Asymmetric Synthesis of α-Substituted β-Nitrophosphonic Acids by Phospha-Analogous Michael Addition to Aromatic Nitroalkenes**

Dieter Enders,* Livio Tedeschi, and Jan Willem Bats

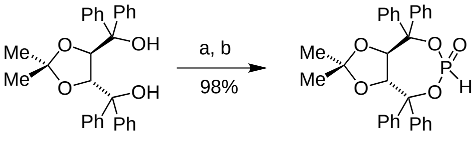
Dedicated to Professor Hans Jürgen Bestmann
on the occasion his 75th birthday

Considering the enormous significance of organophosphorus compounds in nature, it is surprising that naturally occurring phosphonates[1] that contain a C–P bond, have only been known since 1959[2] when (aminoethyl)phosphonic acid was isolated from sheep rumen. Since then numerous compounds of this class have been isolated, synthesized, and tested for their biological activity. In particular, phosphonates[3] bearing heteroatomic substituents in the α- or β-position to the phosphorus atom have shown strong activities as antibiotics, anticancer drugs, herbicides, and enzyme inhibitors.[4] Their activity may be attributed to the similarity to the natural α- and β-amino acids and to the relative hydrolytic stability of the C–P bond compared to that of the P–O bond. Optically active α-hydroxy and α-aminophosphonic acids can nowadays be prepared by a variety of methods.[5]

In contrast, only a few methods have been developed for the asymmetric synthesis of β-aminophosphonic acids[6] and of their precursors. A convenient route to β-aminophosphonic acids is provided by the addition of phosphorus compounds bearing a labile phosphorus–hydrogen bond to nitroalkenes, first developed by Pudovik et al.,[7] and the subsequent reduction of the nitro group.[8] However, the addition of dialkylphosphites to aromatic nitroalkenes leads to extensive polymerization of the nitro compounds. Examples of addition of di- and trialkylphosphites to unsaturated nitro compounds were also described by Yoshimura et al.,[9] who were able to add diethylphosphite to aliphatic nitroalkenes at 100 °C in moderate yields. Yamamoto et al.[10] developed the first substrate-controlled diastereoselective addition of dialkylphosphites to unsaturated nitrosaccharides, albeit only with moderate stereoselectivities. An efficient general method for the asymmetric Michael addition of phosphorus nucleophiles to unsaturated nitro compounds has not yet been described. Chiral catalysts[11] and chiral phosphorus nucleophiles[12, 13] have already been employed in the asymmetric hydrophosphonylation of aldehydes and imines by 1,2-addition.

We report here on the synthesis of an enantiomerically pure phosphite and its application as a chiral phosphorus nucleophile in the asymmetric Michael addition to aromatic nitroalkenes.

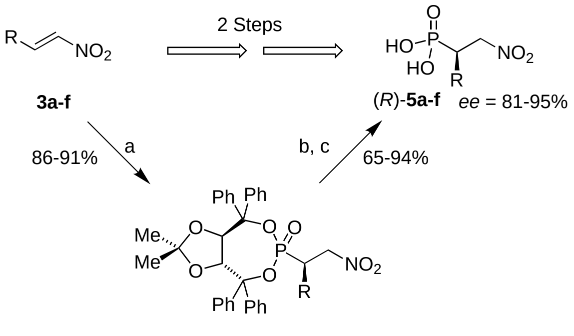
We obtained phosphite (*R*,*R*)-**2** in a two-step synthesis starting from TADDOL[14] ((*R*,*R*)-4,5-bis(diphenylhydroxymethyl)-2,2-dimethyl-1,3-dioxolane) (*R*,*R*)-**1**, which was converted into the corresponding chloride with PCl_3 and finally hydrolyzed in almost quantitative yield (Scheme 1).[15] The C_2-symmetry of the ligand avoided the formation of a new stereogenic center at phosphorus and the otherwise necessary separation of diastereomers.



(*R*,*R*,)-**1** (*R*,*R*,)-**2**

Scheme 1. Synthesis of phosphite (*R*,*R*)-**2**. a) 1.3 equiv PCl_3/Et_3N, THF, 0 °C; b) H_2O/Et_3N, THF, 0 °C.

Phosphite (*R*,*R*)-**2** was allowed to react with nitroalkenes **3a–f** in the presence of Et_2Zn and *N*,*N*,*N'N'*-tetramethylenediamine (TMEDA) and the resulting β-nitrophosphonates **4a–f** were obtained in very good yields and very high diastereomeric excesses (*de* = 84–96%) (Scheme 2, Table 1).



(*R*,*R*,*R*)-**4a-f** *de* = 84-96%

Scheme 2. Synthesis of β-nitrophosphonic acids (*R*)-**5**. a) (*R*,*R*)-**2**, TMEDA, Et_2Zn, THF, −78 °C; b) TMSCl, NaI, CH_3CN, reflux; c) CH_2Cl_2/H_2O, room temperature.

The reaction of diethylzinc with diphenylphosphane leads to the formation of reactive organozinc–phosphorus adducts, which were already described by Noltes[16] as very reactive but very insoluble. Also in our case we observed, after the addition of Et_2Zn to (*R*,*R*)-**2**, the precipitation of a solid substance which proved to be unreactive at −78 °C but easily underwent addition to the nitroalkenes at 0 °C. The solubility of the adduct was greatly improved by addition of TMEDA, so that it was possible to perform the reaction at low temperature and thus to obtain the addition products with higher *de* values (Table 1).

The configuration of the newly formed stereogenic center was determined to be *R* by single-crystal X-ray analysis for the

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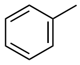
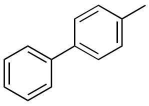
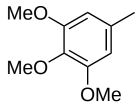
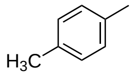
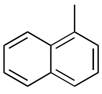
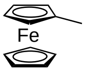
Table 1. Michael addition of phosphite **2** to nitroalkenes **3** to give β-nitrophosphonates **4**.

4	R	Yield [%]	*de* [%][a]	δ^{31}P	$[\alpha]_D^{20}$
a		89	89	17.0/16.8	–195.5
b		88	92(>96)[b]	15.9/15.5	–158.4
c		91	88(>96)[b]	17.2/16.8	–203.3
d		86	96	17.2/16.9	–187.3
e		87	93(>96)[b]	15.2/15.9	–219.3
f		86	84	17.7/17.5	–84.4

[a] Determined by ^{31}P NMR spectroscopy and by HPLC (Whelk 01, cyclohexane/2-propanol 9/1). [b] *de* values after chromatographic epimer separation (prep. HPLC: Merck Lichrosorb Si60, pentane/diethyl ether 1/1).

case of the 1,4-addition product **4b** (Figure 1).[17] Since we can postulate a common reaction mechanism all the described examples **4a–f** should possess this configuration.

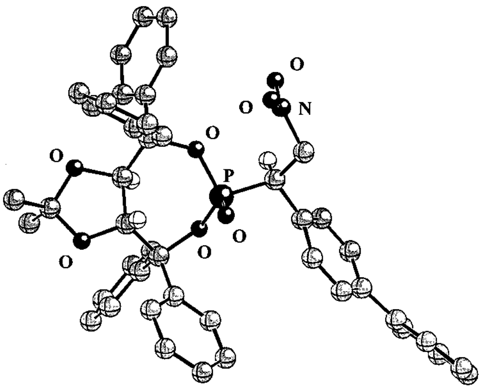


Figure 1. X-ray crystal structure of **4b**.[17]

The chiral auxiliary was cleaved under mild conditions by a modification of a procedure by Morita et al.[18] Reaction of nitrophosphonates **4a–f** with trimethylsilyl chloride (TMSCl) and NaI in acetonitrile led to bis(trimethysilyl)phosphonates, which were finally hydrolyzed in a mixture of water/dichloromethane (Scheme 2, Table 2).

Dimethyl- or diethylphosphonates can be converted to the corresponding silyl esters with NaI/TMSCl at room temperature or 40 °C, respectively, and then hydrolyzed with water. Owing to the steric hindrance of the esters **4a–f** it was necessary in our case to use longer reaction times and a higher temperature. The free nitrophosphonic acids **5a–f** were isolated from the aqueous phase after separation of the organic phase. We could show by HPLC over a chiral stationary phase that the cleavage of the auxiliary occurred practically without racemization (*ee* = 81–95 %). The β-nitrophosphonic acids were esterified with trimethylsilyl diazomethane and the enantiomeric excesses determined by HPLC (Table 2).

Table 2. Cleavage of TADDOL auxiliary to yield β-nitrophosphonic acids **5**.

(*R*)-**5**	Yield [%]	*ee* [%][a]	δ^{31}P	$[\alpha]_D^{20}$
a	87	92	19.7	+9.2
b	88	88	20.1	+11.1
c	92	86	20.5	+9.8
d	94	95	20.4	+15.3
e	65	91	20.2	+8.7
f	85	81	19.9	+4.7

[a] Determined by HPLC over a chiral stationary phase of the methyl ester derivatives (Whelk 01, *n*-heptane/2-propanol 9/1).

Aliphatic nitroalkenes (R = Me, Et) can also be used as Michael acceptors (yields: 85–95 %), but the asymmetric inductions are currently still unsatisfactory.

The described asymmetric phospha-analogous Michael addition to aromatic nitroalkenes provides an efficient route to optically active β-nitrophosphonic acids in good yields and enantiomeric excesses by a C–P bond-forming reaction. The products are valuable synthetic bifunctional building blocks and constitute potential precursors of β-aminophosphonic acids.

Experimental Section

(*R*,*R*)-**2**: In an oven-dried Schlenk flask triethylamine (1.3 equiv) was added under argon at 0 °C to a solution of phosphorus trichloride (1.3 equiv) in dry degassed THF (3 mL mmol^{-1}). A solution of TADDOL **1** (1 equiv) in THF (7 mL mmol^{-1}) was then added dropwise over 30 min. After one hour the solid triethylammonium chloride was filtered off under argon, and a mixture of water (1 equiv) and triethylamine (1 equiv) was added to the solution. The resulting mixture was stirred for 1 h, filtered, and the product was purified by chromatography (SiO_2, pentane/diethyl ether 1/1). (*R*,*R*)-**2** was obtained as a colorless solid in 98 % yield.

(*R*,*R*,*R*)-**4a–f**: In an oven-dried Schlenk flask phosphite (*R*,*R*)-**2** was added under argon at 0 °C to a solution of TMEDA (1 equiv) in THF (2 mL mmol^{-1}), and then Et_2Zn (1 equiv) was added dropwise. The nitroalkenes **3a–f** dissolved in THF (2 mL mmol^{-1}) were added directly and the resulting solution was stirred for 12 h at –78 °C. The reaction was quenched at 0 °C with a saturated aqueous solution of ammonium chloride, extracted three times with diethyl ether, and the organic phase was washed with brine. After removal of the solvent under reduced pressure the β-nitrophosphonates (*R*,*R*,*R*)-**4a–f** were obtained as colorless solids which were purified by chromatography (SiO_2, pentane/diethyl ether).

(*R*)-**5a–f**: In a round-bottomed flask NaI (1 equiv) and TMSCl (1 equiv) were added to a solution of nitrophosphonates (*R*,*R*,*R*)-**4a–f** (1 equiv) in CH_3CN (10 mL mmol^{-1}) and the resulting mixture was refluxed for 12 h. The precipitated NaCl was filtered off. After removal of the solvent under reduced pressure, a mixture of CH_2Cl_2 (3 mL mmol^{-1}) and H_2O (2.5 mL mmol^{-1}) was added. After the mixture had been stirred at room temperature for 2 h and the organic phase had been removed, the water was removed under high vacuum and the β-nitrophosphonic acids (*R*,*R*,*R*)-**5a–f** were obtained as colorless solids, which were purified by recrystallization.

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[17] Crystal data for **4b**: single crystals were obtained by recrystallization from diethyl ether. The substance ($C_{45}H_{40}NO_7P$ $M_r = 737.75$) crystallized in the monoclinic space group $P2_1$, $a = 15.052(2)$, $b = 10.1503(14)$, $c = 27.203(4)$ Å, $\beta = 95.738°$, $V = 4135.2(10)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.185$ g cm^{-3}, $F(000) = 1552$, $T = 147(2)$ K. Data collection: Siemens-Smart diffractometer with graphite-monochromated $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å). Crystal dimensions: $0.03 \times 0.08 \times 1.55$ mm $3.0° \leq 2\theta \leq 54.4°$; 41782 measured reflections, of which 16113 were independent and were used for the structure refinement of 994 parameters. Empirical absorption correction (SADABS). The structure was solved by direct methods (SHELXS), the hydrogen atoms were placed at idealized positions and refined according to the riding model. Disordered solvent was described with five isotropic C and O atoms. The structure was refined according to the full-matrix least-squares method on F^2 (SHELX-96). At convergence $R1 = 0.0618$ ($I > 2\sigma(I)$) and w$R2 = 0.1036$; min./max. residual electron density: -0.26/$+0.41$ e Å^2., Flack parameter 0.07(9). Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-147316. 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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Breakdown of Bond Length-Bond Strength Correlation: A Case Study[**]

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"Shorter bonds are stronger bonds". This is still the tenet of essentially all interpretations of molecular structure, for example in the analysis of crystallographic data,[1] formalized by a plethora of empirical bond length–bond strength correlations.[2] However, the number of cases where shorter bonds have been found to exhibit smaller bond energies or force constants has increased slowly but steadily during the past decade. Most examples (see, however, refs. [3, 4]) pertain to the effects of substitution by very electronegative groups, such as fluorine. Thus, for example, increased fluorine substitution in the $NH_{3-n}F_n$ and $OH_{2-n}F_n$ series shortens the N–F or O–F bonds but apparently reduces the force constants and dissociation energies.[5] Fluorine substitution in lead(IV) compounds $PbR_{4-n}F_n$ (R = H, CH_3) was shown computationally to contract bonds but to facilitate reductive elimination.[6] Similarly, in a number of titanium–phosphane complexes $[Ti(2,4\text{-}C_7H_{11})_2PX_3]$, Ti–P bond lengths *and* dissociation energies were found experimentally to decrease along the series X = CH_3, OC_2H_5, F.[7] In contrast, in some polyfluorinated hydrocarbons, C–C bond lengths *and* dissociation energies apparently *increase* with increasing fluorine substitution.[8]

There is clearly a need for systematic studies aimed at elucidating under which circumstances and in which direction deviations from the usual correlations may be expected. Here we report a high-level ab initio case study on the Sn–Sn bond lengths, homolytical dissociation energies, and force constants in distannane, Sn_2H_6, and several of its fluorine-substituted derivatives. This particular choice of model systems has several advantages: 1) a homonuclear bond is studied, and thus polar bonding contributions may be minimized or, for symmetrical substitution, eliminated; 2) in contrast to first-row compounds,[8] complicating effects of negative hyperconjugation are expected to be minor for the properties discussed; 3) the systems are still sufficiently small to obtain definite results from highly accurate coupled-cluster calculations with extended basis sets.[9]

Table 1 provides computed Sn–Sn bond lengths, dissociation energies, and force constants.[9] We will concentrate on the CCSD data, as the available computational resources did not allow CCSD(T) calculations at this basis-set level for all systems (the available data indicate that contributions from triple excitations will not alter the conclusions). Figure 1 shows clearly that bond lengths and dissociation energies do

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