on tandem 1,4-1,2-phosphite additions some tentative mechanisms were proposed.[8, 40-42] Nonetheless, this particular work has resulted in several new mechanistic insights and the current hypotheses are presented herein (Scheme 2). Without any acid present no phosphite addition to the unsaturated system takes place, and this is clearly visible, since upon addition of H_2SO_4 to the reaction medium may even start to boil. Once imine **A** is suitably activated (species **B**) phosphite addition can take place and result in initial 1,6, 1,4 or 1,2-addition. Careful follow-up of the reaction revealed that 1,2-addition initially proceeds (**B** to **C**),[8] but it can be reversible depending on the amount of acid present.

When a stoichiometric amount of H^+ is present in the reaction medium (0.5 equiv H_2SO_4), the secondary amine in **C** will not be protonated (**C** to **E** does not take place) and 1,2-addition is reversible. However, **C** might undergo intramolecular TMS-transfer to **D**.[8] This TMS-shift is reversible as well and as a consequence, **C** can again be formed.[8]

Subsequently, this unstable intermediate will either revert to iminium **B** due to expulsion of phosphite, or it will undergo S_N' yielding species **G** or **I** when excess phosphite is present. In the former case, iminium **B** will then undergo 1,6- or 1,4-addition, which are probably irreversible. In case of 1,4-addition to **B**, compound **I** will then equilibrate to iminium **K**, which will eventually undergo 1,2-addition. In case of 1,6-addition, compound **G** will be protonated in the α-position before undergoing 1,2-addition, overall resulting in a shift of the double bond. As such, no 1,4-addition can ensue. These pathways account for the observed tandem 1,6-1,2- or 1,4-1,2-phosphite addition products (Table 1). In case an excess of H^+ is present in the

reaction medium (> 0.5 equiv H_2SO_4, generally 2 equiv, cfr. Table 3) the initial 1,2-addition will be rendered irreversible. Compound **C** will immediately be protonated due to an excess of H_2SO_4 giving rise to compound **E**. This would result in a doubly positively charged species which is highly unlikely. Therefore, protonation and desilylation may take place simultaneously, assisted by one (as depicted) or more molecule(s) of $R^5{}_2SO_4$, yielding species D. After aqueous work-up the 1,2-addition adduct is isolated. It must be noted that 1,2-adducts may also be isolated after reaction using 1 equiv of DMPTMS and 0.5 equiv H_2SO_4, corroborating that 1,2-addition is kinetically favored.



Scheme 2. Proposed mechanism for tandem and mono-phosphite additions.

In summary, it is in the first place the amount of DMPTMS and H_2SO_4 that will dictate the regioselectivity of the phosphite addition. However, the intrinsic reactivity of the

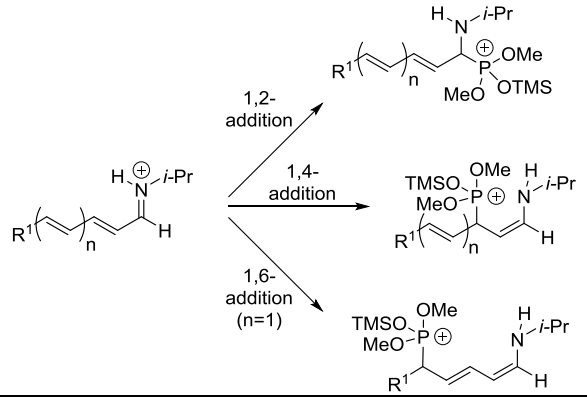
substrate will also differentiate between 1,6- or 1,4-addition. Temperature or reaction time do not seem to exert any effect onto the regioselectivity.

Theoretical rationalization

A computational study was performed to understand the reactivities of *mono*- and *di*unsaturated imines towards Michael-type additions of silylated phosphites. DFT calculations utilizing the M06-2X/6-31+G(d,p)[50] level of theory implemented in the G09 program package[51] have elucidated the underlying rationale for the experimentally observed regioselectivity.

Reaction mechanisms have been explored in an effort to rationalize the ease of addition of the phosphite nucleophile, $P(OTMS)(OMe)_2$, across α,β-unsaturated imines **1** and *α,β,γ,δ*-diunsaturated imines **3** (Scheme 1). Energetics for the first phosphite addition step are illustrated in Table 4. The difference in free energy barriers for the 1,2-, 1,4- and 1,6- phosphite additions to iminium ions of *mono*-unsaturated systems **1a**, **1b** and *di*-unsaturated systems **3a** and **3b** are shown. The 1,2-addition is clearly the most feasible (lowest free energy of activation, $\Delta G^{\ddagger}$) reaction for all four systems, revealing the 1,2-adduct as the kinetic product. However, it is also the most reversible type of addition (lowest barrier for reverse reaction, 20-30 kJ/mol for all systems), as inferred from the relative stabilities of the respective adducts.

Table 4. Activation ($\Delta G^{\ddagger}$) and reaction (ΔG_{rxn}) free energies (M06-2X/6-31+G(d,p), 298 K, 1 atm, in kJ/mol) for initial 1,2-, 1,4- and 1,6- phosphite addition to iminium ions of *mono*- and *di*-unsaturated imines **1** and **3**.[a,b]

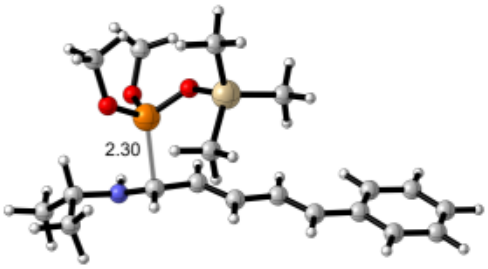


			1,2-addition		1,4-addition		1,6-addition	
	n	R^1	$\Delta G^{\ddagger}$	ΔG_{rxn}	$\Delta G^{\ddagger}$	$\Delta G^{\ddagger}_{rxn}$	$\Delta G^{\ddagger}$	ΔG_{rxn}
1a	0	Ph	23.0	0.8	23.8	-37.9		
1b	0	Me	12.2	-21.6	15.7	-51.2		
3a	1	Ph	33.1	10.6	40.8	-13.5	42.8	-30.2
3b	1	Me	28.5	1.6	30.1	-27.2	32.3	-49.2

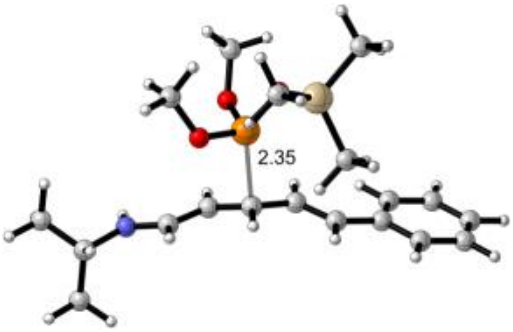
[a]Barriers and reaction energies calculated from separate reactants, namely the corresponding iminium ion and the silylated phosphite, $P(OTMS)(OMe)_2$. [b] The identity of the N-substituent was shown to have minimal effect on the relative energetics, with similar energetics for N-*t*-Bu, N-Bn and N-*i*-Pr.

Nevertheless, the highly exergonic 1,4- and 1,6-additions are also likely since they require only slightly higher activation energies than the 1,2-addition for the corresponding system, but lead to remarkably more stable adducts with higher reverse reaction barriers (in the order of ~60 and ~80 kJ/mol for the 1,4- and 1,6-additions, respectively). For the initial phosphite addition step (Table 4), the 1,4-adduct is clearly the thermodynamic product for systems **1**. For systems **3**, while the relative stabilities of 1,4- and 1,6-adducts favor the latter due to the disruption of conjugation ensued by 1,4-addition, their respective activation energies are quite close. Hence, both adducts are expected to form although the 1,6-adduct is the thermodynamic product. The final product, however, will be the most stable tandem

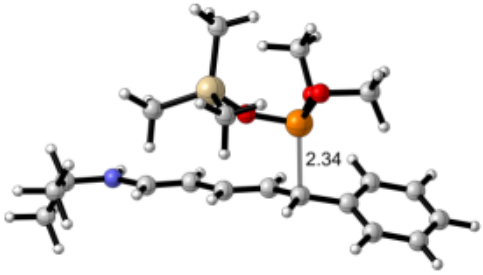
diadduct.For *mono*-unsaturated system **1a** (R^1 = Ph), a slightly larger activation energy compared to **1b** (R^1 = Me) is observed for both 1,2- and 1,4-addition ($\Delta G^{\ddagger}$ = 23.0 and 23.8 kJ/mol, respectively). This is understandably due to the additional conjugation brought to the system by the phenyl ring; hence, disrupting it costs more energy. Similarly, for *di*unsaturated system **3a**, which comprises extended conjugation with the phenyl group (R^1), 1,4- and 1,6-additions disrupting the conjugation have ~10 kJ/mol higher barriers than **3b**. Figure 1 depicts transitions state structures 1,2- 1,4- and 1,6-phosphite additions to iminium ion of **3a**.



1,2-addition TS



1,4- addition TS

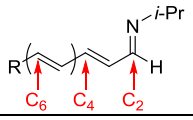


1,6-addition TS

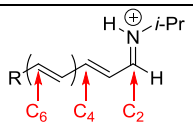
Figure 1. M06-2X/6-31+G(d,p) optimized geometries for the transition state structures of 1,2- 1,4- and 1,6- phosphite addition to iminium ion of **3a**. Critical distances in Å.

Natural Population Analysis (NPA)[52] and Iterative Hirshfeld (HI)[53-54] atomic charges depict a clear difference between the neutral imines and their 'activated' iminium counterparts (Table 5). The iminium ions of **1** and **3** (Table 5) show a higher positive charge on carbon C2 with both population schemes, indicating higher reactivity compared to C4 and C6 (for **3**).

Table 5. Natural Population Analysis (NPA), Iterative Hirshfeld (HI) atomic charges and π-orbital LUMO coefficients (M06-2X/6-31+G(d,p)) for *mono*- and *di*-unsaturated imines **1** and **3** and their iminium ions.



	NPA charges			HI charges			LUMO coefficients		
	C2	C4	C6	C2	C4	C6	C2	C4	C6
1a	0.057	-0.198		0.207	-0.102		0.153	0.264	
1b	0.062	-0.188		0.215	0.022		0.242	0.336	
3a	0.053	-0.221	-0.202	0.203	-0.061	-0.128	0.127	0.200	0.261
3b	0.057	-0.215	-0.191	0.208	-0.049	0.004	0.182	0.277	0.291



	NPA charges			HI charges			LUMO coefficients		
	C2	C4	C6	C2	C4	C6	C2	C4	C6
1a	0.193	-0.034		0.308	0.102		0.322	0.348	
1b	0.214	-0.019		0.321	0.199		0.392	0.366	
3a	0.177	-0.075	-0.060	0.298	0.123	0.060	0.289	0.314	0.292
3b	0.191	-0.063	-0.049	0.306	0.134	0.155	0.332	0.343	0.283

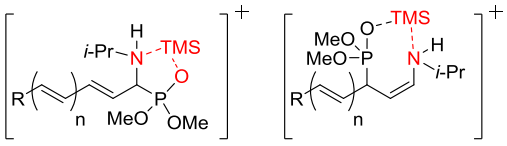
This is consistent with the lower barrier of formation for the 1,2-adduct indicated earlier (Table 4). Nonetheless, note that all carbons are more positive compared to their imine counterparts. For systems **3**, charges on C4 and C6 are comparable, which also correlates well with the barriers calculated for attack on these carbons.

Meanwhile, π-orbital LUMO coefficients (Table 5) depict no difference among C2, C4 and C6, indicating the reaction is electrostatically-driven rather than orbital-controlled.

There are several possible fates for the mono-addition products of **1** and **3**, as indicated in Scheme 2: a) a TMS shift from oxygen to the neighboring nitrogen could occur for 1,2- (**C** to **D**) and 1,4-adducts (**I** to **J**), b) an intramolecular S_N' reaction could take place in the case of the 1,2-adduct (Scheme 2, **C** to **I**), c) a second phosphite attack could occur for the 1,4- and 1,6-mono-adducts, leading to the tandem addition products experimentally observed (Table 1). The energetic feasibilities of all aforementioned reactions were computationally explored in order to rationalize the experimental findings.

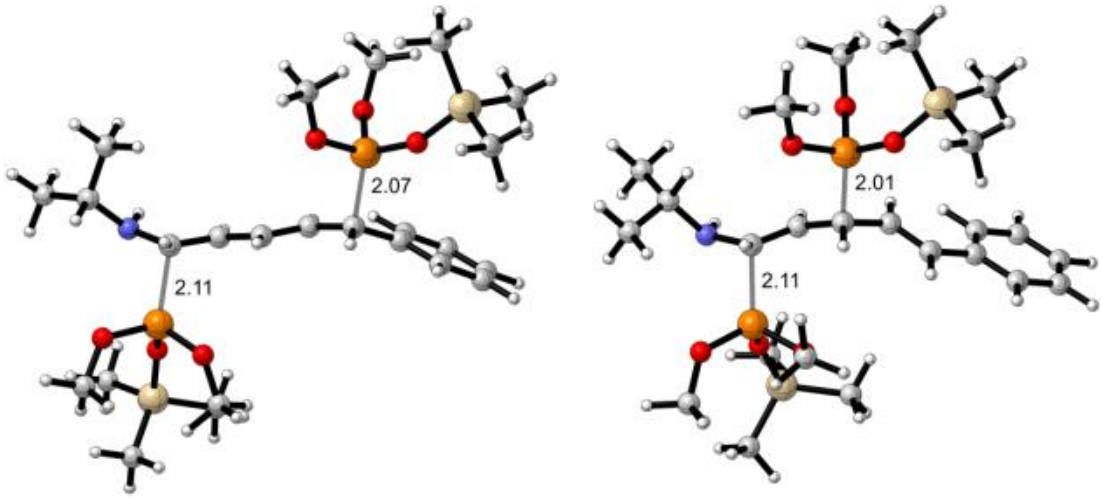
The O-TMS to N-TMS shift was modeled for both 1,2- and 1,4-adducts of **1** and **3** (Table 6). This shift is shown to be both kinetically and thermodynamically unfavorable in all four systems Silicon's propensity for oxygen is well-known as evidenced in the high bond dissociation energies (BDE) previously reported[55] indicating high bond strength, hence this result is expected.

Table 6. Activation ($\Delta G^{\ddagger}$) and reaction (ΔG_{rxn}) free energies (M06-2X/6-31+G(d,p), 298 K, 1 atm, in kJ/mol) for TMS shift from oxygen to nitrogen in 1,2- and 1,4-adducts of *mono*- and *di*-unsaturated imines **1** and **3**.[a]



	TMS-Shift for 1,2-Adduct		TMS-Shift for 1,4-Adduct	
	$\Delta G^{\ddagger}$	ΔG_{rxn}	$\Delta G^{\ddagger}$	ΔG_{rxn}
1a	104.4	68.8	186.4	51.7
1b	103.7	69.0	187.9	52.6
3a	98.5	58.7	181.9	63.4
3b	99.1	58.5	181.3	61.2

[a]O-TMS monoadducts are taken as reference.



S_N'-TS (1,2 to 1,6) S_N'-TS (1,2 to 1,4)

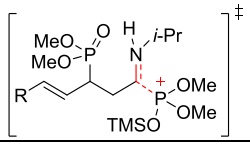
Figure 2. Transition state structures for the conversion of 1,2-adduct to 1,4- and 1,6-adducts *via* an S_N' pathway for 3a (PM3, critical distances in Å).

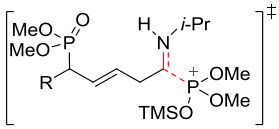
All efforts to locate the S_N' transition states for the concerted conversion of 1,2-adducts to 1,4- and 1,6-adducts failed at the DFT (M06-2X and B3LYP) level of theory. However, S_N' transition state geometries converting the 1,2- to a 1,4-adduct (**C** to **I**, Scheme 2) as well as the 1,2- to a 1,6-adduct (**C** to **G**) were located at the semi-empirical level of theory (PM3, Figure 2). Thus, their existence cannot be fully refuted. The final fate of the mono-addition products is the nucleophilic attack of a second phosphite nucleophile, leading to a tandem addition product, as observed experimentally (Table 1) for systems **3**.

Table 7 depicts activation and reaction free energies for 1,2-phosphite attack on 1,4- as well as 1,6-adducts. Transition state geometries for **3a** are shown in Figure 3. When compared to activation barriers for the initial step (Table 4) the second addition step is clearly not rate determining. Hence, the product distributions will most likely

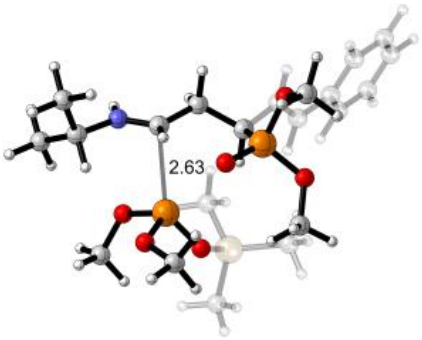
be dictated by thermodynamic stability of the final tandem adducts rather than the intermediates and thermodynamic equilibration will prevail. Relative product stabilities (Table 8), depict a significant difference favoring the 1,2-1,4-adduct in the case of **3a**, consistent with experimental results. Similarly, the product stabilities are in line with observations for **3b**, which gave a 50/50 product distribution for both tandem addition products.

Table 7. Relative free energies (M06-2X/6-31+G(d,p), 298 K, 1atm, in kJ/mol) of the transition states for the second phosphite attack in the formation of 1,4-1,2 and 1,6-1,2 tandem adducts of *di*-unsaturated imines 3.

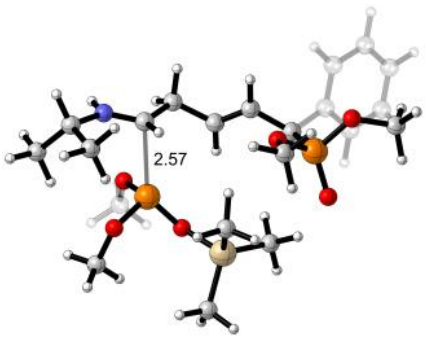




	ΔΔG‡ — 1,4 addition	ΔΔG‡ — 1,6 addition
3a	0.0	31.6
3b	0.0	40.6



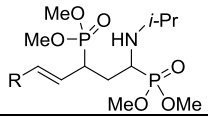
TS1,4 addition

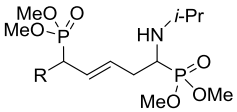


TS1,6 addition

Figure 3. Transition state structures for the second phosphite attack in the formation of 1,4-1,2 and 1,6-1,2 tandem adducts of *di*unsaturated imine 3a (M06-2X/6-31+G(d,p), critical distances in Å).

Table 8. Relative product free energies for the tandem 1,2-1,4- and 1,2-1,6-addition of $P(OTMS)(OMe)_2$ to *mono*- and *di*unsaturated imines 1 and 3. (M06-2X/6-31+G(d,p), 298 K, 1 atm, in kJ/mol)





	4	5
3a	0.0	16.7
3b	0.0	4.6

The combination of these experimental and theoretical results has shed new light on the precise mechanism of tandem phosphite additions (Scheme 2). After acidic activation of the linear unsaturated system, phosphite addition takes place in a 1,2-, 1,4- or 1,6-fashion. The resulting phosphonium ion either readily collapses with concomitant loss of the TMS-moiety, or it is expelled, after which a second phosphite attack takes place. Calculations have demonstrated that an intramolecular O-to-N TMS-shift is not feasible (**C** to **D**).In contrast, it was shown earlier that N-to-O TMS-shift does take place.[8] However, intermolecular TMS-shift is possible (**C-E-D**, **I-J** and **B-G**), assisted by one or more molecules of sulfuric acid, or a TMS-derivative thereof. In addition, calculations have shown that S_N' is somewhat less likely to occur, but it cannot fully be ruled out (**C** to **I**). As such, the mechanism depicted in Scheme 2 is the most plausible stream of events in tandem phosphite additions to acyclic unsaturated systems, taken into account the results of the computational analysis.

Conclusion

This work has expanded the scope of tandem phosphite additions to *α,β,γ,δ*-diunsaturated imines. To the best of our knowledge, a 1,6-conjugate addition of a phosphite nucleophile has been reported for the first time. Selective mono-1,2-addition could also be obtained by controlling the stoichiometry of the reagents. The

observed regioselectivities were dictated by both electronic and steric properties of the substrates and were supported by theoretical calculations. These findings suggest that the regioselectivity of the phosphite additions is rather electrostatically-driven than orbital-controlled. In addition, with the aid of calculations the most comprehensive mechanism up to date has been presented here, allowing to rule out previous hypotheses.

Experimental Section

Commercially available products were used as received without any purification unless otherwise noted. Dry diethyl ether (Et_2O), tetrahydrofuran (THF) and toluene were freshly distilled from sodium/benzophenone ketyl. Dry dichloromethane (CH_2Cl_2) was freshly distilled over calcium hydride (CaH_2). Column chromatography was performed in a glass column with silica gel (particle size 70−200 μm, pore diameter 60 Å) using mixtures of ethyl acetate (EtOAc) and hexanes. Visualisation was performed on TLC-plates using UV irradiation and oxidation by a $KMnO_4$ solution or elemental iodine. NMR spectra were recorded on a 400 MHz spectrometer at room temperature at 400 MHz (^{1}H), 100 MHz (^{13}C) and 162 MHz (^{31}P) in $CDCl_3$ unless otherwise noted, with tetramethylsilane (TMS) as internal standard. ^{31}P-spectra were externally referenced to 85% H_3PO_4. All chemical shifts are expressed as parts per million (ppm). HPLC and HPLC-MS analyses were performed on an liquid chromatograph using a reversed phase column (C18 column, 50 x 4.6 mm, particle size 3.5 μm, or C18 column, 30 x 4.6 mm, particle size 2.7 μm) connected to a UV-VIS detector and a mass spectrometer (ESI, 70 eV) using a mass selective single quadrupole detector. A mixture of 5 mM NH_4OAc in H_2O and CH_3CN was used as eluent. Preparative HPLC was performed using a reversed phase column (C18 column, 150 x 21.2 mm, particle size 5 μm) that was thermostatized at 25 °C. The

column is connected to a UV-VIS Variable Wavelength Detector (VWD). A mixture of H_2O and CH_3CN is used as eluent, with TFA or diethylamine as additives if needed. Low-resolution mass spectra were obtained with an LC/MSD type SL mass spectrometer (ESI, 70 eV) using a mass selective single quadrupole detector. High-resolution mass spectra were obtained with a Time-Of-Flight (TOF) mass spectrometer (ESI or APCI).

Synthesis of *α,β,γ,δ*-diunsaturated aldehydes **S1**[44]

In a flame-dried round-bottom flask equipped with a stirring bar a suitable *α,β*-unsaturated aldehyde was dissolved in dry THF under an inert atmosphere. Next, (1,3-dioxolan-2-ylmethyl)triphenylphosphonium bromide (1.5 equiv) and LiOMe (2.2 equiv) were added and the reaction mixture was heated to reflux temperature for 16 h. A solution of 2 M HCl with a volume equal to the reaction solvent was then added to the reaction mixture at room temperature and was left to stir for 1 hour. Afterwards the THF was evaporated *in vacuo* until only the aqueous phase remained. Ethyl acetate was added and the mixture was extracted 3x using ethyl acetate. The combined organic layers were washed once using $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated *in vacuo*.[44] The crude product was then triturated using a 9/1 mixture of hexanes/EtOAc and filtered: the desired *α,β,γ,δ,*-diunsaturated aldehyde **S1** was present in the filtrate while the residue consisted of triphenylphosphine oxide. The filtrate was concentrated *in vacuo* and purified using column chromatography.

(2*E*,4*E*)-5-phenylpenta-2,4-dienal S1a[44]

Cinnamaldehyde (2.04 g, 15.4 mmol) was transformed into **S1a**. After column chromatography, 2.15 g was obtained (13.6 mmol, 88% yield, yellow solid). Spectral

data are in accordance with reported values. R_f = 0.25. (hexanes/EtOAc 95/5). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.28 (1H, dd, *J* = 15.1 Hz, *J* = 7.9 Hz), 7.00-7.03 (2H, m), 7.24-7.31 (1H, m), 7.33-7.41 (3H, m), 7.49-7.53 (2H, m), 9.63 (1H, d, *J* = 7.9 Hz).

(*E*)-3-((1*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)acrylaldehyde S1c

(1*R*)-(−)-Myrtenal (1.74 g, 11.6 mmol) was transformed into **S1c**. After column chromatography, 1.23 g was obtained as an *E*/*Z* mixture in a 93/7 ratio (6.97 mmol, 60% yield, yellow oil). Spectral data are given for the major isomer. R_f = 0.34 (hexanes/EtOAc 95/5). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.78 (3H, s), 1.16 (1H, d, *J* = 9.0 Hz), 1.35 (3H, s), 2.15-2.20 (1H, m), 2.46-2.53 (3H, m), 2.57 (1H, m), 6.06 (1H, dd, *J* = 15.6 Hz, *J* = 7.8 Hz), 6.17-6.20 (1H, m), 7.10 (1H, d, *J* = 15.6 Hz), 9.58 (1H, d, *J* = 7.8 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 20.8, 26.0, 31.1, 33.0, 37.8, 40.5, 41.4, 125.6, 136.9, 146.3, 153.2, 194.3. IR (ATR, cm^{-1}) v_{max}: 1121, 1609, 1678, 2921. MS (ESI, pos): *m/z* (%) 177.1/178.1 ($M+H^+$, 100/12).

Synthesis of dimethyl trimethylsilyl phosphite (DMPTMS)

In a flame-dried round-bottom flask equipped with a magnetic stirring bar dimethyl phosphite (DMP) was dissolved in dry dichloromethane (0.2M) under a N_2-atmosphere. Next the flask was cooled to 0 °C using an ice bath before Et_3N (1.2 equiv) was added. Then TMSCl (1.1 equiv) was added in a dropwise fashion and the reaction mixture was kept at 0 °C for 30 minutes. Afterwards the resulting suspension was filtered using an oven-dried filter and flame-dried glassware (which was allowed to cool in a dessicator prior to use). The residue was washed using dry diethyl ether and the filtrate was concentrated *in vacuo*. The resulting suspension was again filtered using an oven-dried filter and flame-dried glassware and was washed using dry diethyl ether. The filtrate was concentrated *in vacuo*. This filtration/concentration

procedure was repeated until no more salt was visibly present (typically 3x) and a clear colorless solution was obtained, typically in 75% yield. The resulting DMPTMS was stored in a flame-dried flask under a N_2-atmosphere in the freezer at -18 °C and could be kept as such without significant hydrolysis for several months. Prior to use, the exact concentration was determined using ^{1}H- and ^{31}P-NMR spectroscopy (relevant signals: DMPTMS: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.40 (6H, d, $^{3}J_{HP}$ = 10.4 Hz) and ^{31}P-NMR (162 MHz, $CDCl_3$) δ 128.1. DMP: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.72 (6H, d, $^{3}J_{HP}$ = 11.9 Hz) and ^{31}P-NMR (162 MHz, $CDCl_3$) δ 10.4.)

Synthesis of *α,β,γ,δ*-diunsaturated imines **3**

In a round-bottom flask equipped with a magnetic stirring bar, a diunsaturated aldehyde was dissolved in dichloromethane (0.2 M). Then 2 equivalents of $MgSO_4$ and 1 equivalent of a suitable amine were added to the flask. The mixture was heated to reflux temperature and the reaction progress was monitored using ^{1}H-NMR spectroscopy. After consumption of all starting material, the $MgSO_4$ was filtered off and washed three times using dichloromethane. The filtrate was concentrated *in vacuo* and the resulting crude was used as such in the next step if, according to ^{1}H-NMR spectroscopy ,no hydrolysis had taken place during work-up.

Synthesis of phosphonylated α-aminophosphonates **5** and **6**

In a flame-dried round-bottom flask equipped with a magnetic stirring bar *α,β,γ,δ*-diunsaturated imines **3** were dissolved in dry dichloromethane under a N_2-atmosphere. Next, an appropriate amount of DMPTMS was added using a syringe and the reaction mixture was heated to reflux temperature. H_2SO_4 was then added via a syringe in a dropwise fashion. The reaction progress was monitored using HPLC-MS and after complete consumption of the starting material, the reaction

mixture was poured into 10 mL of a 2 M HCl-solution. Diethyl ether was added and the mixture was extracted thrice using diethyl ether. The resulting aqueous layer was then rendered alkaline to a pH of 14 using a 2 M NaOH solution. Next, the alkaline aqueous phase was extracted thrice using ethyl acetate (3x 10 mL). The combined ethyl acetate fractions were dried over $MgSO_4$, filtered and concentrated *in vacuo*, yielding the crude desired phosphonylated α-aminophosphonates. The regio- and diastereomers were separated using HPLC in order to obtain analytically pure samples.

328 mg (1.33 mmol) of **3a1** was converted into **5a1** and using 2 equiv of DMPTMS and 0.5 equiv of H_2SO_4 at reflux temperature. After work-up, 478 mg of crude product was obtained as diastereomers in a 3/7 ratio (1.02 mmol, 77% yield, yellow oil). The 1,4-1,2-adducts were separated using preparative HPLC (reversed-phase C18-column, water/acetonitrile eluent). Two fractions were isolated for characterization.

tetramethyl (1-(benzylamino)-5-phenylpent-4-ene-1,3-diyl)(E)-bis(phosphonate) 5a1 (diastereomer 1)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.89-2.05 (1H, m), 2.29-2.41 (1H, m), 3.12 (1H, ddd, $^2J_{HP}$ = 13.7 Hz, J = 6.9 Hz, J = 6.9 Hz), 3.22 (1H, dddd, $^2J_{HP}$ = 21.9 Hz, J = 9.4 Hz, J = 9.4 Hz, J = 5.1 Hz), 3.73 (3H, d, $^3J_{HP}$ = 10.6 Hz), 3.74 (3H, d, $^3J_{HP}$ = 10.7 Hz), 3.76 (3H, d, $^3J_{HP}$ = 10.5 Hz), 3.81 (3H, d, $^3J_{HP}$ = 10.4 Hz), 3.88 (2H, br s), 6.04 (1H, ddd, J = 15.8 Hz, J = 9.3 Hz, $^3J_{HP}$ = 6.4 Hz), 6.53 (1H, dd, J = 15.8 Hz, $^4J_{HP}$ = 5.0 Hz), 7.16-7.32 (10H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 29.8 (dd, $^2J_{CP}$ = 3.9 Hz, $^2J_{CP}$ = 3.9 Hz), 38.5 (dd, $^1J_{CP}$ = 138.7 Hz, $^3J_{CP}$ = 6.6 Hz), 51.4 (dd, $^1J_{CP}$ = 149.0 Hz, $^3J_{CP}$ = 13.3 Hz), 51.7 (d, $^3J_{CP}$ = 7.2 Hz), 52.8 (d, $^2J_{CP}$ = 7.2 Hz), 53.2 (d, $^2J_{CP}$ = 7.1 Hz), 53.4 (d, $^2J_{CP}$ = 7.2 Hz), 123.8 (d, $^2J_{CP}$ = 10.7 Hz), 126.41, 126.42, 127.1, 127.8, 128.35 (2x CH_{ar}),

128.39 (2x CH_{ar}), 128.6 (2x CH_{ar}), 134.6 (d, $^{3}J_{CP}$ = 13.8 Hz), 136.5 (d, $^{4}J_{CP}$ = 3.5 Hz), 139.5. ^{31}P-NMR (162 MHz, $CDCl_3$) δ 29.91, 30.47. IR (ATR, cm^{-1}) v_{max}: 1024, 1223, 1452, 3395. MS (ESI, pos): *m/z* (%) 358.3/359.3 (M-[P(O)$(OMe)_2$]$^-$, 60/10), 468.3/469.3 ($M+H^+$, 100/20). HRMS: *m/z* calcd for $C_{22}H_{31}NO_6P_2+H^+$ 468.1699, found 468.1711.

tetramethyl (1-(benzylamino)-5-phenylpent-4-ene-1,3-diyl)(E)-bis(phosphonate) 5a1 (diastereomer 2)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.88 (1H, br s), 1.94-2.10 (2H, m), 2.91 (1H, ddd, $^{2}J_{HP}$ = 11.5 Hz, J = 11.5 Hz, J = 3.2 Hz), 3.24 (dddd, $^{2}J_{HP}$ = 20.8 Hz, J = 10.4 Hz, J = 10.4 Hz, J = 3.0 Hz), 3.74 (3H, d, $^{3}J_{HP}$ = 10.5 Hz), 3.75 (3H, d, $^{3}J_{HP}$ = 10.6 Hz), 3.77 (1H, dd, J = 13.1 Hz, $^{4}J_{HP}$ = 1.3 Hz) 3.78 (3H, d, $^{3}J_{HP}$ = 10.4 Hz), 3.79 (3H, d, $^{3}J_{HP}$ = 10.4 Hz), 4.05 (1H, dd, J = 13.1 Hz, $^{4}J_{HP}$ = 1.4 Hz), 5.91 (1H, ddd, J = 15.8 Hz, J = 9.8 Hz, $^{3}J_{HP}$ = 6.2 Hz), 6.2 (1H, dd, J = 15.8 Hz, $^{4}J_{HP}$ = 4.8 Hz), 7.20-7.36 (10H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 29.7 (dd, $^{2}J_{CP}$ = 8.0 Hz, $^{2}J_{CP}$ = 2.7 Hz), 37.7 (dd, $^{1}J_{CP}$ = 140.5 Hz, $^{3}J_{CP}$ = 14.7 Hz), 50.6 (dd, $^{1}J_{CP}$ = 141.6 Hz, $^{3}J_{CP}$ = 16.6 Hz), 51.9, 52.6 (d, $^{2}J_{CP}$ = 7.3 Hz), 52.8 (d, $^{2}J_{CP}$ = 7.3 Hz), 53.3 (d, $^{2}J_{CP}$ = 7.1 Hz), 122.9 (d, $^{2}J_{CP}$ = 10.2 Hz), 126.40, 126.42, 127.3, 127.8, 128.4, 128.5, 128.6, 135.5 (d, $^{3}J_{CP}$ = 14.1 Hz), 136.4 (d, $^{4}J_{CP}$ = 3.5 Hz), 140.1. ^{31}P-NMR (162 MHz, $CDCl_3$) δ 30.92 (d, $^{4}J_{PP}$ = 10.2 Hz), 31.50 (d, $^{4}J_{PP}$ = 10.2 Hz). IR (ATR, cm^{-1}) v_{max}: 1024, 1223, 1641, 3394. MS (ESI, pos): *m/z* (%) 358.3/359.3 (M-[P(O)$(OMe)_2$]$^-$, 90/20), 468.3/469.3 ($M+H^+$, 100/20). HRMS: *m/z* calcd for $C_{22}H_{31}NO_6P_2+H^+$ 468.1699, found 468.1726.

233 mg (1.17 mmol) of **3a2** was converted into **5a2** using 2 equiv of DMPTMS and 0.5 equiv of H_2SO_4 at reflux temperature. After work-up, 347 mg of crude product was obtained as diastereomers in a 3/7 ratio (0.83 mmol, 71% yield, yellow oil). The

1,4-1,2-adducts were separated using preparative HPLC (reversed-phase C18-column, water/acetonitrile eluent). Two fractions were isolated for characterization.

tetramethyl (5-phenyl-1-(propylamino)pent-4-ene-1,3-diyl)(E)-bis(phosphonate) 5a2 (diastereomer 1)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.87 (3H, t, J = 7.3 Hz), 1.12 (1H, br), 1.42 (2H, sextet, J = 7.3 Hz), 1.85-2.01 (1H, m), 2.25-2.39 (1H, m), 2.64 (2H, t, J = 7.3 Hz), 3.07 (1H, ddd, $^{2}J_{HP}$ = 13.2 Hz, J = 6.9 Hz, J = 6.9 Hz), 3.24 (dddd, $^{2}J_{HP}$ = 21.9 Hz, J = 9.4 Hz, J = 9.4 Hz, J = 5.2 Hz), 3.75 (3H, d, $^{3}J_{HP}$ = 10.6 Hz), 3.76 (3H, d, $^{3}J_{HP}$ = 10.7 Hz), 3.78 (3H, d, $^{3}J_{HP}$ = 10.6 Hz), 3.81 (3H, d, $^{3}J_{HP}$ = 10.4 Hz), 6.11 (1H, ddd, J = 15.9 Hz, J = 9.5 Hz, $^{3}J_{HP}$ = 6.4 Hz), 6.60 (1H, dd, J = 15.9 Hz, $^{4}J_{HP}$ = 5.0 Hz), 7.25 (1H, dd, J = 7.4 Hz, J = 7.4 Hz), 7.32 (2H, dd, J = 7.4 Hz, J = 7.4 Hz), 7.38 (2H, d, J = 7.4 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 11.6, 23.4, 29.8 (dd, $^{2}J_{CP}$ = 4.3 Hz, $^{2}J_{CP}$ = 4.3 Hz), 38.5 (dd, $^{1}J_{CP}$ = 138.6 Hz, $^{3}J_{CP}$ = 6.9 Hz), 49.9 (d, $^{3}J_{CP}$ = 7.2 Hz), 52.5 (dd, $^{1}J_{CP}$ = 149.8 Hz, $^{3}J_{CP}$ = 12.0 Hz), 52.6 (d, $^{2}J_{CP}$ = 7.3 Hz), 52.8 (d, $^{2}J_{CP}$ = 7.2 Hz), 53.2 (d, $^{2}J_{CP}$ = 7.2 Hz), 53.4 (d, $^{2}J_{CP}$ = 7.0 Hz), 123.9 (d, $^{2}J_{CP}$ = 10.7 Hz), 126.35, 126.37, 127.8, 128.6 (2x CH_{ar}), 134.5 (d, $^{3}J_{CP}$ = 13.9 Hz), 136.6 (d, $^{4}J_{CP}$ = 3.2 Hz). IR (ATR, cm^{-1}) ν_{max}: 1016, 1230, 1647, 2955. ^{31}P-NMR (162 MHz, $CDCl_3$) δ 30.09, 30.53. MS (ESI, pos): *m/z* (%) 310.3/311.3 (M-[P(O)(OMe)$_2$]$^-$, 100/20), 420.3/421.3 (M+H$^+$, 90/20). HRMS: *m/z* calcd for $C_{18}H_{31}NO_6P_2$+H$^+$ 420.1699, found 420.1698.

tetramethyl (5-phenyl-1-(propylamino)pent-4-ene-1,3-diyl)(E)-bis(phosphonate) 5a2 (diastereomer 2)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.94 (3H, t, J = 7.4 Hz), 1.45 (2H, dqd, J = 9.0 Hz, J = 7.4 Hz, J = 7.1 Hz), 1.93-2.10 (2H, m), 2.47 (1H, dtd, J = 11.0 Hz, J = 7.1 Hz, J = 1.3 Hz), 2.82-2.90 (2H, m), 3.35 (1H, dddd, $^{2}J_{HP}$ = 20.6 Hz, J = 10.6 Hz, J = 10.2 Hz, J =

2.6 Hz), 3.74-3.75 (6H, m), 3.76-3.77 (6H, m), 6.01 (1H, ddd, J = 15.7 Hz, J = 9.8 Hz, $^{3}J_{HP}$ = 6.1 Hz), 6.56 (1H, dd, J = 15.7 Hz, $^{4}J_{HP}$ = 4.9 Hz), 7.25 (1H, dd, J = 7.4 Hz, J = 7.4 Hz), 7.32 (2H, dd, J = 7.4 Hz, J = 7.4 Hz), 7.38 (2H, d, J = 7.4 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 11.8, 23.9, 29.3 (dd, $^{2}J_{CP}$ = 8.7 Hz, $^{2}J_{CP}$ = 1.9 Hz), 37.8 (dd, $^{1}J_{CP}$ = 138.0 Hz, $^{3}J_{CP}$ = 16.8 Hz), 50.1, 51.5 (dd, $^{1}J_{CP}$ = 139.6 Hz, $^{3}J_{CP}$ = 18.3 Hz), 52.59 (d, $^{2}J_{CP}$ = 7.5 Hz), 52.60 (d, $^{2}J_{CP}$ = 7.4 Hz), 52.8 (d, $^{2}J_{CP}$ = 7.0 Hz), 53.3 (d, $^{2}J_{CP}$ = 6.8 Hz), 123.1 (d, $^{2}J_{CP}$ = 10.3 Hz), 126.37, 126.39, 127.9, 128.6 (2x CH_{ar}), 135.6 (d, $^{3}J_{CP}$ = 14.0 Hz), 136.5 (d, $^{4}J_{CP}$ = 3.1 Hz). ^{31}P-NMR (162 MHz, $CDCl_3$) δ 31.22 (d, $^{4}J_{PP}$ = 9.8 Hz), 31.64 (d, $^{4}J_{PP}$ = 9.8 Hz).). IR (ATR, cm^{-1}) v_{max}: 1016, 1231, 1449, 2955. MS (ESI, pos): *m/z* (%) 310.3/311.3 (M-[P(O)(OMe)$_2$]$^-$, 100/20), 420.3/421.3 (M+H$^+$, 70/10). HRMS: *m/z* calcd for $C_{18}H_{31}NO_6P_2$+H$^+$ 420.1699, found 420.1733.

123 mg (0.62 mmol) of **3a3** was converted into **5a3** using 2 equiv of DMPTMS and 0.5 equiv of H_2SO_4 at reflux temperature. After work-up, 214 mg of crude product was obtained as diastereomers in a 3/7 ratio (0.51 mmol, 82% yield, yellow oil). The 1,4-1,2-adducts were separated using preparative HPLC (reversed-phase C18-column, water/acetonitrile eluent). Two fractions were isolated for characterization.

tetramethyl (1-(isopropylamino)-5-phenylpent-4-ene-1,3-diyl)(E)-bis(phosphonate) 5a3 (diastereomer 1)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.96 (3H, d, J = 6.2 Hz), 1.02 (3H, d, J = 6.2 Hz), 1.80-1.97 (1H, m), 2.25-2.38 (1H, m), 3.00 (1H, septet, J = 6.2 Hz), 3.13 (1H, ddd, $^{2}J_{HP}$ = 15.1 Hz, J = 8.5 Hz, J = 5.4 Hz), 3.25 (1H, dddd, $^{2}J_{HP}$ = 22.0 Hz, J = 9.5 Hz, J = 9.5 Hz, J = 4.7 Hz), 3.75 (3H, d, $^{3}J_{HP}$ = 10.7 Hz), 3.76 (3H, d, $^{3}J_{HP}$ = 10.7 Hz), 3.78 (3H, d, $^{3}J_{HP}$ = 10.6 Hz), 3.81 (3H, d, $^{3}J_{HP}$ = 10.3 Hz), 6.09 (1H, ddd, J = 15.8 Hz, J = 9.5 Hz, $^{3}J_{HP}$ = 6.4 Hz), 6.60 (1H, dd, J = 15.9 Hz, $^{4}J_{HP}$ = 5.1 Hz), 7.25 (1H, dd, J = 7.8 Hz,

J = 7.8 Hz), 7.32 (2H, dd, J = 7.4 Hz, J = 7.4 Hz), 7.38 (2H, d, J = 7.5 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 22.8, 23.1, 30.3 (dd, $^2J_{CP}$ = 4.3 Hz, $^2J_{CP}$ = 4.3 Hz), 38.4 (dd, $^1J_{CP}$ = 138.7 Hz, $^3J_{CP}$ = 5.3 Hz), 46.4 (d, $^3J_{CP}$ = 9.1 Hz), 49.5 (dd, $^1J_{CP}$ = 152.2 Hz, $^3J_{CP}$ = 13.7 Hz), 52.7 (d, $^2J_{CP}$ = 7.3 Hz), 52.8 (d, $^2J_{CP}$ = 7.1 Hz), 53.4 (d, $^2J_{CP}$ = 7.1 Hz), 53.5 (d, $^2J_{CP}$ = 7.1 Hz), 123.8 (d, $^2J_{CP}$ = 10.8 Hz), 126.3, 126.4, 127.8, 128.6 (2x CH_{ar}), 134.9 (d, $^3J_{CP}$ = 13.9 Hz), 136.6 (d, $^4J_{CP}$ = 3.1 Hz). ^{31}P-NMR (162 MHz, $CDCl_3$) δ 30.16, 30.54. IR (ATR, cm^{-1}) v_{max}: 1016, 1233, 2957, 3458. MS (ESI, pos): *m/z* (%) 310.3/311.3 (M-[P(O)(OMe)$_2$]$^-$, 100/20), 420.3/421.3 (M+H$^+$, 85/20). HRMS: *m/z* calcd for $C_{18}H_{31}NO_6P_2$+H$^+$ 420.1699, found 420.1693.

tetramethyl (1-(isopropylamino)-5-phenylpent-4-ene-1,3-diyl)(E)-bis(phosphonate) 5a3 (diastereomer 2)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, d, J = 6.0 Hz), 1.04 (3H, d, J = 6.0 Hz), 1.85-1.95 (1H, m), 2.05-2.15 (1H, m), 2.94 (1H, ddd, $^2J_{HP}$ = 11.6 Hz, J = 11.6 Hz, J = 2.5 Hz), 3.14 (1H, septet x d, J = 6.1 Hz, $^3J_{HP}$ = 2.7 Hz), 3.32-3.43 (1H, m), 3.74-3.78 (12H, m), 6.00 (1H, ddd, J = 15.6 Hz, J = 9.9 Hz, $^3J_{HP}$ = 5.8 Hz), 6.58 (1H, dd, J = 15.9 Hz, $^4J_{HP}$ = 5.0 Hz), 7.25 (1H, dd, J = 7.1 Hz, J = 7.1 Hz), 7.32 (2H, dd, J = 7.4 Hz, J = 7.4 Hz), 7.38 (2H, d, J = 7.4 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 22.4, 24.1, 30.0 (dd, $^2J_{CP}$ = 7.6 Hz, $^2J_{CP}$ = 2.5 Hz), 37.6 (dd, $^1J_{CP}$ = 141.6 Hz, $^3J_{CP}$ = 12.3 Hz), 46.5, 48.7 (dd, $^1J_{CP}$ = 143.5 Hz, $^3J_{CP}$ = 14.5 Hz), 52.6 (d, $^2J_{CP}$ = 7.3 Hz), 52.7 (d, $^2J_{CP}$ = 7.4 Hz), 52.8 (d, $^2J_{CP}$ = 7.2 Hz), 53.3 (d, $^2J_{CP}$ = 7.0 Hz), 123.2 (d, $^2J_{CP}$ = 10.7 Hz), 126.34, 126.36, 127.8, 128.6 (2x CH_{ar}), 135.6 (d, $^3J_{CP}$ = 13.4 Hz), 136.5 (d, $^4J_{CP}$ = 3.5 Hz). ^{31}P-NMR (162 MHz, $CDCl_3$) δ 31.22 (d, $^4J_{PP}$ = 10.3 Hz), 31.45 (d, $^4J_{PP}$ = 10.3 Hz). IR (ATR, cm^{-1}) v_{max}: 1016, 1232, 2956, 3458. MS (ESI, pos): *m/z* (%)

310.3/311.3 (M-[P(O)(OMe)$_2$]$^-$, 100/15), 420.3/421.3 (M+H$^+$, 60/10). HRMS: *m/z* calcd for $C_{18}H_{31}NO_6P_2$+H$^+$ 420.1699, found 420.1693.

142 mg (0.67 mmol) of **3a4** was converted into **5a4** using 2 equiv of DMPTMS and 0.5 equiv of H_2SO_4 at reflux temperature. After work-up, 211 mg of crude product was obtained as diastereomers in a 1/1 ratio (0.49 mmol, 73% yield, yellow oil). The 1,4-1,2-adducts were separated using preparative HPLC (reversed-phase C18-column, water/acetonitrile eluent). Two fractions were isolated for characterization.

tetramethyl (1-(tert-butylamino)-5-phenylpent-4-ene-1,3-diyl)(E)-bis(phosphonate) 5a4 (diastereomer 1)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.05 (9H), 1.81-1.99 (1H, m), 2.30-2.43 (1H, m), 3.08 (1H, ddd, $^2J_{HP}$ = 17.0 Hz, J = 11.1 Hz, J = 3.2 Hz), 3.31 (1H, dddd, $^2J_{HP}$ = 21.7 Hz, J = 12.2 Hz, J = 9.6 Hz, J = 2.6 Hz), 3.74 (3H, d, $^3J_{HP}$ = 10.6 Hz), 3.77 (6H, d, $^3J_{HP}$ = 10.7 Hz), 3.84 (3H, d, $^3J_{HP}$ = 10.2 Hz), 6.09 (1H, ddd, J = 15.9 Hz, J = 9.7 Hz, $^3J_{HP}$ = 6.5 Hz), 6.64 (1H, dd, J = 15.9 Hz, $^4J_{HP}$ = 4.9 Hz), 7.26 (1H, dd, J = 7.1 Hz, J = 7.1 Hz), 7.33 (2H, dd, J = 7.4 Hz, J = 7.4 Hz), 7.40 (1H, d, J = 7.4 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 29.6, 33.5 (dd, $^2J_{CP}$ = 4.7 Hz, $^2J_{CP}$ = 3.8 Hz), 38.9 (d, $^1J_{CP}$ = 139.1 Hz), 46.7 (dd, $^1J_{CP}$ = 160.6 Hz, $^3J_{CP}$ = 17.5 Hz), 52.0 (d, $^3J_{CP}$ = 10.1 Hz), 52.6 (d, $^2J_{CP}$ = 7.5 Hz), 52.8 (d, $^2J_{CP}$ = 7.3 Hz), 53.4 (d, $^2J_{CP}$ = 6.9 Hz), 54.3 (d, $^2J_{CP}$ = 7.4 Hz), 123.3 (d, $^2J_{CP}$ = 10.8 Hz), 126.37, 126.39, 127.8, 128.6 (2x CH_{ar}), 135.7 (d, $^3J_{CP}$ = 14.5 Hz), 136.5 (d, $^4J_{CP}$ = 3.5 Hz). ^{31}P-NMR (162 MHz, $CDCl_3$) δ 30.10, 30.38. IR (ATR, cm^{-1}) ν_{max}: 1015, 1221, 1450, 2957. MS (ESI, pos): *m/z* (%) 324.3/325.3 (M-[P(O)(OMe)$_2$]$^-$, 70/10), 434.3/435.3 (M+H$^+$, 100/20). HRMS: *m/z* calcd for $C_{19}H_{33}NO_6P_2$+H$^+$ 434.1856, found 434.1850.

tetramethyl (1-(tert-butylamino)-5-phenylpent-4-ene-1,3-diyl)(E)-bis(phosphonate) 5a4 (diastereomer 2)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.09 (9H), 1.86 (1H, br s), 1.95-2.06 (1H, m), 2.11-2.22 (1H, m), 3.16-3.23 (1H, m), 3.36 (1H, dddd, $^{2}J_{HP}$ = 23.0 Hz, J = 9.3 Hz, J = 9.0 Hz, J = 4.0 Hz), 3.75 (3H, d, $^{3}J_{HP}$ = 10.4 Hz), 3.76 (3H, d, $^{3}J_{HP}$ = 10.9 Hz), 3.77 (3H, d, $^{3}J_{HP}$ = 9.8 Hz), 3.79 (3H, d, $^{3}J_{HP}$ = 10.6 Hz), 6.07 (1H, ddd, J = 15.8 Hz, J = 9.0 Hz, $^{3}J_{HP}$ = 5.9 Hz), 6.59 (1H, dd, J = 16.0 Hz, $^{4}J_{HP}$ = 5.4 Hz), 7.25 (1H, dd, J = 7.5 Hz, J = 7.5 Hz), 7.32 (2H, dd, J = 7.6 Hz, J = 7.6 Hz), 7.38 (1H, d, J = 7.4 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 30.3, 32.2 (dd, $^{2}J_{CP}$ = 7.3 Hz, $^{2}J_{CP}$ = 3.0 Hz), 37.4 (dd, $^{1}J_{CP}$ = 138.0 Hz, $^{3}J_{CP}$ = 10.2 Hz), 47.3 (dd, $^{1}J_{CP}$ = 151.4 Hz, $^{3}J_{CP}$ = 14.5 Hz), 51.3, 52.8 (d, $^{2}J_{CP}$ = 7.5 Hz), 52.9 (d, $^{2}J_{CP}$ = 7.1 Hz), 53.3 (d, $^{2}J_{CP}$ = 6.9 Hz), 53.4 (d, $^{2}J_{CP}$ = 7.5 Hz), 124.1 (d, $^{2}J_{CP}$ = 11.4 Hz), 126.34 , 126.35, 127.8, 128.6 (2x CH_{ar}), 134.7 (d, $^{3}J_{CP}$ = 13.3 Hz), 136.6 (d, $^{4}J_{CP}$ = 3.7 Hz). ^{31}P-NMR (162 MHz, $CDCl_3$) δ 30.60 (d, $^{4}J_{PP}$ = 6.5 Hz), 31.09 (d, $^{4}J_{PP}$ = 6.5 Hz). IR (ATR, cm^{-1}) ν_{max}: 1014, 1220, 1450, 2956. MS (ESI, pos): *m/z* (%) 324.3/325.3 (M-[P(O)(OMe)$_2$]$^-$, 100/20), 434.3/435.3 (M+H$^+$, 60/10). HRMS: *m/z* calcd for $C_{19}H_{33}NO_6P_2$+H$^+$ 434.1856, found 434.1852.

155 mg (0.84 mmol) of **3b1** was converted into **5b1** and **6b1** using 2 equiv of DMPTMS and 0.5 equiv of H_2SO_4. After work-up, 255 mg of crude product was obtained as diastereomers (0.63 mmol, 75% yield, yellow oil, ratio **5**/**6** = 1/1). The 1,6-1,2-adducts and 1,4-1,2-adducts were separated using preparative HPLC (reversed-phase C18-column, water/acetonitrile eluent). Three fractions were isolated for characterization.

tetramethyl (1-(benzylamino)hex-4-ene-1,3-diyl)(E)-bis(phosphonate) 5b1 (diastereomer 1, 4/1 E/Z mixture [cfr. determination of E/Z stereochemistry based on the ^{13}C-shift of a vinylic CH_3][56], spectral data of the major isomer)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.66 (3H, dd, J = 6.9 Hz, $^5J_{HP}$ = 4.9 Hz), 1.70 (1H, br s), 1.72-1.90 (1H, m), 2.16-2.31 (1H, m), 2.91-3.03 (1H, m), 3.06 (1H, ddd, $^2J_{HP}$ = 13.6 Hz, J = 7.4 Hz, J = 6.2 Hz), 3.72 (6H, d, $^3J_{HP}$ = 10.1 Hz), 3.76 (3H, d, $^3J_{HP}$ = 10.5 Hz), 3.81 (3H, d, $^3J_{HP}$ = 10.4 Hz), 3.88 (2H, s), 5.24-5.33 (1H, m), 5.56-5.65 (1H, m), 7.22-7.27 (1H, m), 7.30-7.34 (4H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 18.1 (d, $^4J_{CP}$ = 2.3 Hz), 29.6 (dd, $^2J_{CP}$ = 4.4 Hz, $^2J_{CP}$ = 4.4 Hz), 37.8 (dd, $^1J_{CP}$ = 138.8 Hz, $^3J_{CP}$ = 6.5 Hz), 51.2 (dd, $^1J_{CP}$ = 150.0 Hz, $^3J_{CP}$ = 13.4 Hz), 51.6 (d, $^3J_{CP}$ = 7.5 Hz), 52.6 (d, $^2J_{CP}$ = 9.4 Hz), 52.7 (d, $^2J_{CP}$ = 9.4 Hz), 53.18 (d, $^2J_{CP}$ = 7.7 Hz), 53.21 (d, $^2J_{CP}$ = 7.0 Hz), 124.9 (d, $^2J_{CP}$ = 10.0 Hz), 127.2, 128.4 (4x CH_{ar}), 131.0 (d, 3JCP = 13.7 Hz), 139.7. ^{31}P-NMR (162 MHz, $CDCl_3$) δ 30.12, 31.5. IR (ATR, cm^{-1}) v_{max}: 1016, 1222, 1453, 1641, 3428. MS (ESI, pos): *m/z* (%) 296.2/297.2 (M-[P(O)(OMe)$_2$]$^-$, 100/18), 406.3/407.3 (M+H$^+$, 65/10). HRMS: *m/z* calcd for $C_{17}H_{29}NO_6P_2$+H$^+$ 406.1543, found 406.1551.

tetramethyl (1-(benzylamino)hex-4-ene-1,3-diyl)(E)-bis(phosphonate) 5b1 (diastereomer 2, E)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.60 (3H, ddd, J = 6.5 Hz, $^5J_{HP}$ = 5.2 Hz, J = 1.4 Hz), 1.82-1.93 (3H, m), 2.86-2.93 (1H, m), 2.95-3.07 (1H, m), 3.72 (6H, d, $^3J_{HP}$ = 10.6 Hz), 3.78 (1H, dd, J = 12.7 Hz, $^4J_{HP}$ = 1.4 Hz), 3.79 (3H, d, $^3J_{HP}$ = 10.6 Hz), 3.80 (3H, d, $^3J_{HP}$ = 10.6 Hz), 4.03 (1H, dd, J = 12.7 Hz, $^4J_{HP}$ = 1.5 Hz), 5.09-5.17 (1H, m), 5.25-5.35 (1H, m), 7.23-7.28 (1H, m), 7.30-7.35 (4H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 18.2 (d, $^4J_{CP}$ = 2.2 Hz), 29.5 ($^2J_{CP}$ = 7.6 Hz, $^2J_{CP}$ = 2.3 Hz), 37.1 (dd, $^1J_{CP}$ = 141.0 Hz, $^3J_{CP}$ = 14.2 Hz), 50.3 (dd, $^1J_{CP}$ = 142.4 Hz, $^3J_{CP}$ = 16.1 Hz), 51.9, 52.59 (d, $^2J_{CP}$ = 7.3

Hz), 52.64 (d, $^{2}J_{CP}$ = 7.0 Hz), 52.8 (d, $^{2}J_{CP}$ = 7.4 Hz), 53.1 (d, $^{2}J_{CP}$ = 7.1 Hz), 123.9 (d, $^{2}J_{CP}$ = 9.6 Hz), 127.2, 128.4 (2x CH_{ar}), 128.6 (2x CH_{ar}), 132.0 (d, $^{3}J_{CP}$ = 14.0 Hz), 140.1. ^{31}P-NMR (162 MHz, $CDCl_3$) δ 31.19 (d, $^{4}J_{PP}$ = 11.5 Hz), 32.51 (d, $^{4}J_{PP}$ = 11.5 Hz). IR (ATR, cm^{-1}) ν_{max}: 1017, 1222, 1454, 3428. MS (ESI, pos): *m/z* (%) 296.2/297.2 (M-[P(O)$(OMe)_2$]$^-$, 100/18), 406.3/407.3 (M+H$^+$, 45/10). HRMS: *m/z* calcd for $C_{17}H_{29}NO_6P_2$+H$^+$ 406.1543, found 406.1563.

tetramethyl (1-(benzylamino)hex-3-ene-1,5-diyl)(E)-bis(phosphonate) 6b1 (2 diastereomers [d1 and d2], 1/1 mixture):

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.26 (3H, dd, $^{3}J_{HP}$ = 7.0 Hz, J = 7.0 Hz, d1), 1.30 (3H, dd, $^{3}J_{HP}$ = 7.0 Hz, J = 7.0 Hz, d2), 2.00 (2H, br s, d1+d2), 2.32-2.43 (2H, m, d1+d2), 2.51-2.75 (4H, m, d1+d2), 2.96-3.00 (2H, m, d1+d2), 3.67-3.73 (12H, m, d1+d2), 3.77-3.82 (12H, m, d1+d2), 3.86-3.96 (4H, m, d1+d2), 5.52-5.64 (4H, m, d1+d2), 7.22-7.35 (10H, m, d1+d2). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 13.7 (d, $^{2}J_{CP}$ = 5.9 Hz, d1 or d2), 13.8 (d, $^{2}J_{CP}$ = 5.9 Hz, d1 or d2), 32.8 (d1 or d2), 32.9 (d1 or d2), 35.0 (d, $^{1}J_{CP}$ = 139.6 Hz, d1+d2), 52.06 (d, $^{3}J_{CP}$ = 7.3 Hz, d1 or d2), 52.09 (d, $^{3}J_{CP}$ = 7.3 Hz, d1 or d2), 52.8 (d, $^{2}J_{CP}$ = 7.6 Hz, d1 or d2), 52.87 (d, $^{2}J_{CP}$ = 7.6 Hz, d1 or d2), 52.90 (d, $^{2}J_{CP}$ = 6.9 Hz, d1 or d2), 53.05 (d, $^{2}J_{CP}$ = 7.1 Hz, d1 or d2), 53.26 (dd, $^{1}J_{CP}$ = 156.7 Hz, $^{5}J_{CP}$ = 3.5 Hz, d1 or d2), 53.34 (dd, $^{1}J_{CP}$ = 156.7 Hz, $^{5}J_{CP}$ = 3.4 Hz, d1 or d2), 127.1 (2x CH_{ar}, d1+d2), 128.3 (4x CH_{ar}, d1+d2), 128.4 (4x CH_{ar}, d1+d2), 128.8 (dd, $^{3}J_{CP}$ = 12.4 Hz, $^{3}J_{CP}$ = 12.4 Hz, d1+d2), 129.6 (d, $^{2}J_{CP}$ = 5.0 Hz, d1 or d2), 129.7 (d, $^{2}J_{CP}$ = 4.9 Hz, d1 or d2), 139.7 (2x $C_{q,ar}$, d1+d2). ^{31}P-NMR (162 MHz, $CDCl_3$) δ 29.30, 29.33, 32.59 (2x s). IR (ATR, cm^{-1}) ν_{max}: 1016, 1223, 1454, 3428. MS (ESI, pos): *m/z* (%) 296.2/297.2 (M-[P(O)$(OMe)_2$]$^-$, 100/18), 406.3/407.3 (M+H$^+$, 20/10). HRMS: *m/z* calcd for $C_{17}H_{29}NO_6P_2$+H$^+$ 406.1543, found 406.1556.

250 mg (1.82 mmol) of **3b2** was converted into **5b2** and **6b2** using 2 equiv of DMPTMS and 0.5 equiv of H_2SO_4. After work-up, 323 mg of crude product was obtained as diastereomers (0.90 mmol, 50% yield, yellow oil, ratio **5**/**6** = 7/3). The 1,6-1,2-adducts and 1,4-1,2-adducts were separated using preparative HPLC (reversed-phase C18-column, water/acetonitrile eluent). Three fractions were isolated for characterization.

tetramethyl (1-(propylamino)hex-4-ene-1,3-diyl)(E)-bis(phosphonate) 5b2 (diastereomer 1, 4/1 E/Z mixture, spectral data of the major isomer)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, t, J = 7.2 Hz), 1.44 (2H, sext, J = 7.2 Hz), 1.65 (1H, br s), 1.73 (3H, dd, J = 6.5 Hz, $^5J_{HP}$ = 5.2 Hz), 1.69-1.87 (1H, m), 2.14-2.26 (1H, m), 2.63 (2H, t, J = 7.2 Hz), 2.92-3.04 (2H, m), 3.74 (3H, d, $^3J_{HP}$ = 10.6 Hz), 3.74 (3H, d, $^3J_{HP}$ = 10.6 Hz), 3.77 (3H, d, $^3J_{HP}$ = 10.7 Hz), 3.80 (3H, d, $^3J_{HP}$ = 10.4 Hz), 5.30-5.39 (1H, m), 5.64-5.74 (1H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 11.7, 18.2 (d, $^4J_{CP}$ = 2.2 Hz), 23.4, 29.7 (dd, $^2J_{CP}$ = 3.8 Hz, $^2J_{CP}$ = 3.8 Hz), 37.9 (dd, $^1J_{CP}$ = 138.7 Hz, $^3J_{CP}$ = 6.6 Hz), 49.8 (d, $^3J_{CP}$ = 7.5 Hz), 52.5 (dd, $^1J_{CP}$ = 150.7 Hz, $^3J_{CP}$ = 12.7 Hz), 52.6 (d, $^2J_{CP}$ = 7.4 Hz), 53.2 (d, $^2J_{CP}$ = 7.3 Hz), 125.0 (d, $^2J_{CP}$ = 9.9 Hz), 130.9 (d, $^2J_{CP}$ = 13.8 Hz). ^{31}P-NMR (162 MHz, $CDCl_3$) δ 30.27, 31.55. IR (ATR, cm^{-1}) ν_{max}: 1022, 1211, 1649, 3429. MS (ESI, pos): *m/z* (%) 248.2/249.2 (M-$[P(O)(OMe)_2]^-$, 100/15), 358.2/359.2 (M+H^+, 25/5). HRMS: *m/z* calcd for $C_{13}H_{29}NO_6P_2$+H^+ 358.1543, found 358.1534.

tetramethyl (1-(propylamino)hex-4-ene-1,3-diyl)(E)-bis(phosphonate)5b2 (diastereomer 2, E)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, t, J = 7.4 Hz), 1.36-1.48 (2H, m), 1.73 (3H, ddd, J = 6.7 Hz, $^5J_{HP}$ = 5.1 Hz, J = 1.6 Hz), 1.78-1.93 (3H, m), 2.47 (1H, dtd, J = 11.2

Hz, J = 6.9 Hz, $^{4}J_{HP}$ = 1.5 Hz), 2.80-2.88 (2H, m), 3.03-3.15 (1H, m), 3.74 (6H, d, $^{3}J_{HP}$ = 10.6 Hz), 3.77 (6H, d, $^{3}J_{HP}$ = 10.6 Hz), 5.21-5.30 (1H, m), 5.61-5.71 (1H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 11.7, 18.2 (d, $^{4}J_{CP}$ = 2.3 Hz), 23.8, 29.2 (dd, $^{2}J_{CP}$ = 7.9 Hz, $^{2}J_{CP}$ = 2.3 Hz), 37.1 (dd, $^{1}J_{CP}$ = 140.9 Hz, $^{3}J_{CP}$ = 14.1 Hz), 50.0, 51.4 (dd, $^{1}J_{CP}$ = 142.8 Hz, $^{3}J_{CP}$ = 16.0 Hz), 52.58 (d, $^{2}J_{CP}$ = 6.9 Hz), 52.60 (d, $^{2}J_{CP}$ = 6.9 Hz), 52.7 (d, $^{2}J_{CP}$ = 6.9 Hz), 53.1 (d, $^{2}J_{CP}$ = 6.9 Hz), 124.3 (d, $^{2}J_{CP}$ = 9.6 Hz), 131.9 (d, $^{3}J_{CP}$ = 14.0 Hz). ^{31}P-NMR (162 MHz, $CDCl_3$) δ 31.37 (d, $^{4}J_{PP}$ = 10.2 Hz), 32.62 (d, $^{4}J_{PP}$ = 10.2 Hz).). IR (ATR, cm^{-1}) v_{max}: 1022, 1211, 1454, 2957. MS (ESI, pos): *m/z* (%) 248.2/249.2 (M-[P(O)(OMe)$_2$]$^-$, 100/10), 358.2 (M+H$^+$, 20). HRMS: *m/z* calcd for $C_{13}H_{29}NO_6P_2$+H$^+$ 358.1543, found 358.1544.

tetramethyl (1-(propylamino)hex-3-ene-1,5-diyl)(E)-bis(phosphonate) 6b2 (2 diastereomers [d1 and d2], 1/1 mixture)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.91 (6H, t, d1+d2), 1.30 (6H, dd, $^{3}J_{HP}$ = 18.5 Hz, J = 7.2 Hz, d1+d2), 1.46 (4H, sext, J = 7.3 Hz, d1+d2), 2.30-2.42 (2H, m, d1+d2), 2.51-2.60 (2H, m, d1+d2), 2.62-2.76 (6H, m, d1+d2), 2.91 (1H, ddd, $^{2}J_{HP}$ = 12.7 Hz, J = 8.1 Hz, J = 4.6 Hz, d1), 2.92 (1H, ddd, $^{2}J_{HP}$ = 12.7 Hz, J = 8.1 Hz, J = 4.6 Hz, d2), 3.75 (12H, d, $^{3}J_{HP}$ = 10.6 Hz, d1+d2), 3.78 (6H, d, $^{3}J_{HP}$ = 10.6 Hz, d1+d2), 3.80 (6H, d, $^{3}J_{HP}$ = 10.6 Hz, d1+d2), 5.54-5.69 (4H, m, 4x d1+d2). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 11.7 (d1+d2), 13.86 (d, $^{2}J_{CP}$ = 6.0 Hz, d1 or d2), 13.94 (d, $^{2}J_{CP}$ = 6.0 Hz, d1 or d2), 23.3 (d1+d2), 32.9 (d1+d2), 35.04 (d, $^{1}J_{CP}$ = 139.5 Hz, d1 or d2), 35.05 (d, $^{1}J_{CP}$ = 139.5 Hz, d1 or d2), 50.5 (d, $^{3}J_{CP}$ = 7.8 Hz, d1+d2), 52.75 (d, $^{2}J_{CP}$ = 7.3 Hz, d1 or d2), 52.78 (d, $^{2}J_{CP}$ = 7.0 Hz, d1 or d2), 52.9 (d, $^{2}J_{CP}$ = 7.2 Hz, d1 or d2), 53.1 (d, $^{2}J_{CP}$ = 7.2 Hz, d1 or d2), 54.73 (d, $^{1}J_{CP}$ = 157.4 Hz, d1 or d2), 54.76 (d, $^{1}J_{CP}$ = 157.4 Hz, d1 or d2), 128.9 (dd, $^{3}J_{CP}$ = 12.3 Hz, $^{3}J_{CP}$ = 12.3 Hz, d1+d2), 129.6 (d, $^{2}J_{CP}$ = 9.6 Hz,

d1+d2). ^{31}P-NMR (162 MHz, $CDCl_3$) δ 29.38, 29.41, 32.60 (2x s). IR (ATR, cm^{-1}) ν_{max}: 1022, 1229, 1454, 2957. MS (ESI, pos): *m/z* (%) 248.2/249.2 (M-[P(O)(OMe)$_2$]$^-$, 100/15), 358.2 (M+H$^+$, 15). HRMS: *m/z* calcd for $C_{13}H_{29}NO_6P_2$+H$^+$ 358.1543, found 358.1539.

272 mg (1.98 mmol) of **3b3** was converted into **5b3** and **6b3** using 2 equiv of DMPTMS and 0.5 equiv of H_2SO_4. After work-up, 304 mg of crude product was obtained as diastereomers (0.85 mmol, 43% yield, yellow oil, ratio **5**/**6** = 6/4). The 1,6-1,2-adducts and 1,4-1,2-adducts were separated using preparative HPLC (reversed-phase C18-column, water/acetonitrile eluent). Three fractions were isolated for characterization.

tetramethyl (1-(isopropylamino)hex-4-ene-1,3-diyl)(E)-bis(phosphonate) 5b3 (1 diastereomer, 4/1 E/Z mixture, spectral data of the major isomer)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.99 (3H, d, J = 6.2 Hz), 1.02 (3H, d, J = 6.2 Hz), 1.63-1.77 (1H, m), 1.74 (3H, ddd, J = 6.7 Hz, $^5J_{HP}$ = 5.0 Hz, J = 1.5 Hz), 2.13-2.26 (1H, m), 2.93-3.10 (3H, m), 3.74 (6H, d, $^3J_{HP}$ = 10.7 Hz), 3.77 (3H, d, $^3J_{HP}$ = 11.0 Hz), 3.81 (3H, d, $^3J_{HP}$ = 10.3 Hz), 5.30-5.38 (1H, m), 5.66-5.74 (1H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 18.1 (d, $^4J_{CP}$ = 2.5 Hz), 22.7, 23.2, 30.2 (dd, $^2J_{CP}$ = 4.0 Hz, $^2J_{CP}$ = 4.0 Hz), 37.8 (dd, $^1J_{CP}$ = 138.8 Hz, $^3J_{CP}$ = 5.0 Hz), 46.3 (d, $^3J_{CP}$ = 9.6 Hz), 49.4 (dd, $^1J_{CP}$ = 153.5 Hz, $^3J_{CP}$ = 14.1 Hz), 52.64 (d, $^2J_{CP}$ = 7.2 Hz), 52.66 (d, $^2J_{CP}$ = 7.2 Hz), 53.2 (d, $^2J_{CP}$ = 7.2 Hz), 53.6 (d, $^2J_{CP}$ = 7.2 Hz), 124.9 (d, $^2J_{CP}$ = 9.9 Hz), 131.3 (d, $^3J_{CP}$ = 13.7 Hz). ^{31}P-NMR (162 MHz, $CDCl_3$) δ 30.34, 31.54. IR (ATR, cm^{-1}) ν_{max}: 1024, 1206, 1451, 2956. MS (ESI, pos): *m/z* (%) 248.2/249.2 (M-[P(O)(OMe)$_2$]$^-$, 100/10), 358.1/359.1 (M+H$^+$, 30/5). HRMS: *m/z* calcd for $C_{13}H_{29}NO_6P_2$+H$^+$ 358.1543, found 358.1538.

tetramethyl (1-(isopropylamino)hex-4-ene-1,3-diyl)(E)-bis(phosphonate) 5b3 (1 diastereomer, 9/1 E/Z mixture, spectral data of the major isomer)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, d, J = 6.0 Hz), 1.02 (3H, d, J = 6.2 Hz), 1.73 (ddd, J = 7.1 Hz, $^{5}J_{HP}$ = 5.0 Hz, J = 1.6 Hz), 1.73-1.82 (1H, m), 1.89-1.99 (1H, m), 2.91 (1H, ddd, $^{2}J_{HP}$ = 11.5 Hz, J = 11.5 Hz, J = 2.6 Hz), 3.09-3.17 (2H, m), 3.73 (3H, d, $^{3}J_{HP}$ = 10.6 Hz), 3.74 (3H, d, $^{3}J_{HP}$ = 10.5 Hz), 3.76 (3H, d, $^{3}J_{HP}$ = 10.6 Hz), 3.77 (3H, d, $^{3}J_{HP}$ = 10.4 Hz), 5.20-5.29 (1H, m), 5.63-5.73 (1H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 18.2 (d, $^{4}J_{CP}$ = 2.6 Hz), 22.3, 24.1, 29.9 (dd, $^{2}J_{CP}$ = 7.6 Hz, $^{2}J_{CP}$ = 2.4 Hz), 36.9 (dd, $^{1}J_{CP}$ = 140.2 Hz, $^{3}J_{CP}$ = 13.8 Hz), 46.5, 48.6 (dd, $^{1}J_{CP}$ = 142.9 Hz, $^{3}J_{CP}$ = 16.1 Hz), 52.6 (d, $^{2}J_{CP}$ = 7.4 Hz), 52.67 (d, $^{2}J_{CP}$ = 7.1 Hz), 52.69 (d, $^{2}J_{CP}$ = 7.9 Hz), 53.1 (d, $^{2}J_{CP}$ = 6.8 Hz), 124.4 (d, $^{2}J_{CP}$ = 10.2 Hz), 131.9 (d, $^{2}J_{CP}$ = 13.6 Hz). ^{31}P-NMR (162 MHz, $CDCl_3$) δ 31.38 (d, $^{4}J_{PP}$ = 11.6 Hz), 32.48 (d, $^{4}J_{PP}$ = 9.8 Hz). IR (ATR, cm^{-1}) ν_{max}: 1024, 1205, 1450, 2957. MS (ESI, pos): *m/z* (%) 248.2/249.2 (M-$[P(O)(OMe)_2]^-$, 100/15), 358.1 ($M+H^+$, 20). HRMS: *m/z* calcd for $C_{13}H_{29}NO_6P_2+H^+$ 358.1543, found 358.1541.

tetramethyl (1-(isopropylamino)hex-3-ene-1,5-diyl)(E)-bis(phosphonate) 6b3 (2 diastereomers [d1 and d2], 1/1 mixture)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.02 (12H, d, J = 6.2 Hz, d1+d2), 1.30 (6H, dd, $^{3}J_{HP}$ = 18.4 Hz, J = 7.2 Hz, d1+d2), 2.28-2.39 (2H, m, d1+d2), 2.50-2.61 (2H, m, d1+d2), 2.70 (2H, dqd, $^{2}J_{HP}$ = 22.2 Hz, J = 7.2 Hz, J = 7.2 Hz, d1+d2), 2.94-3.06 (4H, m d1+d2), 3.75 (12H, d, $^{3}J_{HP}$ = 10.6 Hz, d1+d2), 3.78 (6H, d, $^{3}J_{HP}$ = 10.6 Hz, d1+d2), 3.81 (6H, d, $^{3}J_{HP}$ = 10.6 Hz, d1+d2), 5.51-5.71 (4H, m, d1+d2). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 13.87 (d, $^{2}J_{CP}$ = 6.8 Hz, d1 or d2), 13.93 (d, $^{2}J_{CP}$ = 6.8 Hz, d1 or d2), 22.86 (d1 or d2), 22.88 (d1 or d2), 33.37 (d, $^{2}J_{CP}$ = 1.9 Hz,d1+d2), 35.0 (d, $^{1}J_{CP}$ = 139.8 Hz,

d1 or d2), 35.1 (d, $^{1}J_{CP}$ = 139.5 Hz, d1 or d2), 46.77 (d, $^{3}J_{CP}$ = 9.1 Hz, d1 or d2), 46.83 (d, $^{3}J_{CP}$ = 9.4 Hz, d1 or d2), 51.81 (dd, $^{1}J_{CP}$ = 159.2 Hz, $^{5}J_{CP}$ = 3.2 Hz, d1 or d2), 51.84 (dd, $^{1}J_{CP}$ = 159.3 Hz, $^{5}J_{CP}$ = 3.1 Hz, d1 or d2), 52.76 (d, $^{2}J_{CP}$ = 7.4 Hz, d1 or d2), 52.78 (d, $^{2}J_{CP}$ = 7.0 Hz, d1 or d2), 52.81 (d, $^{2}J_{CP}$ = 7.3 Hz, d1 or d2), 52.85 (d, $^{2}J_{CP}$ = 7.3 Hz, d1 or d2), 52.94 (d, $^{2}J_{CP}$ = 7.3 Hz, d1 or d2), 53.5 (d, $^{2}J_{CP}$ = 7.3 Hz, d1 or d2), 128.91 (dd, $^{3}J_{CP}$ = 14.0 Hz, $^{3}J_{CP}$ = 10.3 Hz, d1 or d2), 128.95 (dd, $^{3}J_{CP}$ = 14.0 Hz, $^{3}J_{CP}$ = 10.3 Hz, d1 or d2), 129.65 (d, $^{2}J_{CP}$ = 9.5 Hz, d1 or d2), 129.72 (d, $^{2}J_{CP}$ = 9.4 Hz, d1 or d2). ^{31}P-NMR (162 MHz, $CDCl_3$) δ 29.33, 29.37, 32.59, 32.66. IR (ATR, cm^{-1}) v_{max}: 1024, 1205, 1450, 2957. MS (ESI, pos): *m/z* (%) 248.2/249.2 (M-[P(O)(OMe)$_2$]$^-$, 100/12), 358.1 (M+H$^+$, 10). HRMS: *m/z* calcd for $C_{13}H_{29}NO_6P_2$+H$^+$ 358.1543, found 358.1537.

240 mg (1.59 mmol) of **3b4** was converted into **5b4** and **6b4** using 2 equiv of DMPTMS and 0.5 equiv of H_2SO_4. After work-up, 357 mg of crude product was obtained as diastereomers (0.96 mmol, 60% yield, yellow oil, ratio **5**/**6** = 6/4). The 1,6-1,2-adducts were separated using preparative HPLC (reversed-phase C18-column, water/acetonitrile eluent). Two fractions were isolated for characterization.

tetramethyl (1-(tert-butylamino)hex-3-ene-1,5-diyl)(E)-bis(phosphonate) 6b4 (1 diastereomer, E, 90% pure)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.08 (9H, s), 1.31 (3H, dd, $^{3}J_{HP}$ = 18.5 Hz, J = 7.2 Hz), 2.40-2.53 (2H, m), 2.72 (1H, dqd, $^{2}J_{HP}$ = 22.5 Hz, J = 7.3 Hz, J = 7.2 Hz), 3.11 (1H, ddd, $^{2}J_{HP}$ = 18.3 Hz, J = 5.5 Hz, J = 5.5 Hz), 3.75 (9H, d, $^{3}J_{HP}$ = 10.6 Hz), 3.83 (3H, d, $^{3}J_{HP}$ = 10.2 Hz), 5.52-5.59 (1H, m), 5.69-5.78 (1H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 13.9 (d, $^{2}J_{CP}$ = 5.9 Hz), 29.9, 35.0 (d, $^{1}J_{CP}$ = 139.7 Hz), 36.1 (dd, $^{2}J_{CP}$ = 4.3 Hz, J = 2.1 Hz), 49.1 (dd, $^{1}J_{CP}$ = 167.3 Hz, $^{5}J_{CP}$ = 3.6 Hz), 51.6 (d, $^{3}J_{CP}$ = 11.4 Hz), 52.5 (d,

$^{2}J_{CP}$ = 7.8 Hz), 52.8 (d, $^{2}J_{CP}$ = 7.1 Hz), 53.0 (d, $^{2}J_{CP}$ = 7.0 Hz), 54.2 (d, $^{2}J_{CP}$ = 7.4 Hz), 128.8 (dd, $^{3}J_{CP}$ = 13.7 Hz, $^{3}J_{CP}$ = 5.6 Hz), 130.1 (d, $^{2}J_{CP}$ = 9.6 Hz). ^{31}P-NMR (162 MHz, $CDCl_3$) δ 29.15, 32.66. IR (ATR, cm^{-1}) v_{max}: 1018, 1221, 1452, 2957. MS (ESI, pos): *m/z* (%) 262.3/263.3 (M-[P(O)(OMe)$_2$]$^-$, 100/15), 372.3 (M+H$^+$, 10). HRMS: *m/z* calcd for $C_{14}H_{31}NO_6P_2$+H$^+$ 372.1699, found 372.1693.

tetramethyl (1-(tert-butylamino)hex-3-ene-1,5-diyl)(E)-bis(phosphonate) 6b4 (1 diastereomer, E, 75% pure)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.09 (9H, s), 1.30 (3H, dd, $^{3}J_{HP}$ = 18.5 Hz, J = 7.2 Hz), 2.39-2.53 (2H, m), 2.72 (1H, dqd, $^{2}J_{HP}$ = 22.1 Hz, J = 7.4 Hz, J = 7.4 Hz), 3.12 (1H, ddd, $^{2}J_{HP}$ = 18.4 Hz, J = 5.4 Hz, J = 5.4 Hz), 3.74 (3H, d, $^{3}J_{HP}$ = 10.4 Hz), 3.75 (3H, d, $^{3}J_{HP}$ = 10.6 Hz), 3.76 (3H, d, $^{3}J_{HP}$ = 10.6 Hz), 3.82 (3H, d, $^{3}J_{HP}$ = 10.2 Hz), 5.47-5.54 (1H, m), 5.69-5.78 (1H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 13.9 (d, $^{2}J_{CP}$ = 5.9 Hz), 29.9, 35.1 (d, $^{1}J_{CP}$ = 139.2 Hz), 35.9 (dd, $^{2}J_{CP}$ = 4.3 Hz, J = 2.1 Hz), 49.1 (dd, $^{1}J_{CP}$ = 167.8 Hz, $^{5}J_{CP}$ = 3.6 Hz), 51.6 (d, $^{3}J_{CP}$ = 11.2 Hz), 52.5 (d, $^{2}J_{CP}$ = 7.6 Hz), 52.8 (d, $^{2}J_{CP}$ = 6.9 Hz), 52.8 (d, $^{2}J_{CP}$ = 7.1 Hz), 54.2 (d, $^{2}J_{CP}$ = 7.4 Hz), 129.0 (dd, $^{3}J_{CP}$ = 13.9 Hz, $^{3}J_{CP}$ = 5.8 Hz), 130.2 (d, $^{2}J_{CP}$ = 9.7 Hz). ^{31}P-NMR (162 MHz, $CDCl_3$) δ 29.16, 32.83. IR (ATR, cm^{-1}) v_{max}: 1018, 1222, 2957, 3431. MS (ESI, pos): *m/z* (%) 262.3/263.3 (M-[P(O)(OMe)$_2$]$^-$, 100/15), 372.3 (M+H$^+$, 15). HRMS: *m/z* calcd for $C_{14}H_{31}NO_6P_2$+H$^+$ 372.1699, found 372.1694.

150 mg (0.46 mmol) of **3c** was converted into **5c** using 2 equiv of DMPTMS and 0.5 equiv of H_2SO_4 at reflux temperature. After work-up 169 mg of crude product was obtained as 4 chromatographically unseparable diastereomers in a 3/3/1/1 ratio (0.39 mmol, 84% yield, yellow oil).

tetramethyl (1-((1R,5S)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)-3-(isopropylamino)propane-1,3-diyl)bis(phosphonate) 5c

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.75-0.79 (3H, m), 0.81-0.85 (2H, m), 0.86-0.93 (4H, m), 0.95-1.10 (2H, m), 1.15-1.17 (3H, m), 1.51-1.64 (1H, m), 1.88-2.06 (1H, m), 2.10-2.22 (3H, m), 2.27-2.36 (1H, m), 2.66-2.79 (1H, m), 2.86-3.10 (2H, m), 3.55-3.71 (13H, m), 5.32-5.41 (1H, m). ^{31}P-NMR (162 MHz, $CDCl_3$) δ 31.74 (d, $^{4}J_{PP}$ = 11.8 Hz), 31.49 (d, $^{4}J_{PP}$ = 11.8 Hz), 31.16, 31.00 (d, $^{4}J_{PP}$ = 13.8 Hz), 30.92 (d, $^{4}J_{PP}$ = 13.8 Hz), 30.66, 30.23, 30.05. IR (ATR, cm^{-1}) ν_{max}: 1026, 1242, 1458, 2951. MS (ESI, pos): *m/z* (%) 328.3/329.3 (M-[P(O)(OMe)$_2$]$^-$, 40/8) 438.3/439.3 (M+H$^+$, 100/25). HRMS: *m/z* calcd for $C_{19}H_{37}NO_6P_2$+H$^+$ 438.2169, found 438.2180.

Synthesis of α-aminophosphonates **7**:

In a flame-dried round-bottom flask equipped with a magnetic stirring bar *α,β,γ,δ*-diunsaturated imines **3** were dissolved in dry dichloromethane under a N_2-atmosphere. Next, an appropriate amount of DMPTMS was added using a syringe. H_2SO_4 was then added via a syringe in a dropwise fashion, after which the reaction mixture started to boil. The reaction progress was monitored using HPLC-MS and after complete consumption of the starting material, the reaction mixture was poured into 10 mL of a 2 M HCl-solution. Diethyl ether was added and the mixture was extracted thrice using diethyl ether. The resulting aqueous layer was then rendered alkaline to a pH of 14 using a 2 M NaOH solution. Next, the alkaline aqueous phase was extracted thrice using ethyl acetate (3x 10 mL). The combined ethyl acetate fractions were dried over $MgSO_4$, filtered and concentrated *in vacuo*, yielding the crude desired α-aminophosphonates. If necessary, they were purified using column chromatography (hexanes/EtOAc).

150 mg (0.61 mmol) of (1*E*,2*E*,4*E*)-*N*-benzyl-5-phenylpenta-2,4-dien-1-imine **3a1** was converted into dimethyl ((2*E*,4*E*)-1-(benzylamino)-5-phenylpenta-2,4-dien-1-yl)phosphonate **7a1** using 1 equiv DMPTMS and 0.5 equiv H_2SO_4. After work-up, 180 mg was obtained (0.50 mmol, 82% yield, yellow oil). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.95 (1H, br s), 3.66 (1H, dd, $^2J_{HP}$ = 19.9 Hz, J = 8.5 Hz), 3.73 (1H, d, J = 13.4 Hz), 3.79 (3H, d, $^3J_{HP}$ = 10.5 Hz), 3.82 (3H, d, $^3J_{HP}$ = 10.5 Hz), 3.96 (1H, d, J = 13.4 Hz), 5.77 (1H, ddd, J = 15.2 Hz, J = 8.5 Hz, $^3J_{HP}$ = 6.4 H), 6.47 (1H, ddd, J = 15.2 Hz, J = 10.6 Hz, $^4J_{HP}$ = 4.6 Hz), 6.60 (1H, dd, J = 15.7 Hz, J = 1.8 Hz), 6.85 (1H, dd, J = 15.7 Hz, J = 10.6 Hz), 7.23-7.43 (10H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 50.9 (d, $^3J_{CP}$ = 16.3 Hz), 53.1 (d, $^2J_{CP}$ = 6.8 Hz), 53.3 (d, $^2J_{CP}$ = 7.1 Hz), 56.8 (d, $^1J_{CP}$ = 156.3 Hz), 126.1 (2x CH_{ar}), 126.8, 127.3 (d, $^2J_{CP}$ = 7.7 Hz), 127.4, 127.5 (d, $^4J_{CP}$ = 5.2 Hz), 127.9 (2x CH_{ar}), 128.1 (2x CH_{ar}), 128.3 (2x CH_{ar}), 132.9 (d, $^5J_{CP}$ = 4.2 Hz), 134.7 (d, $^3J_{CP}$ = 14.0 Hz), 136.6 (d, $^6J_{CP}$ = 1.5 Hz), 138.9. ^{31}P-NMR (162 MHz, $CDCl_3$) δ 25.91. IR (ATR, cm^{-1}) ν_{max}: 1025, 1241, 1450, 2952. MS (ESI, pos): *m/z* (%) 358.2/359.2 ($M+H^+$, 100/22). HRMS: *m/z* calcd for $C_{20}H_{24}NO_3P+H^+$ 358.1567, found 358.1560.

100 mg (0.50 mmol) of (1*E*,2*E*,4*E*)-*N*-propyl-5-phenylpenta-2,4-dien-1-imine **3a2** was converted into dimethyl ((2*E*,4*E*)-5-phenyl-1-(propylamino)penta-2,4-dien-1-yl)phosphonate **7a2** using 5 equiv of DMPTMS and 2 equiv of H_2SO_4. After work-up, 129 mg was obtained (0.42 mmol, 83% yield, yellow oil). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, t, J = 7.4 Hz), 1.44-1.55 (2H, m), 2.51 (1H, dt, J = 11.3 Hz, J = 7.0 Hz), 2.69 (1H, dt, J = 11.3 Hz, J = 7.4 Hz), 3.63 (1H, dd, $^2J_{HP}$ = 19.6 Hz, J = 8.6 Hz), 3.79 (3H, d, $^3J_{HP}$ = 7.8 Hz), 3.82 (3H, d, $^3J_{HP}$ = 7.8 Hz), 5.72 (1H, ddd, J = 15.2 Hz, J = 8.6 Hz, $^3J_{HP}$ = 6.4 Hz), 6.45 (1H, ddd, J = 15.2 Hz, J = 10.6 Hz, $^4J_{HP}$ = 4.6 Hz), 6.57 (1H, dd, J = 15.7 Hz, J = 1.9 Hz), 6.81 (1H, dd, J = 15.7 Hz, J = 10.6 Hz), 7.23 (1H, dd, J = 7.3 Hz, J = 7.3 Hz), 7.32 (2H, dd, J = 7.3 Hz, J = 7.3 Hz), 7.40 (2H, d, J = 7.3 Hz).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 11.6, 23.0, 50.0 (d, $^3J_{CP}$ = 15.5 Hz), 53.3 (d, $^2J_{CP}$ = 7.2 Hz), 53.5 (d, $^2J_{CP}$ = 7.2 Hz), 58.6 (d, $^1J_{CP}$ = 155.6 Hz), 126.4 (2x CH_{ar}), 127.7, 127.8 (d, $^4J_{CP}$ = 4.3 Hz), 128.3 (d, $^2J_{CP}$ = 7.9 Hz), 128.6 (2x CH_{ar}), 133.0 (d, $^5J_{CP}$ = 4.3 Hz), 134.4 (d, $^3J_{CP}$ = 14.0 Hz), 136.9 (d, $^6J_{CP}$ = 1.9 Hz). ^{31}P-NMR (162 MHz, $CDCl_3$) δ 26.00. IR (ATR, cm^{-1}) ν_{max}: 1025, 1242, 1448, 2955. MS (ESI, pos): *m/z* (%) 200.1/201.0 (M-[P(O)$(OMe)_2$]$^-$, 100/15), 310.0/311.0 (M+H$^+$, 25/5). HRMS: *m/z* calcd for $C_{16}H_{24}NO_3P$+H$^+$ 310.1567, found 310.1562.

105 mg (0.53 mmol) of (1*E*,2*E*,4*E*)-*N*-isopropyl-5-phenylpenta-2,4-dien-1-imine **3a3** was converted into dimethyl ((2*E*,4*E*)-1-(isopropylamino)-5-phenylpenta-2,4-dien-1-yl)phosphonate **7a3** using 5 equiv of DMPTMS and 2 equiv of H_2SO_4. After work-up, 159 mg was obtained (0.51 mmol, 97% yield, yellow oil). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.01 (3H, d, *J* = 6.2 Hz), 1.09 (3H, d, *J* = 6.2 Hz), 2.92 (1H, sept, *J* = 6.2 Hz), 3.74 (1H, d, $^2J_{HP}$ = 21.6 Hz, *J* = 8.5 Hz), 3.79 (3H, d, $^3J_{HP}$ = 10.5 Hz), 3.83 (3H, d, $^3J_{HP}$ = 10.4 Hz), 5.71 (1H, ddd, *J* = 15.2 Hz, *J* = 8.5 Hz, $^3J_{HP}$ = 6.3 Hz), 6.43 (1H, ddd, *J* = 15.2 Hz, *J* = 10.5 Hz, $^4J_{HP}$ = 4.6 Hz), 6.56 (1H, dd, *J* = 15.7 Hz, *J* = 2.1 Hz), 6.80 (1H, dd, 15.7 Hz, *J* = 10.5 Hz), 7.21-7.40 (5H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.5, 23.8, 46.0 (d, $^3J_{CP}$ = 15.4 Hz), 53.3 (d, $^2J_{CP}$ = 7.1 Hz), 53.80 (d, $^2J_{CP}$ = 7.2 Hz), 55.9 (d, $^1J_{CP}$ = 157.2 Hz), 126.4 (2x CH_{ar}), 127.7, 127.8 (d, $^4J_{CP}$ = 4.3 Hz), 128.58 (2x CH_{ar}), 128.61 (d, $^2J_{CP}$ = 5.0 Hz), 133.0 (d, $^5J_{CP}$ = 4.3 Hz), 134.2 (d, $^3J_{CP}$ = 14.2 Hz), 136.9 (d, $^6J_{CP}$ = 1.5 Hz). ^{31}P-NMR (162 MHz, $CDCl_3$) δ 26.27. IR (ATR, cm^{-1}) ν_{max}: 1024, 1244, 1448, 2956. MS (ESI, pos): *m/z* (%) 200.0/201.0 (M-[P(O)$(OMe)_2$]$^-$, 100, 15) 310.0 (M+H$^+$, 8). HRMS: *m/z* calcd for $C_{16}H_{24}NO_3P$+H$^+$ 310.1567, found 310.1561.

102 mg (0.48 mmol) of (1*E*,2*E*,4*E*)-*N*-*t*-butyl-5-phenylpenta-2,4-dien-1-imine **3a4** was converted into dimethyl ((2*E*,4*E*)-1-(tert-butylamino)-5-phenylpenta-2,4-dien-1-yl)phosphonate **7a4** using 5 equiv of DMPTMS and 2 equiv H_2SO_4. After work-up, 133 mg was obtained (0.41 mmol, 86% yield, yellow oil). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.11 (9H, s), 3.76 (3H, d, $^3J_{HP}$ = 10.4 Hz), 3.80 (1H, dd, $^2J_{HP}$ = 24.8 Hz, *J* = 8.4 Hz), 3.84 (3H, d, $^3J_{HP}$ = 10.3 Hz), 5.81 (1H, ddd, *J* = 15.1 Hz, *J* = 7.5 Hz, $^3J_{HP}$ = 7.5 Hz), 6.44 (1H, ddd, *J* = 15.3 Hz, *J* = 10.5 Hz, $^4J_{HP}$ = 5.0 Hz), 6.54 (1H, dd, *J* = 15.6 Hz, *J* = 2.5 Hz), 6.79 (1H, dd, *J* = 15.6 Hz, *J* = 10.5 Hz), 7.22 (1H, dd, *J* = 7.3 Hz, *J* = 7.3 Hz), 7.31 (2H, dd, *J* = 7.3 Hz, *J* = 7.3 Hz), 7.39 (2H, d, *J* = 7.3 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 29.9, 52.1 (d, $^3J_{CP}$ = 14.5 Hz), 53.2 (d, $^2J_{CP}$ = 7.4 Hz), 53.5 (d, $^1J_{CP}$ = 158.5), 54.4 (d, $^2J_{CP}$ = 7.3 Hz), 126.3 (2x CH_{ar}), 127.6, 128.1 (d, $^4J_{CP}$ = 5.0 Hz), 128.6 (2x CH_{ar}), 131.9 (d, $^2J_{CP}$ = 6.2 Hz), 132.6 (d, $^5J_{CP}$ = 4.9 Hz), 132.7 (d, $^3J_{CP}$ = 13.7 Hz), 137.0 (d, $^6J_{CP}$ = 2.1 Hz). ^{31}P-NMR (162 MHz, $CDCl_3$) δ 26.24. IR (ATR, cm^{-1}) ν_{max}: 1022, 1053, 1240, 1447, 2953. MS (ESI, pos): *m/z* (%) 214.1/215.1 (M-[P(O)(OMe)$_2$]$^-$, 100/18) 324.0/325.0 (M+H$^+$, 35/5). HRMS: *m/z* calcd for $C_{17}H_{26}NO_3P$+H$^+$ 324.1723, found 324.1725.

175 mg (0.94 mmol) of **3b1** was converted into dimethyl ((2*E*,4*E*)-1-(benzylamino)hexa-2,4-dien-1-yl)phosphonate **7b1** using 1 equiv of DMPTMS and 0.5 equiv of H_2SO_4. After work-up, 242 mg was obtained as an E/Z mixture in a 86/14 ratio (0.82 mmol, 87% yield, yellow oil). Spectral data are reported only for the major isomer. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.76-1.79 (3H, m), 3.53 (1H, dd, $^2J_{HP}$ = 19.2 Hz, J = 8.5 Hz), 3.69 (1H, d, J = 13.4 Hz), 3.75 (3H, d, $^3J_{HP}$ = 10.5 Hz), 3.79 (3H, d, $^3J_{HP}$ = 10.5 Hz), 3.92 (1H, d, J = 13.4 Hz), 5.47 (1H, ddd, *J* = 15.0 Hz, *J* = 8.5 Hz, $^3J_{HP}$ = 6.1 Hz),5.74 (1H, dqd, J = 15.0 Hz, J = 7.0 Hz, J = 2.3 Hz), 6.08-6.14 (1H, m), 6.23 (1H, ddd, *J* = 15.0 Hz, *J* = 10.4 Hz, $^4J_{HP}$ = 4.4 Hz), 7.24-7.34 (5H, m). ^{13}C-NMR (100

MHz, $CDCl_3$) δ 18.1, 51.1 (d, $^3J_{CP}$ = 16.5 Hz), 53.4 (d, $^2J_{CP}$ = 7.2 Hz), 53.6 (d, $^2J_{CP}$ = 7.2 Hz), 57.0 (d, $^1J_{CP}$ = 156.7 Hz), 124.2 (d, $^2J_{CP}$ = 7.4 Hz), 127.1, 128.3 (2x CH_{ar}), 128.4 (2x CH_{ar}), 130.6 (d, $^5J_{CP}$ = 4.1 Hz), 130.7 (d, $^4J_{CP}$ = 3.8 Hz), 135.3 (d, $^3J_{CP}$ = 13.9 Hz), 139.3. ^{31}P-NMR (162 MHz, $CDCl_3$) δ 26.31. IR (ATR, cm^{-1}) v_{max}: 1024, 1241, 1454, 2953. MS (ESI, pos): *m/z* (%) 186.2/187.2 (M-[P(O)$(OMe)_2$]$^-$, 100/15). HRMS: *m/z* calcd for $C_{15}H_{22}NO_3P+H^+$ 296.1410, found 296.1404.

215 mg (1.56 mmol) of **3b2** was converted into dimethyl ((2*E*,4*E*)-1-(propylamino)hexa-2,4-dien-1-yl)phosphonate **7b2** using 1 equiv of DMPTMS and 0.5 equiv of H_2SO_4. After work-up, 273 mg was obtained as an E/Z mixture in a 85/15 ratio (1.11 mmol, 71% yield, yellow oil). Spectral data are reported only for the major isomer. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, t, J = 7.4 Hz), 1.43-1.53 (2H, m), 1.75-1.78 (3H, m), 2.46 (1H, dt, J = 11.3 Hz, J = 7.4 Hz), 2.65 (1H, dt, J = 11.3 Hz, J = 7.4 Hz), 3.52 (1H, dd, $^2J_{HP}$ = 19.2 Hz, J = 8.5 Hz), 3.77 (3H, d, $^3J_{HP}$ = 10.5 Hz), 3.79 (3H, d, $^3J_{HP}$ = 10.4 Hz), 5.44 (1H, ddd, *J* = 15.0 Hz, *J* = 8.5 Hz, $^3J_{HP}$ = 6.2 Hz), 5.73 (1H, dqd, J = 15.1 Hz, J = 6.6 Hz, J = 2.3 Hz), 6.06-6.12 (1H, m), 6.24 (1H, ddd, *J* = 15.1 Hz, *J* = 10.5 Hz, $^4J_{HP}$ = 4.5 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 11.5, 17.9, 22.8, 49.7 (d, $^3J_{CP}$ = 15.7 Hz), 53.2 (d, $^2J_{CP}$ = 7.2 Hz), 53.3 (d, $^2J_{CP}$ = 7.2 Hz), 58.3 (d, $^1J_{CP}$ = 156.1 Hz), 124.7 (d, $^2J_{CP}$ = 7.6 Hz), 130.2 (d, $^5J_{CP}$ = 3.9 Hz), 130.5 (d, $^4J_{CP}$ = 3.9 Hz), 134.5 (d, $^3J_{CP}$ = 14.1 Hz). ^{31}P-NMR (162 MHz, $CDCl_3$) δ 26.41. IR (ATR, cm^{-1}) v_{max}: 1024, 1223, 1452, 2957. MS (ESI, pos): *m/z* (%) 138.2/139.2 (M-[P(O)$(OMe)_2$]$^-$, 100/10), 248.2 (M+H$^+$, 100). HRMS: *m/z* calcd for $C_{11}H_{22}NO_3P+H^+$ 248.1410, found 248.1402.

165 mg (1.20 mmol) of (1*E*,2*E*,4*E*)-*N*-isopropylhexa-2,4-dien-1-imine **3b1** was converted into dimethyl ((2*E*,4*E*)-1-(isopropylamino)hexa-2,4-dien-1-yl)phosphonate **7b3** using 1 equiv of DMPTMS and 0.5 equiv of H_2SO_4. After work-up, 202 mg was obtained as an *E*/*Z* mixture in a 9/1 ratio (0.81 mmol, 68% yield, pale yellow oil). Spectral data are reported only for the major isomer. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.98 (3H, d, *J* = 6.2 Hz), 1.06 (3H, d, *J* = 6.2 Hz), 1.76 (3H, dd, *J* = 7.0 Hz, *J* = 1.7 Hz), 2.88 (1H, sept, *J* = 6.2 Hz), 3.64 (1H, dd, $^2J_{HP}$ = 21.2 Hz, *J* = 8.6 Hz), 3.76 (3H, d, $^3J_{HP}$ = 10.5 Hz), 3.80 (3H, d, $^3J_{HP}$ = 10.4 Hz), 5.43 (1H, ddd, *J* = 15.0 Hz, *J* = 8.6 Hz, $^3J_{HP}$ = 6.2 Hz), 5.72 (1H, dqd, *J* = 13.4 Hz, *J* = 7.0 Hz, *J* = 2.3 Hz), 6.08 (1H, m), 6.21 (1H, ddd, *J* = 15.0 Hz, *J* = 10.5 Hz, $^4J_{HP}$ = 4.5 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 18.1, 21.4, 23.8, 45.8 (d, $^3J_{CP}$ = 15.6 Hz), 53.3 (d, $^2J_{CP}$ = 7.2 Hz), 53.7 (d, $^2J_{CP}$ = 7.2 Hz), 55.8 (d, $^1J_{CP}$ = 157.7 Hz), 125.1 (d, $^2J_{CP}$ = 6.6 Hz), 130.4 (d, $^5J_{CP}$ = 4.1 Hz), 130.6 (d, $^4J_{CP}$ = 3.8 Hz), 134.4 (d, $^3J_{CP}$ = 14.3 Hz). ^{31}P-NMR (162 MHz, $CDCl_3$) δ 26.67. IR (ATR, cm^{-1}) ν_{max}: 1024, 1233, 1448, 2958. MS (ESI, pos): *m/z* (%) 138.1/139.1 (M-[P(O)(OMe)$_2$]$^-$, 100/10). HRMS: *m/z* calcd for $C_{11}H_{22}NO_3P+H^+$ 248.1410, found 248.1407.

56 mg (0.37 mmol) of **3b4** was converted into dimethyl ((2*E*,4*E*)-1-(tert-butylamino)hexa-2,4-dien-1-yl)phosphonate **7b4** using 5 equiv of DMPTMS and 2 equiv of H_2SO_4. After work-up and column chromatography, 42 mg was obtained as an E/Z mixture in a 85/15 ratio (0.16 mmol, 43% yield, yellow oil). Spectral data are reported only for the major isomer. R_f = 0.13 (EtOAc). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.08 (9H, s), 1.74-1.77 (3H, m), 3.71 (1H, dd, $^2J_{HP}$ = 24.3 Hz, J = 8.1 Hz), 3.74 (3H, d, $^3J_{HP}$ = 10.3 Hz), 3.82 (3H, d, $^3J_{HP}$ = 10.4 Hz), 5.53 (1H, ddd, *J* = 15.0 Hz, *J* = 7.5 Hz, $^3J_{HP}$ = 7.5 Hz), 5.69 (1H, dqd, J = 15.0 Hz, J = 6.7 Hz, J = 2.3 Hz), 6.03-6.09 (1H, m), 6.21 (1H, ddd, *J* = 15.2 Hz, *J* = 10.4 Hz, $^4J_{HP}$ = 5.0 Hz). ^{13}C-NMR (100 MHz,

$CDCl_3$) δ 18.1, 29.9, 52.1 (d, $^3J_{CP}$ = 14.8 Hz), 53.4 (d, $^1J_{CP}$ = 159.3 Hz), 53.2 (d, $^2J_{CP}$ = 7.4 Hz), 54.4 (d, $^2J_{CP}$ = 7.3 Hz), 128.4 (d, $^2J_{CP}$ = 5.7 Hz), 129.9 (d, $^5J_{CP}$ = 4.5 Hz), 130.8 (d, $^4J_{CP}$ = 4.5 Hz), 132.8 (d, $^3J_{CP}$ = 13.6 Hz). ^{31}P-NMR (162 MHz, $CDCl_3$) δ 26.58. IR (ATR, cm^{-1}) v_{max}: 1028, 1233, 1362, 2955. MS (ESI, pos): *m/z* (%)152.2/153.2 (M-[P(O)(OMe)$_2$]$^-$, 100/10), 263.2 (M+H$^+$, 5). HRMS: *m/z* calcd for $C_{12}H_{24}NO_3P+H^+$ 262.1567, found 262.1563.

103 mg of **3c** was converted into dimethyl ((*E*)-3-((1*R**,5*S**)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)-1-(isopropylamino)allyl)phosphonate **7c** using 5 equiv DMPTMS and 2 equiv H_2SO_4. After work-up and column chromatography, 127 mg of **7c** was obtained as diastereomers in a 55/45 ratio (0.39 mmol, 83% yield, yellow oil). Signals were assigned to the major (M) or minor (m) diastereomer. R_f = 0.14 (EtOAc). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.76 (3H, s, m), 0.77 (3H, s, M), 0.98 (3H, d, *J* = 6.1 Hz, m), 0.99 (3H, d, *J* = 6.1 Hz, M), 1.05 (3H, s, m), 1.06 (3H, s, M), 1.12-1.16 (2x 1H, m, M+m), 1.32 (2x 3H, s, M+m), 2.09-2.15 (2x 1H, m, M+m), 2.27-2.39 (2x 2H, m, M+m), 2.40-2.46 (2x 1H, m, M+m), 2.53-2.57 (2x 1H, m, M+m), 2.82-2.94 (2x 1H, m, M+m), 3.61-3.71 (2x 1H, m, M+m), 3.73 (3H, d, $^3J_{HP}$ = 10.1 Hz, M or m), 3.75 (3H, d, $^3J_{HP}$ = 10.2 Hz, M or m), 3.80 (2x 3H, d, $^3J_{HP}$ = 10.4 Hz, M+m), 5.39 (2x 1H, ddd, *J* = 15.4 Hz, *J* = 8.7 Hz, $^3J_{HP}$ = 6.5 Hz, M+m), 5.57 (2x 1H, br s, M+m), 6.24 (2x 1H, dd, *J* = 15.7 Hz, $^4J_{HP}$ = 4.2 Hz, M+m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 20.67, 20.70 (M+m), 21.5, 21.6 (M+m), 23.80, 23.82 (M+m), 26.22 (M+m), 31.2 (M+m), 31.9 (M+m), 37.7 (M+m), 40.9 (M+m), 41.1, 41.2 (M+m), 45.7, 45.8 (M+m), 53.4, 53.6 (2x d, $^2J_{CP}$ = 7.2 Hz, M+m), 53.7 (2x d, $^2J_{CP}$ = 7.2 Hz, M+m), 56.1 (d, $^1J_{CP}$ = 157.1 Hz, m), 56.2 (d, $^1J_{CP}$ = 157.3 Hz, M), 120.0, 120.2 (2x d, $^2J_{CP}$ = 6.0 Hz, M+m), 125.0, 125.1 (2x d, $^5J_{CP}$ = 4.3 Hz, M+m), 135.3, 135.4 (2x d, $^3J_{CP}$ = 14.3 Hz, M+m), 145.6 (d, $^4J_{CP}$ = 3.6 Hz, M+m). ^{31}P-NMR (162 MHz, $CDCl_3$) δ 26.88 (M), 26.74 (m). IR (ATR, cm^{-1})

ν_{max}: 1026, 1242, 1466, 2952. MS (ESI, pos): *m/z* (%) 218.1/219.1 (M-[P(O)(OMe)$_2$]$^-$, 100/18) 328.0/329.0 (M+H$^+$, 40/8). HRMS: *m/z* calcd for $C_{17}H_{30}NO_3P+H^+$ 328.2036, found 328.2036.

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Supporting Information. Cartesian coordinates of the computational part as well as copies of the ^{1}H, ^{31}P and ^{13}C NMR spectra.

References

[1] C. S. Demmer, N. Krogsgaard-Larsen, L. Bunch, *Chem. Rev.* **2011**, *111*, 7981-8006.

[2] I. Wauters, W. Debrouwer, C. V. Stevens, *Beilstein J. Org. Chem.* **2014**, *10*, 1064-1096.

[3] M. Tanaka, in *Hydrofunctionalization, Vol. 43* (Eds.: V. P. Ananikov, M. Tanaka), Springer Berlin Heidelberg, **2013**, pp. 167-201.

[4] J.-L. Montchamp, *Acc. Chem. Res.* **2014**, *47*, 77-87.

[5] C. Spilling, R. Malla, in *Phosphorus Chemistry II, Vol. 361* (Ed.: J.-L. Montchamp), Springer International Publishing, **2015**, pp. 83-136.

[6] D. Zhao, R. Wang, *Chem. Soc. Rev.* **2012**, *41*, 2095-2108.

[7] Ł. Albrecht, A. Albrecht, H. Krawczyk, K. A. Jørgensen, *Chem. Eur. J.* **2010**, *16*, 28-48.

[8] K. Moonen, E. Van Meenen, A. Verwee, C. V. Stevens, *Angew. Chem. Int. Ed.* **2005**, *44*, 7407-7411.

[9] D. Enders, A. Saint-Dizier, M.-I. Lannou, A. Lenzen, *Eur. J. Org. Chem.* **2006**, *2006*, 29-49.

[10] P. A. Badkar, N. P. Rath, C. D. Spilling, *Org. Lett.* **2007**, *9*, 3619-3622.

[11] M. Terada, T. Ikehara, H. Ube, *J. Am. Chem. Soc.* **2007**, *129*, 14112-14113.

[12] A. D. Sadow, I. Haller, L. Fadini, A. Togni, *J. Am. Chem. Soc.* **2004**, *126*, 14704-14705.

[13] A. D. Sadow, A. Togni, *J. Am. Chem. Soc.* **2005**, *127*, 17012-17024.

[14] M. S. Markoulides, A. C. Regan, *Tetrahedron Lett.* **2011**, *52*, 2954-2956.

[15] D. K. Wicht, I. V. Kourkine, B. M. Lew, J. M. Nthenge, D. S. Glueck, *J. Am. Chem. Soc.* **1997**, *119*, 5039-5040.

[16] W. Froestl, S. J. Mickel, G. von Sprecher, P. J. Diel, R. G. Hall, L. Maier, D. Strub, V. Melillo, P. A. Baumann, *J. Med. Chem.* **1995**, *38*, 3313-3331.

[17] M. Hill, W. Krause, M. Sicken, *WO2010051891 (A1)*, **2010**, CAN152:526010.

[18] G. Scheffel, S. Lachhein, *EP0388910 (A2)*, **1990**, CAN114:82127.

[19] Y. Yu, S. Yi, C. Zhu, W. Hu, B. Gao, Y. Chen, W. Wu, H. Jiang, *Org. Lett.* **2016**, *18*, 400-403.

[20] A. Silva, E. Silva, *Synthesis* **2012**, *44*, 3109-3128.

[21] M. Magrez-Chiquet, M. S. Morin, J. Wencel-Delord, S. Drissi Amraoui, O. Basle, A. Alexakis, C. Crevisy, M. Mauduit, *Chem. Eur. J.* **2013**, *19*, 13663-13667.

[22] M. Tissot, A. Alexakis, *Chem. Eur. J.* **2013**, *19*, 11352-11363.

[23] Y. Luo, I. D. Roy, A. G. Madec, H. W. Lam, *Angew. Chem. Int. Ed.* **2014**, *53*, 4186-4190.

[24] Z. Ma, F. Xie, H. Yu, Y. Zhang, X. Wu, W. Zhang, *Chem. Commun.* **2013**, *49*, 5292-5294.

[25] J. Lu, J. Ye, W. L. Duan, *Chem. Commun.* **2014**, *50*, 698-700.

[26] S. C. George, S. Thulasi, S. Anas, K. V. Radhakrishnan, Y. Yamamoto, *Org. Lett.* **2011**, *13*, 4984-4987.

[27] T. Nishimura, A. Noishiki, T. Hayashi, *Chem. Commun.* **2012**, *48*, 973-975.

[28] T. Sawano, A. Ashouri, T. Nishimura, T. Hayashi, *J. Am. Chem. Soc.* **2012**, *134*, 18936-18939.

[29] D. Uraguchi, K. Yoshioka, Y. Ueki, T. Ooi, *J. Am. Chem. Soc.* **2012**, *134*, 19370-19373.

[30] L. Dell'Amico, L. Albrecht, T. Naicker, P. H. Poulsen, K. A. Jorgensen, *J. Am. Chem. Soc.* **2013**, *135*, 8063-8070.

[31] M. Silvi, I. Chatterjee, Y. Liu, P. Melchiorre, *Angew. Chem. Int. Ed.* **2013**, *52*, 10780-10783.

[32] X. Tian, Y. Liu, P. Melchiorre, *Angew. Chem. Int. Ed.* **2012**, *51*, 6439-6442.

[33] Y. Hayashi, D. Okamura, S. Umemiya, T. Uchimaru, *ChemCatChem* **2012**, *4*, 959-962.

[34] M. J. Lear, Y. Hayashi, *ChemCatChem* **2013**, *5*, 3499-3501.

[35] A. G. Csaky, G. de la Herran, M. C. Murcia, *Chem. Soc. Rev.* **2010**, *39*, 4080-4102.

[36] E. M. P. Silva, A. M. S. Silva, J. A. S. Cavaleiro, *Synlett* **2011**, *2011*, 2740-2744.

[37] E. M. P. Silva, K. Grenda, I. N. Cardoso, A. M. S. Silva, *Synlett* **2013**, *24*, 2375-2382.

[38] E. Van Meenen, K. Moonen, A. Verwée, C. V. Stevens, *J. Org. Chem.* **2006**, *71*, 7903-7906.

[39] C. Stevens, E. Van Meenen, K. Masschelein, K. Moonen, A. De Blieck, J. Drabowicz, *Synlett* **2007**, *2007*, 2549-2552.

[40] A. De Blieck, K. G. Masschelein, F. Dhaene, E. Rozycka-Sokolowska, B. Marciniak, J. Drabowicz, C. V. Stevens, *Chem. Commun.* **2010**, *46*, 258-260.

[41] A. De Blieck, S. Catak, W. Debrouwer, J. Drabowicz, K. Hemelsoet, T. Verstraelen, M. Waroquier, V. Van Speybroeck, C. V. Stevens, *Eur. J. Org. Chem.* **2013**, *2013*, 1058-1067.

[42] F. E. A. V. Waes, W. Debrouwer, T. S. A. Heugebaert, C. V. Stevens, *Arkivoc* **2014**, *2014*, 386-427.

[43] E. Sagot, D. S. Pickering, X. Pu, M. Umberti, T. B. Stensbøl, B. Nielsen, M. Chapelet, J. Bolte, T. Gefflaut, L. Bunch, *J. Med. Chem.* **2008**, *51*, 4093-4103.

[44] J. S. Meisner, D. F. Sedbrook, M. Krikorian, J. Chen, A. Sattler, M. E. Carnes, C. B. Murray, M. Steigerwald, C. Nuckolls, *Chem. Sci.* **2012**, *3*, 1007.

[45] D. A. Evans, K. M. Hurst, J. M. Takacs, *J. Am. Chem. Soc.* **1978**, *100*, 3467-3477.

[46] M.-P. Teulade, P. Savignac, *Synthesis* **1987**, *1987*, 1037-1039.

[47] K. Afarinkia, C. W. Rees, J. I. G. Cadogan, *Tetrahedron* **1990**, *46*, 7175-7196.

[48] K. Afarinkia, J. I. G. Cadogan, C. W. Rees, *Synlett* **1992**, *1992*, 123-123.

[49] G. Keglevich, E. Balint, *Molecules* **2012**, *17*, 12821-12835.

[50] Y. Zhao, D. G. Truhlar, *Theor. Chem. Acc.* **2008**, *120*, 215-241.

[51] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, N. J. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev,

A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, Gaussian, Inc., Wallingford, CT, USA, **2009**.

[52] A. E. Reed, R. B. Weinstock, F. Weinhold, *J. Chem. Phys.* **1985**, *83*, 735-746.

[53] T. Verstraelen, V. Van Speybroeck, M. Waroquier, *J. Chem. Phys.* **2009**, *131*.

[54] S. Catak, M. D'hooghe, T. Verstraelen, K. Hemelsoet, A. Van Nieuwenhove, H. J. Ha, M. Waroquier, N. De Kimpe, V. Van Speybroeck, *J. Org. Chem.* **2010**, *75*, 4530-4541.

[55] T. L. Cottrell, *The strengths of chemical bonds*, Butterworths, **1958**.

[56] J. B. Lambert, R. J. Nienhuis, *J. Am. Chem. Soc.* **1980**, *102*, 6659-6665.