C-Alkylation of hydroxyarenes by Michael reaction

Henryk Krawczyk and Ryszard Bodalski*

Institute of Organic Chemistry, Technical University (Politechnika), 90-924 Łódź, Żeromskiego 116, Poland

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Electron-rich hydroxyarenes undergo self-catalytic Michael reaction with the dicyclohexylammonium acrylate **1**. The regiochemistry of this reaction is markedly dependent on structural features of the starting hydroxyarenes. While at 25 °C and in nonpolar solvents phenol and most of its monosubstituted derivatives are converted into the corresponding O-adducts, conjugate addition of disubstituted phenols and naphthols leads to the C-adducts exclusively. An analogous reaction pattern is observed with the dicyclohexylammonium acrylate **2** as the Michael acceptor.

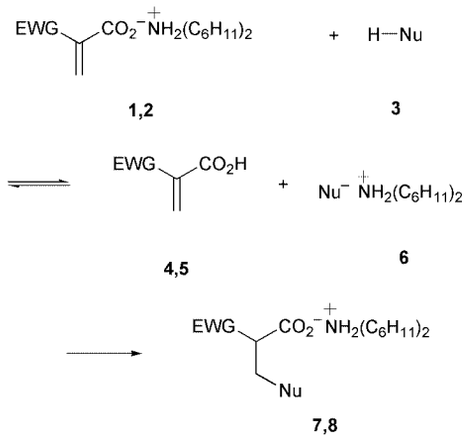
Introduction

The conjugate C-addition of ambident anions to α,β-unsaturated compounds, generally known as the classical Michael reaction, constitutes one of the most convenient methods for the formation of carbon–carbon bonds and has found particularly wide application in both organic and bioorganic syntheses. A large spectrum of different carbanions stabilized by π-conjugation with one or more heteroatoms, including enolates of carbonyl compounds, 1,3-dicarbonyl compounds and related species derived from hydrazones and imines, have been successfully utilized as the Michael donors.[1] Surprisingly, the literature to date contains only a few examples of conjugate C-addition with aryl oxide anions. Miller and Robinson have demonstrated that sodium 2-naphthoxide reacts readily and regiospecifically with methyl vinyl ketone to afford 4-(2-hydroxy-1-naphthyl)butan-2-one.[2] Later Hardman and Lichtenberger's group reported on similar sodium hydroxide-catalyzed addition of 2-naphthol to acrylonitrile leading to 3-(2-hydroxy-1-naphthyl)propionitrile.[3,4] Further investigations by Takemura *et al*. indicated that both the amount of catalyst and the type of solvent play an important role in determining the regiochemistry of this reaction. These findings were convincingly explained in terms of rapid and reversible O-addition and the rate-determining C-addition of sodium naphthoxide.[5]

We have recently shown that no external catalyst is needed to induce the Michael reaction of selected enolizable carbonyl compounds and 1,3-dicarbonyl compounds **3** with dicyclohexylammonium acrylates **1** or **2** possessing an additional electron-withdrawing group at the C-2 carbon atom[6–8] (Scheme 1).

It is likely that proton exchange between the original reaction components generates the dicyclohexylammonium enolates **6** and the acrylic acids **4** or **5**. Being the real Michael donors and acceptors they participate in the conjugate addition which provides dicyclohexylammonium alkanoates **7** or **8** respectively. These self-catalyzed Michael reactions are of noteworthy synthetic value since they can be effectively performed under neutral conditions, thereby helping to exclude undesirable side transformations of the starting materials.

In order to evaluate the potential of the new self-catalysis and to extend the synthetic application of aryl oxide anions as C-nucleophiles we attempted the Michael additions of selected phenols and naphthols to dicyclohexylammonium 2-(diethoxyphosphoryl)acrylate **1** and dicyclohexylammonium 2-cyanoacrylate **2**. We expect that the resulting adducts may prove useful as convenient precursors of some antioxidant, anticorrosive,[9] and anticancer agents.[10] The results of our studies are described in this paper.



1,4,7 EWG = $P(O)(OEt)_2$
2,5,8 EWG = CN
3 aldehydes, 1,3-diketones, alkyl 3-oxoalkanoates, NH- acids

Scheme 1

Results and discussion

The starting acrylates **1** and **2** were prepared according to a previously reported procedure based on the Mannich condensation of diethylphosphonoacetic acid and cyanoacetic acid with formaldehyde.[6,7] All hydroxyarenes **9**–**23** were commercially available. Apart from the simple phenol **9**, 1-naphthol **18**, 2-naphthol **19** and 9-phenanthrol **23** we decided to use a series of their derivatives **10**–**17** and **20**–**22** bearing methyl, hydroxy and methoxy groups as the ring substituents (Chart 1). The functionalization of the parent pronucleophiles was expected to increase the reactivity of the corresponding ambident anions.

Initially, we focused our attention on recognizing the regiochemistry of the reaction between phenol **9** and the acrylate **1**.

The presence of the phosphorus atom in the Michael acceptor **1** as well as in the expected products allowed the use of ^{31}P NMR spectroscopy as a convenient tool for monitoring the reaction's progress. No signs of addition were observed when a benzene solution containing equimolar amounts of starting materials was left at 20 °C for two weeks. However, with an increased proportion of phenol **9** the conjugate O-addition occurred quite effectively, producing the propionate **24**. With a twenty-fold molar excess of phenol **9** after one week at 25 °C the O-adduct **24** was obtained in 70% yield. Identical results

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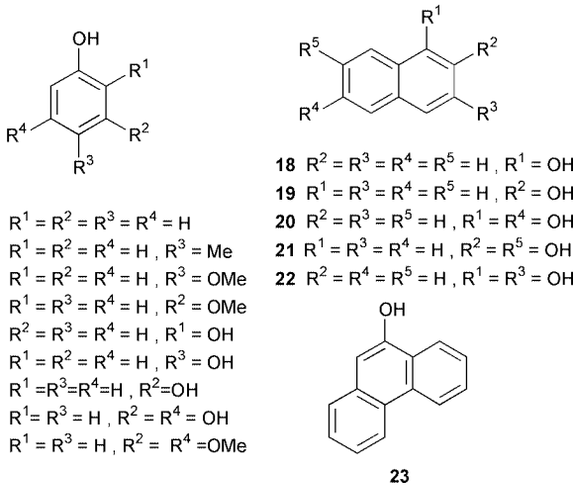


9 $R^1 = R^2 = R^3 = R^4 = H$
10 $R^1 = R^2 = R^4 = H$, $R^3 = Me$
11 $R^1 = R^2 = R^4 = H$, $R^3 = OMe$
12 $R^1 = R^3 = R^4 = H$, $R^2 = OMe$
13 $R^2 = R^3 = R^4 = H$, $R^1 = OH$
14 $R^1 = R^2 = R^4 = H$, $R^3 = OH$
15 $R^1 = R^3 = R^4 = H$, $R^2 = OH$
16 $R^1 = R^3 = H$, $R^2 = R^4 = OH$
17 $R^1 = R^3 = H$, $R^2 = R^4 = OMe$

18 $R^2 = R^3 = R^4 = R^5 = H$, $R^1 = OH$
19 $R^1 = R^3 = R^4 = R^5 = H$, $R^2 = OH$
20 $R^2 = R^3 = R^5 = H$, $R^1 = R^4 = OH$
21 $R^1 = R^3 = R^4 = H$, $R^2 = R^5 = OH$
22 $R^2 = R^4 = R^5 = H$, $R^1 = R^3 = OH$

23

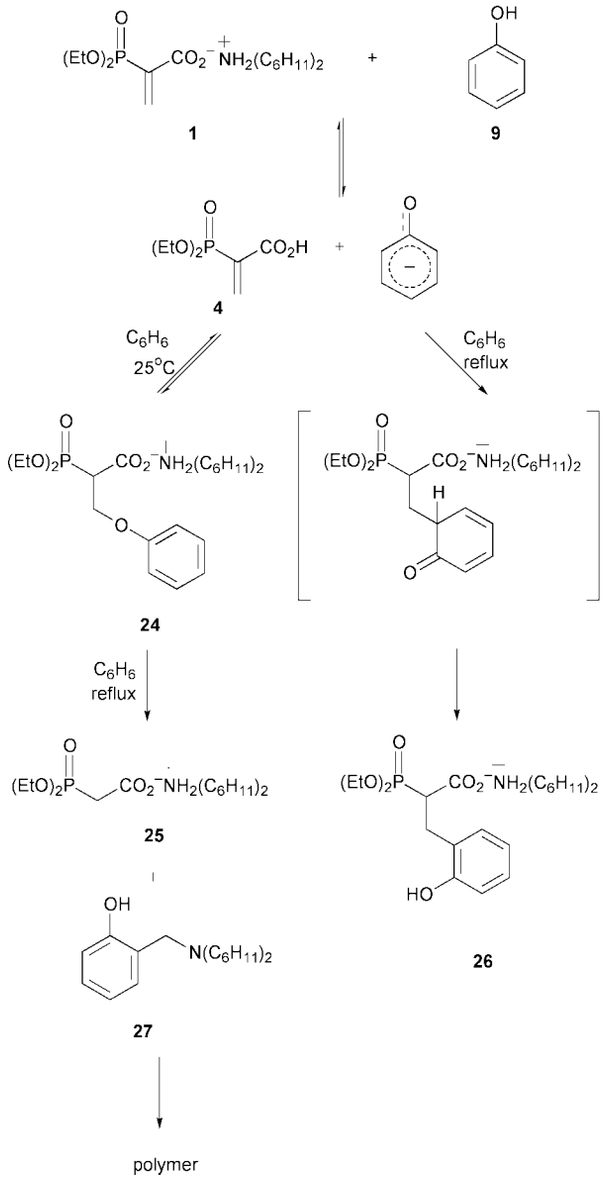
Chart 1

were achieved when the reaction was conducted without a solvent at 35 °C. Although attempts to isolate pure O-adduct **24** proved inefficacious, its structure could be unequivocally confirmed by ^{1}H NMR spectroscopy. Next we discovered that O-adduct **24**, subjected to heating with phenol **9** at 100 °C for 2 h, was converted into a mixture of the acetate **25** and the C-adduct **26** in the ratio 1.00 : 0.05. The formation of polymeric material was also observed. We succeeded in separating both organophosphorus components of this mixture by fractional crystallization. Additionally we found that the C-adduct **26** was quite stable and that it remained unchanged even under prolonged heating under similar conditions (Scheme 2).

Careful analysis of the experimental data collected leads to the conclusion that the conjugate O-addition of phenol **9** to the acrylate **1** is a relatively fast and reversible process. The C-conjugate addition proceeds much more slowly, irreversibly, and requires thermal promotion. Increased temperature induces easy fragmentation of the O-adduct **24**, yielding the acetate **25** and presumably the (aminomethyl)phenol **27**[11] which might be a direct precursor of the polymer.[12]

The close structural relationship between the O-adduct **24** and ethers containing leaving groups at the α-carbon atom[13] led us to anticipate the similar chemical behaviour of these compounds. Thus, considering the well-known tendency of the ethers to undergo dissociative expulsion of the leaving group, we can assume that the fragmentation of the O-adduct **24** will follow an analogous mechanistic pathway. We believe that the proton exchange within the O-adduct **24** leads to the acid **28**, which undergoes oxygen electron pair-assisted carbon–carbon bond cleavage which results in the formation of the enolate **30** and the carbonium ion **29**. While the enolate **30** is next converted to the tautomeric acetate **25**, the carbonium ion **29** reacts with the amine **31** to give the adduct **32**. Further fragmentation of this compound provides the phenolate anion **33** and the iminium cation **34** whose subsequent recombination produces the final product **27** (Scheme 3).

The replacement of a simple phenol by its derivatives with electron-donating substituents brought about essential changes in the reaction pattern presented. Although in benzene solution and at 25 °C the substituted phenols **10**–**14** added to the acrylate **1** preferably through an oxygen atom to give the corresponding O-adducts **35**–**39** respectively (Chart 2), other representatives of these pronucleophiles revealed a different type of reactivity. We observed that under similar conditions C-conjugate addition of such phenols as **15**–**17** was particularly favoured. While the reactions of the acrylate **1** with the phenols **15** and **16** led to the single C-adducts **40** and **41** respectively, the reaction with the phenol **17** afforded a mixture of two regioisomeric C-adducts **42** and **43** in the ratio 1.5 : 1. Careful



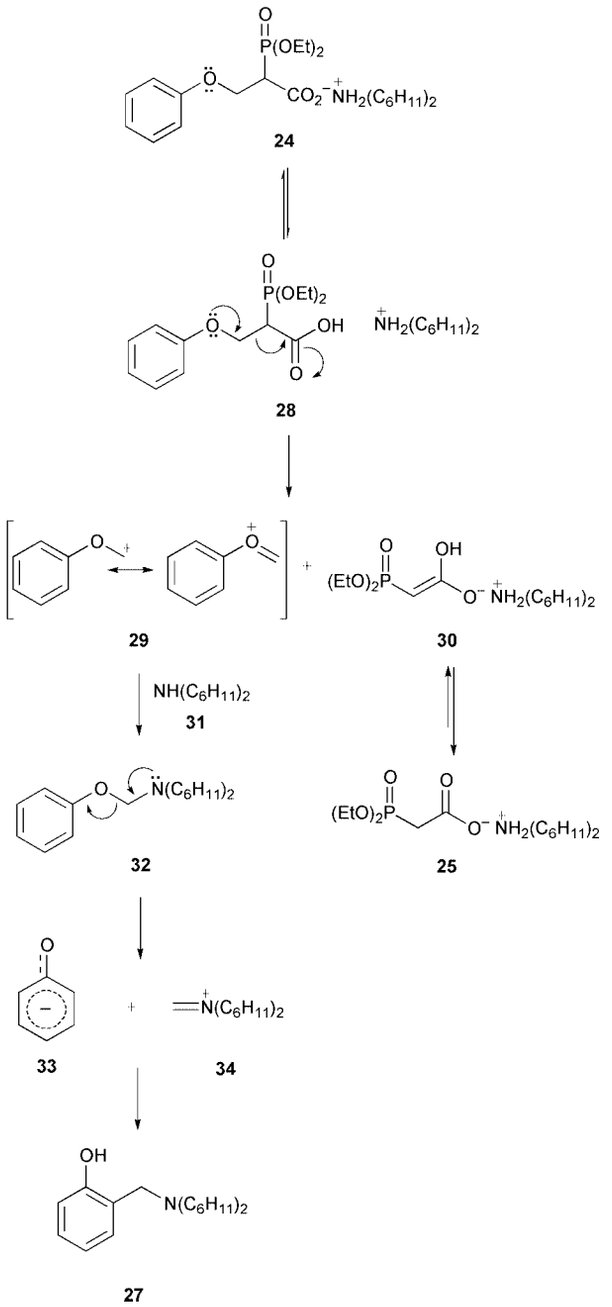
Scheme 2

recrystallization of this mixture allowed the isolation of individual regioisomers (Scheme 4).

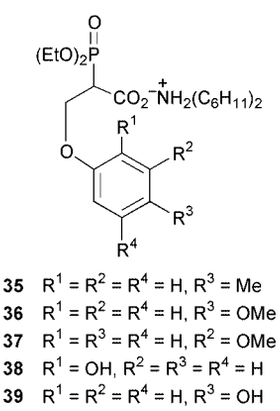
In general, all the performed conjugate additions of naphthols and phenanthrol followed the same reaction pattern. By modifying the proportions of the starting materials and monitoring the formation and disappearance of particular products with ^{31}P NMR spectroscopy, we have demonstrated that, at 25 °C and in benzene solution 2-naphthol **19** reacts relatively fast and reversibly with the acrylate **1** to give the O-adduct **44** which is then entirely and regiospecifically converted into the C-1 adduct **45** (Scheme 5).

Exposing the naphthols **20**, **21** and the phenanthrol **23** to the same reaction sequence gave rise to the formation of the corresponding C-adducts **46**, **47** and **48** as the only regioisomeric products. However, the conjugate C-additions of the naphthols **18** and **22** have not occurred so regioselectively. The reaction of the naphthol **18** with the acrylate **1** provided a mixture of two C-adducts **49** and **50** in the ratio 10 : 1. A two-component mixture containing C-adducts **51** and **52** in the proportions 2 : 1 was also produced when the naphthol **22** was employed as pronucleophile (Scheme 6). Both of the mixtures obtained were separated by fractional crystallization.

To gain better insight into the influence of the substrate structure on the regiochemistry and synthetic utility of the reactions examined we performed further conjugate additions

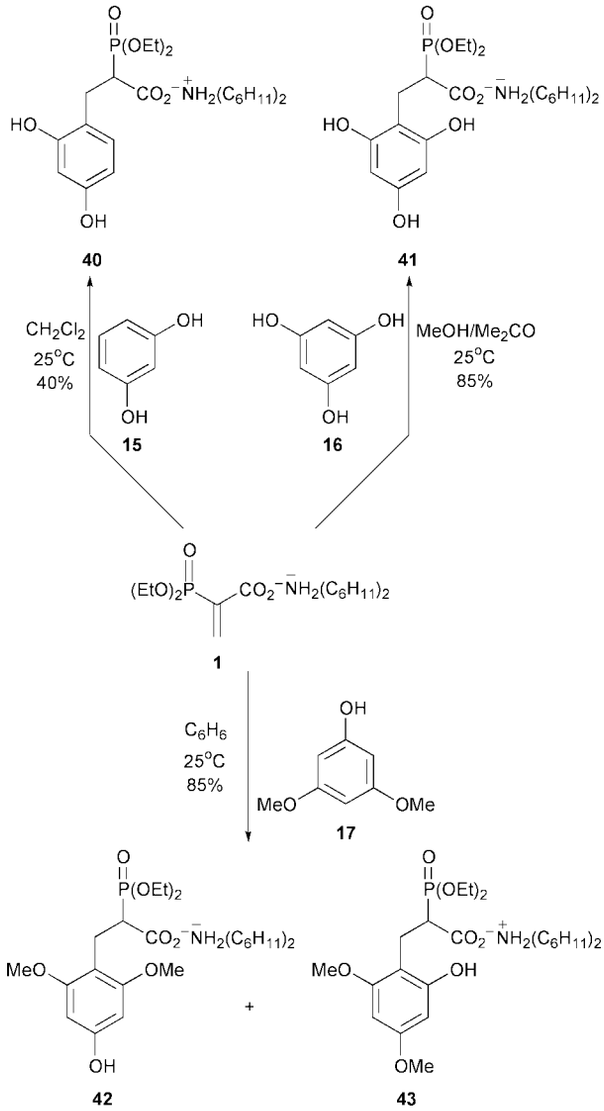


Scheme 3

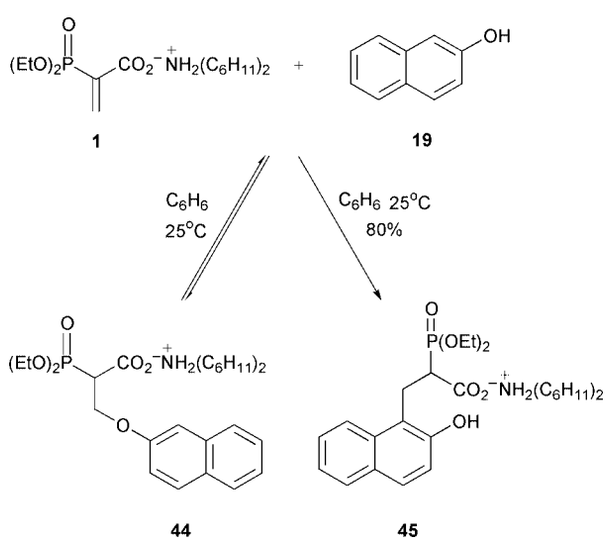


35 $R^1 = R^2 = R^4 = H$, $R^3 = Me$
36 $R^1 = R^2 = R^4 = H$, $R^3 = OMe$
37 $R^1 = R^3 = R^4 = H$, $R^2 = OMe$
38 $R^1 = OH$, $R^2 = R^3 = R^4 = H$
39 $R^1 = R^2 = R^4 = H$, $R^3 = OH$

Chart 2

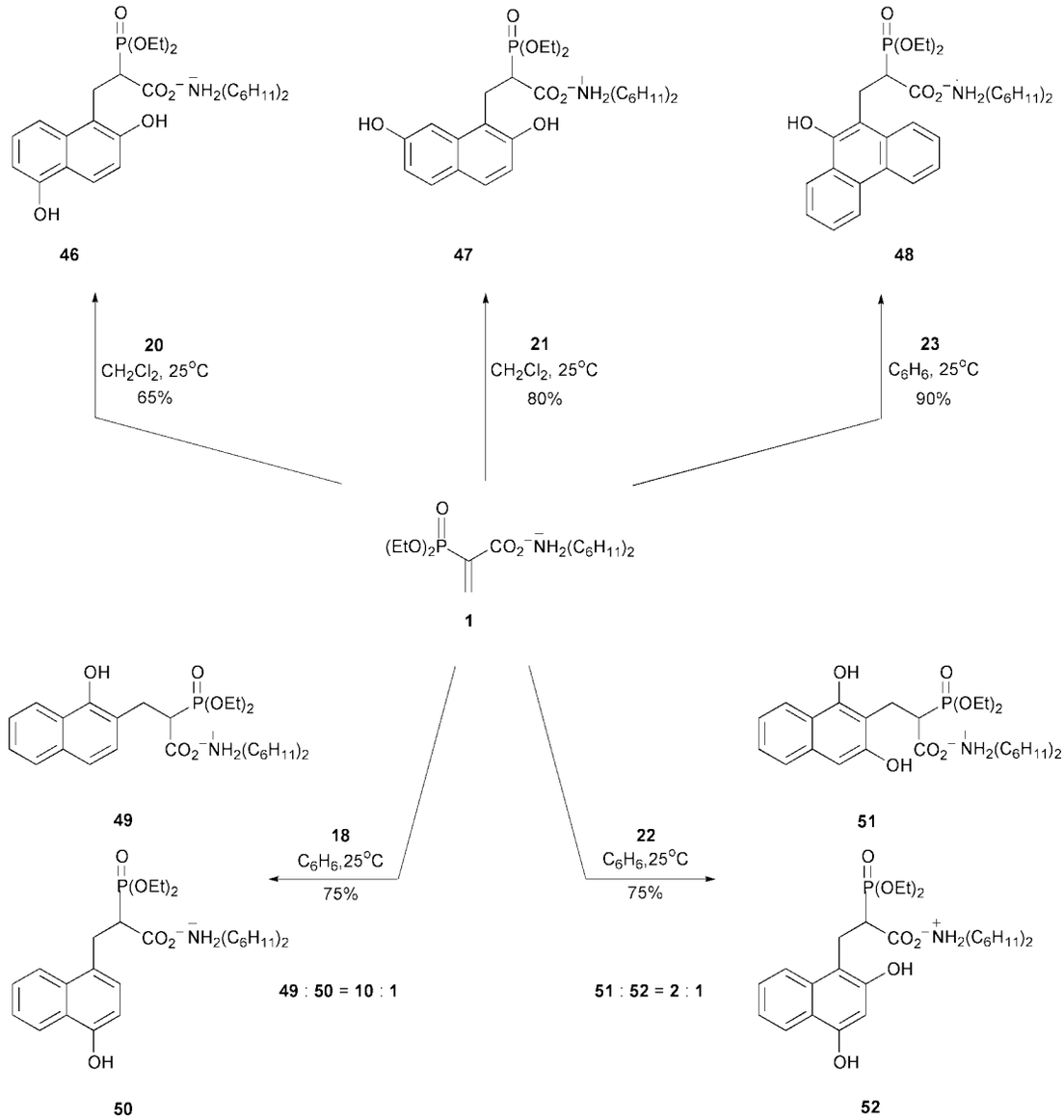


Scheme 4



Scheme 5

using some of the pronucleophiles mentioned above and a new α,β-unsaturated acceptor, the acrylate **2**. The results of these experiments were fully consistent with earlier observations. All the accomplished reactions appeared to proceed regiospecifically, affording the corresponding phenols and naphthols with an aromatic system functionalized in a manner identical to that previously favoured. Thus, the conjugate C-additions of the phenols **15** and **16** as well as those of the naphthols **18**, **19**



Scheme 6

and **21** led to the formation of the single C-adducts **53**–**57** respectively (Scheme 7).

In summary we have succeeded in performing self-catalyzed Michael reactions of selected hydroxyarenes with dicyclohexylammonium acrylates bearing electron-withdrawing groups at the C-2 carbon atom. Orientation in these conjugate C-additions is effectively controlled by the electronic effects of hydroxy groups in the aromatic reagents. This new methodology opens a convenient route towards a number of phenols and naphthols containing highly functionalized carbon substituents.

Experimental

For general experimental details see refs. 7 and 8. FAB/MS were recorded on a PO Electron Modell MI 1201 E mass spectrometer equipped with FAB ion source (thioglycerol matrix).

Reaction of acrylate 1 with phenols 9–14 and 2-naphthol 19. Aryloxypropionates 24, 35–39, and 44. General procedure

A solution of acrylate **1** (0.389 g, 1 mmol) and phenol **9** (1.88 g, 20 mmol) in benzene (5 ml) was left at room temperature for one week. The solvent was evaporated off to afford an oily residue. The aryloxypropionate **24** was identified in the crude mixture on the basis of ^{31}P and ^{1}H NMR analysis. In the ^{1}H NMR spectrum protons of the P–CH–CH_2–OAr groups gave a characteristic AMXP pattern which was a diagnostic tool for determining the structure of the aryloxypropionate **24**.

Selected data of aryloxypropionates:

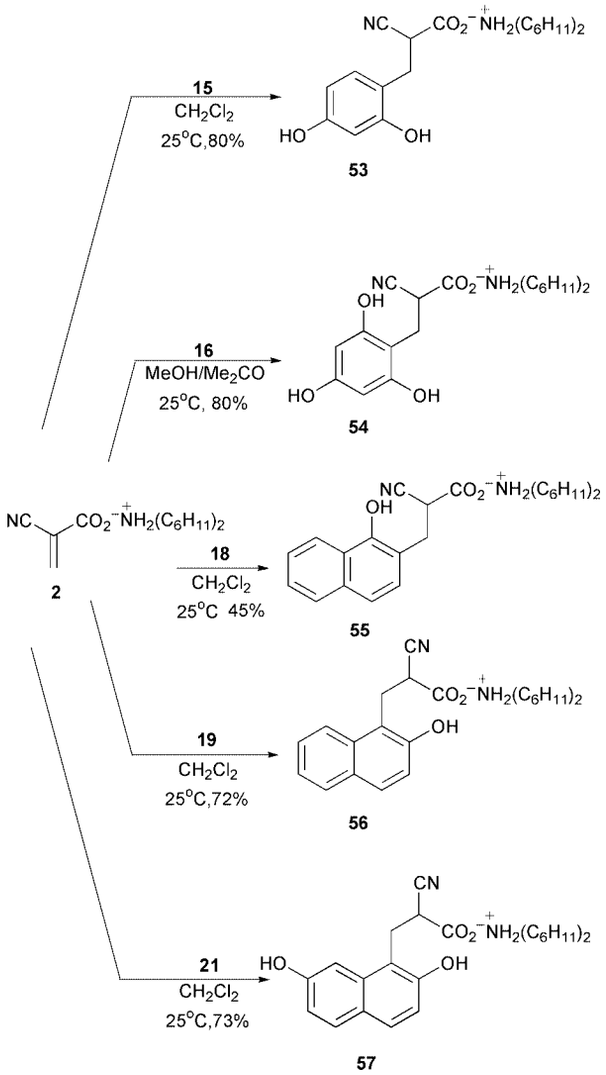
Propionate 24. δ_P (101.26 MHz; $CDCl_3$) 24.43; δ_H (250 MHz; $CDCl_3$) 3.75 (ddd, 1H, *J* 5.0, *J* 9.0, $^{2}J_{HP}$ 20.0, CHP), 4.45 (dt, 1H, *J* 5.0, ^{2}J 9.0, $^{3}J_{HP}$ 9.0, C*H*OAr), 4.75 (q, 1H, *J* 9.0, ^{2}J 9.0, $^{3}J_{HP}$ 9.0, C*H*OAr).

Propionate 35. δ_P (101.26 MHz; $CDCl_3$) 24.34; δ_H (250 MHz; $CDCl_3$) 3.60 (ddd, 1H, *J* 5.0, ^{2}J 9.0, $^{2}J_{HP}$ 22.0, CHP), 4.31 (dt, 1H, *J* 5.0, ^{2}J 9.0, $^{3}J_{HP}$ 9.0, C*H*OAr), 4.60 (q, 1H, *J* 9.0, *J* 9.0, $^{3}J_{HP}$ 9.0, C*H*OAr).

Propionate 36. δ_P (101.26 MHz; $CDCl_3$) 24.34; δ_H (250 MHz; $CDCl_3$) 3.56 (ddd, 1H, *J* 5.0, *J* 9.0, $^{2}J_{HP}$ 22.0, CHP), 4.29 (dt, 1H, *J* 5.0, ^{2}J 9.0, $^{3}J_{HP}$ 9.0, C*H*OAr), 4.57 (q, 1H, *J* 9.0, ^{2}J 9.0, $^{3}J_{HP}$ 9.0, CHOAr).

Propionate 37. δ_P (101.26 MHz; $CDCl_3$) 24.32; δ_H (250 MHz; $CDCl_3$) 3.57 (ddd, 1H, *J* 5.0, *J* 9.0, $^{2}J_{HP}$ 22.0, CHP), 4.33 (dt, 1H, *J* 5.0, ^{2}J 9.0, $^{3}J_{HP}$ 9.0, C*H*OAr), 4.62 (q, 1H, *J* 9.0, ^{2}J 9.0, $^{3}J_{HP}$ 9.0, CHOAr).

Propionate 38. δ_P (101.26 MHz; $CDCl_3$) 24.24; δ_H (250 MHz; $CDCl_3$) 3.50 (ddd, 1H, *J* 5.0, *J* 9.0, $^{2}J_{HP}$ 23.0, CHP), 4.32 (dt,



Scheme 7

1H, *J* 5.0, ^2J 9.0, $^3J_{HP}$ 9.0, C*H*OAr), 4.43 (q, 1H, *J* 9.0, ^2J 9.0, $^3J_{HP}$ 9.0, C*H*OAr).

Propionate 44. δ_P (101.26 MHz; $CDCl_3$) 22.45; δ_H (250 MHz; $CDCl_3$) 3.81 (ddd, 1H, *J* 5.0, *J* 9.0, $^2J_{HP}$ 22.0, CHP), 4.56 (dt, 1H, *J* 5.0, ^2J 9.0, $^3J_{HP}$ 9.0, C*H*OAr), 4.88 (q, 1H, *J* 9.0, ^2J 9.0, $^3J_{HP}$ 9.0, C*H*OAr).

Propionate 39. To a solution of acrylate **1** (1.945 g, 5 mmol) in benzene (10 ml) was added hydroquinone **14** (0.55 g, 5 mmol) and the mixture was briefly heated to 50 °C until a clear solution was obtained (10 min). The reaction mixture was left at room temperature for one week. The precipitated crystals were collected by filtration to give the crude propionate **39** (1.87 g) as a white solid. The product was identified by its ^{1}H and ^{31}P NMR spectra which indicated the presence of 7% unchanged acrylate **1**; δ_P (101.26 MHz; $CDCl_3$) 25.07; δ_H (250 MHz; $CDCl_3$) 1.04–1.46 (m, 10H), 1.26 (t, 6H, *J* 7.0, 2 × C*H*$_3$CH$_2$O), 1.59 (m, 2H), 1.74 (m, 4H), 1.94 (m, 4H), 2.87 (m, 2H, 2 × CHN), 3.28 (ddd, 1H, *J* 5.0, *J* 9.0, $^3J_{HP}$ 22.0, CHP), 4.10 (m, 5H, 2 × CH$_2$O, C*H*OAr), 4.40 (q, *J* 9.0, ^2J 9.0, $^3J_{HP}$ 9.0, C*H*OAr), 6.62 (s, 2H), 6.66 (s, 2H). Attempted recrystallization of the solid from chloroform failed and led to a mixture of acrylate **1** and propionate **39** in the ratio 1 : 2.

Dicyclohexylammonium 2-(diethoxyphosphoryl)-3-(2-hydroxyphenyl)propionate 26

A mixture of acrylate **1** (1.945 g, 5 mmol) and phenol **9** (1.88 g, 100 mmol) was heated at 100 °C for 2 h. Excess of phenol was distilled off under reduced pressure to leave a brown oil, which crystallized on storage. The precipitated crystals were collected by filtration and washed with hexane to afford the crude compound **26** (120 mg). Recrystallization from chloroform–acetone gave the pure propionate **26** as a white solid (95 mg, 3.9%), mp 185–187 °C; δ_P (101.26 MHz; $CDCl_3$) 27.15; δ_H (250 MHz; $CDCl_3$) 1.0–1.4 (m, 10H), 1.33 (t, 3H, *J* 7.0, C*H*$_3$CH$_2$O), 1.34 (t, 3H, *J* 7.0, C*H*$_3$CH$_2$O) 1.60 (m, 2H), 1.72 (m, 4H), 1.92 (m, 4H), 2.92 (m, 4H, 2 × CHN, CHP, C*H*Ar), 3.41 (ddd, 1H, $^3J_{HP}$ 5.5, *J* 11.5, *J* 13.5, C*H*Ar), 4.18 (m, 4H, 2 × CH$_2$O), 6.80 (m, 2H), 7.05 (m, 2H); ν_{max}(KBr)/cm^{-1} 1627 (COO$^-$), 1227 (P=O); FAB/MS MH$^+$ 484 (Found: C, 61.93; H, 8.71. $C_{25}H_{42}NO_6P$ requires C, 62.09; H, 8.75%).

Dicyclohexylammonium 2-(diethoxyphosphoryl)-3-(2,4-dihydroxyphenyl)propionate 40

A solution of acrylate **1** (3.89 g, 10 mmol) and resorcinol **15** (1.65 g, 15 mmol) in methylene dichloride (20 ml) was left for two weeks at room temperature. The precipitated crystals were collected by filtration to give the crude product **40**. Recrystallization from methanol–acetone afforded the analytically pure propionate **40** as a white powder (2.0 g, 40%), mp 189–192 °C; δ_P (101.26 MHz; CD_3OD) 28.31; δ_H (250 MHz; CD_3OD) 1.20–1.60 (m, 10H), 1.42 (t, 6H, *J* 7.0, 2 × C*H*$_3$CH$_2$O), 1.80 (m, 2H), 1.97 (m, 4H), 2.15 (m, 4H), 2.98–3.35 (m, 5H, CH$_2$, CH, 2 × CHN), 4.26 (m, 4H, 2 × CH$_2$O), 6.31 (dd, 1H, *J* 3.0, *J* 8.0), 6.35 (d, 1H, *J* 3.0), 7.04 (d, 1H, *J* 8.0); ν_{max}(KBr)/cm^{-1} 1632 (COO$^-$), 1224 (P=O); FAB/MS MH$^+$ 500 (Found: C, 59.93; H, 8.39. $C_{25}H_{42}NO_7P$ requires C, 60.10; H, 8.47%).

Dicyclohexylammonium 2-(diethoxyphosphoryl)-3-(2,4,6-trihydroxyphenyl)propionate 41

To α solution of phloroglucinol **16** (2.52 g, 20 mmol) in methanol (30 ml) was added acrylate **1** (3.89 g, 10 mmol) and resulting solution was evaporated to give an oily residue, which was dissolved in acetone (20 ml) and left for crystallization. After one week the precipitated crystals were collected by filtration to give the crude product **41**. Recrystallization from methanol–acetone afforded the propionate **41** as a white solid (4.37 g, 85%), mp 198–200 °C; δ_P (101.26 MHz; CD_3OD) 28.11; δ_H (250 MHz; CD_3OD) 1.05–1.40 (m, 10H), 1.34 (t, 6H, *J* 7.0, 2 × C*H*$_3$CH$_2$O), 1.67 (m, 2H), 1.85 (m, 4H), 2.03 (m, 4H), 3.00–3.30 (m, 5H, 2 × CHN, CH$_2$, CH), 4.19 (m, 4H, 2 × CH$_2$O), 5.85 (s, 2H); ν_{max}(KBr)/cm^{-1} 1636 (COO$^-$), 1222 (P=O); FAB/MS MH$^+$ 516 (Found: C, 58.11; H, 8.26. $C_{25}H_{42}NO_8P$ requires C, 58.24; H; 8.21%).

Dicyclohexylammonium 2-(diethoxyphosphoryl)-3-(4-hydroxy-2,6-dimethoxyphenyl)propionate 42 and dicyclohexylammonium 2-(diethoxyphosphoryl)-3-(2-hydroxy-4,6-dimethoxyphenyl)-propionate 43

To a solution of acrylate **1** (3.89 g, 10 mmol) in benzene (20 ml) was added 3,5-dimethoxyphenol **17** (1.54 g, 10 mmol) and the mixture was left for one week at room temperature. The solution was evaporated and the solid residue was triturated with diethyl ether and filtered to give a mixture of the products **42** and **43** as a white solid (4.6 g, 85%). The solid was crystallised from methylene dichloride–acetone to furnish the propionate **42** (2.2 g, 40%), from the mother liquor a further crop of the propionate **42** was obtained (0.22 g). Overall yield of the recrystallized product **42** was 2.42 g (44%). The mother liquor was evaporated and the solid residue was recrystallized from acetone–diethyl ether to afford (1.63 g, 30%) of the propionate **43** as a white solid.

Propionate 42. Mp 167–169 °C; δ_P (101.26 MHz; $CDCl_3$) 29.30; δ_H (250 MHz; $CDCl_3$) 1.05–1.50 (m, 10H), 1.31 (t, 3H,

J 7.0, CH_3CH$_2$O), 1.34 (t, 3H, *J* 7.0, CH_3CH$_2$O), 1.65 (m, 2H), 1.81 (m, 4H), 2.04 (m, 4H), 2.70–3.00 (m, 3H), 3.35 (m, 2H), 3.48 (s, 6H, 2 × CH$_3$O), 4.15 (m, 4H, 2 × CH$_2$O), 5.96 (s, 2H); ν_{max}(KBr)/cm^{-1} 1632 (COO$^-$), 1235 (P=O); FAB/MS MH$^+$ 544 (Found: C, 59.54; H, 8.39. $C_{27}H_{46}NO_8P$ requires C, 59.65; H, 8.53%).

Propionate 43. Mp 135–137 °C; δ_P (101.26 MHz; $CDCl_3$) 27.51; δ_H (250 MHz; $CDCl_3$) 1.00–1.45 (m, 10H), 1.33 (t, 3H, *J* 7.0, CH_3CH$_2$O), 1.36 (t, 3H, *J* 7.0, CH_3CH$_2$O), 1.60 (m, 2H), 1.73 (m, 4H), 1.93 (m, 4H), 2.90–3.15 (m, 5H, 2 × CHN, CH$_2$, CH), 3.71 (s, 3H, CH$_3$O), 3.73 (s, 3H, CH$_3$O), 4.18 (m, 4H, 2 × CH$_2$O), 5.99 (d, 1H, *J* 2.0), 6.08 (d, 1H, *J* 2.0); ν_{max}(KBr)/cm^{-1} 1628 (COO$^-$), 1232 (P=O); FAB/MS MH$^+$ 544 (Found: C, 59.47; H, 8.59. $C_{27}H_{46}NO_8P$ requires C, 59.65; H, 8.53%).

Dicyclohexylammonium 2-(diethoxyphosphoryl)-3-(2-hydroxy-1-naphthyl)propionate 45

To a solution of acrylate **1** (3.89 g, 10 mmol) in benzene (30 ml) was added 2-naphthol **19** (1.44 g, 10 mmol) and the reaction mixture was left for 2 weeks at room temperature. The solvent was evaporated off. The solid residue was suspended in diethyl ether and the crystals were collected by filtration to afford the crude product **45** (4.6 g). Recrystallization of the solid from chloroform–acetone afforded the propionate **45** as a white powder (4.25 g, 80%), δ_P (101.26 MHz; $CDCl_3$) 27.10; δ_H (250 MHz; $CDCl_3$) 0.92–1.50 (m, 12H), 1.38 (t, 3H, *J* 7.0, CH_3CH$_2$O), 1.44 (t, 3H, *J* 7.0, CH_3CH$_2$O), 1.65 (m, 4H), 1.82 (m, 4H), 2.84 (m, 2H, 2 × CHN), 3.18 (ddd, 1H, *J* 2.0, *J* 12.0, $^2J_{HP}$ 24.7, CHP), 3.46 (ddd, 1H, *J* 2.0, $^3J_{HP}$ 12.0, ^2J 15.0, C*H*Ar), 3.68 (ddd, 1H, $^3J_{HP}$ 4.0, *J* 12.0, ^2J 15.0, C*H*Ar), 4.22 (m, 4H, 2 × CH$_2$O), 7.10 (d, 1H, *J* 8.7), 7.28 (t, 1H, *J* 8.2), 7.45 (t, 1H, *J* 8.2), 7.58 (d, 1H, *J* 8.7), 7.72 (d, 1H, *J* 8.2), 7.86 (d, 1H, *J* 8.2); ν_{max}(KBr)/cm^{-1} 1630 (COO$^-$), 1227 (P=O); FAB/MS MH$^+$ 534 (Found: C, 65.15; H, 8.24. $C_{29}H_{44}NO_6P$ requires C, 65.27; H, 8.31%).

Dicyclohexylammonium 2-(diethoxyphosphoryl)-3-(2,5-dihydroxy-1-naphthyl)propionate 46

A solution of acrylate **1** (3.89 g, 10 mmol) and 1,6-dihydroxynaphthalene **20** (2.40 g, 15 mmol) in methylene dichloride (25 ml) was left at room temperature for 2 weeks. After the reaction was complete the precipitated crystals were collected by filtration, washed with acetone, and recrystallized from methanol–acetone to afford the propionate **46** as a white powder (3.56 g, 65%), mp 214–216 °C; δ_P (101.26 MHz; CD_3OD) 27.63; δ_H (250 MHz; CD_3OD) 1.11–1.42 (m, 10H), 1.38 (t, 6H, *J* 7.0, 2 × CH_3CH$_2$O), 1.69 (m, 2H), 1.83 (m, 4H), 2.01 (m, 4H), 3.20 (m, 2H, 2 × CHN), 3.20–3.50 (m, 2H, CHP, C*H*Ar), 3.69 (ddd, 1H, $^3J_{HP}$ 5.0, *J* 12.0, *J* 14.0, C*H*Ar), 4.20 (m, 4H, 2 × CH$_2$O), 6.68 (d, 1H, *J* 9.0), 7.02 (d, 1H, *J* 9.0), 7.27 (t, 1H, *J* 9.0), 7.38 (d, 1H, *J* 9.0), 8.02 (d, 1H, *J* 9.0); ν_{max}(KBr)/cm^{-1} 1616 (COO$^-$), 1224 (P=O); FAB/MS MH$^+$ 550 (Found: C, 63.21; H, 7.89. $C_{29}H_{44}NO_7P$ requires C, 63.37; H, 8.06%).

Dicyclohexylammonium 2-(diethoxyphosphoryl)-3-(2,7-dihydroxy-1-naphthyl)propionate 47

A solution of acrylate **1** (3.89 g, 10 mmol) and 2,7-dihydroxynaphthalene **21** (1.60 g, 10 mmol) in methylene dichloride (25 ml) was left aside for one week at room temperature. After the reaction was complete the solvent was evaporated off and the solid residue was recrystallized from acetone to afford the propionate **47** as a white solid (4.39 g, 80%), mp 196–198 °C; δ_P (101.26 MHz; $CDCl_3$) 27.55; δ_H (250 MHz; $CDCl_3$) 0.96–1.40 (m, 10H), 1.33 (t, 3H, *J* 7.1, CH_3CH$_2$O), 1.39 (t, 3H, *J* 7.1, CH_3CH$_2$O), 1.58 (m, 2H), 1.70 (m, 4H), 1.90 (m, 4H), 2.88 (m, 2H, 2 × CHN), 3.20 (dd, 1H, *J* 11.0, $^2J_{HP}$ 25, CHP), 3.45 (dt, 1H, ^2J, $^3J_{HP}$ 14.5, C*H*Ar), 3.65 (ddd, 1H, $^3J_{HP}$ 4.0, *J* 11.0, ^2J 14.5, C*H*Ar), 6.90 (d, 1H, *J* 9.0), 6.92 (d, 1H, *J* 2.0, *J* 9.0), 7.26 (d, 1H, *J* 2.0), 7.48 (d, 1H, *J* 9.0), 7.59 (d, 1H, *J* 9.0); ν_{max}(KBr)/cm^{-1} 1632 (COO$^-$), 1218 (P=O); FAB/MS MH$^+$ 550 (Found: C, 63.24; H, 7.89. $C_{29}H_{44}NO_7P$ requires C, 63.37; H, 8.06%).

Dicyclohexylammonium 2-(diethoxyphosphoryl)-3-(10-hydroxy-9-phenanthryl)propionate 48

A solution of acrylate 1 (0.778 g, 2 mmol) and 9-phenanthrol **23** (0.388 g, 2 mmol) in benzene (7 ml) was stirred at room temperature for 24 h. After the reaction was complete, the solvent was evaporated off and the solid residue was crystallized from methylene dichloride–acetone to afford the propionate **48** as a white solid (1.05 g, 90%), mp 174–176 °C; δ_P (101.26 MHz; $CDCl_3$) 27.08; δ_H (250 MHz; $CDCl_3$) 0.80–1.50 (m, 16H), 1.38 (t, 3H, *J* 7.0, CH_3CH$_2$O), 1.40 (t, 3H, *J* 7.0, CH_3CH$_2$O), 1.78 (m, 4H), 2.80 (m, 2H, 2 × CHN), 3.32 (ddd, 1H, *J* 1.0, *J* 12.0, $^2J_{HP}$ 25.0, CHP), 3.47 (ddd, 1H, *J* 1.0, ^2J 15.0, $^3J_{HP}$ 11.0, C*H*Ar), 3.83 (ddd, 1H, $^3J_{HP}$ 4.0, ^2J 15.0, *J* 12.0, C*H*Ar), 4.34 (m, 4H, 2 × CH$_2$O), 7.46 (m, 1H), 7.56 (m, 3H), 7.92 (d, 1H, *J* 7.0), 8.36 (m, 1H), 8.60 (m, 2H); ν_{max}(KBr)/cm^{-1} 1630 (COO$^-$), 1224 (P=O); FAB/MS MH$^+$ 584 (Found: C, 67.74; H, 7.87. $C_{33}H_{46}NO_6P$ requires C, 67.90; H, 7.94%).

Dicyclohexylammonium 2-(diethoxyphosphoryl)-3-(1-hydroxy-2-naphthyl)propionate 49 and dicyclohexylammonium 2-(diethoxyphosphoryl)-3-(4-hydroxy-1-naphthyl)propionate 50

A solution of acrylate **1** (3.89 g, 10 mmol) and 1-naphthol **18** (2.16 g, 15 mmol) in benzene (25 ml) was left for 6 weeks at room temperature. After the reaction was complete the solvent was evaporated off and the oily residue was dissolved in diethyl ether (20 ml) and left for crystallization. The precipitated solid was filtered off, washed with diethyl ether to afford the propionate **49** (3.2 g, 60%). The mother liquor was partially evaporated to give a further crystalline crop (0.89 g, 15%) containing both products **49** and **50** in the ratio 1 : 1 (^{31}P NMR). Recrystallization of the solid from acetone–methylene dichloride afforded the analytically pure propionate **50** (200 mg).

Propionate 49. White solid, mp 135–137 °C; δ_P (101.26 MHz; $CDCl_3$) 26.94; δ_H (250 MHz; $CDCl_3$) 0.80–1.46 (m, 12H), 1.33 (t, 3H, *J* 7.0, CH_3CH$_2$O), 1.35 (t, 3H, *J* 7.0, CH_3CH$_2$O), 1.55 (m, 4H), 1.84 (m, 4H), 2.88 (m, 3H, 2 × CHN, C*H*Ar), 3.08 (ddd, 1H, *J* 2.5, *J* 12.5, $^2J_{HP}$ 24.0, CHP), 3.60 (ddd, 1H, $^3J_{HP}$ 5.5, *J* 12.5, ^2J 14.5, C*H*Ar), 4.20 (m, 4H, 2 × CH$_2$O), 7.18 (d, 1H, *J* 8.5), 7.29 (d, 1H, *J* 8.5), 7.40 (m, 2H), 7.67 (m, 1H), 8.21 (m, 1H); ν_{max}(KBr)/cm^{-1} 1634 (COO$^-$), 1235 (P=O); FAB/MS MH$^+$ 534 (Found: C, 65.12; H, 8.23. $C_{29}H_{44}NO_6P$ requires C, 65.27; H, 8.31%).

Propionate 50. White solid, mp 158–160 °C; δ_P (101.26 MHz; CD_3OD) 28.47; δ_H (250 MHz; CD_3OD) 1.12–1.45 (m, 10H), 1.34 (t, 3H, *J* 7.0, CH_3CH$_2$O), 1.37 (t, 3H, *J* 7.0, CH_3CH$_2$O), 1.69 (m, 2H), 1.86 (m, 4H), 2.01 (m, 4H), 3.10 (m, 2H, 2 × CHN), 3.24 (dt, 1H, *J* 7.2, $^2J_{HP}$ 22.2, CHP), 3.55 (dd, 2H, *J* 7.2, $^3J_{HP}$ 10.0, CH$_2$Ar), 4.21 (m, 4H, 2 × CH$_2$O), 6.71 (d, 1H, *J* 7.8), 7.30 (d, 1H, *J* 7.8), 7.42 (m, 1H), 7.52 (m, 1H), 8.03 (br d, 1H, *J* 8.2), 8.23 (br d, 1H, *J* 8.2); ν_{max}(KBr)/cm^{-1} 1632 (COO$^-$), 1230 (P=O); FAB/MS MH$^+$ 534 (Found: C, 65.09; H, 8.27. $C_{29}H_{44}NO_6P$ requires C, 65.27; H, 8.31%).

Dicyclohexylammonium 2-(diethoxyphosphoryl)-3-(1,3-dihydroxy-2-naphthyl)propionate 51 and dicyclohexylammonium 2-(diethoxyphosphoryl)-3-(2,4-dihydroxy-1-naphthyl)propionate 52

A mixture of acrylate **1** (3.89 g, 10 mmol) and naphthoresorcinol **22** (1.60 g, 10 mmol) in benzene (40 ml) was stirred for 24 h at room temperature. After the addition was complete the precipitated crystals were collected by filtration and washed with diethyl ether to afford a mixture of the propionates **51** and

52 in the ratio 2 : 1 (^{31}P NMR) as an orange solid (4.7 g, 86%). The solid was recrystallized from methanol–chloroform to afford the propionate **51** as an orange solid (2.1 g, 38%); from the mother liquor a further crop of the propionate **51** was obtained (0.6 g, 11%). Overall yield of the recrystallized product **51** (2.7 g, 49%). The mother liquor was evaporated and the solid residue was recrystallized from chloroform–acetone to afford the propionate **52** as an orange solid (1.4 g, 25%).

Propionate 51. Mp 202–204 °C; δ_P (101.26 MHz; CD_3OD) 28.01; δ_H (250 MHz; CD_3OD) 1.09–1.45 (m, 10H), 1.39 (t, 6H, *J* 7.0, 2 × C*H*$_3$CH$_2$O), 1.66 (m, 2H), 1.80 (m, 4H), 2.04 (m, 4H), 3.14 (m, 2H, 2 × CHN), 3.15–3.40 (m, 3H, CHP, CH_2Ar), 4.22 (m, 4H, 2 × CH_2O), 6.69 (s, 1H), 7.15 (m, 1H), 7.28 (m, 1H), 7.49 (d, 1H, *J* 8.0), 8.07 (d, 1H, *J* 8.0); ν_{max}(KBr)/cm^{-1} 1624 (COO^-), 1216 (P=O); FAB/MS MH^+ 550 (Found: C, 63.10; H, 7.99. $C_{29}H_{44}NO_7P$ requires C, 63.37; H, 8.06%).

Propionate 52. Mp 196–198 °C; δ_P (101.26 MHz; CD_3OD) 27.88; δ_H (250 MHz; CD_3OD) 1.11–1.45 (m, 10H), 1.41 (t, 6H, *J* 7.0, C*H*$_3$CH$_2$O), 1.65 (m, 2H), 1.85 (m, 4H), 2.05 (m, 4H), 3.16 (m, 2H, 2 × CHN), 3.30–3.70 (m, 3H, CHP, C*H*$_2$Ar), 4.25 (m, 4H, 2 × CH_2O), 6.49 (s, 1H), 7.21 (m, 1H), 7.45 (m, 1H), 7.81 (d, 1H, *J* 8.5), 8.17 (d, 1H, *J* 8.5); ν_{max}(KBr)/cm^{-1} 1624 (COO^-), 1216 (P=O); FAB/MS MH^+ 550 (Found: C, 63.14; H, 7.97. $C_{29}H_{44}NO_7P$. requires C, 63.37; H, 8.06%).

Compounds **53**–**57** were prepared in the same manner to that described above.

Dicyclohexylammonium 2-cyano-3-(2,4-dihydroxyphenyl)propionate 53

White solid (80%), mp 127–129 °C; δ_H (250 MHz; CD_3OD) 1.10–1.40 (m, 10H), 1.63 (m, 2H), 1.82 (m, 4H), 2.01 (m, 4H), 2.85 (dd, 1H, *J* 8.5, *J* 13.5, C*H*Ar), 3.11 (dd, 1H, *J* 6.2, *J* 13.5, C*H*Ar), 3.32 (m, 2H, 2 × CHN), 3.67 (dd, 1H, *J* 6.2, *J* 8.5, CHCN), 6.20 (dd, 1H, *J* 3.0, *J* 8.0), 6.27 (d, 1H, *J* 3.0), 6.92 (d, 1H, *J* 8.0); ν_{max}(KBr)/cm^{-1} 2248 (CN), 1636 (COO^-); FAB/MS MH^+ 389 (Found: C, 67.83; H, 8.22. $C_{22}H_{33}N_2O_4$ requires C, 68.01; H, 8.30%).

Dicyclohexylammonium 2-cyano-3-(2,4,6-trihydroxyphenyl)-propionate 54

White solid (80%), δ_H (250 MHz; DMSO-d_6) 1.05–1.27 (m, 10H), 1.60 (m, 2H), 1.80 (m, 4H), 1.97 (m, 4H), 2.80 (d, 2H, *J* 6.5, C*H*$_2$Ar), 3.04 (m, 2H, 2 × CHN), 3.27 (t, 1H, *J* 6.5, CHCN), 5.71 (s, 2H); ν_{max}(KBr)/cm^{-1} 2260 (CN), 1636 (COO^-); FAB/MS MH^+ 405 (Found: C, 65.11; H, 7.44. $C_{22}H_{32}N_2O_5$ requires C, 65.32; H, 7.57%).

Dicyclohexylammonium 2-cyano-3-(1-hydroxy-2-naphthyl)-propionate 55

Light-green solid (45%), mp 159–161 °C; δ_H (250 MHz; $CDCl_3$) 0.90–1.88 (m, 20H), 2.98 (m, 2H, 2 × CHN), 3.14 (dd, 1H, *J* 6.2, *J* 14.2, C*H*Ar), 3.53 (dd, 1H, *J* 3.2, *J* 14.2, C*H*Ar), 3.77 (1H, dd, *J* 3.2, *J* 6.2, CHCN), 7.40 (m, 4H), 7.71 (m, 1H), 8.21 (m, 1H); ν_{max}(KBr)/cm^{-1} 2252 (CN), 1625 (COO^-); FAB/MS MH^+ 423 (Found: C, 73.75; H, 8.02. $C_{26}H_{34}N_2O_3$ requires C, 73.90; H, 8.11%).

Dicyclohexylammonium 2-cyano-3-(2-hydroxy-1-naphthyl)-propionate 56

Light-green solid (72%), mp 150–152 °C; δ_H (250 MHz; $CDCl_3$) 1.0–1.37 (m, 10H), 1.58 (m, 2H), 1.72 (m, 4H), 1.91 (m, 4H), 3.05 (m, 2H, 2 × CHN), 3.51–3.78 (m, 3H, C*H*$_2$Ar, CHCN), 7.13 (d, 1H, *J* 9.0), 7.33 (m, 1H), 7.52 (m, 1H), 7.66 (d, 1H, *J* 9.0), 7.77 (d, 1H, *J* 8.5), 7.86 (d, 1H, *J* 8.5); ν_{max}(KBr)/cm^{-1} 2252 (CN), 1625 (COO^-); FAB/MS MH^+ 423 (Found: C, 73.79; H, 8.04. $C_{26}H_{34}N_2O_3$ requires C, 73.90; H, 8.11%).

Dicyclohexylammonium 2-cyano-3-(2,7-dihydroxy-1-naphthyl)-propionate 57

Light-green solid (73%), mp 185–187 °C; δ_H (250 MHz; CD_3OD) 1.07–1.36 (m, 10H), 1.70 (m, 2H), 1.85 (m, 4H), 2.05 (m, 4H), 3.49–3.77 (m, 3H, CH_2Ar, CHCN), 6.85 (dd, 1H, *J* 2.0, *J* 9.0), 6.89 (d, 1H, *J* 9.0), 7.23 (d, 1H, *J* 2.0), 7.52 (d, 1H, *J* 9.0), 7.59 (d, 1H, *J* 9.0); ν_{max}(KBr)/cm^{-1} 2264 (CN), 1628 (COO^-); FAB/MS MH^+ 439 (Found C, 71.03; H, 7.65. $C_{26}H_{34}N_2O_4$ requires C, 71.20; H, 7.81%).

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