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Ring-closing metathesis and ring-closing metathesis–isomerisation approach to 1-phosphonylated 2-benzazocines

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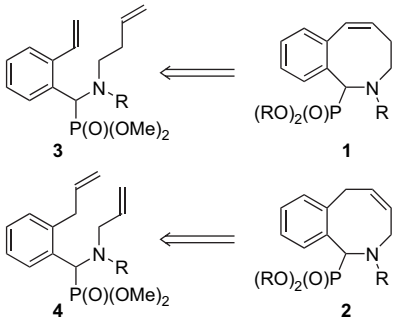
Abstract

An RCM strategy has been developed for the synthesis of phosphonylated benzazocines and their corresponding isomerised analogues. The aminophosphonate precursors were obtained by a one-pot three-component condensation in moderate yield.

1. Introduction

Benzo-fused heterocyclic ring systems have received a lot of attention over the years because of their ubiquitous appearance in natural products and modern pharmaceuticals.[1] Benzazocines are a class of benzo-fused nitrogen-containing eight-membered heterocyclic rings and include the 1-benzazocine and 2-benzazocine skeletons. The first is described in the literature for the use as inhibitors of phenylethanolamine *N*-methyltransferase.[2] One way of constructing this type of compounds is by cyclisation of a suitable precursor using ring-closing metathesis,[3–5] as demonstrated by us[6] and others.[7] The synthesis of benzazocines by RCM has received relatively little attention[8] until very recently van Otterlo and co-workers reported on the synthesis of these compounds using ring-closing metathesis as a key step.[9] Because related bioactive structures of these benzazocines frequently appear to contain other functionalities and other heteroatoms,[10] we became interested in constructing 1-phosphonylated benzazocines **1** and **2**, in our ongoing effort to synthesise aza-heterocyclic phosphonates with potential pharmaceutical and agrochemical applications,[11] which have to date never been described.[12] Retrosynthetic analysis shows that these new compounds **1** and **2** could be obtained by metathesis of suitable precursors **3** and **4**, respectively (Scheme 1).



Scheme 1.

2. Results

The key step in the synthesis of compound **3** was a one-pot three-component coupling mediated by $LiClO_4$ (Scheme 2).[13] Amine **7** was prepared in two straightforward steps starting from 4-bromobutene **5**. In the first step the halogenide was treated with NH_3 in methanol in a pressure tube and **6** was isolated by evaporation of the volatiles.[14] Subsequently, amine **7** was obtained by a simple reductive amination using suitable

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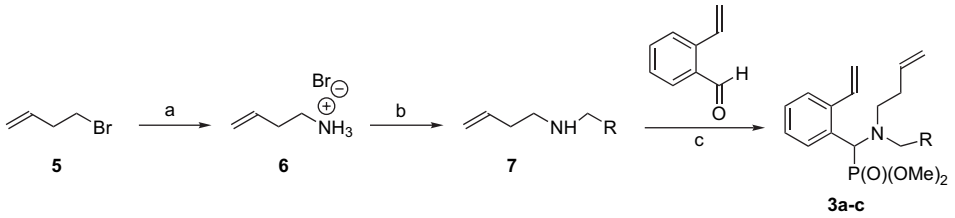


Scheme 2. Reagents and conditions: (a) 100 equiv NH_3 (7 N in MeOH), pressure vessel, 90 °C, 16 h, 95%. (b) (i) CH_2Cl_2, 2 equiv NEt_3, 2 equiv $MgSO_4$, 1 equiv aldehyde, 16 h; (ii) MeOH, 1.1 equiv $NaBH_4$, 4 h. (c) ether, 6 equiv $LiClO_4$, 0.5 equiv 2-vinylbenzaldehyde, 2 equiv $P(OMe)_3$ (10–80%).

aldehydes and $NaBH_4$. As a final step, a mixture of 2-vinylbenzaldehyde[6] and 2 equiv of amine **7** was treated with 6 equiv of $LiClO_4$ in ether. This resulted in the formation of an iminium ion, which is stabilised by $LiClO_4$. Subsequent addition of trimethyl phosphite to this mixture resulted in the formation of the desired compounds **3**. Although this reaction works fine, a difficult purification requiring column chromatography is necessary to remove the excess of amine resulting in a reduced yield of the aminophosphonates **3a–c**, since part of the product tends to stick to the column because of a partial decomposition (Table 1).

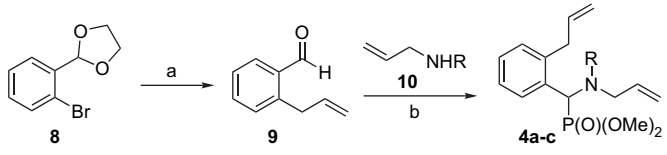
Compounds **4a–c** were also prepared using the $LiClO_4$ method (Table 2). Aldehyde **9** was obtained starting from commercially available acetal **8** (Scheme 3).[15] In a first step, this bromide **8** is treated with 1 equiv of BuLi at −78 °C for 1 h. Next, 1 equiv of $MgBr_2$ etherate is added and stirring is continued for 15 min at 0 °C. After this, 1 equiv of allyl bromide and 0.1 equiv of CuI are added. After extraction, the crude reaction product is dissolved in acetone and treated with a catalytic amount of *p*-TosOH. Aldehyde **9** was isolated in 50% yield.

Table 1
Synthesis of aminophosphonates **3a–c**

Compound	R	Yield (%)
3a	*p*-ClBn	63
3b	*o*-BrBn	80
3c	*p*-MeOBn	10

Table 2
Synthesis of aminophosphonates **4a–c**

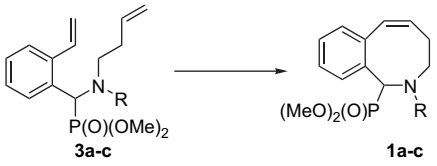
Compound	R	Yield (%)
4a	Bn	30
4b	*m*-FBn	24
4c	*m*-OMeBn	20



Scheme 3. Reagents and conditions: (a) (i) 1 equiv *n*-BuLi; (ii) 1 equiv $MgBr_2.Et_2O$; (iii) 1 equiv allyl bromide, 0.1 equiv CuI; (iv) acetone, cat. *p*-TosOH, rt, 16 h. (b) ether, 6 equiv $LiClO_4$, 2 equiv **10**, 2 equiv $P(OMe)_3$ (20–30%).

After the three-component coupling between **9**, **10** and trimethyl phosphite, compounds **4a–c** were isolated requiring column chromatography to obtain the pure product with a low yield due to a partial decomposition of the product.

With both starting materials in hands, the ring-closing metathesis could be evaluated. Treatment of derivatives **3** with 5% of the second generation Grubbs' catalyst[16] at reflux temperatures in a variety of solvents (toluene, benzene, EtOAc) resulted in a clean conversion into the expected compounds **1a–c** (Scheme 4). Little or no effect of the solvent choice on the yield was observed. The benzazocines **1a–c** were purified using column chromatography resulting again in a major drop of the yield to obtain the pure products (Table 3).

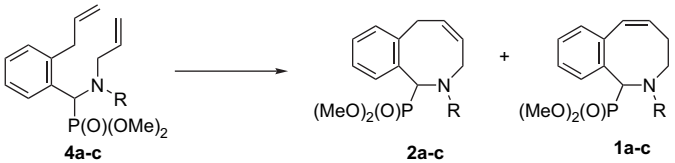


Scheme 4. Reagents and conditions: 5% Grubbs' II, Δ, benzene, 14 h.

When the same reaction conditions were applied on derivatives **4a–c**, a rather unexpected result was obtained. Next to the expected compounds **2**, the isomerised compounds **1** were also formed (Scheme 5). This observation can be explained by non-metathesis behaviour of Grubbs' carbenes.[17] Probably decomposition products of the catalyst, namely ruthenium hydrides,[18,19] isomerise the double bond towards the aromatic centre creating a more elaborate PCMO (polycyclic molecular orbital). When reflux was continued for a prolonged time (48 h), the entire product was converted to the isomerised form

Table 3
Synthesis of 1-phosphonylated benzazocines **1a–c**

Starting material	R	Yield of **1** (%)
3a	*p*-ClBn	**1a** (65)
3b	*o*-BrBn	**1b** (90)
3c	*p*-MeOBn	**1c** (60)



Scheme 5. Reagents and conditions: 5% Grubbs' II, Δ, benzene, 14 h.

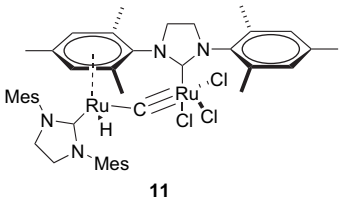


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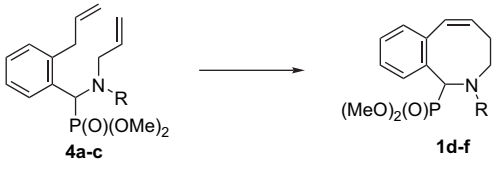
Figure 1.

1. This seems to indicate that this isomer is energetically favoured over isomer **2**. The fact that the double bond shifts towards the aromatic centre cannot solely account for this stabilisation since this type of isomerisation was not observed by van Otterlo and co-workers.[9] Therefore, we speculate that the extra stabilisation of form **1** also arises from the electron withdrawing nature of the nearby phosphonate group.

The explanation of the isomerisation is based on two key assumptions: (1) ruthenium hydrides are capable of converting compounds **2** to compounds **1** and (2) these ruthenium compounds are formed by decomposition of the second generation catalyst. When all ruthenium products were removed from a mixture containing **2** and **1** by chromatography, it proved impossible to convert **2** to **1** by refluxing in benzene or toluene. This indicates that indeed Ru-species are responsible for the isomerisation. When a catalytic amount of a commercially available RuH-catalyst ($RuClH(CO)(PPh_3)_3$),[20] which has already been used in RCM-isomerisation sequences,[21] was added to this refluxing mixture, a rapid conversion to **1** was observed. These two experiments confirm the first assumption. The decomposition of Grubbs' carbenes into RuH-species has been well documented and can be attributed to solvent,[22] temperature,[23]or other[24] effects. It has been shown that prolonged heating of the second generation catalyst results in decomposition towards **11** (Fig. 1) and that this compound is capable of isomerising double bonds.[21]

The most convenient way of fully converting derivatives **4** to derivatives **1** was to add 2% of the isomerisation catalyst $RuClH(CO)(PPh_3)_3$ to the metathesis mixture and to continue reflux for an additional 2 h. Compounds **1d–f** were isolated using column chromatography (Scheme 6 and Table 4).



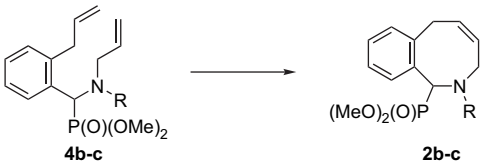
4a-c **1d-f**

Scheme 6. Reagents and conditions: 5% Grubbs' II, Δ, benzene, 14 h; then 2% $RuClH(CO)(PPh_3)_3$, Δ, benzene, 2 h.

Table 4
Synthesis of 1-phosphonylated benzazocines **1d–f**

Starting material	R	Yield of **1** (%)
4a	Bn	**1d** (74)
4b	*m*-FBn	**1e** (70)
4c	*m*-MeOBn	**1f** (72)

Fustero and co-workers recently also observed an unexpected sequence of RCM and isomerisation.[25] They observed that isomerisation only occurred using the second generation catalyst and not using the first generation catalyst.[26] Indeed, we also determined that when compounds **4b**,**c** were treated with 5% of the first generation catalyst, compounds **2b**,**c** were isolated by column chromatography without any trace of the isomerised compounds (Scheme 7 and Table 5). Next to the well known differences between the first and second generation catalyst,[27] this observation is important to select the right catalyst for any given reaction.



4b-c **2b-c**

Scheme 7. Reagents and conditions: 5% Grubbs' I, Δ, benzene, 16 h.

Table 5
Synthesis of 1-phosphonylated benzazocines **2b**,**c**

Starting material	R	Yield of **2** (%)
4b	*m*-FBn	**2b** (75)
4c	*m*-MeOBn	**2c** (75)

In conclusion, we have disclosed in this paper the synthesis of 2-phosphonylated benzazocines, which have to date not been described. The key step in this synthesis is the ring-closing metathesis of substituted nitrogen-containing precursors. An interesting difference in reactivity of the RCM-substrates towards the first and second generation Grubbs' catalysts was also observed. This allows the synthesis of both 1,2,3,4-tetrahydro-2-benzazocines and 1,2,3,6-tetrahydro-2-benzazocines starting from the same precursors.

3. Experimental

3.1. General

High-resolution ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded with a Jeol JNM-EX 300 NMR spectrometer. Peak assignments were obtained using DEPT, 2D-HETCOR, 2D-HSQC and 2D-COSY spectra. The compounds were diluted in deuterated solvent, which is indicated for each compound. Mass spectra were recorded on an Agilent 1100 Series VS (ES, 4000 V) mass spectrometer. The elemental analysis was performed with a Perkin–Elmer 2400 Elemental Analyser. IR-spectra were obtained from a Perkin–Elmer Spectrum One infrared spectrometer. For liquid samples the spectra were collected by preparing a thin film of compound between two sodium chloride plates. The crystalline compounds were mixed with potassium bromide and pressed until a transparent potassium bromide plate was obtained. Melting points of crystalline compounds were measured with a Büchi 540 apparatus and are uncorrected. The

purification of reaction mixtures was performed by an acid/base extraction and chromatography using a glass column with silica gel (Across, particle size: 0.035–0.070 mm, pore diameter: ca. 6 nm) or preparative TLC.

3.2. Synthesis of the hydrobromide salt of but-3-ene-1-amine (**6**)[14]

In a pressure tube, 125 mL of 7 M NH_3 in MeOH (875.0 mmol) was added to 4-bromo-1-butene **5** (1.18 g, 8.7 mmol). The reaction was stirred at 90 °C for 16 h. The solvent was removed in vacuo. The hydrobromide salt of but-3-ene-1-amine **6** was recovered as a white powder (1.60 g, yield: 95%).

3.3. Synthesis of secondary amines **7a–c**: general procedure

To a solution of alkylammonium bromide **6** (2.7 g, 17.8 mmol) in dry CH_2Cl_2 was added $MgSO_4$ (4.29 g, 35.5 mmol), Et_3N (3.6 g, 35.5 mmol) and an appropriate aldehyde (17.8 mmol). The reaction was stirred overnight at room temperature. After filtration of the solids and evaporation of the solvent in vacuo, the residue was dissolved in MeOH. The resulting solution was cooled in an ice bath and $NaBH_4$ (0.74 g, 19.6 mmol) was added carefully. After 4 h, the reaction was quenched with water and the solvent was removed in vacuo. The crude product was purified by an acid/base extraction and the amines **7a–c** were obtained as oils.

3.3.1. Synthesis of N-(4-chlorobenzyl)but-3-ene-1-amine (**7a**)

Yield: 75%.

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.60 (1H, s, NH), 2.23–2.31 (2H, m, CH_2CH_2N), 2.66 (2H, t, J=6.9 Hz, CH$_2$CH_2N), 3.76 (2H, s, C_{ar}CH_2N), 5.02–5.12 (2H, m, CH_2=CH), 5.71–5.85 (1H, m, CH$_2$=CH), 7.23–7.30 (4H, m, CH_{ar}). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 34.32 (*C*H$_2$CH$_2$N), 48.27 (CH$_2$*C*H$_2$N), 53.20 (C_{ar}*C*H$_2$N), 116.58 (*C*H$_2$=CH), 128.26 (2×CH_{ar}), 129.52 (2×CH_{ar}), 132.64 ($C_{ar,q}$), 136.44 (CH$_2$=*C*H), 138.98 ($C_{ar,q}$). IR (NaCl, cm^{-1}): 3312 (NH); 1640 (C=C). MS (ESI, pos mode) (%) *m*/*z*: 196/198 (M+H$^+$, 100).

3.3.2. Synthesis of N-(2-bromobenzyl)but-3-ene-1-amine (**7b**)

Yield: 87%.

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.79 (1H, br s, NH), 2.29 (2H, dtt, J=6.9 Hz, J=6.9 Hz, J=1.0 Hz, CH_2CH$_2$N), 2.70 (2H, t, J=6.9 Hz, CH$_2$CH_2N), 3.87 (2H, s, C_{ar}CH$_2$N), 5.03–5.14 (2H, m, CH_2=CH), 5.72–5.86 (1H, m, CH$_2$=CH), 7.12 (1H, ddd, J=7.7 Hz, J=7.7 Hz, J=1.4 Hz, CH_{ar}), 7.28 (1H, ddd, J=7.7 Hz, J=7.7 Hz, J=1.4 Hz, CH_{ar}), 7.38 (1H, dd, J=7.7 Hz, J=1.4 Hz, CH_{ar}), 7.54 (1H, dd, J=7.7 Hz, J=1.4 Hz, CH_{ar}). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 34.38 (*C*H$_2$CH$_2$N), 48.18 (CH$_2$*C*H$_2$N), 53.77 (C_{ar}*C*H$_2$N), 116.54 (*C*H$_2$=CH), 124.06 ($C_{ar,q}$), 127.51 (CH_{ar}), 128.67 (CH_{ar}), 130.37 (CH_{ar}), 132.87 (CH_{ar}), 136.43 (CH$_2$=*C*H), 139.28 ($C_{ar,q}$). IR (NaCl, cm^{-1}): 3321 (NH); 1644 (C=C). MS (ESI, pos mode) (%) *m*/*z*: 241/243 (M+H$^+$, 100).

3.3.3. Synthesis of N-(4-methoxybenzyl)but-3-ene-1-amine (**7c**)

Yield: 84%.

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.85 (1H, s, NH), 2.24–2.31 (2H, m, CH_2CH$_2$N), 2.69 (2H, t, J=6.8 Hz, CH$_2$CH_2N), 3.72 (2H, s, C_{ar}CH$_2$N), 3.79 (3H, s, CH_3O), 5.01–5.12 (2H, m, CH_2=CH), 5.71–5.84 (1H, m, CH$_2$=CH), 6.86 (2H, d, J=8.5 Hz, 2×CH_{ar}), 7.23 (2H, d, J=8.5 Hz, 2×CH_{ar}). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 34.24 (*C*H$_2$CH$_2$N), 48.20 (CH$_2$*C*H$_2$N), 53.29 (C_{ar}*C*H$_2$N), 55.35 (CH_3O), 113.86 (2×CH_{ar}), 116.47 (*C*H$_2$=CH), 129.45 (2×CH_{ar}), 132.38 ($C_{q,ar}$), 136.49 (CH$_2$=*C*H), 158.72 ($C_{q,ar}$). IR (NaCl, cm^{-1}): 3308 (NH); 1639 (C=C). MS (ESI, pos mode) (%) *m*/*z*: 192 (M+H$^+$, 100).

3.4. Synthesis of dimethyl [(but-3-enyl)benzylamino]-(2-vinylphenyl)methylphosphonates **3a–c**: general procedure

To a solution of $LiClO_4$ (4.5 g, 42.5 mmol) in dry diethyl ether was added vinylbenzaldehyde (1 g, 7.5 mmol).[6] Under a nitrogen atmosphere, the resulting reaction mixture was stirred at room temperature for 10 min. Subsequently, secondary amine **7** was added (15 mmol) and stirring was continued at room temperature. After 1 h, trimethyl phosphite (1.1 g, 9 mmol) was added to the solution and the reaction was allowed to stir for 30 min. The reaction was quenched with water and an extraction with diethyl ether was performed. The organic phase was dried ($MgSO_4$), the solids were removed by filtration and the solvent was evaporated in vacuo. Subsequently, the residue was treated with 1.5 M HCl and the resulting solution was extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$) and after filtration of the solids, the solvent was removed in vacuo. Dimethyl [(but-3-enyl)benzylamino)](2-vinylphenyl)methylphosphonates **3a–c** were obtained as viscous oils. In case of **3b** no further purification was needed. However, in case of **3a** and **3c** column chromatography was performed resulting in an important drop of the yield.

3.4.1. Synthesis of dimethyl [(but-3-enyl)(4-chlorobenzyl)-amino](2-vinylphenyl)methylphosphonate (**3a**)

Yield after column chromatography: 32%.

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.12–2.25 (2H, m, CH_2CH$_2$N), 2.50–2.59 (1H, m, CH$_2$CH_AH$_B$N), 2.88–2.98 (1H, m, CH$_2$CH$_A$$H_B$N), 3.41 (3H, d, $^3J_{HP}$=10.5 Hz, CH_3OP), 3.48 (1H, d, J=14.3 Hz, NCH_AH$_B$C$_{ar}$), 3.84 (3H, d, $^3J_{HP}$=10.5 Hz, CH_3OP), 4.13 (1H, dd, J=14.3 Hz, $^4J_{HP}$=2.0 Hz, NCH$_A$$H_BC_{ar}$), 4.60 (1H, d, $^2J_{HP}$=23.7 Hz, CHP), 4.91–4.98 (2H, m, CH_2=CHCH$_2$), 5.29 (1H, dd, J=11.0 Hz, J=1.4 Hz, CH_AH$_B$=CHC$_{ar}$), 5.60 (1H, dd, J=17.3 Hz, J=1.4 Hz, CH$_A$$H_B$=CHC$_{ar}$), 5.59–5.72 (1H, m, CH$_2$=C$HCH_2$), 6.88 (2H, dd, J=17.3 Hz, J=11.0 Hz, CH$_2$=CHC$_{ar}$), 7.19–7.36 (6H, m, CH_{ar}), 7.46–7.51 (1H, m, CH_{ar}), 7.86–7.91 (1H, m, CH_{ar}). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 32.30 (*C*H$_2$CH$_2$N), 50.87 (d, $^3J_{CP}$=6.9 Hz, CH$_2$*C*H$_2$N), 53.05 (d, $^2J_{CP}$=6.9 Hz, 2×CH_3OP), 54.96 (d, $^3J_{CP}$=6.9 Hz, NCH_2C$_{ar}$), 57.09 (d,

$^1J_{CP}$=158.0 Hz, CHP), 115.80 (*C*H_2=CHCH$_2$), 117.82 (*C*H_2=CHC$_{ar}$), 127.20 (CH$_{ar}$), 127.56 (CH$_{ar}$), 128.29 (2×CH$_{ar}$), 128.46 (CH$_{ar}$), 130.09 (2×CH$_{ar}$), 130.72 (d, J_{CP}=4.6 Hz, CH$_{ar}$), 131.15 (d, J_{CP}=4.6 Hz, C$_{q,ar}$), 132.52 (C$_{q,ar}$), 134.93 (CH$_2$=*C*HC$_{ar}$), 136.41 (CH$_2$=*C*HCH$_2$), 138.51 (C$_{q,ar}$), 139.29 (d, J_{CP}=11.5 Hz, C$_{q,ar}$). ^{31}P NMR (CDCl$_3$, 121 MHz) δ: 26.96. IR (NaCl, cm^{-1}): 1628 (C=C); 1246 (P=O); 1057, 1034 (P–O). MS (ESI, pos mode) (%) *m/z*: 420/422 (M+H$^+$, 100). Chromatography: PE/EtOAc (3/1) R_f=0.17. $C_{22}H_{27}ClNO_3P$: calcd C 62.93, H 6.48, N 3.34; found C 62.95, H 6.56, N 3.28.

3.4.2. Synthesis of dimethyl [(but-3-enyl)(2-bromobenzyl)-amino](2-vinylphenyl)methylphosphonate (**3b**)

Yield after acid extraction: 80%.

^{1}H NMR (CDCl$_3$, 300 MHz) δ: 2.08–2.30 (2H, m, CH_2CH$_2$N), 2.57–2.66 (1H, m, CH$_2$CH_AH$_B$N), 2.95–3.05 (1H, m, CH$_2$CH$_A$$H_B$N), 3.40 (3H, d, $^3J_{HP}$=10.5 Hz, CH$_3$OP), 3.44 (1H, d, J=15.7 Hz, NCH_AH$_B$C$_{ar}$), 3.85 (3H, d, $^3J_{HP}$=10.5 Hz, CH$_3$OP), 4.07 (1H, dd, J=15.7 Hz, $^4J_{HP}$=2.3 Hz, NCH$_A$$H_BC_{ar}$), 4.64 (1H, d, $^2J_{HP}$=24.0 Hz, CHP), 4.91–4.98 (2H, m, CH_2=CHCH$_2$), 5.24 (1H, dd, J=11.0 Hz, J=1.4 Hz, CH_AH$_B$=CHC$_{ar}$), 5.57 (1H, dd, J=17.3 Hz, J=1.4 Hz, CH$_A$$H_B$=CHC$_{ar}$), 5.62–5.76 (1H, m, CH$_2$=C*H*CH$_2$), 6.83 (2H, dd, J=17.3 Hz, J=11.0 Hz, CH$_2$=C*H*C$_{ar}$), 7.05–7.10 (1H, m, CH$_{ar}$), 7.26–7.33 (3H, m, CH$_{ar}$), 7.45–7.49 (2H, m, CH$_{ar}$), 7.66–7.69 (1H, m, CH$_{ar}$), 7.90–7.93 (1H, m, CH$_{ar}$). ^{13}C NMR (CDCl$_3$, 75 MHz) δ: 32.38 (*C*H$_2$CH$_2$N), 51.58 (d, $^3J_{CP}$=8.0 Hz, CH$_2$*C*H$_2$N), 53.02 (d, $^2J_{CP}$=6.9 Hz, CH$_3$OP), 53.19 (d, $^2J_{CP}$=6.9 Hz, CH$_3$OP), 55.23 (d, $^3J_{CP}$=8.0 Hz, NCH$_2$C$_{ar}$), 57.50 (d, $^1J_{CP}$=158.1 Hz, CHP), 115.86 (*C*H$_2$=CHCH$_2$), 118.07 (*C*H$_2$=CHC$_{ar}$), 123.86 (C$_{q,ar}$), 127.31 (CH$_{ar}$), 127.36 (CH$_{ar}$), 127.63 (CH$_{ar}$), 128.18 (CH$_{ar}$), 128.48 (CH$_{ar}$), 130.21 (CH$_{ar}$), 130.59 (d, J_{CP}=4.6 Hz, CH$_{ar}$), 131.07 (d, J_{CP}=4.6 Hz, C$_{q,ar}$), 132.51 (CH$_{ar}$), 134.69 (CH$_2$=*C*HC$_{ar}$), 136.49 (CH$_2$=*C*HCH$_2$), 138.89 (C$_{q,ar}$), 139.58 (d, J_{CP}=11.5 Hz, C$_{q,ar}$). ^{31}P NMR (CDCl$_3$, 121 MHz) δ: 27.09. IR (NaCl, cm^{-1}): 1639 (C=C); 1248 (P=O); 1057, 1027 (P–O). MS (ESI, pos mode) (%) *m/z*: 464/466 (M+H$^+$, 100).

3.4.3. Synthesis of dimethyl [(but-3-enyl)(4-methoxybenzyl)-amino](2-vinylphenyl)methylphosphonate (**3c**)

Yield after column chromatography: 10%.

^{1}H NMR (CDCl$_3$, 300 MHz) δ: 2.09–2.26 (2H, m, CH_2CH$_2$N), 2.52–2.61 (1H, m, CH$_2$CH_AH$_B$N), 2.93–3.04 (1H, m, CH$_2$CH$_A$$H_B$N), 3.41 (3H, d, $^3J_{HP}$=10.5 Hz, CH$_3$OP), 3.44 (1H, d, J=14.0 Hz, NCH_AH$_B$C$_{ar}$), 3.79 (3H, s, CH$_3$O), 3.85 (3H, d, $^3J_{HP}$=10.5 Hz, CH$_3$OP), 4.07 (1H, dd, J=14.0 Hz, $^4J_{HP}$=2.5 Hz, NCH$_A$$H_BC_{ar}$), 4.61 (1H, d, $^2J_{HP}$=23.7 Hz, CHP), 4.88–4.98 (2H, m, CH_2=CHCH$_2$), 5.26 (1H, dd, J=11.0 Hz, J=1.4 Hz, CH_AH$_B$=CHC$_{ar}$), 5.59 (1H, dd, J=17.3 Hz, J=1.4 Hz, CH$_A$$H_B$=CHC$_{ar}$), 5.59–5.73 (1H, m, CH$_2$=C*H*CH$_2$), 6.86 (1H, dd, J=17.3 Hz, J=11.0 Hz, CH$_2$=C*H*C$_{ar}$), 6.83 (2H, d, J=8.8 Hz, 2×CH$_{ar}$), 7.24 (2H, d, J=8.8 Hz, 2×CH$_{ar}$), 7.26–7.34 (2H, m, 2×CH$_{ar}$), 7.46–7.50 (1H, m, CH$_{ar}$), 7.88–7.92 (1H, m, CH$_{ar}$). ^{13}C NMR (CDCl$_3$, 75 MHz) δ: 32.45 (*C*H$_2$CH$_2$N), 50.53 (d, $^3J_{CP}$=8.1 Hz, CH$_2$*C*H$_2$N), 53.00 (d, $^2J_{CP}$=6.9 Hz, CH$_3$OP), 53.11 (d, $^2J_{CP}$=6.9 Hz, CH$_3$OP), 54.98 (d, $^3J_{CP}$=8.0 Hz, NCH$_2$C$_{ar}$), 55.31 (CH$_3$O), 57.11 (d, $^1J_{CP}$=156.9 Hz, CHP), 113.57 (2×CH$_{ar}$), 115.57 (*C*H$_2$=CHCH$_2$), 117.48 (*C*H$_2$=CHC$_{ar}$), 127.07 (CH$_{ar}$), 127.48 (CH$_{ar}$), 128.31 (2×CH$_{ar}$), 130.00 (CH$_{ar}$), 130.83 (d, J_{CP}=4.6 Hz, CH$_{ar}$), 131.44 (d, J_{CP}=4.6 Hz, C$_{q,ar}$), 131.77 (C$_{q,ar}$), 135.08 (CH$_2$=*C*HC$_{ar}$), 136.68 (CH$_2$=*C*HCH$_2$), 139.28 (d, J_{CP}=11.5 Hz, C$_{q,ar}$), 158.69 (C$_{q,ar}$). ^{31}P NMR (CDCl$_3$, 121 MHz) δ: 27.58. IR (NaCl, cm^{-1}): 1639 (C=C); 1247 (P=O); 1056, 1034 (P–O). MS (ESI, pos mode) (%) *m/z*: 416 (M+H$^+$, 100). Chromatography: PE/EtOAc (70/30) R_f=0.14. $C_{23}H_{30}NO_4P$: calcd C 66.49, H 7.28, N 3.37; found C 66.48, H 7.25, N 3.36.

3.5. Synthesis of secondary amines **10b**,**c**: general procedure

To a solution of allylamine (1.50 g, 26.0 mmol) in dry CH$_2$Cl$_2$ were added MgSO$_4$ (6.30 g, 52.0 mmol) and an appropriate aldehyde (26.0 mmol). The reaction was allowed to stir overnight at room temperature. After filtration of the solids and evaporation of the solvent in vacuo, MeOH was added to the residue. At 0 °C, NaBH$_4$ (1.10 g, 28.6 mmol) was added carefully. After 4 h of stirring, water was added to quench the reaction and the solvent was evaporated in vacuo. The crude product was purified by an acid/base extraction. The secondary amines **10b**,**c** were obtained as oils.

3.5.1. Synthesis of N-(3-fluorobenzyl)prop-2-ene-1-amine (**10b**)

Yield: 96%.

^{1}H NMR (CDCl$_3$, 300 MHz) δ: 1.76 (1H, br s, NH), 3.27 (2H, dt, J=6.1 Hz, J=1.4 Hz, CHCH_2N), 3.85 (2H, s, C$_{ar}$CH_2N), 5.12 (1H, ddt, J=10.5 Hz, J=1.7 Hz, J=1.4 Hz, CH_AH$_B$=CH), 5.20 (1H, ddt, J=17.1 Hz, J=1.7 Hz, J=1.4 Hz, CH$_A$$H_B$=CH), 5.93 (1H, ddt, J=17.1 Hz, J=10.5 Hz, J=6.1 Hz, C*H*=CH$_2$), 7.00–7.39 (4H, m, CH$_{ar}$). ^{13}C NMR (CDCl$_3$, 75 MHz) δ: 46.11 (d, J_{CF}=2.3 Hz, C$_{ar}$CH$_2$N), 51.26 (CHCH$_2$N), 115.43 (d, J_{CF}=21.9 Hz, CH$_{ar}$), 117.24 (*C*H$_2$=CH), 124.25 (d, J_{CF}=3.5 Hz, CH$_{ar}$), 126.02 (d, J_{CF}=15.0 Hz, C$_{q,ar}$), 129.14 (d, J_{CF}=8.1 Hz, CH$_{ar}$), 130.81 (d, J_{CF}=4.6 Hz, CH$_{ar}$), 135.57 (CH$_2$=*C*H), 161.31 (d, J_{CF}=245.8 Hz, C$_{q,ar}$). ^{19}F NMR (CDCl$_3$, 282 MHz) δ: −118.86 (m). IR (NaCl, cm^{-1}): 3314 (NH); 1643 (C=C). MS (ESI, pos mode) (%) *m/z*: 166 (M+H$^+$, 100).

3.5.2. Synthesis of N-(3-methoxybenzyl)prop-2-ene-1-amine (**10c**)

Yield: 95%.

^{1}H NMR (CDCl$_3$, 300 MHz) δ: 1.44 (1H, br s, NH), 3.28 (2H, dt, J=6.1 Hz, J=1.4 Hz, CHCH_2N), 3.78 (2H, s, C$_{ar}$CH$_2$N), 3.81 (3H, s, CH$_3$O), 5.12 (1H, ddt, J=10.2 Hz, J=1.7 Hz, J=1.4 Hz, CH_AH$_B$=CH), 5.20 (1H, ddt, J=17.1 Hz, J=1.7 Hz, J=1.4 Hz, CH$_A$$H_B$=CH), 5.93 (1H, ddt, J=17.1 Hz, J=10.2 Hz, J=6.1 Hz, C*H*=CH$_2$), 6.78–6.82 (1H, m, CH$_{ar}$), 6.89–6.92 (2H, m, CH$_{ar}$), 7.21–7.27 (1H, m, CH$_{ar}$). ^{13}C NMR (CDCl$_3$, 75 MHz) δ: 49.52 (C$_{ar}$CH$_2$N), 52.30 (CHCH$_2$N), 54.98 (CH$_3$O), 112.03 (CH$_{ar}$),

114.83 (CH_{ar}), 117.32 (CH_2=CH), 126.51 ($C_{q,ar}$), 128.09 (CH_{ar}), 129.76 (CH_{ar}), 135.03 (CH_2=CH), 160.07 ($C_{q,ar}$). IR (NaCl, cm^{-1}): 3314 (NH); 1643 (C=C). MS (ESI, pos mode) (%) *m/z*: 178 ($M+H^+$, 100).

*3.6. Synthesis of dimethyl (allylbenzylamino)(2-allylphenyl)methylphosphonates **4a–c**: general procedure*

The synthesis of dimethyl (allylbenzylamino)(2-allylphenyl)methylphosphonates **4a–c** is analogous to the synthesis of dimethyl [(but-3-enyl)benzylamino](2-vinylphenyl)methylphosphonates **3a–c**. However, allylbenzaldehyde **9** was used instead of vinylbenzaldehyde **8** and secondary amines **10** were used instead of secondary amines **7**.

*3.6.1. Synthesis of dimethyl (allylbenzylamino)(2-allylphenyl)methylphosphonate (**4a**)*

Yield after column chromatography: 30%.

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.11 (1H, dd, J=14.6 Hz, J=6.9 Hz, NCH_AH$_B$CH), 3.21–3.40 (2H, m, $C_{ar}CH_2$CH), 3.40 (3H, d, $^3J_{HP}$=10.5 Hz, CH_3OP), 3.59 (1H, d, J=14.3 Hz, NCH_AH$_B$C$_{ar}$), 3.61–3.71 (1H, m, NCH$_A$$H_B$CH), 3.85 (3H, d, $^3J_{HP}$=10.5 Hz, CH_3OP), 4.15 (1H, dd, J=14.3 Hz, $^4J_{HP}$=2.8 Hz, NCH$_A$$H_BC_{ar}$), 4.56 (1H, d, $^2J_{HP}$=22.8 Hz, CHP), 4.85 (1H, ddt, J=17.1 Hz, J=1.7 Hz, J=1.7 Hz, CH_AH$_B$=CHCH$_2$C$_{ar}$), 5.00 (1H, ddt, J=10.2 Hz, J=1.7 Hz, J=1.7 Hz, CH$_A$$H_B$=CHCH$_2C_{ar}$), 5.11–5.24 (2H, m, C$H_2$=CHCH$_2$N), 5.74–5.91 (2H, m, 2×CH=CH$_2$), 7.19–7.34 (7H, m, CH_{ar}), 7.93–7.96 (1H, m, CH_{ar}). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 37.10 ($C_{ar}CH_2$CH), 52.90 (d, $^2J_{CP}$=6.9 Hz, CH_3OP), 53.04 (d, $^2J_{CP}$=6.9 Hz, CH_3OP), 54.00 (d, $^3J_{CP}$=6.9 Hz, NCH_2CH), 54.90 (d, $^3J_{CP}$=7.0 Hz, NCH_2C_{ar}), 56.64 (d, $^1J_{CP}$=154.6 Hz, CHP), 116.07 (CH_2=CHCH$_2$C$_{ar}$), 117.65 (CH_2=CHCH$_2$N), 126.15 (CH_{ar}), 126.94 (CH_{ar}), 128.27 (2×CH_{ar}), 128.32 (CH_{ar}), 128.67 (2×CH_{ar}), 130.29 (CH_{ar}), 131.15 (d, J_{CP}=4.6 Hz, CH_{ar}), 132.23 (d, J_{CP}=4.6 Hz, $C_{q,ar}$), 136.18 (CH=CH$_2$), 136.96 (CH=CH$_2$), 139.93 ($C_{q,ar}$), 140.07 (d, J_{CP}=11.6 Hz, $C_{q,ar}$). ^{31}P NMR ($CDCl_3$, 121 MHz) δ: 27.83. IR (NaCl, cm^{-1}): 1638 (C=C); 1247 (P=O); 1057, 1030 (P–O). MS (ESI, pos mode) (%) *m/z*: 386 ($M+H^+$, 100). Chromatography: PE/EtOAc (7/3) R_f=0.25. $C_{22}H_{28}NO_3P$: calcd C 68.55, H 7.32, N 3.63; found C 68.53, H 7.41, N 3.64.

*3.6.2. Synthesis of dimethyl [allyl(3-fluorobenzyl)amino]-(2-allylphenyl)methylphosphonate (**4b**)*

Yield after column chromatography: 24%.

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.13 (1H, dd, J=14.6 Hz, J=6.9 Hz, NCH_AH$_B$CH), 3.23–3.39 (2H, m, $C_{ar}CH_2$CH), 3.40 (3H, d, $^3J_{HP}$=10.5 Hz, CH_3OP), 3.68–3.72 (1H, m, NCH$_A$$H_B$CH), 3.75 (1H, d, J=14.3 Hz, NCH_AH$_B$C$_{ar}$), 3.86 (3H, d, $^3J_{HP}$=10.5 Hz, CH_3OP), 4.12 (1H, dd, J=14.3 Hz, J_{HP}=1.8 Hz, NCH$_A$$H_BC_{ar}$), 4.55 (1H, d, $^2J_{HP}$=23.1 Hz, CHP), 4.85 (1H, ddt, J=17.1 Hz, J=1.7 Hz, J=1.4 Hz, CH_AH$_B$=CHCH$_2$C$_{ar}$), 5.00 (1H, ddt, J=10.2 Hz, J=1.7 Hz, J=1.4 Hz, C$H_A$$H_B$=CHCH$_2C_{ar}$), 5.10–5.24 (2H, m, C$H_2$=CHCH$_2$N), 5.75–5.88 (2H, m, 2×CH=CH$_2$), 6.94–7.00 (1H, m, CH_{ar}), 7.07–7.14 (1H, m, CH_{ar}), 7.16–7.41 (4H, m, CH_{ar}), 7.50–7.63 (1H, m, CH_{ar}), 7.93–8.02 (1H, m, CH_{ar}). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 37.08 ($C_{ar}CH_2$CH), 47.60 (dd, $^3J_{CP}$=7.0 Hz, J_{CF}=2.3 Hz, NCH_2C_{ar}), 53.01 (d, $^2J_{CP}$=6.9 Hz, CH_3OP), 53.14 (d, $^2J_{CP}$=6.9 Hz, CH_3OP), 54.30 (d, $^3J_{CP}$=6.9 Hz, NCH_2CH), 56.76 (d, $^1J_{CP}$=154.6 Hz, CHP), 115.12 (d, J_{CF}=21.9 Hz, CH_{ar}), 116.11 (CH_2=CHCH$_2$C$_{ar}$), 117.71 (CH_2=CHCH$_2$N), 124.05 (d, J_{CF}=3.5 Hz, CH_{ar}), 126.22 (CH_{ar}), 126.79 (d, J_{CF}=15.0 Hz, $C_{q,ar}$), 128.36 (d, J_{CF}=8.1 Hz, CH_{ar}), 128.41 (CH_{ar}), 130.34 (CH_{ar}), 130.57 (d, J_{CF}=4.6 Hz, CH_{ar}), 131.12 (d, J_{CP}=4.6 Hz, CH_{ar}), 131.87 (d, J_{CP}=4.6 Hz, $C_{q,ar}$), 135.99 (CH=CH$_2$), 136.90 (CH=CH$_2$), 140.11 (d, J_{CP}=11.6 Hz, $C_{q,ar}$), 159.20 (d, J_{CF}=162.1 Hz, $C_{q,ar}$). ^{31}P NMR ($CDCl_3$, 121 MHz) δ: 27.59. ^{19}F NMR ($CDCl_3$, 282 MHz) δ: −119.84 (m). IR (NaCl, cm^{-1}): 1638 (C=C); 1244 (P=O); 1057, 1032 (P–O). MS (ESI, pos mode) (%) *m/z*: 404 ($M+H^+$, 100). Chromatography: PE/EtOAc (3/1) R_f=0.10. $C_{22}H_{27}FNO_3P$: calcd C 65.50, H 6.75, N 3.47; found C 65.54, H 6.81, N 3.46.

*3.6.3. Synthesis of dimethyl [allyl(3-methoxybenzyl)amino]-(2-allylphenyl)methylphosphonate (**4c**)*

Yield after column chromatography: 20%.

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.11 (1H, dd, J=14.9 Hz, J=6.9 Hz, NCH_AH$_B$CH), 3.21–3.47 (2H, m, $C_{ar}CH_2$CH), 3.41 (3H, d, $^3J_{HP}$=10.5 Hz, CH_3OP), 3.56 (1H, d, J=14.3 Hz, NCH_AH$_B$C$_{ar}$), 3.65–3.75 (1H, m, NCH$_A$$H_B$CH), 3.77 (3H, s, CH_3O), 3.87 (3H, d, $^3J_{HP}$=10.5 Hz, CH_3OP), 4.13 (1H, dd, J=14.3 Hz, $^4J_{HP}$=2.8 Hz, NCH$_A$$H_BC_{ar}$), 4.57 (1H, d, $^2J_{HP}$=23.1 Hz, CHP), 4.86 (1H, ddt, J=17.1 Hz, J=1.7 Hz, J=1.4 Hz, CH_AH$_B$=CHCH$_2$C$_{ar}$), 5.00 (1H, ddt, J=17.1 Hz, J=1.7 Hz, J=1.4 Hz, C$H_A$$H_B$=CHCH$_2C_{ar}$), 5.12–5.16 (1H, m, C$H_AH_B$=CHCH$_2$N), 5.18–5.25 (1H, m, CH$_A$$H_B$=CHCH$_2$N), 5.76–5.91 (2H, m, 2×CH=CH$_2$), 6.74–7.00 (3H, m, CH_{ar}), 7.16–7.28 (4H, m, CH_{ar}), 7.92–8.02 (1H, m, CH_{ar}). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 37.13 ($C_{ar}CH_2$CH), 52.94 (d, $^2J_{CP}$=6.9 Hz, CH_3OP), 53.07 (d, $^2J_{CP}$=6.9 Hz, CH_3OP), 54.10 (d, $^3J_{CP}$=6.9 Hz, NCH_2CH), 54.79 (d, $^3J_{CP}$=6.9 Hz, NCH_2C_{ar}), 55.19 (CH_3O), 60.17 (d, $^1J_{CP}$=161.5 Hz, CHP), 112.69 (CH_{ar}), 113.70 (CH_{ar}), 116.09 (CH_2=CHCH$_2$C$_{ar}$), 117.70 (CH_2=CHCH$_2$N), 120.90 (CH_{ar}), 126.17 (CH_{ar}), 128.35 (CH_{ar}), 129.21 (CH_{ar}), 130.29 (CH_{ar}), 131.16 (d, J=4.6 Hz, CH_{ar}), 132.08 (d, J=4.6 Hz, $C_{q,ar}$), 136.19 (CH=CH$_2$), 136.96 (CH=CH$_2$), 140.12 (d, J=12.7 Hz, $C_{q,ar}$), 141.70 ($C_{q,ar}$), 159.74 ($C_{q,ar}$). ^{31}P NMR ($CDCl_3$, 121 MHz) δ: 27.82. IR (NaCl, cm^{-1}): 1638 (C=C); 1247 (P=O); 1051, 1035 (P–O). MS (ESI, pos mode) (%) *m/z*: 416 ($M+H^+$, 100). Chromatography: PE/EtOAc (3/1) R_f=0.04. $C_{23}H_{30}NO_4P$: calcd C 66.49, H 7.28, N 3.37; found C 66.59, H 7.32, N 3.34.

*3.7. Synthesis of dimethyl 2-(benzyl)-1,2,3,4-tetrahydro-2-benzazocin-1-ylphosphonates **1a–c**: general procedure*

In a flask of 10 mL, aminophosphonate **3** (0.36 mmol) was refluxed in 7 mL of benzene. To this solution, the second generation Grubbs' catalyst (0.02 mmol) was added. After

refluxing overnight, benzene was evaporated in vacuo. The crude product was purified by chromatography.

*3.7.1. Synthesis of dimethyl 2-(4-chlorobenzyl)-1,2,3,4-tetrahydro-2-benzazocin-1-ylphosphonate (**1a**)*

Yield after chromatography: 65% (viscous oil).

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.96–2.04 (2H, m, CH_2CH$_2$N), 2.38–2.46 (1H, m, CH$_2$CH_AH$_B$N), 2.71–2.77 (1H, m, CH$_2$CH$_A$$H_B$N), 2.89 (1H, dd, J=13.5 Hz, $^4J_{HP}$=1.4 Hz, NCH_AH$_B$C$_{ar}$), 3.56 (3H, d, $^3J_{HP}$=10.5 Hz, CH$_3$OP), 3.93 (3H, d, $^3J_{HP}$=10.5 Hz, CH$_3$OP), 4.48 (1H, d, $^2J_{HP}$=26.4 Hz, CHP), 4.59 (1H, d, J=13.5 Hz, NCH_AH$_B$C$_{ar}$), 6.05 (1H, dt, J=11.3 Hz, J=8.0 Hz, CH=CHCH$_2$), 6.69 (1H, d, J=11.2 Hz, CH=CHCH$_2$), 7.23–7.37 (7H, m, CH$_{ar}$), 8.04–8.07 (1H, m, CH$_{ar}$). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 23.07 (CH_2CH$_2$N), 46.31 (d, $^3J_{CP}$=15.0 Hz, CH$_2$CH$_2$N), 51.60 (NCH$_2$C$_{ar}$), 52.55 (d, $^2J_{CP}$=6.9 Hz, CH$_3$OP), 54.42 (d, $^2J_{CP}$=6.9 Hz, CH$_3$OP), 59.64 (d, $^1J_{CP}$=171.9 Hz, CHP), 127.03 (CH$_{ar}$), 127.73 (CH$_{ar}$), 128.36 (2×CH$_{ar}$), 128.70 (CH$_{ar}$), 129.59 (CH=CHCH$_2$), 130.11 (d, J_{CP}=9.4 Hz, C$_{q,ar}$), 130.67 (d, J_{CP}=4.6 Hz, CH$_{ar}$), 130.78 (2×CH$_{ar}$), 132.61 (C$_{q,ar}$), 133.30 (CH=CHCH$_2$), 137.70 (d, J_{CP}=16.2 Hz, C$_{q,ar}$), 138.27 (C$_{q,ar}$). ^{31}P NMR ($CDCl_3$, 121 MHz) δ: 24.75. IR (NaCl, cm^{-1}): 1619 (C=C); 1248 (P=O); 1061, 1036 (P–O). MS (ESI, pos mode) (%) m/z: 392/394 (M+H$^+$, 100). Chromatography: PE/EtOAc (3/1) R_f=0.08. $C_{20}H_{23}ClNO_3P$: calcd C 61.31, H 5.92, N 3.57; found C 61.27, H 5.87, N 3.54.

*3.7.2. Dimethyl 2-(2-bromobenzyl)-1,2,3,4-tetrahydro-2-benzazocin-1-ylphosphonate (**1b**)*

Crude yield: 99% (viscous oil).

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.05–2.11 (2H, m, CH_2CH$_2$N), 2.43–2.51 (1H, m, CH$_2$CH_AH$_B$N), 2.75–2.82 (1H, m, CH$_2$CH$_A$$H_B$N), 3.38 (1H, dd, J=14.1 Hz, $^4J_{HP}$=1.1 Hz, NCH_AH$_B$C$_{ar}$), 3.54 (3H, d, $^3J_{HP}$=10.5 Hz, CH$_3$OP), 3.90 (3H, d, $^3J_{HP}$=10.5 Hz, CH$_3$OP), 4.46 (1H, d, $^2J_{HP}$=26.7 Hz, CHP), 4.48 (1H, d, J=14.1 Hz, NCH$_A$$H_BC_{ar}$), 6.08 (1H, dt, J=11.0 Hz, J=8.0 Hz, CH=CHCH$_2$), 6.72 (1H, d, J=11.0 Hz, CH=CHCH$_2$), 7.04–7.10 (1H, m, CH$_{ar}$), 7.22–7.54 (5H, m, CH$_{ar}$), 7.92–8.08 (2H, m, CH$_{ar}$). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 24.35 (CH_2CH$_2$N), 46.91 (d, $^3J_{CP}$=15.0 Hz, CH$_2$CH$_2$N), 51.11 (NCH$_2$C$_{ar}$), 52.51 (d, $^2J_{CP}$=6.9 Hz, CH$_3$OP), 54.57 (d, $^2J_{CP}$=6.9 Hz, CH$_3$OP), 59.60 (d, $^1J_{CP}$=173.1 Hz, CHP), 124.58 (C$_{q,ar}$), 127.15 (CH$_{ar}$), 127.59 (CH$_{ar}$), 127.74 (CH$_{ar}$), 128.38 (CH$_{ar}$), 128.66 (CH$_{ar}$), 129.64 (CH=CHCH$_2$), 130.38 (d, J_{CP}=10.2 Hz, C$_{q,ar}$), 130.61 (d, J_{CP}=4.6 Hz, CH$_{ar}$), 132.15 (CH$_{ar}$), 132.32 (CH$_{ar}$), 133.61 (CH=CHCH$_2$), 137.63 (d, J_{CP}=16.2 Hz, C$_{q,ar}$), 139.13 (C$_{q,ar}$). ^{31}P NMR ($CDCl_3$, 121 MHz) δ: 24.85. IR (NaCl, cm^{-1}): 1633 (C=C); 1247 (P=O); 1062, 1037 (P–O). MS (ESI, pos mode) (%) m/z: 436/438 (M+H$^+$, 100).

*3.7.3. Synthesis of dimethyl 2-(4-methoxybenzyl)-1,2,3,4-tetrahydro-2-benzazocin-1-ylphosphonate (**1c**)*

Yield after chromatography: 60% (viscous oil).

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.96–2.01 (2H, m, CH_2CH$_2$N), 2.36–2.44 (1H, m, CH$_2$CH_AH$_B$N), 2.77–2.83 (1H, m, CH$_2$CH$_A$$H_B$N), 2.86 (1H, dd, J=13.2 Hz, $^4J_{HP}$=1.4 Hz, NCH_AH$_B$C$_{ar}$), 3.56 (3H, d, $^3J_{HP}$=10.5 Hz, CH$_3$OP), 3.78 (3H, s, CH$_3$O), 3.96 (3H, d, $^3J_{HP}$=10.5 Hz, CH$_3$OP), 4.49 (1H, d, $^2J_{HP}$=26.4 Hz, CHP), 4.56 (1H, d, J=13.2 Hz, NCH$_A$$H_BC_{ar}$), 6.04 (1H, dt, J=11.3 Hz, J=8.0 Hz, CH=CHCH$_2$), 6.68 (1H, d, J=11.3 Hz, CH=CHCH$_2$), 6.82 (2H, d, J=8.8 Hz, 2×CH$_{ar}$), 7.27 (2H, d, J=8.8 Hz, 2×CH$_{ar}$), 7.29–7.37 (3H, m, CH$_{ar}$), 8.06–8.09 (1H, m, CH$_{ar}$). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 23.05 (CH_2CH$_2$N), 46.05 (d, $^3J_{CP}$=15.0 Hz, CH$_2$CH$_2$N), 51.54 (NCH$_2$C$_{ar}$), 52.42 (d, $^2J_{CP}$=6.9 Hz, CH$_3$OP), 54.55 (d, $^2J_{CP}$=6.9 Hz, CH$_3$OP), 55.28 (CH$_3$O), 59.87 (d, $^1J_{CP}$=171.9 Hz, CHP), 113.62 (2×CH$_{ar}$), 126.95 (CH$_{ar}$), 127.57 (CH$_{ar}$), 128.61 (CH$_{ar}$), 129.52 (CH=CHCH$_2$), 130.26 (d, J_{CP}=11.5 Hz, C$_{q,ar}$), 130.58 (2×CH$_{ar}$), 130.79 (d, J_{CP}=4.6 Hz, CH$_{ar}$), 131.74 (C$_{q,ar}$), 133.41 (CH=CHCH$_2$), 137.67 (d, J_{CP}=16.2 Hz, C$_{q,ar}$), 158.68 (C$_{q,ar}$). ^{31}P NMR ($CDCl_3$, 121 MHz) δ: 24.79. IR (NaCl, cm^{-1}): 1611 (C=C); 1248 (P=O); 1062, 1035 (P–O). MS (ESI, pos mode) (%) m/z: 388 (M+H$^+$, 100). Chromatography: PE/EtOAc (70/30) R_f=0.08. $C_{21}H_{26}NO_4P$: calcd C 65.11, H 6.76, N 3.62; found C 65.19, H 6.83, N 3.59.

*3.8. Synthesis of dimethyl 2-(benzyl)-1,2,3,4-tetrahydro-2-benzazocin-1-ylphosphonates **1d–f**: general procedure*

In a flask of 10 mL, aminophosphonate **4** (0.24 mmol) was refluxed in 5 mL of benzene. To this solution, the second generation Grubbs' catalyst (0.01 mmol) was added. After refluxing overnight, the isomerisation catalyst $RuClH(CO)(PPh_3)_3$ (0.01 mmol) was added to the metathesis mixture and refluxing was continued for an additional 2 h. Benzene was evaporated in vacuo. The crude product was purified by chromatography.

*3.8.1. Synthesis of dimethyl 2-benzyl-1,2,3,4-tetrahydro-2-benzazocin-1-ylphosphonate (**1d**)*

Yield: 74% (brownish oil).

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.97–2.03 (2H, m, CH_2CH$_2$N), 2.35–2.47 (1H, m, CH$_2$CH_AH$_B$N), 2.76–2.83 (1H, m, CH$_2$CH$_A$$H_B$N), 2.93 (1H, dd, J=13.2 Hz, $^4J_{HP}$=1.4 Hz, NCH_AH$_B$C$_{ar}$), 3.57 (3H, d, $^3J_{HP}$=10.5 Hz, CH$_3$OP), 3.97 (3H, d, $^3J_{HP}$=10.5 Hz, CH$_3$OP), 4.50 (1H, d, $^2J_{HP}$=26.1 Hz, CHP), 4.64 (1H, d, J=13.2 Hz, NCH$_A$$H_BC_{ar}$), 6.05 (1H, dt, J=11.3 Hz, J=8.0 Hz, CH=CHCH$_2$), 6.69 (1H, d, J=11.3 Hz, CH=CHCH$_2$), 7.20–7.38 (8H, m, CH$_{ar}$), 8.06–8.10 (1H, m, CH$_{ar}$). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 23.11 (CH_2CH$_2$N), 46.29 (d, $^2J_{CP}$=16.1 Hz, CH$_2$CH$_2$N), 52.29 (NCH$_2$C$_{ar}$), 52.50 (d, $^2J_{CP}$=6.9 Hz, CH$_3$OP), 54.57 (d, $^2J_{CP}$=6.9 Hz, CH$_3$OP), 59.80 (d, $^1J_{CP}$=173.1 Hz, CHP), 126.92 (CH$_{ar}$), 127.01 (CH$_{ar}$), 127.65 (CH$_{ar}$), 128.22 (2×CH$_{ar}$), 128.66 (CH$_{ar}$), 129.50 (CH=CHCH$_2$+2×CH$_{ar}$), 130.20 (d, J_{CP}=9.2 Hz, C$_{q,ar}$), 130.77 (d, J_{CP}=4.6 Hz, CH$_{ar}$), 133.42 (CH=CHCH$_2$), 137.71 (d, J_{CP}=16.1 Hz, C$_{q,ar}$), 139.70 (C$_{q,ar}$). ^{31}P NMR ($CDCl_3$, 121 MHz) δ: 24.83. IR (NaCl, cm^{-1}): 1654 (C=C); 1248 (P=O); 1062, 1037 (P–O). MS (ESI, pos mode) (%) m/z: 358 (M+H$^+$, 100). Chromatography: PE/EtOAc (70/30)

R_f=0.11. $C_{20}H_{24}NO_3P$: calcd C 67.21, H 6.77, N 3.92; found C 67.21, H 6.80, N 3.91.

3.8.2. Synthesis of dimethyl 2-(3-fluorobenzyl)-1,2,3,4-tetrahydro-2-benzazocin-1-ylphosphonate (**1e**)

Yield: 70% (viscous oil).

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.02–2.08 (2H, m, CH_2CH$_2$N), 2.40–2.49 (1H, m, CH$_2$CH_AH$_B$N), 2.74–2.82 (1H, m, CH$_2$CH$_A$$H_B$N), 3.28 (1H, d, J=13.2 Hz, NCH_AH$_B$C$_{ar}$), 3.56 (3H, d, $^3J_{HP}$=10.5 Hz, CH$_3$OP), 3.93 (3H, d, $^3J_{HP}$=10.5 Hz, CH$_3$OP), 4.41 (1H, d, J=13.2 Hz, NCH$_A$$H_BC_{ar}$), 4.47 (1H, d, $^2J_{HP}$=23.4 Hz, CHP), 6.06 (1H, dt, J=11.3 Hz, J=8.0 Hz, CH=CHCH$_2$), 6.69 (1H, d, J=11.3 Hz, CH=CHCH$_2$), 6.92–6.98 (1H, m, CH$_{ar}$), 7.09–7.15 (1H, m, CH$_{ar}$), 7.16–7.39 (4H, m, CH$_{ar}$), 7.69–7.75 (1H, m, CH$_{ar}$), 8.08–8.11 (1H, m, CH$_{ar}$). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 23.23 (CH_2CH$_2$N), 44.46 (NCH_2C$_{ar}$), 46.67 (d, $^3J_{CP}$=15.0 Hz, CH$_2$CH_2N), 52.41 (d, $^2J_{CP}$=6.9 Hz, CH$_3$OP), 54.52 (d, $^2J_{CP}$=6.9 Hz, CH$_3$OP), 59.59 (d, $^1J_{CP}$=172.0 Hz, CHP), 114.90 (d, J=23.1 Hz, CH$_{ar}$), 124.10 (d, J=2.3 Hz, CH$_{ar}$), 126.24 (d, J=15.0 Hz, C$_{q,ar}$), 126.97 (CH$_{ar}$), 127.61 (CH$_{ar}$), 128.46 (d, J=8.1 Hz, CH$_{ar}$), 128.61 (CH$_{ar}$), 129.46 (CH=CHCH$_2$), 130.02 (d, J=10.4 Hz, C$_{q,ar}$), 130.62 (d, J=4.6 Hz, CH$_{ar}$), 132.30 (d, J=4.6 Hz, CH$_{ar}$), 133.40 (CH=CHCH$_2$), 137.62 (d, J=16.2 Hz, C$_{q,ar}$), 161.44 (d, J=245.8 Hz, C$_{q,ar}$). ^{31}P NMR ($CDCl_3$, 121 MHz) δ: 24.62. ^{19}F NMR ($CDCl_3$, 282 MHz) δ: −119.61. IR (NaCl, cm^{-1}): 1625 (C=C); 1246 (P=O); 1061, 1036 (P–O). MS (ESI, pos mode) (%) m/z: 376 (M+H$^+$, 100). Chromatography: PE/EtOAc (3/1) R_f=0.05. $C_{20}H_{23}FNO_3P$: calcd C 63.99, H 6.18, N 3.73; found C 63.98, H 6.16, N 3.72.

3.8.3. Synthesis of dimethyl 2-(3-methoxybenzyl)-1,2,3,4-tetrahydro-2-benzazocin-1-ylphosphonate (**1f**)

Yield: 72% (yellow-brown oil).

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.97–2.04 (2H, m, CH_2CH$_2$N), 2.40–2.48 (1H, m, CH$_2$CH_AH$_B$N), 2.79–2.85 (1H, m, CH$_2$CH$_A$$H_B$N), 2.93 (1H, dd, J=13.2 Hz, $^4J_{HP}$=1.1 Hz, NCH_AH$_B$C$_{ar}$), 3.56 (3H, d, $^3J_{HP}$=10.5 Hz, CH$_3$OP), 3.78 (CH$_3$O), 3.97 (3H, d, $^3J_{HP}$=10.2 Hz, CH$_3$OP), 4.49 (1H, d, $^2J_{HP}$=26.4 Hz, CHP), 4.61 (1H, d, J=13.2 Hz, NCH$_A$$H_BC_{ar}$), 6.05 (1H, dt, J=11.3 Hz, J=7.8 Hz, CH=CHCH$_2$), 6.68 (1H, d, J=11.3 Hz, CH=CHCH$_2$), 6.75–7.04 (3H, m, CH$_{ar}$), 7.16–7.37 (4H, m, CH$_{ar}$), 8.05–8.09 (1H, m, CH$_{ar}$). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 23.21 (CH_2CH$_2$N), 46.40 (d, $^3J_{CP}$=15.0 Hz, CH$_2$CH_2N), 52.49 (d, $^2J_{CP}$=6.9 Hz, CH$_3$OP), 52.51 (d, $^2J_{CP}$=6.9 Hz, CH$_3$OP), 54.47 (d, $^3J_{CP}$=8.1 Hz, NCH_2C$_{ar}$), 55.20 (CH$_3$O), 59.78 (d, $^1J_{CP}$=171.9 Hz, CHP), 112.55 (CH$_{ar}$), 114.76 (CH$_{ar}$), 121.80 (CH$_{ar}$), 127.01 (CH$_{ar}$), 127.65 (CH$_{ar}$), 128.66 (CH$_{ar}$), 129.10 (CH=CHCH$_2$), 129.53 (CH$_{ar}$), 130.22 (d, J_{CP}=9.2 Hz, C$_{q,ar}$), 130.73 (d, J_{CP}=4.6 Hz, CH$_{ar}$), 133.42 (CH=CHCH$_2$), 137.71 (d, J_{CP}=15.0 Hz, C$_{q,ar}$), 141.40 (C$_{q,ar}$), 159.64 (C$_{q,ar}$). ^{31}P NMR ($CDCl_3$, 121 MHz) δ: 24.91. IR (NaCl, cm^{-1}): 1600 (C=C); 1261 (P=O); 1061, 1037 (P–O). MS (ESI, pos mode) (%) m/z: 388 (M+H$^+$, 100). Chromatography: PE/EtOAc (70/30) R_f=0.08. $C_{21}H_{26}NO_4P$: calcd C 65.11, H 6.76, N 3.62; found C 65.11, H 6.81, N 3.64.

3.9. Synthesis of dimethyl 2-(benzyl)-1,2,3,6-tetrahydro-2-benzazocin-1-ylphosphonates **2b**,**c**: general procedure

In a flask of 10 mL, aminophosphonate **4b**,**c** (0.24 mmol) was refluxed in 5 mL of benzene. To this solution, the first generation Grubbs' catalyst (0.01 mmol) was added. After refluxing for 8 h, again 0.03 equiv of the first generation Grubbs' catalyst (0.006 mmol) was added. After refluxing the resulting mixture for another 2 days, benzene was evaporated under vacuum. The crude product was purified by chromatography.

3.9.1. Synthesis of dimethyl 2-(3-fluorobenzyl)-1,2,3,6-tetrahydro-2-benzazocin-1-ylphosphonate (**2b**)

Yield: 75% (viscous oil).

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.02–3.30 (2H, m, NCH_AH$_B$C$_{ar}$+NCH_AH$_B$CH), 3.38 (1H, dd, J=14.6 Hz, J=6.7 Hz, NCH$_A$$H_B$CH), 3.37–3.87 (5H, m, CH$_3$OP+C$_{ar}$CH_2CH), 3.96 (3H, d, $^3J_{HP}$=10.5 Hz, CH$_3$OP), 3.98–4.16 (1H, m, NCH$_A$$H_BC_{ar}$), 4.96 (1H, d, $^2J_{HP}$=24.5 Hz, CHP), 5.47–5.58 (1H, m, CH=CH), 6.12 (1H, dt, J=10.5 Hz, J=7.7 Hz, CH=CH), 6.92–8.02 (8H, m, CH$_{ar}$). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 34.71 (C$_{ar}$CH_2CH), 45.58 (br, NCH_2C$_{ar}$), 49.97 (br, CHCH_2N), 52.56 (d, $^2J_{CP}$=6.9 Hz, CH$_3$OP), 54.63 (d, $^2J_{CP}$=6.9 Hz, CH$_3$OP), 60.27 (d, ^1J=161.5 Hz, CHP), 115.18 (d, J_{CP}=21.9 Hz, CH$_{ar}$), 124.01 (d, J_{CP}=3.5 Hz, CH$_{ar}$), 125.95 (d, J=15.0 Hz, C$_{q,ar}$), 126.40 (CH$_{ar}$), 126.92 (CH=CH), 128.54 (CH$_{ar}$), 128.60 (d, J=9.2 Hz, CH$_{ar}$), 129.10 (CH$_{ar}$), 129.39 (br, CH$_{ar}$), 131.67 (br, C$_{q,ar}$), 132.12 (br, CH$_{ar}$), 135.94 (CH=CH), 141.80 (br, C$_{q,ar}$), 161.49 (d, J=245.8, C$_{q,ar}$). ^{31}P NMR ($CDCl_3$, 121 MHz) δ: 24.55. ^{19}F NMR ($CDCl_3$, 282 MHz) δ: −119.61. IR (NaCl, cm^{-1}): 1657 (C=C); 1248 (P=O); 1058, 1034 (P–O). MS (ESI, pos mode) (%) m/z: 376 (M+H$^+$, 100). Chromatography: PE/EtOAc (3/1) R_f=0.06. $C_{20}H_{23}FNO_3P$: calcd C 63.99, H 6.18, N 3.73; found C 64.05, H 6.23, N 3.72.

3.9.2. Synthesis of dimethyl 2-(3-methoxybenzyl)-1,2,3,6-tetrahydro-2-benzazocin-1-ylphosphonate (**2c**)

Yield: 75% (viscous oil).

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.67–2.84 (1H, m, NCH_AH$_B$C$_{ar}$), 3.05–3.30 (1H, m, NCH_AH$_B$CH), 3.40 (1H, dd, J=14.9 Hz, J=6.3 Hz, NCH$_A$$H_B$CH), 3.46–3.96 (5H, m, CH$_3$OP+C$_{ar}$CH_2CH), 3.78 (3H, s, CH$_3$O), 4.02 (3H, $^3J_{HP}$=10.5 Hz, CH_3OP), 4.07–4.25 (1H, m, NCH$_A$$H_BC_{ar}$), 4.91–5.09 (1H, m, C$H$P), 5.40–5.49 (1H, m, C$H$=CH), 6.11 (1H, dt, J=9.9 Hz, J=8.3 Hz, CH=CH), 6.75–6.79 (1H, m, CH$_{ar}$), 6.91–6.97 (2H, m, CH$_{ar}$), 7.15–7.28 (5H, m, CH$_{ar}$). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 34.57 (C$_{ar}$CH_2CH), 49.81 (br, NCH_2CH), 52.44 (d, $^2J_{CP}$=6.9 Hz, CH$_3$OP), 52.70 (NCH_2C$_{ar}$), 54.81 (d, $^2J_{CP}$=6.9 Hz, CH$_3$OP), 55.20 (CH$_3$O), 63.51 (d, $^1J_{CP}$=175.4 Hz, CHP), 112.73 (CH$_{ar}$), 114.60 (CH$_{ar}$), 121.73 (CH$_{ar}$), 126.32 (CH$_{ar}$), 126.99 (CH=CH), 128.46 (CH$_{ar}$), 129.07 (CH$_{ar}$), 129.27 (br, CH$_{ar}$), 130.70 (br, CH$_{ar}$), 132.09 (d, J=9.2 Hz, C$_{q,ar}$), 135.74 (CH=CH),

140.99 ($C_{q,ar}$), 141.56 (br, $C_{q,ar}$), 159.61 ($C_{q,ar}$). ^{31}P NMR ($CDCl_3$, 121 MHz) δ: 24.12. IR (NaCl, cm^{-1}): 1600 (C=C); 1250 (P=O); 1066, 1039 (P–O). MS (ESI, pos mode) (%) *m/z*: 388 ($M+H^+$, 100). Chromatography: PE/EtOAc (3/1) R_f=0.08. $C_{21}H_{26}NO_4P$: calcd C 65.11, H 6.76, N 3.62; found C 65.12, H 6.82, N 3.60.

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