Cinchona based squaramide catalysed enantioselective Michael addition of α-nitrophosphonates to aryl acrylates: Enantioselective synthesis of quaternary α-aminophosphonates

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Abstract—Several cinchona based squaramide catalysts were applied in asymmetric Michael addition of α-nitroethylphosphonates to acrylic acid aryl esters, resulting in high yield and enantioselectivity. The absolute configuration of one of the quaternary α-nitrophosphonate adducts was deduced from its experimental and calculated CD spectra. The adducts were reduced to their cyclic aminophosphonates by catalytic hydrogenation.

1. Introduction

Racemic and non-racemic α-aminophosphonic acid derivatives are considered to be structural and functional surrogates of the proteinogenic and non-proteinogenic amino acids.[1] Since their mode of action involves the inhibition of enzymes of different type, they were tested for a variety of biological effects ranging from medicine to agrochemistry.[2] This property was exploited in the development of new antibacterial,[3] antihypertensive[4] and anti-HIV agents[5] or herbicides.[6] Among the naturally occurring aminophosphonates K-26, a tripeptide phosphonic acid, shows ACE inhibitory activity.[7] Moreover, due to their metal complexing character, aminobisphosphonic acid derivatives have become important in the treatment of osteoporosis and bone metastases.[8]

Since biological activity is strongly influenced by the configuration of carbon atom adjacent to phosphorus, various synthetic methods providing non-racemic α-aminophosphonates were developed in the last decade and have recently been reviewed.[9] Among them, numerous enantioselective synthetic methods based on chiral auxiliaries were reported.[10] In the last few years interest was focused on catalytic stereoselective strategies involving both P-C[11] and C-C[12] coupling approaches.

As a part of our research program, aiming at the enantioselective synthesis of aminophosphonates, we have recently described stereoselective Michael additions of *N*-protected aminomethyl phosphonates to acrylic acid derivatives catalyzed by TADDOL.[12b] and sugar[12d] and BINOL[12e] based crown ethers. The stereoselective construction of a quaternary carbon stereocenter generated using a chiral catalyst, i.e. the synthesis of α-substituted α-aminophosphonates, appeared to be a logical extension of our research. Quaternary α-aminophosphonates could be useful for biomimetic research, because incorporation them into peptides may lend them increased rigidity and resistance to proteases. Although numerous α-substituted α-aminophosphonates were synthesised as racemates,[13] only a few enantioselective methods have been applied to this class of compounds.[14]

Optically active organocatalysts have acquired ever more importance in the enantioselective synthesis of chiral compounds.[15] Among them cinchona alkaloid derivatives proved to be excellent catalysts in enantioselective Michael additions.[16]

Herein, we report a new organocatalytic, enantioselective Michael addition of α-nitroethylphosphonates (**1**) to acrylic acid esters (**2**) (Scheme 1). The Michael adducts (**3**) can serve as direct precursors of optically active α-substituted α-aminophosphonic acids (**5**) (Scheme 3).

2. Results and discussion

2.1 Synthesis of α-nitrophosphonates

Our earlier attempts to promote addition of diethyl α-nitroethylphosphonate[17] (**1a**) to alkyl acrylates (**2**, R: ethyl or *t*-butyl) and benzyl acrylate (**2**, R: benzyl) failed in the presence of any of the catalysts **4a-n**. Using aryl acrylates[18] (**2a**, R: phenyl), however, the Michael reaction proceeded smoothly providing the expected substituted α-nitroethylphosphonate (**3a**, R: phenyl).

First both catalytic activity and selectivity in the Michael addition of a cyclohexanediamine based thiourea catalyst (**4a**), cinchonine (**4b**), quinidine (**4c**), cinchonidine (**4d**), quinine (**4e**), two bifunctional thiourea derivatives of cinchona alkaloids (**4f** and **4g**) and seven squaramide derivatives of cinchona alkaloids (**4h-n**) were tested (Scheme 1, Figure 1). Note, that while the cinchona based catalysts **4b-j** were already often used in

enantioselective syntheses, the benzyl squaramide derivative (**4k**) was only synthesised recently[19], and applied in a stereoselective C-C coupling reaction. The other benzyl squaramide derivatives (**4l-n**) are new. The reactions were performed at room temperature in toluene using 10 mol% of the catalyst. As it can be gleaned from Table 1, all of the catalysts, except **4m** provided the quaternary nitrophosphonate (**3a**) in excellent yield. While selectivity of the catalysts varied from low (**4a**, entry 1) to medium (**4b-e**, entries 2-5), the enantiomeric excess (ee) values were more promising with catalysts bearing a thiourea moiety (**4f** and **4g**, entries 6, 7).

Among the squaramide type catalysts (**4h-n**, entries 8-14) those in which the aromatic ring is next to the acidic NH showed reduced selectivity (**4h-j**, entries 8-10), while benzyl substituted squaramide derivatives provided the highest *ee* values (**4k, 4m** and **4n**, entries 11, 13 and 14). Although the ethyl chain on the bridged cycle (**4m**, entry 13) enhanced enantioselectivity the reaction slowed down probably due to poor solubility of the catalyst. The squaramide derivative possessing disubstituted benzyl group (**4l**, entry 12) showed one of the lowest selectivities among catalysts tested. Finally in the optimization experiments **4k** proved to be the most effective catalyst.

In order to optimize conditions of the Michael addition the effect of solvent, temperature and catalyst loading were examined using the best catalyst (**4k**). According to data in Table 2, toluene proved to be the best solvent both in terms of yield and stereoselectivity (entry 1). In more polar solvents, such as CH_2Cl_2, CH_3CN, THF, dioxane and anisole, yields were high, but selectivity decreased to medium values (entries 2-6). Relatively low enantioselectivity in xylene may be attributed to poor solubility of the catalyst (entry 7). Lowering the temperature to 0 and -30°C the reaction slowed down and also selectivity decreased (entries 8 and 9). Catalyst loading could be decreased from 10 to 5 mol% without loss of yield and selectivity (entry 10), while there was a slight drop of chiral induction was found when only 2 mol% of the catalyst was used (entry 11). Using butyl and isopropyl phosphonate esters did not affect reaction rate, but decreased enantioselectivity (entries 1-3).

Next, Michael reaction of ethyl α-nitroethylphosphonate (**1a**) with a range of aryl acrylates (**2a-t**) was examined. It can be seen from Table 3 that the reactions were quantitative with medium to excellent enantioselectivity with all aryl acrylates. It turned out, that acrylates having an electron-withdrawing group in any position in the aromatic ring afforded the adducts **3** with lower *ee* (entries 4-7 and 20) while aryl acrylates bearing electron-donating groups all gave good to excellent enantioselectivities (entries 8-13 and 15-19). No significant differences in ee values were, however, observed between the alkyl (entries 8-13) and the stronger electron-donating methoxy substituents (entries 15-19) whereas the position of the substituents seemed to have an impact on the selectivity. Thus. the bulky aryl esters furnished the adducts with best enantioselectivities, although with slightly lower rates (entries 13, 14 and 19). The highest *ee* values were observed for the 2,6-dimethoxyphenyl (**3t**, 96%, entry 19), the 2,6-dimethylphenyl (**3k**, 90%, entry 11) and the 2-methyl-4-*tert*-butylphenyl (**3m**, 89%, entry 13) derivatives.

2.2 Synthesis of α-aminophophonates

Since the most important synthetic utility of quaternary α-nitrophosphonate adducts (**3**) is the straightforwad access to quaternary α-aminophosphonates, catalytic hydrogenation of three representative examples (**3a, 3r** and **3t**) was performed to their cyclic α-aminophosphonates (Scheme 3). All hydrogenation reactions were carried out over a 10% Pd/C catalyst (Selcat Q[20]), in ethanol, under pressure. After 4 h reaction time, the conversion of **3** was complete at 10 bar and 30 °C. It was found that a mixture of two cyclic phosphonates, the expected lactame (**5**) and a cyclic imine (**6**) were formed in all cases. The ratio of **5** and **6** depended on both the pressure and the bulkiness of R group of **3**. At higher pressure (30 bar) the formation of **5** was favoured.

Furthermore, it was observed that the ratio of the expected **5** and the by-product **6** was the highest (6:1) in case of **3a** (R: phenyl) at 10 bar, while for **3r** (R: 2-MeOPh) it was 4.5:1, and for **3t** (R: 2,6-diMeOPh) was only 1:1. Increasing the pressure to 30 bar the latter ratio increased to 1.6:1. These significant differences, presumably, were due to the very stable and good leaving group (2,6-dimethylphenol) formed in a hydrogenolytic step providing an aldehyde intermediate, which could be responsible for the cyclic imine by-product in a higher ratio.

2.3 Calculations

The absolute configuration of a representative example (**3r**) of our Michael adducts was supported by quantum chemical calculations using the Gaussian 09 package.[21] Conformation analysis was carried out for the molecule using the Austin model 1 (AM1) method.[22] The five lowest energy conformers, which lie at maximum 6 kJ/mol above the most stable one, were considered in the subsequent calculations. The geometries for all of these conformers were further optimized at the density functional theory (DFT) level choosing the PBE0 functional[23,24] and the $6\text{-}311\text{++}G^{**}$ basis set. The optimized geometry for the most stable conformer is presented in Fig. 2. Vertical excitation energies as well as oscillator and rotator strengths (in the velocity gauge) were calculated for the conformers using the time-dependent DFT method[25] with the same functional and basis set. The theoretical absorption and CD curves were calculated as superpositions of individual Gaussian functions centered at the wavelengths of the theoretically calculated transitions and having heights proportional to the corresponding calculated oscillator and rotator strengths, respectively. The spectra of the individual conformers were Boltzmann-weighted. The simulated spectra were normalized so that the height of the most intense band should be identical to that of the experimental spectra. Further the spectra were shifted by 20 nm towards red so that the position of the most intense band of the absorption spectra should be identical (Figure 3). The agreement of the experimental and theoretical absorption spectra of the compound is satisfactory and justifies the selection of the applied theoretical model. The signs of the dominant features in the measured and computed CD spectra are identical, thus the absolute configuration of the synthesized compound is identical to that for the isomers considered in the calculations. Consequently, we can conclude that the absolute configuration of the obtained stereoisomer is *S* (Figure 2).

It is expected that the absolute configuration for the remaining examples can be assigned by analogy to be the same with all catalysts, except for **4d** and **4e**. These catalysts generated the opposite enantiomer (see Table 1, entries 4, 5).

3. **Conclusions**

In summary, benzyl substituted cinchona based squaramide were used the first time to catalyse a highly enantioselective Michael addition of α-nitroethylphosphonates to acrylic acid aryl esters. By comparing the experimental and quantum chemically calculated CD spectra the absolute configuration of one of the adducts (**3r**) could be deduced to be *S*. The cyclic quaternary aminophosphonate (**5**) has been obtained by catalytic hydrogenation of any of the three the Michael adducts **3a**, **3r** and **3t**.

4. **Experimental**

4.1. General

NMR spectra were recorded on Bruker Avance-DRX-500 and 300 instruments using tetramethylsilane (^{1}H, ^{13}C) as internal standard and 85% H_3PO_4 (^{31}P) as external standard, in $CDCl_3$ solution, except as otherwise stated. Low resolution MS measurements were carried out on an AB Sciex API2000 tandem mass spectrometer coupled with a Perkin Elmer Series 200 LC system. Samples were measured either in electrospray (ESI) or in atmospheeric pressure chemical ionization (APCI) mode. Source conditions were: spray voltage (ESI): 5000 V, needle current (APCI): 4 μA, drying temperature (ESI): 300 °C, vaporizer temperature (APCI): 300 °C, nebulizing gas: 40 psi, drying gas: 40 psi, declustering potential: 30 V, scan range: 50-Da, scan time: 1 sec. All parameters were controlled and the data were processed by Analyst 1.5 software. High-resolution MS measurements were carried out on a Waters Q-TOF Premier mass spectrometer operated in ESI positive ionization mode. The HPLC measurements were carried out on a Jasco PU 1580 apparatus equipped with a Jasco UV1575 detector. Optical rotations were measured with Perkin Elmer 241 polarimeter at room temperature. Circular dichroism spectra were taken on a Jasco J-810 spectropolarimeter.

4.2. Synthesis of α-nitroethylphosphonates 1

The procedure described in ref. 17 was followed.

4.2.1. (1-Nitroethyl)-phosphonic acid diethyl ester (1a)[17b] Purification by distillation, bp: 82–92 °C/0.2 mmHg. Pale yellow oil. Yield: 68%. ^{1}H NMR (500 MHz): δ 1.38 (t, J = 6.8 Hz, 3H), 1.39 (t, J = 6.9 Hz, 3H), 1.82 (dd, J_{HP} = 16.2 Hz, J_{HH} = 7.2 Hz, 3H), 4.10–4.35 (m, 4H), 4.95–5.06 (m, 1H). ^{13}C NMR (75.5 MHz) δ 14.51 (d, J_{HP} = 3.7 Hz CH_3), 16.30 (d, J_{HP} = 3.9 Hz, CH_3), 16.38 (d, J_{HP} = 3.6 Hz, CH_3), 64.25 (d, J_{PC} = 6.4 Hz, OCH_2), 64.42 (d, J_{PC} = 6.9 Hz, OCH_2), 79.51 (d, J_{HP} = 144.5 Hz, PCH). ^{31}P NMR (121.5 MHz) δ 13.62.

4.2.2. (1-Nitroethyl)-phosphonic acid diisopropyl ester (1b)[17a] Purification by distillation, bp: 88–95 °C/0.2 mmHg. Pale yellow oil. Yield: 63%. ^{1}H NMR (500 MHz) δ 1.64 (m, 12H), 1.79 (dd, J_{HP} = 16.1 Hz, J_{HH} = 7.1 Hz, 3H), 4.71–4.85 (m, 2H), 4.86–5.05 (m, 1H). ^{13}C NMR (75.5 MHz) δ 14.74 (d, J_{HP} = 3.8 Hz, CH_3), 23.78 (d, J_{HP} = 5.4 Hz, CH_3), 23.83 (d, J_{HP} = 5.3 Hz, CH_3), 24.15 (d, J_{HP} = 5.2 Hz, CH_3), 24.22 (d, J_{HP} = 5.0 Hz, CH_3), 73.53 (d, J_{HP} = 2.5 Hz, CH), 73.62, (d, J_{HP} = 2.9 Hz, CH) 80.2 (d, J_{HP} = 145.1 Hz, PCH). ^{31}P NMR (121.5 MHz) δ 11.5.

4.2.3. (**1-Nitroethyl)-phosphonic acid dibutyl ester (1c)** Purification by column chromatography (eluent: ethyl acetate–hexane = 7:3) Oil. Yield: 71%. ^{1}H NMR (500 MHz) δ 0.88 (t, J = 7.3 Hz, 3H), 1.23–1.40 (m, 2H), 1.53–1.65 (m, 2H), 1.74 (dd, J_{HP} = 16.2 Hz, J_{HH} = 7.2 Hz, 3H), 4.06–4.16 (m, 2H), 4.85–5.03 (m, 1H). ^{13}C NMR (75.5 MHz) δ 13.75 (CH_3), 14.71 (d, J_{PC} = 3.8 Hz, CH_3), 18.80 (d, J_{PC} = 2.2 Hz, CH_2), 32.56 (d, J_{PC} = 4.0 Hz, CH_2), 32.64 (d, J_{PC} = 3.9 Hz, CH_2), 68.09 (d, J_{PC} = 6.9 Hz, OCH_2), 68.22 (d, J_{PC} = 7.2 Hz, OCH_2), 79.59 (d, J_{PC} = 144.3 Hz, PCH). ^{31}P NMR (121.5 MHz) 13.5. MS (APCI) M/z (rel intensity) 268.3 ([MH^+], 48), 212.0 (52), 156.0 (100), 110.1 (34).

4.3. Synthesis of aryl acrylates 2

The procedure discribed in ref. 18 was followed. The crude products were purified by column chromatography (eluent: hexane–ethyl acetate = 8:2).

4.3.1. **Acrylic acid phenyl ester (2a)**[18] Oil. Yield: 78%. ^{1}H NMR (300 MHz) δ 6.01 (d, J = 10.4 Hz, 1H), 6.32 (dd, J = 17.3, 10.4 Hz, 1H), 6.60 (d, J = 17.3 Hz, 1H), 7.18 (d, J = 7.6 Hz, 2H_{Ar}), 7.24 (t, J = 8.3 Hz, 1H_{Ar}), 7.34 (dd, J = 8.3, 7.6 Hz, 2H_{Ar}). ^{13}C NMR (75.5 MHz) δ 121.75 (Ar), 126.09 (Ar), 128.20 (CH_2=$\underline{CH}$), 129.66 (Ar), 132.73 ($\underline{CH_2}$=CH), 150.82 (Ar_q), 164.77 (CO).

4.3.2. Acrylic acid 4-chlorophenyl ester (2b) Oil. Yield: 85%. ^{1}H NMR (300 MHz) δ 6.02 (d, J = 11.6 Hz, 1H), 6.30 (dd, J = 17.3, 11.6 Hz, 1H), 6.60 (d, J = 17.3 Hz, 1H), 7.08 (d, J = 8.8 Hz, 2H), 7.35 (d, J = 8.8 Hz, 2H). ^{13}C NMR (75.5 MHz) δ 122.87 (Ar), 126.45 (CH_2=$\underline{CH}$), 130.90 (Ar_q), 131.81 (Ar), 133.10 ($\underline{CH_2}$=CH), 149.64 (Ar_q), 161.25 (CO).

4.3.3. Acrylic acid 4-nitrophenyl ester (2c) Oil. Yield: 83%. ^{1}H NMR (300 MHz) δ 6.13 (d, J = 10.5 Hz, 1H), 6.36 (dd, J = 17.4, 10.5 Hz, 1H), 6.65 (d, J = 17.4 Hz, 1H), 8.21 (d, J = 9.0 Hz, 2H), 8.29 (d, J = 9.0 Hz, 2H). ^{13}C NMR (75.5 MHz) δ 120.42 (Ar), 126.87 (CH_2=$\underline{CH}$), 127.11 (Ar), 132.38 ($\underline{CH_2}$=CH), 143.65, (Ar_q), 158.64 (Ar_q), 161.35 (CO).

4.3.4. Acrylic acid 3-nitrophenyl ester (2d) Oil. Yield: 77%. ^{1}H NMR (300 MHz): δ 6.17 (d, J = 10.4 Hz, 1H), 6.37 (dd, J = 17.3, 10.4 Hz, 1H), 6.66 (d, J = 17.3 Hz, 1H), 7.31–7.65 (m, 2H), 7.95–8.16 (m, 2H). ^{13}C NMR (75.5 MHz) δ 117.71 (Ar), 120.81 (Ar), 127.15 (CH$_2$=$\underline{CH}$), 127.52 (Ar), 131.75 (Ar), 132.91 ($\underline{CH_2}$=CH), 149.12 (Ar$_q$), 151.72 (Ar$_q$), 161.45 (CO).

4.3.5. Acrylic acid 2-nitrophenyl ester (2e) Oil. Yield: 78%. ^{1}H NMR (300 MHz): δ 6.12 (d, J = 10.5 Hz, 1H), 6.37 (dd, J = 17.3, 10.5 Hz, 1H), 6.67 (d, J = 17.3 Hz, 1H), 7.30 (d, J = 8.1 Hz, 1H), 7.40–7.44 (m, 1H), 7.66–7.69 (m, 1H), 8.11 (d, J = 8.2 Hz, 1H). ^{13}C NMR (75.5 MHz) δ 122.42 (Ar), 125.22 (Ar), 126.87 (CH$_2$=$\underline{CH}$), 127.52 (Ar), 132.38 ($\underline{CH_2}$=CH), 133.67 (Ar), 138.20 (Ar$_q$), 146.75 (Ar$_q$), 162.88 (CO).

4.3.6. Acrylic acid *p*-tolyl ester (2f) Oil. Yield: 70%. ^{1}H NMR (300 MHz) δ 2.39 (s, 3H), 6.02 (d, J =10.4 Hz, 1H), 6.38 (dd, J = 17.2, 10.4 Hz, 1H), 6.62 (d, J = 17.2 Hz, 1H), 7.05 (d, J = 8.3 Hz, 2H$_{Ar}$), 7.22 (d, J = 8.3 Hz, 2H$_{Ar}$). ^{13}C NMR (75.5 MHz) δ 21.05 (CH$_3$), 121.37 (Ar), 128.22 (CH$_2$=$\underline{CH}$), 130.12 (Ar), 132.49 ($\underline{CH_2}$=CH), 135.67 (Ar$_q$), 148.34 (Ar$_q$), 164.92 (CO).

4.3.7. Acrylic acid *m*-tolyl ester (2g) Oil. Yield: 75%. ^{1}H NMR (300 MHz) δ 2.39 (s, 3H), 6.02 (d, J =10.4 Hz, 1H), 6.34 (dd, J = 17.4, 10.4 Hz, 1H), 6.62 (d, J = 17.4 Hz, 1H), 6.93–7.02 (m, 2H$_{Ar}$), 7.07 (d, J = 7.07 Hz, 1H$_{Ar}$), 7.29 (m, 1H$_{Ar}$). ^{13}C NMR (75.5 MHz) δ 21.38 (CH$_3$), 118.51 (Ar), 122.16 (Ar), 126.32 (Ar), 128.09 (CH$_2$=$\underline{CH}$), 129.20 (Ar), 132.44 ($\underline{CH_2}$=CH), 139.69 (Ar$_q$), 150.59 (Ar$_q$), 164.72 (CO).

4.3.8. Acrylic acid *o*-tolyl ester (2h) Oil. Yield: 77%. ^{1}H NMR (300 MHz) δ 2.35 (s, 3H), 6.03 (d, J = 10.5 Hz, 1H), 6.37 (dd, J = 17.3, 10.5 Hz, 1H), 6.62 (d, J = 17.3 Hz, 1H), 7.02–7.04(m, 2H$_{Ar}$), 7.12–7.16 (m, 1H$_{Ar}$), 7.18–7.19 (m, 1H$_{Ar}$). ^{13}C NMR (75.5 MHz) δ 16.31 (CH$_3$), 119.03 (Ar), 125.74 (Ar), 126.71 (Ar), 127.18 (CH$_2$=$\underline{CH}$), 128.32 (Ar), 129.78 (Ar$_q$), 133.26 ($\underline{CH_2}$=CH), 152.74 (Ar$_q$), 164.67 (CO).

4.3.9. Acrylic acid 2,6-dimethylphenyl ester (2i) Oil. Yield: 74%. ^{1}H NMR (300 MHz) δ 2.15 (s, 6H), 6.01 (d, J = 10.4 Hz, 1H), 6.37 (dd, J = 17.3, 10.4 Hz, 1H), 6.64 (d, J = 17.3 Hz, 1H), 7.06 (s, 3H$_{Ar}$). ^{13}C NMR (75.5 MHz) δ 16.51 (CH$_3$), 126.12 (CH$_2$=$\underline{CH}$), 127.79 (Ar), 128.79 (Ar), 130.42 (Ar), 132.71 ($\underline{CH_2}$=CH), 148.22 (Ar$_q$), 164.03 (CO).

4.3.10. Acrylic acid 4-*tert*-butylphenyl ester (2j) Oil. Yield: 81%. ^{1}H NMR (300 MHz) δ 1.32 (s, 9H), 5.99 (d, J = 10.4 Hz, 1H), 6.32 (dd, J = 17.3, 10.4 Hz, 1H), 6.59 (d, J= 17.3 Hz, 1H), 7.05 (d, J = 8.6 Hz, 2H$_{Ar}$), (d, J = 8.6 Hz, 2H$_{Ar}$). ^{13}C NMR (75.5 MHz) δ 31.64 (CH$_{3q}$), 34.70 (C$_q$), 121.02 (Ar), 126.54 (CH$_2$=$\underline{CH}$), 128.29 (Ar), 132.53 ($\underline{CH_2}$=CH), 148.44 (Ar$_q$), 148.87 (Ar$_q$), 164.93 (CO).

4.3.11. Acrylic acid 4-*tert*-butyl-2-methylphenyl ester (2k) Oil. Yield: 68%. ^{1}H NMR (300 MHz) δ 1.38 (s, 9H), 2.25 (s, 3H), 6.03 (d, J = 10.4 Hz, 1H), 6.39 (dd, J = 17.3, 10.4 Hz, 1H), 6.66 (d, J = 17.3 Hz, 1H), 7.04 (d, J = 8.2 Hz, 1H), (d, J = 9.6 Hz, 2H). ^{13}C NMR (75.5 MHz) δ 16.65 (CH$_3$), 31.64 (CH$_{3q}$), 34.70 (C$_q$), 121.32 (Ar), 124.10 (Ar), 128.15 (CH$_2$=$\underline{CH}$), 128.37 (Ar), 129.38 (Ar$_q$), 132.51 ($\underline{CH_2}$=CH), 147.06 (Ar$_q$), 149.02 (Ar$_q$), 164.69 (CO).

4.3.12. Acrylic acid naphtalen-2-yl ester (2l) Oil. Yield: 78%. ^{1}H NMR (300 MHz) δ 6.04 (d, J = 10.4 Hz, 1H), 6.37 (dd, J = 17.2, 10.4 Hz, 1H), 6.65 (d, J = 17.2 Hz, 1H), 7.27 (dd, J = 8.9 Hz, 2.1 Hz, 1H$_{Ar}$), 7.41-7.54 (m, 2H$_{Ar}$), 7.61 (d, J = 1.4 Hz, 1H), 7.76- 7.81 (m, 3H$_{Ar}$). ^{13}C NMR (75.5 MHz) δ 118.58 (Ar), 126.64 (Ar), 127.74 (CH$_2$=$\underline{CH}$), 127.84 (Ar), 128.04 (Ar), 129.48 (Ar), 131.56 (Ar$_q$), 132.72 ($\underline{CH_2}$=CH), 133.83 (Ar$_q$), 148.31 (Ar$_q$), 164.77 (CO).

4.3.13. Acrylic acid 4-methoxyphenyl ester (2m) Oil. Yield: 81%. ^{1}H NMR (300 MHz, CDCl$_3$) δ 3.81 (s, 3H), 6.02 (d, J = 10.4 Hz, 1H), 6.32 (dd, J = 17.4, 10.4 Hz, 1H), 6.61 (d, J = 17.4 Hz, 1H), 6.92 (d, J = 9.0 Hz, 2H), 7.06 (d, J = 9.0 Hz, 2H). ^{13}C NMR (75.5 MHz) δ 55.54 (CH$_3$), 116.51 (Ar), 122.95 (Ar), 127.18 (CH$_2$=$\underline{CH}$), 133.21 ($\underline{CH_2}$=CH), 147.78 (Ar$_q$), 158.72 (Ar$_q$), 162.58 (CO).

4.3.14. Acrylic acid 3-methoxyphenyl ester (2n) Oil. Yield: 77%. ^{1}H NMR (300 MHz) δ 3.81 (s, 3H), 6.02 (d, J = 10.4 Hz, 1H), 6.34 (dd, J = 17.3, 10.4 Hz, 1H), 6.63 (d, J = 17.3 Hz, 1H), 6.66 (t, J = 2.2 Hz, 1H$_{Ar}$), 6.77 (dd, J = 8.2 Hz, 2.2 Hz, 1H) 6.82 (dd, J = 8.2 Hz, 2.1 Hz, 1H), 7.31 (t, J = 8.2 Hz, 1H). ^{13}C NMR (75.5 MHz) δ 55.65 (CH$_3$), 107.75

(Ar), 112.03 (Ar), 113.95 (Ar), 128.18 (CH$_2$=$\underline{CH}$), 130.05 (Ar), 132.76 ($\underline{CH_2}$=CH), 151.78 (Ar$_q$), 160.74 (Ar$_q$), 164.67 (CO).

4.3.15. Acrylic acid 2-methoxyphenyl ester (2o) Oil. Yield: 77%. ^{1}H NMR (300 MHz) δ 3.77 (s, 3H), 5.95 (d, J = 10.5 Hz, 1H), 6.33 (dd, J = 17.3, 10.5 Hz, 1H), 6.68 (d, J = 17.3 Hz, 1H), 7.04–7.06 (m, 2H), 7.16–7.17 (m, 1H), 7.18–7.19 (m, 1H). ^{13}C NMR (75.5 MHz) δ 55.84 (CH$_3$), 119.75 (Ar), 125.55 (Ar), 125.74 (Ar), 126.61 (Ar), 127.18 (CH$_2$=$\underline{CH}$), 133.26 ($\underline{CH_2}$=CH), 148.78 (Ar$_q$), 152.74 (Ar$_q$), 162.67 (CO).

4.3.16. Acrylic acid 3,5-dimethoxyphenyl ester (2p) Oil. Yield: 81%. ^{1}H NMR (300 MHz) δ 3.79 (s, 6H), 6.03 (d, J = 10.4 Hz, 1H), 6.32 (dd, J = 17.3, 10.4 Hz, 1H), 6.33 (d, J = 2.1 Hz, 2H$_{Ar}$), 6.38 (d, J = 2.1 Hz, 1H$_{Ar}$), 6.62 (d, J = 17.3 Hz, 1H). ^{13}C NMR (75.5 MHz) δ 55.73 (CH$_3$), 98.63 (Ar), 100.37 (Ar), 128.15 (CH$_2$=$\underline{CH}$), 132.81 ($\underline{CH_2}$=CH), 152.35 (Ar$_q$), 161.38 (Ar$_q$), 164.59 (CO).

4.3.17. Acrylic acid 2,6-dimethoxyphenyl ester (2r) Oil. Yield: 70%. ^{1}H NMR (300 MHz) δ 3.81 (s, 6H), 6.01 (d, J = 10.4 Hz, 1H), 6.35 (dd, J = 17.3, 10.4 Hz, 1H), 6.62 (d, J = 8.4 Hz, 2H$_{Ar}$), 6.63 (d, J = 17.3 Hz, 1H), 7.14 (t, J = 8.4 Hz, 1H$_{Ar}$). ^{13}C NMR (75.5 MHz) δ 56.36 (CH$_3$), 105.12 (Ar), 126.51 (Ar), 127.68 (CH$_2$=$\underline{CH}$), 128.76 (Ar$_q$), 132.63 ($\underline{CH_2}$=CH), 152.58 (Ar$_q$), 164.04 (CO).

4.3.18. 4-Acryloyloxy benzoic acid methyl ester (2s) Pale yellow solid. mp: 69–72°C. Yield: 58%. ^{1}H NMR (300 MHz) δ 3.92 (s, 3H), 6.06 (d, J = 10.4 Hz, 1H), 6.32 (dd, J = 17.3, 10.5 Hz, 1H), 6.63 (d, J = 17.3 Hz, 1H), 7.23 (d, J = 8.5 Hz, 2H$_{Ar}$), 8.09 (d, J = 8.5 Hz, 2H$_{Ar}$). ^{13}C NMR (75.5 MHz) δ 50.85 (CH$_3$), 121.51 (Ar), 127.22 (CH$_2$=$\underline{CH}$), 128.13 (Ar$_q$), 133.69 ($\underline{CH_2}$=CH), 133.91 (Ar), 155.78 (Ar$_q$), 162.58 (CO), 165.33 (CO).

4.3.19. Acrylic acid benzo[1,3]dioxolyl ester (2t) Oil. Yield: 80%. ^{1}H NMR (300 MHz) δ 5.97 (s, 2H), 5.99 (dd, J = 10.4, 1.2 Hz, 1H), 6.28 (dd, J = 17.3, 10.4 Hz, 1H), 6.57 (dd, J = 8.4 Hz, 2.3 Hz, 1H$_{Ar}$), 6.58 (dd, J = 17.2 Hz, 1.3 Hz, 1H), 6.65 (d, J = 2.3 Hz 1H$_{Ar}$), 6.78 (d, J= 8.4 Hz, 1H$_{Ar}$). ^{13}C NMR (75.5 MHz) δ 101.76 (OCH$_2$O), 103.58 (Ar), 108.03 (Ar), 113.94 (Ar), 127.88 (CH$_2$=$\underline{CH}$), 132.61 ($\underline{CH_2}$=CH), 144.93 (Ar$_q$), 145.50 (Ar$_q$), 148.07 (Ar$_q$), 164.87 (CO).

4.4. Typical procedure for the synthesis of 3

To a solution of 0.25 mmol dialkyl α-nitroethyl-phosphonate **1** and 0.125 mmol catalyst **4** in toluene (4 ml) aryl acrylate **2** (0.3 mmol) dissolved also in toluene (2ml) was added. The reaction mixture was stirred at room temperature and monitored by TLC. The toluene was evaporated and the residue was purified by column chromatography on silica gel using ethyl acetate–hexane = 7:3 as an eluent. The catalyst was also recovered during column chromatography.

4.4.1. 4-(Diethoxyphosphoryl)-4-nitropentanoic acid phenyl ester (3a) Oil. Yield: 93%. HPLC conditions: Kromasil Amycoat (hexane–EtOH = 95:5, flow rate 0.3 ml/min, 220 nm, 5 °C) t_{minor} = 91.0 min and t_{major} = 102.3 min. ^{1}H NMR (500 MHz) δ 1.38 (t, J = 7.2 Hz, 6H), 1.85 (d, J = 14.4 Hz 3H), 2.48–2.63 (m, 1H), 2.65–2.75 (m, 2H), 2.75–2.81 (m, 1H), 4.19–4.31 (m, 4H), 7.08 (d, J = 8.4 Hz, 2H), 7.24 (t, J = 7.7 Hz, 1H), 7.29–7.4 (m, 2H). ^{13}C NMR (75.5 MHz) δ 16.54 (CH$_3$), 16.64 (CH$_3$), 20.29 (d, J_{PC} = 1.6 Hz, CH$_3$), 28.29 (d, J_{PC} = 8.3 Hz, CH$_2$), 30.57 (CH$_2$), 64.68 (d, J_{PC} = 7.1 Hz, OCH$_2$), 64.75 (d, J_{PC} = 6.9 Hz, OCH$_2$), 89.24 (d, J_{PC} = 150.2 Hz, PC), 126.23 (Ar), 128.86 (Ar), 130.17 (Ar), 148.20 (Ar$_q$), 169.89 (CO). ^{31}P NMR (121.5 MHz) δ 16.3. MS (ESI) M/z (rel intensity) 360.1 ([MH$^+$], 100), 266.2 (31), 238.2 (4).

4.4.2. 4-(Diisopropyloxyphosphoryl)-4-nitropentanoic acid phenyl ester (3b) Oil. Yield: 85%. HPLC conditions: Kromasil Amycoat (hexane–EtOH = 95:5, flow rate 0.3 ml/min, 220 nm, 5°C) t_{minor} = 54.3 min and t_{major} = 58.7 min. ^{1}H NMR (500 MHz) δ 1.37 (d, J = 6.2 Hz, 6H), 1.38 (d, J = 5.9 Hz, 3H), 1.39 (d, J = 6.3 Hz, 3H), 1.84 (d, J_{PH} = 14.4 Hz, 3H), 2.44–2.57 (m, 1H), 2.62–2.78 (m, 2H), 2.80–2.92 (m, 1H), 4.76–4.88 (m, 2H), 7.08 (d, J = 8.4 Hz, 2H), 7.24 (t, J = 7.5 Hz, 1H), 7.38 (dd, J = 8.4, 5.5 Hz, 2H). ^{13}C NMR (75.5 MHz) δ 20.09 (d, J_{PC} = 1.7 Hz, CH$_3$), 23.77 (d, J_{PC} = 1.5 Hz, CH$_3$), 23.85 (d, J_{PC} = 1.5 Hz, CH$_3$), 24.39 (d, J_{PC} = 3.5 Hz, CH$_3$), 24.44 (d, J_{PC} = 3.5 Hz, CH$_3$), 29.15 (d, J_{PC} = 3.5 Hz, CH$_2$), 30.82 (CH$_2$), 89.31 (d, J_{PC} = 150.3 Hz, PC), 121.62 (Ar), 126.21 (Ar), 129.68 (Ar), 150.71 (Ar$_q$), 170.74 (CO). [31]P

NMR (121.5 MHz) δ 14.3. MS (APCI) M/z (rel intensity) 388.2 ([MH$^+$], 51), 346.4 (27), 304.1 (34), 294.7 (7), 252.2 (19), 210.0 (100), 122.9 (16).

4.4.3. 4-(Dibutoxyphosphoryl)-4-nitropentanoic acid phenyl ester (3c) Oil. Yield: 82%. HPLC conditions: Kromasil Amycoat (hexane–EtOH = 95:5, flow rate 0.3 ml/min, 220 nm, 5°C) t_{minor} = 21.8 min and t_{major} = 24.8 min. ^{1}H NMR (500 MHz) δ 0.95 (t, J = 7.3 Hz, 3H), 1.37–1.45 (m, 2H), 1.62–1.73 (m, 2H), 1.86 (d, J = 14.4 Hz, 3H), 2.48–2.64 (m, 1H), 2.62–2.81 (m, 2H), 2.81–2.94 (m, 1H), 4.11–4.25 (m, 4H), 7.08 (d, J = 7.7 Hz, 2H), 7.25 (t, J = 7.4 Hz, 1H), 7.38–7.41 (m, 2H). ^{13}C NMR (75.5 MHz) δ 13.60 (CH$_3$), 13.64 (CH$_3$), 18.70 (CH$_2$), 20.07 (d, J_{PC} = 1.7 Hz, CH$_3$), 28.95 (d, J_{PC} = 8.3 Hz, CH$_2$), 30.74 (CH$_2$), 32.34 (d, J_{PC} = 1.1 Hz, CH$_2$), 32.50 (d, J_{PC} = 1.1 Hz, CH$_2$), 68.18 (d, J_{PC} = 7.7 Hz, OCH$_2$), 68.28 (d, J_{PC} = 7.7 Hz, OCH$_2$), 89.05 (d, J_{PC} = 150.2 Hz, PC), 121.44 (Ar), 126.06 (Ar), 129.52 (Ar), 150.51 (Ar$_q$), 170.45 (CO). ^{31}P NMR (121.5 MHz) δ 16.8. MS (APCI) M/z (rel intensity) 416.2 ([MH$^+$], 94), 340.2 (20), 322.3 (93), 266.3 (85), 210.0 (100).

4.4.4. 4-(Diethoxyphosphoryl)-4-nitropentanoic acid 4-chlorophenyl ester (3d) Oil. Yield: 92%. HPLC conditions: Kromasil Cellucoat (hexane–EtOH = 9:1, flow rate 0.3 ml/min, 220 nm, 10 °C) t_{major} = 36.0 min and t_{minor} = 39.4 min. ^{1}H NMR (500 MHz) δ 1.38 (t, J = 7.1 Hz, 3H), 1.85 (d, J = 14.3 Hz, 3H), 2.44–2.60 (m, 1H), 2.62–2.79 (m, 2H), 2.79–2.90 (m, 1H), 4.20–4.38 (m, 4H), 7.03 (d, J = 8.8 Hz, 2H), 7.34 (d, J = 8.8 Hz, 2H). ^{13}C NMR (75.5 MHz) δ 16.60 (CH$_3$), 16.64 (CH$_3$), 20.37 (d, J_{PC} = 1.4 Hz, CH$_3$), 29.11 (d, J_{PC} = 8.2 Hz, CH$_2$), 30.86 (CH$_2$), 64.74 (d, J_{PC} = 7.1 Hz, OCH$_2$), 64.79 (d, J_{PC} = 7.1 Hz, OCH$_2$), 89.11 (d, J_{PC} = 150.5 Hz, PC), 123.0 (Ar), 129.76 (Ar), 131.63 (Ar$_q$), 149.14 (Ar$_q$), 170.44 (CO). ^{31}P NMR (121.5 MHz) δ 16.2. MS (APCI) M/z (rel intensity) 394.4 ([MH$^+$], 44), 266.3 (100), 238.2 (57), 210.2 (56), 163.1 (10), 123.1 (11).

4.4.5. 4-(Diethoxyphosphoryl)-4-nitropentanoic acid 4-nitrophenyl ester (3e) Oil. Yield: 92%. HPLC conditions: Kromasil Cellucoat (hexane–EtOH = 9:1, flow rate 0.5 ml/min, 256 nm, 10 °C) t_{major} = 54.2 min and t_{minor} = 63.4 min ^{1}H NMR (500 MHz) δ 1.39 (t, J = 7.1 Hz, 3H), 1.87 (d, J = 14.4 Hz, 3H), 2.43–2.61 (m, 1H), 2.79–2.90 (m, 3H), 4.20–4.38 (m, 4H), 7.29 (d, J = 9.1 Hz, 2H), 8.28 (d, J = 9.1 Hz, 2H). ^{13}C NMR (75.5 MHz) δ 16.40 (CH$_3$), 16.48 (CH$_3$), 20.45 (d, J_{PC} = 1.8 Hz, CH$_3$), 29.03 (d, J_{PC} = 7.8 Hz, CH$_2$), 30.57 (CH$_2$), 64.66 (d, J_{PC} = 7.0 Hz, OCH$_2$), 64.75 (d, J_{PC} = 7.0 Hz, OCH$_2$), 88.81 (d, J_{PC} = 151.1 Hz, PC), 122.40 (Ar), 125.31 (Ar), 145.51 (Ar$_q$), 155.13 (Ar$_q$), 169.61 (CO). ^{31}P NMR (121.5 MHz) δ 16.1. M/z (APCI) (rel intensity) 405.3 ([MH$^+$], 48), 266.4 (100), 238.2 (73), 210.3(66), 163.2 (18), 123.0 (21).

4.4.6. 4-(Diethoxyphosphoryl)-4-nitropentanoic acid 3-nitrophenyl ester (3f) Oil. Yield: 93%. HPLC conditions: Kromasil Cellucoat (hexane–EtOH = 9:1, flow rate 0.5 ml/min, 256 nm, 10 °C) t_{major} = 46.4 min and t_{minor} = 51.6 min. ^{1}H NMR (500 MHz) δ 1.39 (t, J = 7.1 Hz, 3H), 1.88 (d, J = 14.3 Hz, 3H), 2.45–2.62 (m, 1H), 2.78–2.90 (m, 3H), 4.21–4.38 (m, 4H), 7.47 (dd, J = 8.1, 1.3 Hz, 1H), 7.58 (dd, J = 8.2, 8.1 Hz, 1H), 8.01 (s, 1H), 8.12 (dd, J = 8.2, 1.3 Hz, 1H). ^{13}C NMR (75.5 MHz) δ 16.56 (CH$_3$), 16.63 (CH$_3$), 20.60 (d, J_{PC} = 1.8 Hz, CH$_3$), 29.11 (d, J_{PC} = 7.9 Hz, CH$_2$), 30.79 (CH$_2$), 64.67 (d, J_{PC} = 7.5 Hz, OCH$_2$), 64.83 (d, J_{PC} = 7.2 Hz, OCH$_2$), 89.02 (d, J_{PC} = 150.9 Hz, PC), 117.49 (Ar), 121.17 (Ar), 128.16 (Ar), 130.34 (Ar), 148.99 (Ar$_q$), 150.91 (Ar$_q$), 170.11 (CO). ^{31}P NMR (121.5 MHz) δ 16.1. MS (APCI) M/z (rel intensity) 405.3 ([MH$^+$], 65), 266.0 (100), 238.0 (54), 219.9 (14), 209.9 (32), 179.3 (10), 126.1 (11).

4.4.7. 4-(Diethoxyphosphoryl)-4-nitropentanoic acid 2-nitrophenyl ester (3g) Oil. Yield: 90%. HPLC conditions: Chiralpak AD-H (hexane–EtOH = 95:5, flow rate 0.8 ml/min, 254 nm, 10 °C) t_{minor} = 74.9 min and t_{major} = 83.6 min. ^{1}H NMR (500 MHz) δ 1.40 (t, J = 7.2 Hz, 3H), 1.89 (d, J = 14.4 Hz, 3H), 2.43–2.64 (m, 1H), 2.80–3.0 (m, 3H), 4.21–4.41 (m, 4H), 7.27 (d, J = 7.9 Hz, 1H), 7.43 (dd, J = 8.3, 1.1 Hz, 1H), 7.69 (dd, J = 7.9, 1.3 Hz, 1H), 8.14 (dd, J = 8.3, 1.3 Hz, 1H). ^{13}C NMR (75.5 MHz) δ 16.57 (CH$_3$), 16.64 (CH$_3$), 20.40 (d, J_{PC} = 1.6 Hz, CH$_3$), 28.99 (d, J_{PC} = 8.1 Hz, CH$_2$), 30.65 (CH$_2$), 64.71 (d, J_{PC} = 7.2 Hz, OCH$_2$), 64.80 (d, J_{PC} = 7.0 Hz, OCH$_2$), 89.13 (d, J_{PC} = 150.5 Hz, PC), 125.40

(Ar), 126.15 (Ar), 127.09 (Ar), 135.16 (Ar), 141.74 (Ar$_q$), 144.13 (Ar$_q$), 169.97 (CO). ^{31}P NMR (121.5 MHz) δ 15.6. MS (ESI) M/z (rel intensity) 405.3 ([MH$^+$], 100), 390.4 (14), 266.3 (95), 238.0(10), 210.1(4).

4.4.8. 4-(Diethoxyphosphoryl)-4-nitropentanoic acid *p*-tolyl ester (3h) Oil. Yield: 91%. HPLC conditions: Kromasil Amycoat (hexane–EtOH = 95:5, flow rate 0.3 ml/min, 256 nm, 10 °C) t_{minor} = 117.5 min and t_{major} = 127.1 min. ^{1}H NMR (500 MHz) δ 1.38 (t, *J* = 7.1 Hz, 3H), 1.85 (d, *J* = 14.4 Hz), 2.34 (s, 3H), 2.44–2.60 (m, 1H), 2.62–2.79 (m, 2H), 2.80–2.91 (m, 1H), 4.21–4.31 (m, 4H), 6.95 (d, *J* = 8.3 Hz, 2H), 7.17 (d, *J* = 8.3 Hz, 2H). ^{13}C NMR (75.5 MHz) δ 16.58 (CH$_3$), 16.65 (CH$_3$), 20.18 (d, J_{PC} = 1.6 Hz, CH$_3$), 21.08 (CH$_{3Ar}$), 29.10 (d, J_{PC} = 8.4 Hz, CH$_2$), 30.93 (CH$_2$), 64.63 (d, J_{PC} = 7.1 Hz, OCH$_2$), 64.78 (d, J_{PC} = 7.1 Hz, OCH$_2$), 89.20 (d, J_{PC} = 150.3 Hz, PC), 121.26 (Ar), 130.19 (Ar), 135.88 (Ar$_q$), 148.46 (Ar$_q$), 170.82 (CO). ^{31}P NMR (121.5 MHz) δ 16.3. MS (APCI) M/z (rel intensity) 374.1 ([MH$^+$], 40), 266.3 (100), 238.2 (38), 210.3 (13).

4.4.9. 4-(Diethoxyphosphoryl)-4-nitropentanoic acid *m*-tolyl ester (3i) Oil. Yield: 90%. HPLC conditions: Kromasil Cellucoat (hexane–EtOH = 9:1, flow rate 0.3 ml/min, 256 nm, 10 °C) t_{major} = 37.1 min and t_{minor} = 40.0 min. ^{1}H NMR (500 MHz) δ 1.38 (t, *J* = 7.1 Hz, 3H), 1.85 (d, *J* = 14.6 Hz, 3H), 2.36 (s, 3H), 2.42–2.61 (m, 1H), 2.63–2.79 (m, 2H), 2.80–2.91 (m, 1H), 4.20–4.31 (m, 4H), 6.84–6.91 (m, 2H$_{Ar}$), 7.04 (d, *J* = 7.6 Hz, 1H$_{Ar}$), 7.24 (d, *J* = 7.7 Hz, 1H$_{Ar}$). ^{13}C NMR (75.5 MHz) δ 16.40 (CH$_3$), 16.47 (CH$_3$), 20.02 (d, J_{PC} = 1.7 Hz, CH$_3$), 21.36 (CH$_{3Ar}$), 28.98 (d, J_{PC} = 8.3 Hz, CH$_2$), 30.75 (CH$_2$), 64.48 (d, J_{PC} = 7.1 Hz, OCH$_2$), 64.62 (d, J_{PC} = 7.1 Hz, OCH$_2$), 89.02 (d, J_{PC} = 150.3 Hz, PC), 118.37 (Ar), 122.02 (Ar), 126.88 (Ar), 129.23 (Ar), 139.75 (Ar$_q$), 150.45 (Ar$_q$), 170.57 (CO). ^{31}P NMR (121.5 MHz) δ 16.3. MS (APCI) M/z (rel intensity) 374.2 ([MH$^+$], 79), 265.9 (100), 238.2 (74), 210.3 (38), 163.1 (14).

4.4.10. 4-(Diethoxyphosphoryl)-4-nitropentanoic acid *o*-tolyl ester (3j) Oil. Yield: 89%. HPLC conditions: Kromasil Cellucoat (hexane–EtOH = 9:1, flow rate 0.3 ml/min, 256 nm, 10 °C) t_{major} = 35.3 min and t_{minor} = 42.1 min. ^{1}H NMR (500 MHz) δ 1.38 (t, *J* = 7.1 Hz, 3H), 1.85 (d, *J* = 14.5 Hz, 3H), 2.26 (s, 3H), 2.41–2.60 (m, 1H), 2.62–2.80 (m, 2H), 2.81–2.91 (m, 1H), 4.20–4.33 (m, 4H), 6.94–7.06 (m, 2H$_{Ar}$), 7.06-15 (m, 2H$_{Ar}$). ^{13}C NMR (75.5 MHz) δ 16.46 (CH$_3$), 16.52 (CH$_3$), 19.13 (d, J_{PC} = 1.7 Hz, CH$_3$), 20.22 (CH$_{3Ar}$), 28.55 (d, J_{PC} = 8.3 Hz, CH$_2$), 30.65 (CH$_2$), 64.42 (d, J_{PC} = 7.1 Hz, OCH$_2$), 64.58 (d, J_{PC} = 7.1 Hz, OCH$_2$), 89.11 (d, J_{PC} = 150.2 Hz, PC), 119.75 (Ar), 122.84 (Ar), 126.43 (Ar), 131.22 (Ar), 139.54 (Ar$_q$), 149.40 (Ar$_q$), 170.49 (CO). ^{31}P NMR (121.5 MHz) δ 16.3. MS (APCI) M/z (rel intensity) 374.2 ([MH$^+$], 54), 265.9 (100), 238.0 (69), 210.3 (46), 163.1 (10).

4.4.11. 4-(Diethoxyphosphoryl)-4-nitropentanoic acid 2,6-dimethylphenyl ester (3k) Oil. Yield: 92%. [α]$_D^{20}$ = -2.1 (c 1.4, CHCl$_3$). HPLC conditions: Chiralpak AD-H (hexane–EtOH = 95:5, flow rate 0.3 ml/min, 254 nm, 10°C) t_{minor} = 29.2 min and t_{major} = 30.9 min. ^{1}H NMR (500 MHz) δ 1.40 (t, *J* = 7.0 Hz, 3H), 1.88 (d, *J* = 14.4 Hz, 3H), 2.15 (s, 6H), 2.51–2.71 (m, 1H), 2.72–2.82 (m, 2H), 2.82–2.93 (m, 1H), 4.20–4.38 (m, 4H), 7.07 (s, 3H). ^{13}C NMR (75.5 MHz) δ 16.53 (CH$_3$), 16.62 (CH$_3$), 20.29 (d, J_{PC} = 1.6 Hz, CH$_3$), 23.61(CH$_{3\ Ar}$), 29.12 (d, J_{PC} = 8.3 Hz, CH$_2$), 30.85 (CH$_2$), 64.48 (d, J_{PC} = 7.1 Hz, OCH$_2$), 64.62 (d, J_{PC} = 7.1 Hz, OCH$_2$), 89.02 (d, J_{PC} = 150.3 Hz, PC), 126.88 (Ar), 129.23 (Ar), 139.75 (Ar$_q$), 148.47 (Ar$_q$), 170.32 (CO). ^{31}P NMR (121.5 Hz) δ (ppm) 16.3. MS (ESI) M/z (rel intensity) 388.3 ([MH$^+$], 100), 266.3 (23), 238.3 (3).

4.4.12. 4-(Diethoxyphosphoryl)-4-nitropentanoic acid 4-*tert*-butylphenyl ester (3l) Oil. Yield: 93%. HPLC conditions: Kromasil Cellucoat (hexane–EtOH = 7:3, flow rate 0.1 ml/min, 256 nm, 10 °C) t_{major} = 41.4 min and t_{minor} = 51.2 min. ^{1}H NMR (500 MHz) δ 1.31 (s, 9H), 1.38 (t, *J* = 7.0 Hz, 3H), 1.85 (d, *J* = 14.4 Hz), 2.46–2.60 (m, 1H), 2.62–2.75 (m, 2H), 2.79–2.86 (m, 1H), 4.20–4.31 (m, 4H), 7.0 (d, *J* = 8.6 Hz, 2H$_{Ar}$), 7.38 (d, *J* = 8.6 Hz, 2H$_{Ar}$). ^{13}C NMR (75.5 MHz) δ 16.54 (CH$_3$), 16.62 (CH$_3$), 20.14 (d, J_{PC} = 1.6 Hz, CH$_3$), 29.10 (d, J_{PC} = 8.4 Hz, CH$_2$), 30.90 (CH$_2$), 31.60 (CC̲H$_3$)$_3$), 34.69 (C̲CH$_3$)$_3$), 64.62 (d, J_{PC} = 7.2 Hz, OCH$_2$), 64.76 (d, J_{PC} = 7.1 Hz, OCH$_2$), 89.20 (d, J_{PC} = 150.2 Hz, PC), 120.88 (Ar), 126.56 (Ar), 148.31 (Ar$_q$), 149.04 (Ar$_q$), 170.78 (CO). ^{31}P NMR (121.5 MHz) δ 16.3. MS (APCI) M/z (rel intensity) 416.1 ([MH$^+$], 69), 266.2 (100), 238.3 (8.5), 210.3 (18).

13. 4-(Diethoxyphosphoryl)-4-nitropentanoic acid 4-*tert*-butyl-2-methylphenyl ester (3m) Oil. Yield: 93%. $[\alpha]_D^{20}$ = -0.63 (c 1.75, CHCl$_3$). HPLC conditions: Chiralpak AD-H (hexane–EtOH = 95:5, flow rate 0.3 ml/min, 254 nm, 10 °C) t_{minor} = 37.9 min and t_{major} = 47.1 min. ^{1}H NMR (500 MHz) δ 1.29 (s, 9H), 1.37 (t, J = 7.1 Hz, 6H), 1.86 (d, J = 14.3 Hz, 3H), 2.15 (s, 3H), 2.49–2.62 (m, 1H), 2.63–2.75 (m, 2H), 2.75–2.92 (m, 1H), 4.21–4.31 (m, 4H), 6.91 (d, J = 8.1 Hz, 1H$_{Ar}$), 7.18–7.21 (m, 2H$_{Ar}$). ^{13}C NMR (75.5 MHz) δ 16.51 (CH$_3$), 16.58 (CH$_{3Ar}$), 16.61 (CH$_3$), 20.11 (d, J_{PC} = 1.3 Hz, CH$_3$), 28.83 (d, J_{PC} = 8.4 Hz, CH$_2$), 30.93 (CH$_2$), 31.58 (CH$_{3q}$), 34.54 (C$_q$), 64.59 (d, J_{PC} = 7.5 Hz, OCH$_2$), 64.98 (d, J_{PC} = 7.5 Hz, OCH$_2$), 89.20 (d, J_{PC} = 150.2 Hz, PC), 121.15 (Ar), 124.07 (Ar), 128.34 (Ar), 129.09 (Ar$_q$), 146.95 (Ar$_q$), 149.10 (Ar$_q$), 170.47 (CO). ^{31}P NMR (121.5 MHz) δ 16.3. MS (ESI) M/z (rel intensity) 430.3 ([MH$^+$], 100), 266.2 (7).

4.4.14. 4-(Diethoxyphosphoryl)-4-nitropentanoic acid naphthalen-2-yl ester (3n) Oil. Yield: 89%. HPLC conditions: Kromasil Cellucoat (hexane–EtOH = 9:1, flow rate 0.8 ml/min, 256 nm, 10 °C) t_{major} = 33.1 min and t_{minor} = 53.1 min. ^{1}H NMR (500 MHz) δ 1.39 (t, J = 7.1 Hz, 6H), 1.88 (d, J = 14.6 Hz 3H), 2.54–2.64 (m, 1H), 2.72–2.81 (m, 2H), 2.81–2.91 (m, 1H), 4.19–4.31 (m, 4H), 7.22 (dd, J = 8.9, 2.2 Hz, 1H$_{Ar}$), 7.48 (t, J = 7.7 Hz, 2H$_{Ar}$), 7.56 (d, 2Hz, 1H$_{Ar}$), 7.79 (d, J = 2.0 Hz, 1H$_{Ar}$), 7.82–7.91 (m, 2H$_{Ar}$). ^{13}C NMR (75.5 MHz) δ 16.55 (CH$_3$), 16.64 (CH$_3$), 20.28 (d, J_{PC} = 1.6 Hz, CH$_3$), 29.19 (d, J_{PC} = 8.3 Hz, CH$_2$), 30.95 (CH$_2$), 64.71 (d, J_{PC} = 7.2 Hz, OCH$_2$), 64.83 (d, J_{PC} = 7.2 Hz, OCH$_2$), 89.21 (d, J_{PC} = 150.5 Hz, PC), 118.6 (Ar), 121.07 (Ar), 126.03 (Ar), 126.86 (Ar), 127.88 (Ar), 127.98 (Ar), 129.71 (Ar), 131.73 (Ar$_q$), 133.92 (Ar$_q$), 148.31 (Ar$_q$), 170.81 (CO). ^{31}P NMR (121.5 MHz) δ 16.3. MS (APCI) M/z (rel intensity) 410.2 ([MH$^+$], 100), 265.9 (66), 238.2 (55), 220.2 (21), 210.3 (65), 179.3 (19), 123.1 (19).

4.4.15. 4-(Diethoxyphosphoryl)-4-nitropentanoic acid 4-methoxyphenyl ester (3o) Oil. Yield: 93%. HPLC conditions: Kromasil Cellucoat (hexane–EtOH = 9:1, flow rate 0.3 ml/min, 256 nm, 10 °C) t_{major} = 50.7 min and t_{minor} = 58.2 min. ^{1}H NMR (500 MHz) δ 1.39 (t, J = 7.0 Hz, 6H), 1.87 (d, J = 14.4 Hz, 3H), 2.44–2.62 (m, 1H),2.62–2.78 (m, 2H), 2.79–2.93 (m, 1H), 3.81 (s, 3H), 4.19–4.38 (m, 4H), 6.90 (d, J = 9.0 Hz, 2H$_{Ar}$), 7.01 (d, J = 9.0 Hz, 2H$_{Ar}$). ^{13}C NMR (75.5 MHz) δ 16.58 (CH$_3$), 16.65 (CH$_3$), 20.20 (d, J_{PC} = 1.5 Hz, CH$_3$), 29.11 (d, J_{PC} = 8.4 Hz, CH$_2$), 30.94 (CH$_2$), 55.82 (OCH$_3$), 64.63 (d, J_{PC} = 7.2 Hz, OCH$_2$), 64.77 (d, J_{PC} = 7.2 Hz, OCH$_2$), 89.20 (d, J_{PC} = 150.3 Hz, PC), 114.70 (Ar), 122.36 (Ar), 144.18 (Ar$_q$), 157.57 (Ar$_q$), 170.99 (CO). ^{31}P NMR (121.5 MHz) δ 16.3. MS (ESI) M/z (rel intensity) 390.2 ([MH$^+$], 100), 266.2 (29).

4.4.16. 4-(Diethoxyphosphoryl)-4-nitropentanoic acid 3-methoxyphenyl ester (3p) Oil. Yield: 93%. HPLC conditions: Chiralpak AD-H (hexane–EtOH = 9:1, flow rate 0.5 ml/min, 254 nm, 10 °C) t_{minor} = 58.2 min and t_{major} = 68.3 min. ^{1}H NMR (500 MHz) δ 1.38 (t, J = 7.1 Hz, 6H), 1.86 (d, J = 14.4 Hz, 3H), 2.44–2.60 (m, 1H), 2.62–2.79 (m, 2H), 2.81–2.92 (m, 1H), 3.80 (s, 3H), 4.19–4.38 (m, 4H), 6.64 (s, 1H$_{Ar}$), 6.68 (d, J = 8.2 Hz, 1H$_{Ar}$), 6.79 (d, J = 8.2 Hz, 1H$_{Ar}$), 7.27 (t, J = 8.2 Hz, 1H$_{Ar}$). ^{13}C NMR (75.5 MHz) δ 16.56 (CH$_3$), 16.62 (CH$_3$), 20.20 (d, J_{PC} = 1.6 Hz, CH$_3$), 29.09 (d, J_{PC} = 8.4 Hz, CH$_2$), 30.88 (CH$_2$), 55.64 (OCH$_3$), 64.69 (d, J_{PC} = 7.2 Hz, OCH$_2$), 64.81 (d, J_{PC} = 6.2 Hz, OCH$_2$), 89.15 (d, J_{PC} = 150.5 Hz, PC), 107.64 (Ar), 112.06 (Ar), 113.78 (Ar), 130.06 (Ar), 151.59 (Ar$_q$), 160.70 (Ar$_q$), 170.51 (CO). ^{31}P NMR (121.5 MHz) δ 16.3. MS (APCI) M/z (rel intensity) 390.2 ([MH$^+$], 100), 265.9 (81), 238.0 (82), 210.3 (68), 163.1 (16).

4.4.17. (*S*)-4-(Diethoxyphosphoryl)-4-nitropentanoic acid 2-methoxyphenyl ester (3r) Oil. Yield: 93%. $[\alpha]_D^{20}$ = -1.0 (c 1.0, CHCl$_3$). HPLC conditions: Kromasil Amycoat (hexane–IPA = 9:1, flow rate 0.5 ml/min, 254 nm, 10 °C) t_{minor} = 91.0 min and t_{major} = 102.3 min. ^{1}H NMR (500 MHz) δ 1.39 (t, J = 7.1 Hz, 6H), 1.87 (d, J = 14.4 Hz, 3H), 2.42–2.63 (m, 1H), 2.63–2.81 (m, 2H), 2.81–2.98 (m, 1H), 3.83 (s, 3H), 4.20–4.41 (m, 4H), 6.96–7.06 (m, 3H$_{Ar}$), 7.22 (t, J = 8.2 Hz, 1H$_{Ar}$). ^{13}C NMR (75.5 MHz) δ 16.40 (CH$_3$), 16.49 (CH$_3$), 19.73 (d, J_{PC} = 1.5 Hz, CH$_3$), 28.53 (d, J_{PC} = 8.7 Hz, CH$_2$), 30.75 (CH$_2$), 55.86 (OCH$_3$), 64.41 (d, J_{PC} = 7.2 Hz, OCH$_2$), 64.62 (d, J_{PC} = 7.1 Hz, OCH$_2$), 89.17 (d, J_{PC} = 149.9 Hz, PC), 112.45 (Ar), 120.84 (Ar), 122.69 (Ar), 127.11 (Ar), 139.61 (Ar$_q$), 151.02 (Ar$_q$), 170.08 (CO). ^{31}P NMR (121.5 MHz) δ 16.4. MS (ESI) M/z (rel intensity) 390.1 ([MH$^+$], 100), 266.2 (58), 220.2 (48).

4.4.18. 4-(Diethoxyphosphoryl)-4-nitropentanoic acid 3,5-dimethoxyphenyl ester (3s) Oil. Yield: 92%. HPLC conditions: Chiralpak AD-H (hexane–EtOH = 9:1, flow rate 0.8 ml/min, 214 nm, 10 °C) t_{minor} = 74.7 min and t_{major} = 101.1 min. ^{1}H NMR (500 MHz) δ 1.37 (t, J = 7.1 Hz, 6H), 1.84 (d, J = 14.3 Hz, 3H), 2.42-2.61 (m, 1H), 2.62–2.76 (m, 2H), 2.76–2.94 (m, 1H), 3.76 (s, 6H), 4.17–4.37 (m, 4H), 6.25 (d, J = 2.0 Hz, $2H_{Ar}$), 6.33 (t, J = 2.0 Hz, $1H_{Ar}$). ^{13}C NMR (75.5 MHz) δ 16.56 (d, J_{PC} = 1.2 Hz, CH_3), 16.64 (d, J_{PC} = 1.2 Hz, CH_3), 20.23 (d, J_{PC} = 1.6 Hz, CH_3), 29.11 (d, J_{PC} = 8.3 Hz, CH_2), 30.89 (CH_2), 55.71 (OCH_3), 64.65 (d, J_{PC} = 7.6 Hz, OCH_2), 64.75 (d, J_{PC} = 7.3 Hz, OCH_2), 89.16 (d, J_{PC} = 150.3 Hz, PC), 98.61 (Ar), 100.25 (Ar), 152.17 (Ar_q), 161.36 (Ar_q), 170.42 (CO). ^{31}P NMR (121.5 Hz) δ 16.3. MS (ESI) M/z (rel intensity) 420.3 ([MH^+], 100), 334.2 (29), 266.3 (28).

4.4.19. 4-(Diethoxyphosphoryl)-4-nitropentanoic acid 2,6-dimethoxyphenyl ester (3t) Oil. Yield: 92%. $[α]_D^{20}$ = +3.7 (c 1.5, $CHCl_3$). HPLC conditions: Chiralpak AD-H (hexane–EtOH = 9:1, flow rate 0.8 ml/min, 214 nm, 10 °C) t_{minor} = 34.4 min and t_{major} = 37.9 min; ^{1}H NMR (500 MHz) δ 1.38 (t, J = 6.9 Hz, 6H), 1.86 (d, J = 14.5 Hz, 3H), 2.42–2.62 (m, 1H), 2.62–2.78 (m, 2H), 2.78–2.95 (m, 1H), 3.81 (s, 6H), 4.18–4.38 (m, 4H), 6.61 (d, J = 8.4 Hz, $2H_{Ar}$), 7.14 (t, J = 8.4 Hz, $1H_{Ar}$). ^{13}C NMR (75.5 MHz) δ 16.55 (CH_3), 16.62 (CH_3), 19.60 (d, J_{PC} = 1.2 Hz, CH_3), 28.47 (d, J_{PC} = 8.3 Hz, CH_2), 30.91 (CH_2), 58.30 (OCH_3), 64.51 (d, J_{PC} = 7.1 Hz, OCH_2), 64.78 (d, J_{PC} = 7.1 Hz, OCH_2), 89.41 (d, J_{PC} = 149.7 Hz, PC), 105.03 (Ar), 126.62 (Ar), 128.76 (Ar_q), 152.43 (Ar_q), 170.02 (CO). ^{31}P NMR (121.5 MHz) δ (ppm) 16.6. MS (ESI) M/z (rel intensity) 420.2 ([MH^+], 100), 266.1 (55).

4.4.20. 4-[4-(Diethoxyphosphoryl)-4-nitropentanoyloxy]-benzoic acid methyl ester (3u) Oil. Yield: 91%. HPLC conditions: Chiralpak AD-H (hexane–EtOH = 9:1, flow rate 0.8 ml/min, 240 nm, 10 °C) t_{minor} = 82.1 min and t_{major} = 95.3 min. ^{1}H NMR (500 MHz) δ 1.39 (t, J = 7.0 Hz, 6H), 1.86 (d, J = 14.3 Hz, 3H), 2.44–2.62 (m, 1H), 2.62–2.78 (m, 2H), 2.79–2.94 (m, 1H), 3.92 (s, 3H), 4.19–4.37 (m, 4H), 7.17 (d, J = 8.7 Hz, $2H_{Ar}$), 8.07 (d, J = 8.2 Hz, $2H_{Ar}$). ^{13}C NMR (75.5 MHz) δ 16.40 (CH_3), 16.47 (CH_3), 20.25 (d, J_{PC} = 1.6 Hz, CH_3), 29.03 (d, J_{PC} = 6.1 Hz, CH_2), 30.68 (CH_2), 52.27 (OCH_3), 64.54 (d, J_{PC} = 7.1 Hz, OCH_2), 64.59 (d, J_{PC} = 7.1 Hz, OCH_2), 88.93 (d, J_{PC} = 150.5 Hz, PC), 121.50 (Ar), 127.97 (Ar), 131.25 (Ar_q), 154.08 (Ar_q), 166.27 (CO), 169.96 (CO). ^{31}P NMR (121.5 MHz) δ 16.1. MS (ESI) M/z (rel intensity) 418.2 ([MH^+], 100), 266.2 (23).

4.4.21. 4-(Diethoxyphosphoryl)-4-nitropentanoic acid benzo[1,3]dioxolyl ester (3v) Oil. Yield: 90%. HPLC conditions: Chiralpak AD-H (hexane–EtOH = 9:1, flow rate 0.8 ml/min, 254 nm, 10 °C) t_{minor} = 77.1 min and t_{major} = 89.5 min. ^{1}H NMR (500 MHz) δ 1.39 (t, J = 7.1 Hz, 6H), 1.86 (d, J = 14.4 Hz, 3H), 2.42–2.59 (m, 1H), 2.60–2.66 (m, 2H), 2.76–2.91 (m, 1H), 4.19–4.38 (m, 4H), 5.99 (s, 2H), 6.53 (dd, J = 8.4, 2.3 Hz, $1H_{Ar}$), 6.56 (d, J = 2.3 Hz, $1H_{Ar}$), 6.77 (d, J = 8.4 Hz, $1H_{Ar}$). ^{13}C NMR (75.5 MHz) δ 16.45 (d J_{PC} = 1.3 Hz, CH_3), 16.52 (d, J_{PC} = 1.1 Hz, CH_3), 20.09 (d, J_{PC} = 1.6 Hz, CH_3), 28.88 (d, J_{PC} = 8.4 Hz, CH_2), 30.77 (CH_2), 64.50 (d, J_{PC} = 7.2 Hz, OCH_2), 64.66 (d, J_{PC} =7.2 Hz, OCH_2), 89.07 (d, J_{PC} = 150.3 Hz, PC), 101.87 (OCH_2O), 103.65 (Ar), 108.06 (Ar), 113.87 (Ar), 144.86 (Ar_q), 145.58 (Ar_q), 148.13 (Ar_q), 170.81 (CO). ^{31}P NMR (121.5 Hz) δ 16.3. MS (ESI) M/z (rel intensity) 404.1 ([MH^+], 100), 266.3 (25).

4.5. Synthesis of catalysts 4l-4m

Procedure described in ref 19 was followed starting from the corresponding alkaloid amine.

4.5.1. 3-((3,5-Bis(trifluoromethyl)benzyl)amino)-4-(((1S)-(6-methoxyquinolin-4-yl)((2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)amino)cyclobut-3-ene-1,2-dione (4l) White solid. H[1]NMR (300 MHz, $CDCl_3$:CD_3OD 1:1) δ 0.62-0.77 (m, 1H), 1.46-1.76 (m, 5H), 2.32-2.47 (m, 1H), 2.67-2.90 (m, 2H), 3.32-3.62 (m, 2H), 4.00 (s, 3H), 4.80 (d, J = 15 Hz, 1H), 4.93 (d, J = 15 Hz, 1H), 5.01 (s, 1H), 5.06 (d, J = 8 Hz, 1H), 5.82 (ddd, J = 2, 8, 17 Hz, 1H), 6.23(d, J = 10 Hz, 1H), 7.35-7.46 (m, 2H), 7.74-7.85 (m, 5H), 7.94 (d, J = 10 Hz, 1H), 8.66 (d, J = 4 Hz, 1H). C[13]NMR (75 MHz) δ 182.543, 182.398, 167.436, 167.418, 167.054, 159.042, 146.660, 144.063, 140.772, 132.113, 131.670, 130.435, 128.011, 127.869, 127.830, 124.821, 123.382, 123.363, 121.455, 121.406, 121.355, 121.209, 114.731, 114.696, 114.671, 114.633, 100.770, 59.752, 55.779, 55.600, 46.657, 40.650, 38.733, 38.707, 38.678, 27.056, 26.942, 25.988. HRMS calculated for $C_{33}H_{30}F_6N_4O_3$ (MH^+): 645.2295 found: 645.2296.

4.5.2 **3-(Benzylamino)-4-(((1*S*)-((2S,4S,5R)-5-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl)amino)cyclobut-3-ene-1,2-dione (4m)** White solid. H[1]NMR (300 MHz, CDCl$_3$:CD$_3$OD 1:1) δ 0.54-0.72 (m, 1H), 0.83 (t, *J* = 7 Hz, 3H), 1.16-1.74 (m, 7H), 2.35-2.51 (m, 1H), 2.61-2.81 (m, 1H), 3.16-3.40 (m, 2H), 3.41-3.61 (m, 1H), 3.99 (s, 3H), 4.55 (bs, 2H), 4.69 (q, *J* = 15 Hz, 2H), 6.22 (d, *J* = 10 Hz, 1H), 7.10-7.30 (m, 5H), 7.38 (bs, 1H), 7.40 (dd, *J* = 12, 2 Hz, 1H), 7.83 (bs, 1H), 7.93 (d, *J* = 9 Hz, 1H), 8.64 (d, *J* = 4 Hz, 1H). C[13]NMR (75MHz) δ 182.457, 182.057, 167.586, 166.820, 159.017, 146.707, 144.658, 144.084, 137.583, 130.430, 128.629, 128.105, 127.707, 127.482, 123.354, 100.980, 59.672, 57.487, 55.832, 47.890, 40.705, 36.622, 27.739, 27.172, 25.888, 24.932, 11.490, HRMS calculated for C$_{31}$H$_{34}$N$_4$O$_3$ (MH[+]): 511.2704 found: 511.2705.

4.5.3. **3-(Benzylamino)-4-(((1*S*)-((2S,4S,5S)-5-ethynylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl)amino)cyclobut-3-ene-1,2-dione (4n)** White solid. H[1]NMR (300 MHz, CDCl$_3$:CD$_3$OD 1:1) δ 0.57-0.86 (m, 1H), 1.05-1.34 (m, 4H), 1.41-1.69(m, 2H), 1.70-1.88(m, 2H), 2.07-2.18(m,. 4H), 2.47-2.80(m, 2H), 2.87-3.10 (m, 1H), 3.26-3.42 (m, 1H), 3.42-3.70 (m, 2H), 3.94 (s, 3H), 4.53-4.76 (m, 2H), 7.07-7.27 (m, 5H), 7.28-7.50 (m, 4H), 7.74 (bs, 1H), 7.90 (d, J=9 Hz, 1H), 8.62 (d, *J* = 4 Hz, 1H). C[13]NMR (75.5 MHz) δ 181.060, 165.536, 165.516, 157.920, 142.989, 136.367, 129.414, 127.497, 126.917, 126.890, 126.579, 126.510, 126.441, 126.382, 122.274, 122.250, 122.230, 99.786, 99.667, 58.197, 55.578, 54.779, 39.134, 28.373, 28.358, 25.693, 25.296, 25.097, 23.983. HRMS calculated for C$_{31}$H$_{30}$N$_4$O$_3$ (MH[+]): 507,2391 found: 507.2396.

4.6. Typical procedure for the synthesis of *(S)*-(2-methyl-5-oxopyrrolidin-2-yl)-phosphonic acid diethyl ester (5). Over 10% Pd/C catalyst (Selcat Q, 0.53 g) Michael adduct **3** (2.5 mmol) was hydrogenated in ethanol (50 cm^3), in a 250 cm^3 stainless steel autoclave equipped with a magnetic stirrer (stirring speed: 1100 rpm). The reduction was carried out at 30 bar and room temperature. After finishing the hydrogen uptake (4 h), the catalyst was filtered off and the filtrate was evaporated under vacuum. The residue was subjected to column chromatography on silica using CH$_2$Cl$_2$–EtOAc 9:1 as an eluent. By-product **6** was also isolated during column chromatography. Oil. Yield: 51%. [α]$_D^{20}$ = +1.0 (c 1.25, CHCl$_3$), HPLC conditions: Chiralpak AD-H (hexane–IPA = 95:5, flow rate 1 ml/min, 220 nm, 10 °C) t_{minor} = 38.9 min and t_{major} = 46.5 min.; 97% ee. ^{1}H NMR (500 MHz) δ 1.34 (t, *J* = 7.1 Hz, 3H), 1.50 (d, *J* = 14.5 Hz, 3H), 1.87–1.94 (m, 1H), 2.34–2.42 (m, 1H), 2.48–2.62 (m, 2H), 4.09–4.22 (m, 4H), 6.01 (s, 1NH). ^{13}C NMR (75.5 MHz) δ 16.72 (CH$_3$), 16.79 (CH$_3$), 16.83 (d, J_{PC} = 5.5 Hz, CH$_3$), 24.02 (d, J_{PC} = 8.1 Hz, CH$_2$), 30.41 (d, J_{PC} = 7.4 Hz, CH$_2$), 56.89 (d, J_{PC} = 162.5 Hz, PC), 62.97 (d, J_{PC} = 7.7 Hz, OCH$_2$), 63.57 (d, J_{PC} = 7.4 Hz, OCH$_2$), 177.48 (d, J_{PC} = 3.5 Hz, CO).). ^{31}P NMR (121.5 MHz) δ 26.6. MS (ESI) M/z (rel intensity) 236.2 ([MH$^+$], 100).

(2-Methyl-3,4-dihydro-2*H*-pyrrol-2-yl)-phosphonic acid diethyl ester (by-product 6): Oil. Yield: 39%. HPLC conditions: Chiralpak AD-H (hexane–IPA = 95:5, flow rate 1 ml/min, 220 nm, 20 °C) t_{major} = 14.9 min and t_{minor} = 17.8 min.; 91% ee. ^{1}H NMR (500 MHz) δ 1.35 (t, *J* = 6.9 Hz, 6H), 1.58 (d, *J* = 14.2 Hz, 3H), 1.80–1.91 (m, 1H), 2.31–2.41 (m, 1H), 2.46–2.61 (m, 2H), 4.11–4.25 (m, 4H), 8.08 (d, *J* = 7.8 Hz, 1H). ^{13}C NMR (75.5 MHz) δ 16.43 (CH$_3$), 16.51 (CH$_3$), 16.58 (CH$_3$), 22.69 (d, J_{PC} = 14.3 Hz, CH$_2$), 23.02 (d, J_{PC} = 16.6 Hz, CH$_2$), 35.94 (d, J_{PC} = 4.5 Hz, CH$_2$), 36.33 (d, J_{PC} = 4.5 Hz, CH$_2$), 59.1 (d, J_{PC} = 157.4 Hz, PC), 59.2 (d, J_{PC} = 159.2 Hz, PC), 169.65 (d, J_{PC} = 3.8 Hz, PC). ^{31}P NMR (121.5 MHz) δ 25.3. MS (ESI) M/z (rel intensity) 220.3 ([MH$^+$], 100).

Acknowledgments

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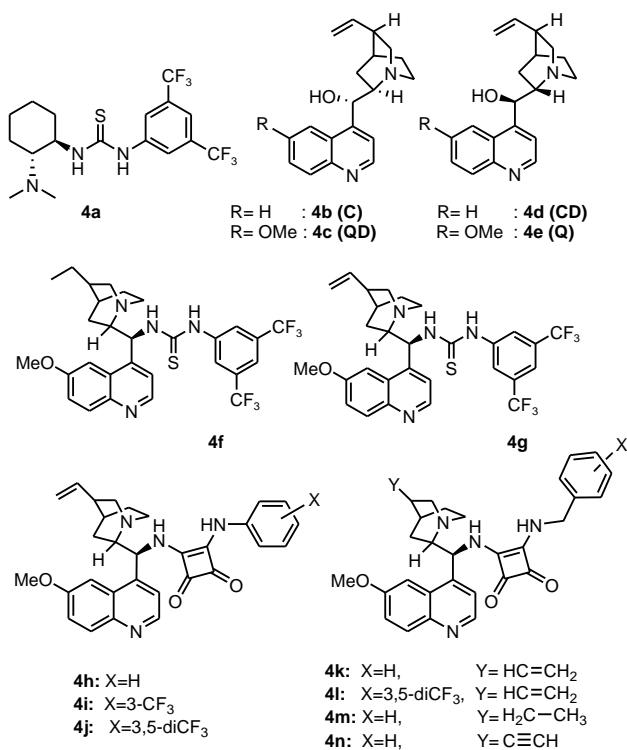
Figure 1. Bifunctional organocatalysts tested in the Michael addition.
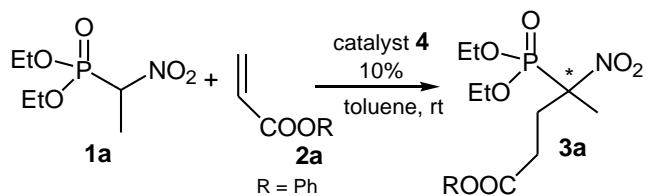
Scheme 1.

Table 1. Michael addition of α-nitroethylphosphonate **1a** to phenyl acrylate **2a** in toluene, at rt, in the presence of catalysts **4a**-**n**.

Entry	Catalyst	Time (day)	Conversion[a] (%)	Yield[b] (%)	ee (%)[c]
1	**4a**	7	94	83	21
2	**4b**	5	100	85	58
3	**4c**	5	100	86	61
4	**4d**	5	100	86	61[d]
5	**4e**	5	100	90	62[d]
6	**4f**	3	100	92	70
7	**4g**	3	100	91	69
8	**4h**	2	100	92	53
9	**4i**	2	100	93	67
10	**4j**	2	100	92	51
11	**4k**	2	100	93	76
12	**4l**	2	100	92	58
13	**4m**	4	40	35	86

| 14 | **4n** | 2 | 100 | 90 | 70 |

[a]Determined by ^{31}P NMR.

[b]Yields of the isolated products.

[c]Determined by chiral HPLC in comparison with authentic racemic compounds.

[d]Reverse enantioselection.
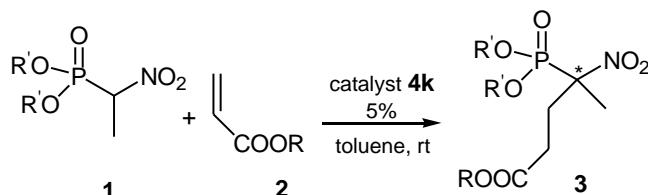
Scheme 2.

Table 2. Dependence on solvent, temperature and catalyst loading in the Michael addition of α-nitroethylphosphonate **1a** to phenyl acrylate **2a**, in the presence of catalyst **4k**.

| Entry	Solvent	Time (day)	Conversion[a] (%)	Yield[b] (%)	ee (%)[c]
1	Toluene	2	100	93	76
2	CH$_2$Cl$_2$	14	100	79	59
3	CH$_3$CN	14	84	63	53
4	THF	14	91	84	58
5	Dioxane	14	92	84	63
6[e]	Anisole	14	100	93	55
7	Xylene	14	97	89	57
8[d]	Toluene	10	63	51	62
9[e]	Toluene	10	85	77	70
10[f]	Toluene	7	100	92	75
11[g]	Toluene	7	84	76	70

[a-c]See Table 1.

[d]-30 °C.

[e]0 °C.

[f]With 5 mol% catalyst.

[g]With 2 mol% catalyst.
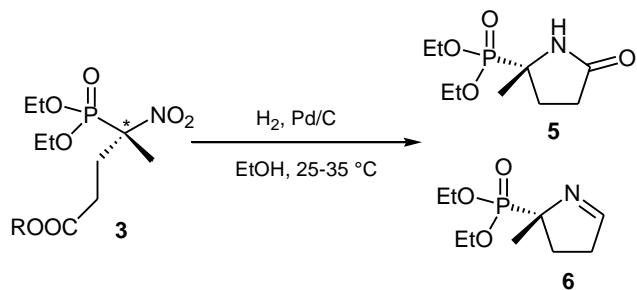
Scheme 3.

Table 3. Enantioselective Michael addition of nitroethyl phosphonate esters (**1a-c**) to aryl acrylates (**2a-o**) using 5 mol% of catalyst **4k**.

Entry	R'	R	Time (day)[aa]	Yield of **3** (%)[b]	ee (%)[c]
1	Et (**1a**)	Ph (**2a**)	2	93 (**3a**)	76
2	iPr (**1b**)	Ph (**2a**)	2	85 (**3b**)	64
3	Bu (**1c**)	Ph (**2a**)	2	82 (**3c**)	52
4	Et (**1a**)	4-ClC$_6$H$_4$ (**2b**)	2	92 (**3d**)	68
5	Et (**1a**)	4-NO$_2$C$_6$H$_4$ (**2c**)	1	92 (**3e**)	64
6	Et (**1a**)	3-NO$_2$C$_6$H$_4$ (**2d**)	1	93 (**3f**)	67
7	Et (**1a**)	2-NO$_2$C$_6$H$_4$ (**2e**)	4	90 (**3g**)	40
8	Et (**1a**)	4-MeC$_6$H$_4$ (**2f**)	2	91 (**3h**)	81
9	Et (**1a**)	3-MeC$_6$H$_4$ (**2g**)	2	90 (**3i**)	79
10	Et (**1a**)	2-MeC$_6$H$_4$ (**2h**)	2	89 (**3j**)	83
11	Et (**1a**)	2,6-diMeC$_6$H$_3$ (**2i**)	3	92 (**3k**)	90
12	Et (**1a**)	4-tBuC$_6$H$_4$ (**2j**)	3	93 (**3l**)	84
13	Et (**1a**)	2-Me,4-tBuC$_6$H$_3$ (**2k**)	4	93 (**3m**)	89
14	Et (**1a**)	β-Naphtyl (**2l**)	4	89 (**3n**)	60
15	Et (**1a**)	4-MeOC$_6$H$_4$ (**2m**)	2	93 (**3o**)	80
16	Et (**1a**)	3-MeOC$_6$H$_4$ (**2n**)	2	93 (**3p**)	79
17	Et (**1a**)	2-MeOC$_6$H$_4$ (**2o**)	3	93 (**3r**)	85[d]
18	Et (**1a**)	3,5-diMeOC$_6$H$_3$ (**2p**)	3	92 (**3s**)	80
19	Et (**1a**)	2,6-diMeOC$_6$H$_3$ (**2r**)	3	92 (**3t**)	96
20	Et (**1a**)	4-MeO$_2$CC$_6$H$_4$ (**2s**)	4	91(**3u**)	62
21	Et (**1a**)	3,4-(OCH$_2$O)C$_6$H$_3$ (**2t**)	4	90 (**3v**)	69

[a]The reactions were led until 100% conversion and determined by ^{31}P NMR.

[b,c]See Table 1.

[d]Absolute configuration of **3r** was derived to be *S* from the CD spectrum (see Section 2.3).
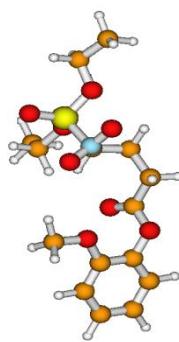
Fig. 2. Optimized geometry for the lowest-energy conformer of 4-(diethoxyphosphoryl)-4-nitropentanoic acid phenyl ester (**3r).**

1.
(a)

2.
(b)
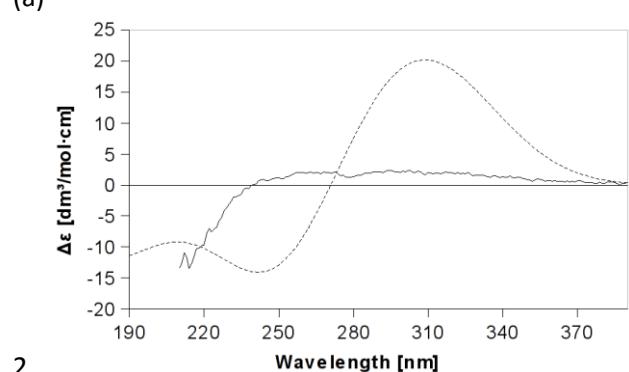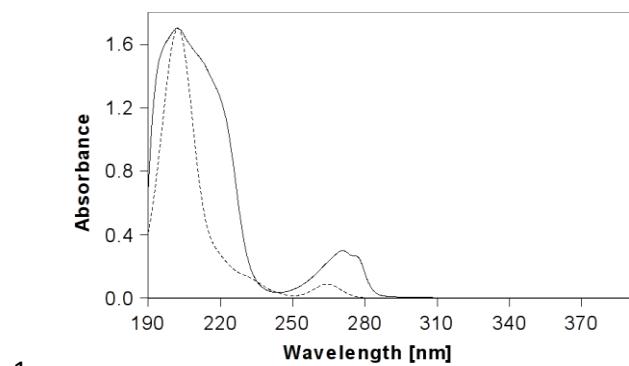
Figure 3. Absorption (a) and CD (b) spectra of **3r,** experimental**: ——— ,** calculated**: ---------**