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[4+2] Cycloaddition of 1-phosphono-1,3-butadiene with azo- and nitroso-heterodienophiles

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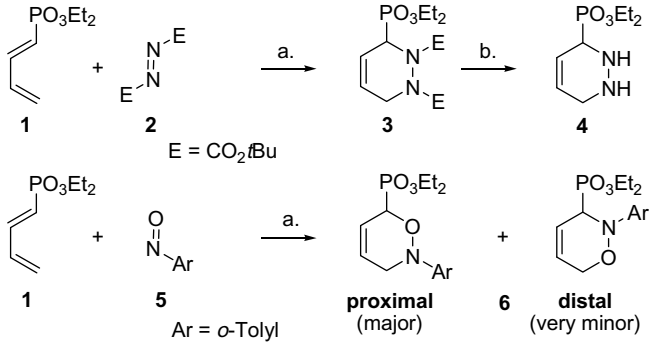
Abstract

Under microwave activation, diethyl 1-phosphono-1,3-butadiene (**1**) reacted with *t*-butyl azodicarboxylate (**2**) and *o*-nitrosotoluene (**5**) to furnish quantitatively [4+2] cycloadducts, 3-phosphono-3,6-dihydro-1,2-pyridazine (**3**) and 6-phosphono-3,6-dihydro-1,2-oxazine (**6**), respectively. Selective oxidation and/or reduction of **6** led to functionalized δ-aminophosphonic derivatives in cyclic (**7**, **8**) and aliphatic series (**9**, **10**). Intermediate **10** may be cyclized into 2-phosphono-2,5-dihydro-1-pyrrole (**12**).

Keywords: Hetero Diels–Alder reaction; 1-Phosphono-1,3-butadiene; Azo dienophile; Nitroso dienophile; Microwave activation; Aminophosphonic derivatives

With its well-known potential of forming highly functionalized molecules, in a convergent way compatible with a wide range of substituents, the Diels–Alder (DA) reaction (i.e., [4+2] cycloaddition) is a versatile synthetic tool that can be used for the synthesis of aminophosphonic derivatives.[1] These compounds are recognized as an important class of pharmacologically active molecules effective in several diseases.[2] Surprisingly, aminophosphonic derivatives other than the α-ones have been obtained only via punctual methods. This stimulates the development of novel synthetic routes towards such compounds.[2,3] Our interest in cycloaddition reactions leads us to investigate HDA (hetero-Diels–Alder) reaction[4] as a valuable strategy towards δ-aminophosphonic derivatives of potential interest in medicinal chemistry.[5,6] In this Letter, we describe the [4+2] reaction of phosphono-butadiene (**1**) with *t*-butyl azodicarboxylate (**2**) and 2-nitrosotoluene (**5**) as heterodienophile model compounds (Scheme 1). We further demonstrate that cycloadduct **6** is a versatile intermediate leading to various aminophosphonic derivatives both in cyclic and aliphatic series.

1-(Diethylphosphono)-1,3-butadiene (**1**) could be readily obtained in two steps from 1,4-*trans*-dichlorobutene.[7] The DA reactivity of **1** was initially studied in 1963 by Pudovik et al.[8] Cycloadditions occurred with acrylonitrile,



Scheme 1. Reagents and conditions: (a) $(CH_2Cl)_2$, 95 °C or MW activation; (b) TFA, DCM, rt, 15 h.

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acroleine, ethyl methacrylate and dimethylmaleate, at high temperature in an autoclave, but in poor yields because dimerization of the diene was the major process. Similar observations were reported later by Griffin and co-workers,[9] opposing **1** to other electron-poor dienophiles such as diethyl vinylphosphonate and dimethyl acetylenedicarboxylate. In the case of electron-rich dienophiles, namely enamines, the cycloadditions of **1** were even more sluggish according to Darling and Subramanian.[10]

We found that **1** reacted smoothly with *t*-butyl azodicarboxylate (**2**) under classical thermal conditions to furnish 1,2-(di-*t*-butyloxycarbonyl)-3-diethoxyphosphono-3,6-dihydro-1,2-pyridazine (**3**) (Scheme 1), while microwave activation[11] provided a significant increase in yields and reaction rate (Table 1). The cycloadduct was easily purified by column chromatography on silica gel and characterized by the usual spectroscopies.[12] Deprotection of the Boc groups with trifluoroacetic acid (TFA) gave the corresponding hydrazine derivative **4** in 95% yield.[13]

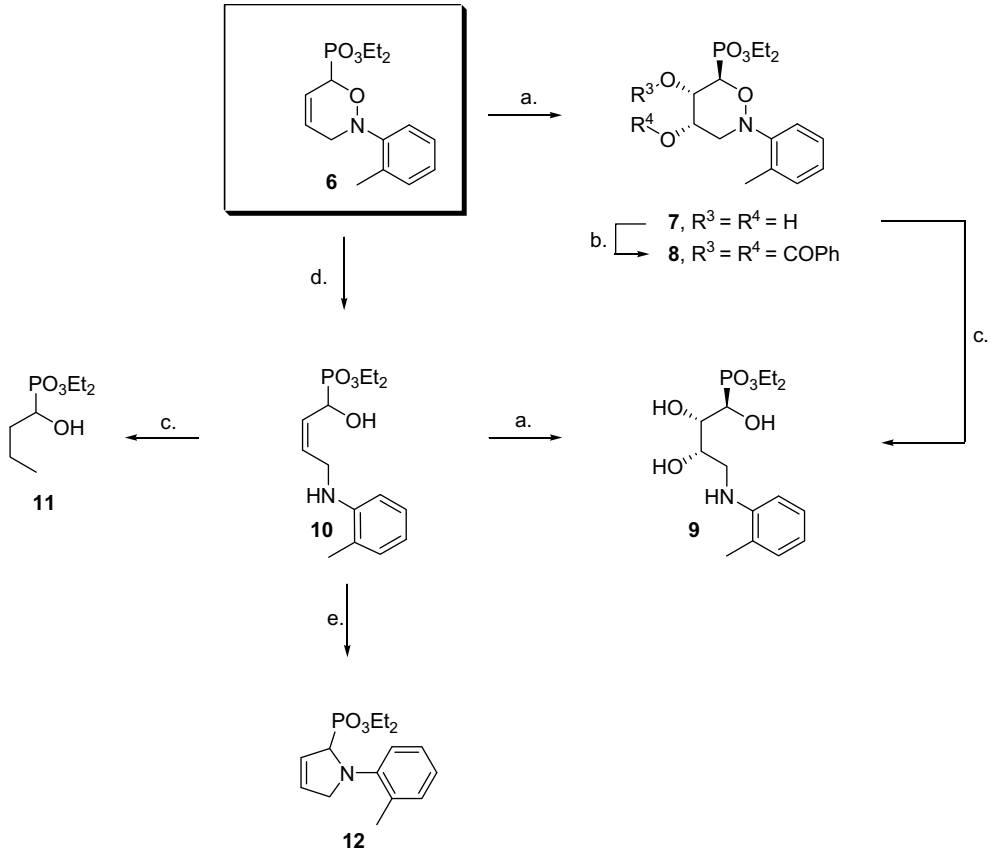
Next, we found that diene **1** reacted more easily with 2-nitrosotoluene[14] in refluxing dichloroethane (DCE) to afford dihydro-1,2-oxazine cycloadducts **6** (Scheme 1) as a 10:1 mixture of proximal and distal regioisomers, which were easily separated by column chromatography on silica gel.[15] Interestingly, when microwave activation was applied, the regioselectivity became complete in favour of the proximal isomer and the reaction time was shortened (Table 1). This can be explained by the greater synchronicity of the *distal* transition state versus the *proximal* one.[16]

Table 1
Microwave activation of diene **1** in HDA reactions

Entry	Reagent	Conditions	Conv.[a] (%)	Regioselectivity proximal/distal[a]
1	**2**	DCE, 95 °C, 7 d	55	—
2	**2**	μW, 650 W, 120 °C, 1 h	>99	—
3	**5**	DCE, 95 °C, 15 h	>99	10:1
4	**5**	DCE, μW, 500 W, 100 °C, 1 h	>99	Proximal

[a] From 500 MHz ^{1}HNMR on the crude mixture.

Oxidation of **6** without cleavage of the C–C double bond was investigated (Scheme 2). Treatment with $K_2OsO_2(OH)_4$ and *N*-methyl morpholine oxide (NMO)[17] to effect cis-dihydroxylation of the double bond gave the *syn*-diol **7** in high yield (92%).[18] ^{1}H, ^{13}C and ^{31}P NMR data are consistent with the formation of one stereoisomer, suggesting a control of the relative stereochemistry by the bulky phosphonate. Esterification of **7** with benzoyl chloride afforded



Scheme 2. Reagents and conditions: (a) $K_2OsO_2(OH)_4$, acetone–water, rt, 24 h, 92%; (b) benzoyl chloride, DMAP, pyridine, DCM, rt, 2 h, >95%; (c) H_2, Pd–C, EtOH, rt, 12 h, >99%; (d) Zn, AcOH, water, 70 °C, 15 h, >99%; (e) CBr_4, Imidazole, Et_3N, PPh_3, DCM, rt, 15 h, 75%.

diester **8** that smoothly crystallized from a benzene–ether 5:1 mixture. X-ray diffraction analysis of a monocrystal confirmed that the phosphonate group is in *anti* relationship regarding the two *syn* hydroxyl groups.[19]

Reductive cleavage of the 1,2-oxazine motif of **7** under catalytic hydrogenation conditions (Scheme 2) led quantitatively to diethyl 4-(*o*-tolylamino)-1,2,3-trihydroxybutylphosphonate (**9**).[20]

A useful synthetic application of 3,6-dihydro-1,2-oxazine **6** could be the selective reductive cleavage of the N–O bond to generate 1,4-difunctional 2-butene derivatives with preserved (*Z*)-configuration. The currently most popular way of oxazine cleavage uses freshly prepared $Mo(CO)_3(CH_3CN)_3$.[21] But in our case the reductive cleavage with Zn in AcOH[22] was the most efficient method for preparing (*Z*)-diethyl 4-(*o*-tolylamino)-1-hydroxybut-2-enylphosphonate (**10**) in quantitative yield.[23] The (*Z*)-relationship of olefinic protons was confirmed by the observation of a $^3J_{H-H}$ value of 6 Hz. Oxidation of **10** by using $K_2OsO_2(OH)_4$ as previously described led to **9** in low yields. Thus, the best route to synthesize **9** from **6** is C=C dihydroxylation followed by O–N cleavage (91% yield) and not the reversed reaction sequence (42% yield).

Treatment of **10** by hydrogen in the presence of Pd catalyst reduced the C=C double bond and simultaneously cleaved the *o*-tolylamine group. This unexpected reaction furnished the known diethyl 1-hydroxybutylphosphonate (**11**).[24] Lastly, ring closure of **10** into pyrrolidine-2-phosphonic derivative was possible by using PPh_3/CBr_4 activation.[25] The reactive intermediate (not isolated) underwent an intramolecular nucleophilic substitution by the aniline moiety, in the presence of imidazole, leading to diethyl 2,5-dihydro-1-*o*-tolyl-1-pyrrol-2-yl-2-phosphonate (**14**)[26] (Scheme 2).

In conclusion, we have demonstrated that under microwave activation, HDA reaction of 1-phosphono-butadiene could be readily performed. This is most probably due to the high polarizability of reagent **1**.[27] Reaction with azo partner **2** followed by N-deprotection represents the best way to prepare 3-phosphono-1,2,3,6-tetrahydropyridazine (**4**), an already known biologically active molecule.[5] Reaction with nitroso partner **3** followed by either oxidation or reduction illustrates the versatility of our strategy towards δ-aminophosphonic derivatives, in particular poly-hydroxylated compounds such as **9**. Also, a novel entry into the 2-phosphono-pyrrolidine (**12**) family[28] has been shown.

Acknowledgements

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12. *Procedure for 1,2-(di-t-butyloxycarbonyl)-3-diethoxyphosphono-3,6-dihydro-1,2-pyridazine* **3**: A mixture of *t*-butyl azodicarboxylate (5.3 mmol) and **1** (5.3 mmol) with a few drops of toluene was stirred in a microwave oven under 650 W irradiation at 120 °C for 1 h. The reaction mixture was concentrated in vacuo and purified by column chromatography on silica gel to give **3** as a yellow oil (>99%). R_f (ethyl acetate) = 0.6; ^{1}H NMR (500 MHz; 50 °C, $CDCl_3$) δ: 5.94 (br s, 2H), 5.04 (br d, 1H, $J = 19.6$ Hz), 4.41 (dd, 1H, $J = 7$ and 7.7 Hz), 4.27–4.15 (m, 4H), 3.76–3.63 (m, 1H), 1.47 (br s, 18H), 1.31 (t, 3H, $J = 7.2$ Hz), 1.25 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR (125 MHz; $CDCl_3$, major rotamer) δ: 154.17, 152.68, 126.07, (d, $J_{C-P} = 7.7$ Hz) 121.25, 81.02, 63.58 (d, $J_{C-P} = 6.5$ Hz), 62.77 (d, $J_{C-P} = 6.1$ Hz), 51.3 (d, $J_{C-P} = 162.3$ Hz), 41.55 (d, $J_{C-P} = 2.1$ Hz), 28.58 (m), 16.71 (m); ^{31}P NMR (121 MHz; $CDCl_3$, H_3PO_4) δ: 21.23; IR (NaCl, ν, cm^{-1}) 2984, 2934, 1734, 1420, 1284, 1015, 952; ESI HRMS *m/z* for $C_{18}H_{33}N_2O_7PNa$ [M+Na$^+$]: calcd 443.1918; found 443.1921.
13. *Procedure for diethyl 1,2,3,6-tetrahydropyridazin-3-yl-3-phosphonate* **4**: To a solution of **3** (0.34 mmol) in chloroform (2.5 cm^3) at room temperature was added TFA (2.72 mmol). After 15 h, the reaction mixture was concentrated in vacuo affording **4** as a yellow oil (95%). R_f [ethyl acetate/*i*PrOH 95:5] = 0.25; ^{1}H NMR (300 MHz; $CDCl_3$) δ: 6.06 (br s, 2H), 4.21 (m, 5H), 3.91–3.81 (m, 2H), 1.35 (t, 6H, $J = 6.3$ Hz); ^{13}C NMR (75 MHz; $CDCl_3$) δ: 122.81 (d, $J_{C-P} = 9.5$ Hz), 121.19, 65.44 (d, $J_{C-P} = 155.4$ Hz); 42.79, 16.56; ^{31}P NMR (121 MHz; $CDCl_3$, H_3PO_4) δ: 19.99; IR (NaCl, ν, cm^{-1}) 3325, 1280, 1023; ESI HRMS *m/z* for $C_8H_{17}N_2O_3PNa$ [M+Na$^+$]: calcd 243.0875; found 243.0878.
14. 2-Nitrosotoluene **5** was purchased from commercial source (Aldrich) as a dimeric form (colourless). In dichloroethane solution, the dissociation towards monomeric form was instantaneous (deep green solution). See: Lee, J.; Chen, L.; West, A. H.; Richter-Addo, G. B. *Chem. Rev.* **2002**, *102*, 1019–1065.
15. *Procedure for diethyl 3,6-dihydro-2-o-tolyl-1,2-oxazin-6-yl-6-phosphonate* **6**: A solution of **1** (6.58 mmol) in dichloroethane (10 cm^3) and 2-nitrosotoluene (6.58 mmol) was stirred in a microwave oven

under 500 W irradiation at 100 °C for 1 h. The reaction mixture was concentrated in vacuo and purified by column chromatography on silica gel to give **6** as a brown oil (>99%). R_f (ethyl acetate) = 0.6; ^{1}H NMR (500 MHz; $CDCl_3$) δ: 7.16 (m, 4H), 6.13 (m, 2H), 5.1 (ddd, 1H, J = 7.6, 5.3 and 3 Hz), 4.14 (m, 4H), 3.88 (m, 1H), 3.57 (tdd, 1H, J = 7, 4.1 and 1.9 Hz), 2.33 (s, 3H), 1.28 (m, 6H); ^{13}C NMR (125 MHz; $CDCl_3$) δ: 147.76, 133.1, 130.99, 126.47, 126.34 (d, J_{C-P} = 10 Hz), 125.85, 122.87 (d, J_{C-P} = 5 Hz), 118.57, 75.68 (d, J_{C-P} = 160 Hz), 63.49 (d, J_{C-P} = 6.2 Hz), 62.86 (d, J_{C-P} = 6.2 Hz), 52.15 (d, J_{C-P} = 2.8 Hz), 18.33, 16.61 (dd, J_{C-P} = 5.7 Hz); ^{31}P NMR (121 MHz; $CDCl_3$, H_3PO_4) δ: 18.2; IR (NaCl, ν, cm^{-1}) 2935, 1495, 1454, 1209, 1068; ESI HRMS m/z for $C_{15}H_{22}NO_4PNa$, [M+Na$^+$]: calcd 334.1184; found 334.1171.

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18. *Procedure for diethyl syn-4,5-dihydroxy-2-o-tolyl-3,4,5,6-tetrahydro-1,2-oxazin-6-yl-6-phosphonate* **7**: A solution of **6** (9.4 mmol) in acetone (30 cm^3) was treated successively by water (20 cm^3), NMO (20.68 mmol) and $K_2OsO_2(OH)_4$ (0.47 mmol) at room temperature. After 24 h, toluene (30 cm^3) was added and concentrated in vacuo. The resulting dark oil was directly purified by column chromatography on silica gel to give **7** as a slightly yellow oil (>95%). R_f (ethyl acetate/*i*PrOH 95:5) = 0.43; ^{1}H NMR (500 MHz; CD_3CN) δ: 7.54 (m, 4H), 4.55 (dd, 1H, J = 10.3 and 9.6 Hz), 4.12 (m, 5H), 3.97 (ddd, 1H, J = 12.9, 8.4 and 4.4 Hz), 3.86 (large s, 1H), 3.55 (large s, 1H), 3.4 (dd, 2H, J = 7.1 and 2.8 Hz), 2.36 (s, 3H), 1.30 (t, 3H, J = 6.9 Hz), 1.26 (t, 3H, J = 7.1 Hz); ^{13}C NMR (125 MHz; CD_3CN) δ: 148.28, 134.28, 131.54, 127.17, 126.8, 119.22, 76.41 (d, J_{C-P} = 158.1 Hz), 67.76 (d, J_{C-P} = 13.8 Hz), 66.9 (d, J_{C-P} = 11.3 Hz), 63.81 (d, J_{C-P} = 6.7 Hz), 63.44 (d, J_{C-P} = 6.3 Hz), 58.54, 18.04, 16.65 (d, J_{C-P} = 5.8 Hz); ^{31}P NMR (121 MHz; CDCN, H_3PO_4) δ: 20.37; IR (NaCl, ν, cm^{-1}) 3389, 2982, 1489, 1230, 1047, 976; ESI HRMS m/z for $C_{15}H_{24}NO_6PNa$ [M+Na$^+$]: calcd 368.1239; found 368.1245.
19. This structure has been deposited at the Cambridge Crystallographic Data Centre with the number 666038.
20. *Procedure for diethyl 4-(o-tolylamino)-1,2,3-trihydroxybutylphosphonate* **9**: A solution of **7** (1.6 mmol) in ethanol (25 cm^3) was stirred for 15 h at room temperature under H_2 atmosphere in the presence of Pd–C as catalyst (5 mol %). Afterwards, the reaction mixture was concentrated in vacuo and purified by column chromatography on silica gel to give **7** as a white solid (>99%). R_f (ethyl acetate/*i*PrOH 95:5) = 0.6; mp 105–106 °C; ^{1}H NMR (500 MHz; $CDCl_3$) δ: 7.04 (m, 2H), 6.65 (m, 2H), 4.39 (br s, 3H), 4.14 (m, 6H), 3.96 (m, 1H), 3.47 (dd, 1H J = 12.6 and 4.2 Hz), 3.22 (dd, 1H, J = 12.6 and 6.5 Hz), 2.12 (s, 3H), 1.28 (dt, 6H, J = 7.1 and 3.9 Hz); ^{13}C NMR (125 MHz; $CDCl_3$) δ: 146.23, 130.33, 127.29, 123.49, 118.17, 111.23, 73.77, 71.19, 71.12, 69.54 (d, J_{C-P} = 158.3 Hz), 63.70 (d, J_{C-P} = 6.9 Hz), 63.31 (d, J_{C-P} = 6.9 Hz), 46.56, 17.73, 16.62 (t, J_{C-P} = 6.1 Hz); ^{31}P NMR (121 MHz; $CDCl_3$, H_3PO_4) δ: 24.62; IR (NaCl, ν, cm^{-1}) 3366, 1608, 1514, 1213, 1028; ESI HRMS m/z for $C_{15}H_{27}NO_6P$ [M+H$^+$]: calcd 348.1576; found 348.1577.
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23. *Procedure for (Z)-diethyl 4-(o-tolylamino)-1-hydroxybut-2-enyl-phosphonate* **10**: To a solution of **6** (6.4 mmol) in a AcOH/water 1:2 mixture (90 cm^3) was added zinc dust (10.2 mmol). The reaction mixture was heated at 70 °C for 12 h with vigorous stirring. The mixture was cooled down (20 °C) and solid K_2CO_3 was added portionwise to pH 7, and then 3 N aqueous KOH to pH 9. The mixture was then extracted with ethyl acetate (3 × 50 cm^3). The organic phase was dried over $MgSO_4$ and concentrated in vacuo, affording **10** as a brown solid (>99%). R_f (ethyl acetate) = 0.32; mp 72–73 °C; ^{1}H NMR (500 MHz; $CDCl_3$): 7.15–7.07 (m, 2H), 6.73–6.64 (m, 2H), 5.89 (td, 1H, J = 10.1 and 6.1 Hz), 5.73 (m, 1H), 4.83 (t, 1H, J = 10 and 7.5 Hz), 4.23–4.19 (m, 4H), 3.94–3.85 (m, 2H), 2.18 (s, 3H), 1.36 (t, 6H, J = 7.1 Hz); ^{13}C NMR (125 MHz; $CDCl_3$) δ: 145.97, 132.32 (d, J_{C-P} = 12.6 Hz), 130.52, 127.53 (d, J_{C-P} = 3.8 Hz), 123.20, 118.14, 110.75, 66.13 (d, J_{C-P} = 160.9 Hz), 63.52 (t, J_{C-P} = 7.9 Hz), 41.12, 17.89, 16.86 (d, J_{C-P} = 5.5 Hz); ^{31}P NMR (121 MHz; $CDCl_3$, H_3PO_4) δ: 23.05; IR (NaCl, ν, cm^{-1}) 3323, 1605, 1514, 1238, 1051; ESI HRMS m/z for $C_{15}H_{24}NO_4PNa$ [M+Na$^+$]: calcd 336.1341; found 336.1342.
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26. *Procedure for diethyl 2,5-dihydro-1-o-tolyl-1-pyrrol-2-yl-2-phosphonate* **12**: To a solution of **10** (0.91 mmol), imidazole (0.91 mmol), triethylamine (0.91 mmol) and freshly recrystallized CBr_4 (0.91 mmol) in dry dichloromethane (5 cm^3) was added portionwise PPh_3 (0.91 mmol) at 20 °C for 10 min. After 15 h, the reaction mixture was concentrated in vacuo, diluted with AcOEt, washed with 10% aqueous NH_4Cl (1×), brine (1×) and water (2×). The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. The oily residue was purified by column chromatography on silica gel to give **12** as a yellow oil (75%). R_f (dichloromethane/ethyl acetate 3:1) = 0.33; ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.09 (ddd, 2H, J = 12, 9.9 and 4.7 Hz), 6.91 (dt, 2H, J = 7.2 and 1.9 Hz), 5.99 (tq, 1H, J = 6.1 and 3.1 Hz), 5.99–5.95 (m, 1H), 5.02 (dq, 1H, J = 5.9, 5.8 and 2.3 Hz), 4.58–4.41 (m, 1H), 3.92 (m, 4H), 3.70 (tddd, 1H, J = 19.5, 14.1, 3.7, and 2 Hz), 2.33 (s, 3H), 1.13 (dt, 6H, J = 7.1 and 5.5 Hz); ^{13}C NMR (125 MHz; $CDCl_3$) δ: 149.02 (d, J_{C-P} = 2.7 Hz), 133.52, 131.40, 129.87 (d, J_{C-P} = 11.3 Hz), 126.70, 124.46 (d, J_{C-P} = 5.6 Hz), 123.33, 120.71, 66.18 (d, J_{C-P} = 168.3 Hz), 62.65 (d, J_{C-P} = 7.1 Hz), 62.65 (d, J_{C-P} = 7.3 Hz), 61.87, 19.54, 16.50 (dd, J_{C-P} = 11.7 and 5.7 Hz); ^{31}P NMR (121 MHz; $CDCl_3$, H_3PO_4) δ: 21.98; IR (NaCl, ν, cm^{-1}) 3446, 2249, 1493, 1240, 1055, 1026; ESI MS m/z (%) for $C_{15}H_{23}NO_3P$ [M+H$^+$]: 296.12 (10), 279.27 (100).
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