Table 1. Indirect nucleophilic addition to cycloalkenols **1** and **7**.[a]

Entry	Substrate	Nucleophile	Catalyst [mol %]	t[b] [h]	Yield[c,d] [%]
1	**1**	**2**	Al(O*t*Bu)$_3$(100)	24	90[e]
2	**1**	**2**	Al(O*t*Bu)$_3$(10)	24	<5
3	**1**	**2**	Me$_2$AlCl(100)[f]	24	45
4	**1**	**2**	Me$_2$AlCl(10)	24	<5
5	**1**	**6**	Al(O*t*Bu)$_3$(100)	24	81
6	**7**	**2**	Al(O*t*Bu)$_3$(100)	24	27
7	**7**	**6**	Al(O*t*Bu)$_3$(100)	24	19

[a] The reactions were carried out on a 1 mmol scale in dichloromethane (5 mL) at reflux (Al(O*t*Bu)$_3$); or at room temperature (Me$_2$AlCl). [b] Rate studies indicated that the reaction reached near completion after 6–8 h. [c] Yield of isolated product after column chromatography. [d] The maximum expected yield is 90%. [e] Reaction carried out on a 5 mmol scale. [f] Tetrabutylammonium bromide (4 mol%) added to increase dissolution of methylmalononitrile salt.

Table 2. Catalytic indirect nucleophilic addition to cycloalkenols **1** and **7**.[a]

Entry	Substrate	Nucleophile	Al(O*t*Bu)$_3$ [mol %]	t [h]	Yield[b] [%]
1	**1**	**2**	10	24	90
2	**1**	**2**	10	24	70[c]
3	**1**	**6**	10	24	64
4	**7**	**2**	100	24	60
5	**7**	**6**	100	24	21

[a] The reactions were carried out on a 1 mmol scale in dichloromethane (3 mL) at 100 °C. [b] Yield of isolated product after column chromatography. [c] Cyclohexanone (10 mol%) used as oxidant.

cyclohexanone as an alternative catalytic oxidant (Table 2, entry 2).

However, the increase in temperature does not provide an enhancement in the yields obtained for the cyclopentyl system that we would have anticipated (Table 2, entries 4 and 5). Further experiments using scandium triflate and cerium chloride heptahydrate additives to activate 2-cyclopenten-1-one proved equally unsuccessful. It is suspected that the lower recovered yield at these temperatures is attributed to a competing side reaction (e.g. Pinner[7] reaction).

In summary, we have demonstrated that whilst nucleophiles will not normally add to allylic alcohols, this reaction becomes possible by a procedure involving catalytic electronic activation of the substrate.[8] We anticipate that the concept of catalytic electronic activation could be applied to other reactions that are more successful for electron-deficient alkenes than for electron-rich alkenes.

Experimental Section

Typical procedure for the domino Oppenauer/Michael addition/MPV process: Compounds **1** (0.098 g, 1.0 mmol) and **3** (0.009 g, 0.1 mmol) were added to a suspension of **6** (0.156 g, 1.0 mmol) and KO*t*Bu (0.011 g, 0.1 mmol) in CH_2Cl_2 (3 mL). The solution was heated to reflux under nitrogen and aluminum *tert*-butoxide (0.246 g, 1.0 mmol) in CH_2Cl_2 (2 mL) was added dropwise. After 24 h, the reaction was cooled, diluted with diethyl ether (50 mL), and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with diethyl ether (3 × 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Purification by flash column chromatography (SiO_2, 50% petroleum ether/diethyl ether) gave **5b** (0.206 g, 81% yield). $\mathbf{5b}_{\text{axial alcohol}}$: m.p. 106–108 °C; ^1H NMR (500 MHz, C_6D_6, 25 °C): $\delta = 0.35$ (br s, 1H; OH), 0.81 (app. ddt, $^3J(H,H) = 2$ Hz, $^3J(H,H) = 4$ Hz, $^2J(H,H) = 13.5$ Hz, 1H; H_{6ax}), 0.96 (app. dq, $^3J(H,H) = 4$ Hz, $^2J(H,H) = 13$ Hz, 1H; H_{4ax}), 1.12 (app. dt, $^3J(H,H) = 2$ Hz, $^2J(H,H) = 13$ Hz, 1H; H_{2ax}), 1.17–1.21 (m, 1H; H_{5eq}), 1.25 (br d, $^2J(H,H) = 14$ Hz, 1H; H_{6eq}), 1.37 (app. tq, $^2J(H,H) = 4$ Hz, $^3J(H,H) = 13$ Hz, 1H; H_{5ax}), 1.64 (br d, $^2J(H,H) = 12.5$ Hz, 1H; H_{4eq}), 1.70 (br d, $^2J(H,H) = 13$ Hz, 1H; H_{2eq}), 1.99 (app. tt, $^3J(H,H) = 3$ Hz, $^3J(H,H) = 12$ Hz, 1H; H_{3ax}), 2.41 (d, $^2J(H,H) = 14$ Hz, 1H; C*H*Ph), 2.51 (d, $^2J(H,H) = 14$ Hz, 1H; C*H*Ph), 3.53 (br s, 1H; H_{1eq}), 7.02–7.25 (m, 5H; Ph); IR (C_6D_6): $\tilde{\nu} = 2282$ (C≡N), 3592 cm^{-1} (O–H); MS (70 eV): m/z (%): 254 [$M^{\bullet+}$], 91 (100) [$PhCH_2^+$].

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The tmbp Dianion in the Contact Ion Pair $[(\mathrm{tmbp})\mathrm{Na}_2(\mathrm{dme})_{1.5}]_n$ and in the Solvent-Separated Ion Pair $[\mathrm{tmbp}][(2.2.1)\mathrm{Li}]_2$**

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Multiple reductions of unsaturated π systems generally provide important information on delocalization processes. Furthermore they often yield fascinating structures that illustrate aggregation and solvation phenomena of cations,[1] and constitute good models for the modification of solid

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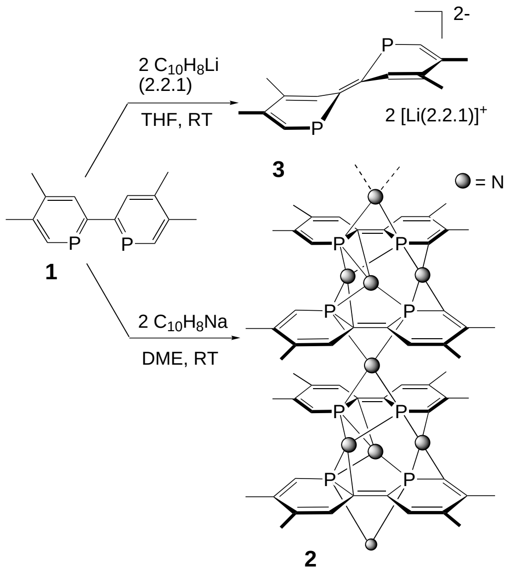
surfaces by adsorption of alkali metals.[2] Whereas reduction processes of unsaturated carbon[3] and nitrogen derivatives are now well documented,[4] that of sp^2-hybridized phosphorus-based molecules and their related transition metal complexes constitute a new field.[5] Recently, we have shown that 2,2′-biphosphinine dianions[6a] could be used efficiently to synthesize highly reduced transitions metal complexes through their reactions with various metal precursors;[6] herein we shed some light on their very peculiar geometrical and electronic structures. The twofold reduction of 4,4′,5,5′-tetramethyl-2,2′-biphosphinine (**1**; tmbp)[7a] was studied in THF and dimethoxyethane at room temperature with lithium naphthalene or sodium naphthalene with and without cryptands. From dimethoxyethane (DME), a polymeric structure of general formula $[(\text{tmbp})\text{Na}_2(\text{dme})_{1.5}]_n$ (**2**) crystallized,[8] whereas reaction with lithium in THF in the presence of cryptand (2.2.1) yielded the monomeric complex $[(\text{tmbp})][\text{Li}(2.2.1)]_2$ (**3**; Scheme 1).[9]



Scheme 1. Synthesis of polymeric $[(\text{tmbp})\text{Na}_2(\text{dme})_{1.5}]_n$ and monomeric $[(\text{tmbp})][\text{Li}(2.2.1)]_2$ salts.

The structure of **2** is highly unusual (Figure 1). The 2,2′-biphosphinine ligand adopts a cisoid configuration and the Na2, Na2′, and Na3 cations, which are each coordinated by one DME ligand, link two (tmbp) dianionic units. These two units are stacked to columns by Na1 cations. Relatively long distances (> 3.45 Å) indicate that no contact occurs between all these cations and their most noticeable feature is their coordination mode. Indeed, the two cations Na2 and Na2′ are bound both to the two P atoms of one molecule (2.925(2)–3.096(1) Å) and in an η^2-mode to the P1–C5 bond (Na2–C5 = 2.63(3) Å) of the second molecule. These relatively long bond lengths suggest that the bonding between sodium cations and the reduced ligand is mainly electrostatic. This particular geometrical arrangement implies that weak contacts also occur between these two cations and the C4 and C6 carbon atoms (average 3.025 Å). Interestingly, the third cation Na3 is only coordinated on one side of the dimeric unit to the two external P2–C10 bonds and a contact with the two C9 carbon atoms (3.097(3) pm). As a consequence of the loss of aromaticity in each phosphinine subunit, the ligand adopts a curved shape. A similar distorsion was observed upon coordination of **1** to a triosmium core.[10] Intramolecular bond lengths are dramatically affected and the connection between the two rings is short (1.401(4) vs 1.49 Å in **1**)[7b] as are the C3–C4 and C7–C8 bonds (1.363(4) Å). Conversely, the internal P=C bonds P1–C5 (1.815(3) Å) and P2–C6 (1.821(3) pm) are significantly lengthened adopting a single-bond character. All these data are in good agreement with the filling of the π* LUMO of the neutral tmbp ligand.[6c, d]

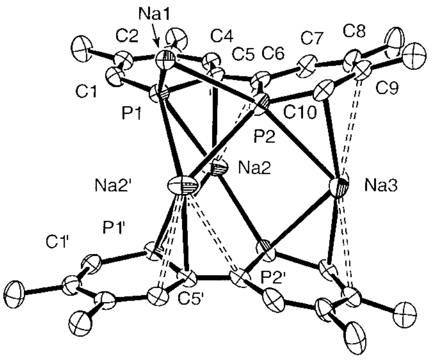


Figure 1. ORTEP view of two units of $[\text{tmbp}][\text{Na}_2(\text{dme})_{1.5}]_n$ (**2**). The DME ligands have been omitted for clarity. Selected bond lengths [Å] and angles [°]: P1–C1 1.773(3), C1–C2 1.357(4) C2–C3 1.446(4), C3–C4 1.363(4), C4–C5 1.439(4), C5–P1 1.815(3), C5–C6 1.401(4), C6–C7 1.425(4), C7–C8 1.363(4), C8–C9 1.447(4), C9–C10 1.367(4), C10–P2 1.772(3), Na1–P1 2.996(2), Na1–P2 3.011(2), Na2′–P1 3.018(2), Na2′–P2 2.927(2), C5–Na2 2.631(3), Na3–P2 3.068(2), Na3–C10 2.759(3); C1-P1-C5 100.1(1), P1-Na1-P2 61.02(4), P1-Na2′-P2 60.77 (3).

In **3**, the ligand adopts a transoid configuration (Figure 2). The overall geometry of **3** is highly distorted and the C5–C5′ connection deviates out of the plane defined by the other carbon atoms of the ring (C1-C2-C3-C4) and the phosphorus atom ($\Theta = 11°$).[10] Except for this distorsion, bond lengths and bond angles are very similar to those of compound **2**.

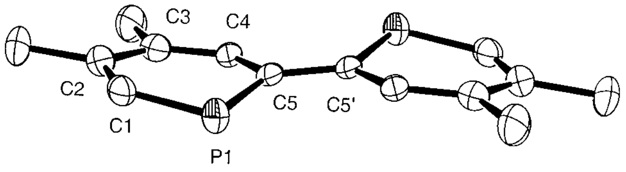
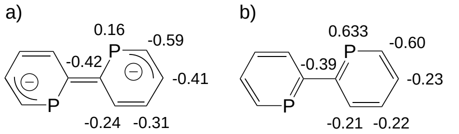


Figure 2. ORTEP view of one molecule of tmbp in **3**. Theoretical data obtained from calculations are given in parentheses. Selected bond lengths [Å] and angles [°]: P1–C1 1.760(7) [1.77], C1–C2 1.36(1) [1.36], C2–C3 1.44(1) [1.43], C3–C4 1.364(8) [1.38], C4–C5 1.431(8) [1.44], C5–P1 1.827(6) [1.87], C5–C6 1.40(1) [1.40]; C5-P1-C1 99.3(3) [100.9], P1-C1-C2 130.1(5) [127.7], C1-C2-C3 119.7(6) [129.9]; C2-C3-C4, 122.1(6) [124.2], C3-C4-C5 129.2(6) [127.7], C4-C5-P1 117.7(4) [117.1].

To assess the effects of the two-electron reduction of **1**, density functional theory (DFT) calculations were carried out on the constituent dianion in **3** (B3LYP/6-31+G* level of theory).[11] A scan of the potential-energy surface indicated the presence of two minima, a *cis* and a *trans* structure, the former being slightly higher in energy ($E_{cis} - E_{trans} =$ 2.02 kcal mol^{-1}, MP2/6-311 + G(2d,p)//B3LYP/6-31 + G* level of theory). Though the energy difference between the two configurations is small, all our crystallization attempts using (2.2.1) crytand yielded the *trans*-configuration product. This clearly shows that the loss of energy *trans* → *cis* in **2** is compensated by the Na–C_π and P_π interaction. The calculated geometry of the *trans* structure perfectly matches the experimental data, even reproducing the out of plane distorsion of the C–C bridge ($\Theta_{theo} = 10.5°$). Additionally, the natural bond order (NBO) analysis[12] shows that the phosphorus atom still behaves as a strong donor towards the carbocyclic system and the natural charge at the phosphorus center in **2** (+0.160; c.f. +0.663 in **1**) compares with those calculated for other delocalized anionic structures such as $(CH_2{=}CH)_2P^-$ (+0.142) and the phospholide anion $C_4H_4P^-$ (+0.227).[13, 14] This observation indicates that dianions **2** and **3** should not be regarded as classical phosphides.[15] Indeed, the negative charge in the two rings is mainly delocalized over the P–Cα–Cβ part of the ring. These different data lead us to propose the pseudo-allylic structure in Scheme 2.



Scheme 2. Comparison between natural charges in computed dianionic (a) and free (b) biphosphinine.

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[8] Preparation and single-crystal growth of **2**: In a dry box a solution of naphthalene/Na (0.2 mmol) in a DME/Et_2O mixture (8:2), was added to solid tmbp (25 mg, 0.1 mmol) under argon. The dark green solution was then transferred to a glass tube which was subsequently sealed. Deep purple crystals of **2** of X-ray quality deposited within a week at room temperature. The tube was taken back into a dry box and the crystals collected on a fine frit, yield (75%). The high sensitivity of the product towards oxygen precluded the determination of elemental analyses. Single crystals of **2** were protected with paratone oil for handling. Crystal structure determination: formula: $C_{46}H_{80}Li_2N_4O_{10}P_2$, dimensions 0.08 × 0.08 × 0.04 mm, monoclinic, space group *P2/n*, $a = 8.440(5)$, $b = 12.760(5)$, $c = 21.340(5)$ Å, $\alpha = 89.970(5)$, $\beta = 90.190(5)$, $\gamma = 89.980(5)°$, $V = 2298.2(17)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.235\ \mathrm{g\,cm^{-3}}$, $\mu = 0.243\ \mathrm{cm^{-1}}$, $F(000) = 908$, $\Theta_{max} = 24.40°$, *h,k,l* ranges, −9 to 8, −14 to 14, −24 to 24; 11266 reflections collected of which 3793 were unique ($R_{int} = 0.0602$), 2899 reflections with $I > 2\sigma(I)$, and 252 parameters refined, GOF(F^2) = 1.130, final *R* indices: $R_1 = 0.0468$, $wR_2 = 0.1402$, max./min. residual electron density 0.582(0.167)/−0.466(0.167) e Å^{-3}. For data collection see ref. [9]. In this structure, Na1 and Na3 atoms both sit on twofold axes. The dimer shown in Figure 1 is obtained by a twofold (55502) rotation of the tmbp dianion about Na3 and applying operation 65501 and 45502 to Na2 (ORTEP notation). The symmetry of the dimer is C_2.

[9] Preparation and single-crystal growth of **3**: In a dry box a solution of naphthalene/Li (0.2 mmol) in DME was added to a mixture of solid tmbp (25 mg, 0.1 mmol) and Kryptofix (2.2.1) (66 mg, 0.2 mmol) under argon. The deep purple solution obtained was then sealed in a glass tube and small X-ray quality crystals deposited within a week at room temperature. The tube was taken back into a dry-box and the crystals collected on a fine frit, yield (65%). The high sensitivity towards oxygen precluded the determination of elemental analyses. Single crystals of **3** were protected with paratone oil for handling. Crystal structure determination: formula: $C_{30}H_{48}LiN_2O_5P_2$, dimensions 0.22 × 0.22 × 0.16 mm, triclinic, space group $P\bar{1}$, $a = 10.639(5)$, $b = 10.703(5)$, $c = 12.503(5)$ Å, $\alpha = 100.590(5)$, $\beta = 106.250(5)$, $\gamma = 11.240(5)°$, $V = 1207.6(9)$ Å^3, $Z = 1$, $\rho_{calcd} = 1.272\ \mathrm{g\,cm^{-3}}$, $\mu = 0.150\ \mathrm{cm^{-1}}$, $F(000) = 500$, $\Theta(\max) = 20.81°$, *h,k,l* ranges, −10 to 10, −10 to 10, −11 to 12; 4330 reflections collected of which 2515 were unique ($R_{int} = 0.0347$), 2201 reflections with $I > 2\sigma(I)$, and 252 parameters refined, GOF(F^2) = 1.272, final *R* indices: $R_1 = 0.0797$, $wR_2 = 0.2185$, max./min. residual electron density 0.476(0.099)/−0.423(0.099) e Å^{-3}. The dianion has a C_i symmetry. Figure 2 shows the assembly resulting from an inversion center at 66602. Data collection for structures **2** and **3**: Nonius Kappa CCD diffractometer, φ and ω scans, $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å), graphite monochromator, $T = 150$ K, structure solution with SIR97,[16] refinement against F^2 (SHELXL97[17]) with anisotropic thermal parameters for all non-hydrogen atoms, calculated hydrogen positions with riding isotropic thermal parameters. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-166429 (for **2**) and CCDC-166430 (for **3**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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[13] All these structures were computed at the same level of theory.

[14] Comparatively, anions which lack π delocalization exhibit a higher negative charge at P: H_2P- (-0.883), Me_2P- (-0.226) computed at the B3LYP/6-31 + G* level of theory.

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Identification of a PLP-Dependent Threonine Transaldolase: A Novel Enzyme Involved in 4-Fluorothreonine Biosynthesis in *Streptomyces cattleya*[**]

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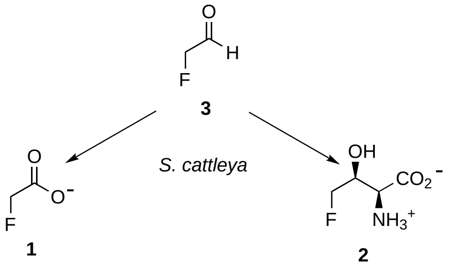
Fluorinated natural products are extremely rare in nature. Fluoroacetate (**1**) is the most widely distributed of this group of natural products and has been identified as a toxin in a range of tropical and sub-tropical plants[1] and in the actinomycete *Streptomyces cattleya*.[2, 3] In this bacterium fluoroacetate is co-produced with 4-fluorothreonine (**2**), the only naturally occurring fluorinated amino acid which has been identified to date. The biosynthetic pathways leading to fluoroacetate and 4-fluorothreonine have been investigated by using ^{13}C- and ^{2}H- enriched precursors.[4–6] These experiments have revealed that the carbon substrate for fluorination is closely related to an intermediate of the glycolytic pathway between glycerol and pyruvate. Furthermore, the labeling studies demonstrated that fluoroacetate and the C-3 and C-4 atoms of 4-fluorothreonine have the same biosynthetic origin and that there is a single fluorination enzyme. Most recently[7] fluoroacetaldehyde (**3**) has been identified as the common precursor of both fluorometabolites (Scheme 1) and the aldehyde dehydrogenase responsible for the oxidation of fluoroacetaldehyde to fluoroacetate has been isolated and purified.[8] Herein we describe the nature of the biotransformation of fluoroacetaldehyde to 4-fluorothreonine. Sanada et al.,[2] who first reported fluorometabolite production by *S. cattleya*, suggested that 4-fluorothreonine may arise by the direct condensation of fluoroacetaldehyde with glycine in a classical aldolase reaction. However, when [2-^{13}C]glycine was incubated with resting cell cultures of the bacterium,[6] the 4-fluorothreonine produced was doubly labeled in the C-1 and C-2 positions. Thus glycine does not directly contribute to 4-fluorothreonine biosynthesis, but is probably metabolized by serine hydroxymethyl transferase. We now report that L-threonine is the amino acid that condenses with fluoroacetaldehyde in *S. cattleya* to generate 4-fluorothreonine in a transaldolase-mediated reaction.



Scheme 1. Fluoroacetaldehyde is the common precursor of fluoroacetate and 4-fluorothreonine.

Upon incubation of a cell-free extract of *S. cattleya* with L-threonine, pyridoxal 5'-phosphate (PLP), and fluoroacetaldehyde, 4-fluorothreonine (ca. 0.25 mM) was detected by ^{19}F NMR spectroscopy. When the assay was conducted in the absence of PLP or L-threonine, or with boiled cell-free extract, there was no production of 4-fluorothreonine. When [1-^{2}H]fluoroacetaldehyde was used, a high level (61 %) of isotopic label was detected in the (C-2 – C-4) fragment of 4-fluorothreonine by GC-MS analysis, which indicates the direct incorporation of this unit into 4-fluorothreonine generated in vitro. This result is consistent with our previous observation in whole cells.[7] The enzyme was partially purified by ammonium sulfate precipitation and assayed with a range of amino acids (glycine, L-serine, L-cysteine, L-aspartate, L-alanine, and L-*allo*-threonine) instead of threonine. In none of the assay mixtures was 4-fluorothreonine production detected. The key observation that glycine is not a substrate for this enzyme is consistent with whole cell studies with [2-^{13}C]glycine.[6] The requirement for PLP and L-threonine suggests that a novel threonine transaldolase activity is responsible for 4-fluorothreonine production in the bacterium (Scheme 2).

The enzyme was purified further by anion-exchange chromatography. Experiments were conducted by using [1,2,2,2-$^{2}H_4$]acetaldehyde and DL-[4,4,4-$^{2}H_3$]threonine to explore the PLP-transaldolase aspect of the enzyme. After incubation of the enzyme with [1,2,2,2-$^{2}H_4$]acetaldehyde, PLP, and L-threonine, GC-MS analysis revealed a 20 % incorporation [M+4] of isotope into the threonine pool. No labeled threonine was detected in a control experiment in which threonine was substituted with glycine. Thus the enzyme – PLP complex accepted acetaldehyde as a substrate and generated a new molecule of L-threonine in a neutral

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