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Asymmetric Synthesis of β-Phosphono Malonates via Fe_2O_3-Mediated Phospha-Michael Addition to Knoevenagel Acceptors

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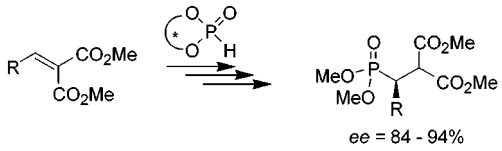
ABSTRACT



The first asymmetric P–C bond formation under heterogeneous conditions was achieved via a Fe_2O_3-mediated conjugate addition of a chiral phosphite to alkylidene malonates. The easy cleavage of the chiral auxiliary from the addition products leads to optically active β-substituted β-phosphono malonates in good yields and high enantiomeric excesses.

The pioneering work on P−C bond formation was carried out by Arbusov in the early 20th century, culminating in the well-known Michaelis−Arbuzov reaction.[1] In the following decades the chemistry of phosphonates has developed relatively slowly because of the difficulty of forming the C−P bond. Its renaissance came after 1959 with the discovery of natural occurring aminophosphonic acids[2] and new biologically active phosphonates.[3]

Phosphonoacetic acid,[4] for example, has been shown to inhibit the replication of cytomegalovirus and herpes virus by interacting directly with the virus-induced DNA polymerase. Phosphonoformate[5] has shown activity in cell cultures against HTLV-III (the virus implicated in AIDS), and a derivative of β-phosphonomalonic acid[6] was used as an inhibitor of ras farnesyl protein transferase in studies directed to the development of new antitumor agents.

The need for testing new optically active highly functionalized phosphonates with different substitution patterns for biological activity has made their synthesis of increasing interest.[7] However, only a few methods have been developed so far for the asymmetric P−C bond formation, generally limited to the asymmetric additions of phosphites to imines or aldehydes[8] in the presence of organometallic bases or catalysts.

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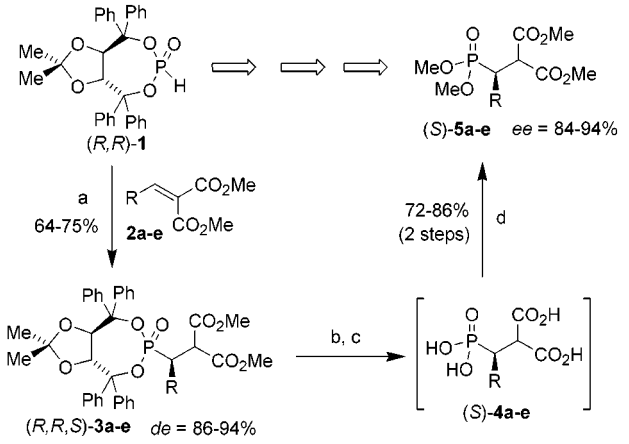
In a previous communication[9] we reported the first general asymmetric Michael addition[10] of a phosphorus nucleophile to nitroalkenes. Herein we describe the conjugate addition of the enantiopure phosphite (*R*,*R*)-**1** to α,*β*-unsaturated malonates **2** as a key step in the synthesis of optically active *β*-substituted *β*-phosphono malonates **5** (Scheme 1). This

Scheme 1. Asymmetric Synthesis of *β*-Substituted *β*-Phosphono Malonates[a]



[a] (a) Fe_2O_3/KOH, CH_2Cl_2, rt. (b) TMSCl, NaI, CH_3CN, reflux. (c) CH_2Cl_2/H_2O. (d) CH_2N_2, MeOH/H_2O.

reaction constitutes the first example of asymmetric P−C bond formation under heterogeneous conditions.

Phosphite (*R*,*R*)-**1** was prepared from TADDOL[11] (*R*,*R*)-4,5-bis(diphenylhydroxymethyl)-2,2-dimethyl-1,3-dioxo-lane in a two-step procedure as previously reported.[9]

The conjugate addition of (*R*,*R*)-**1** to the alkylidene malonates **2a**−**e** in the presence of Fe_2O_3/KOH as a solid base led to chiral *β*-phosphono malonates **3a**−**e** in good yields and high diastereomeric excesses.

The TADDOL auxiliary was easily cleaved[9,12] without detectable epimerization or racemization, by refluxing the addition products in acetonitrile in the presence of TMSCl/NaI and subsequently hydrolyzing the resulting bistrimethylsilyl ester.

The very polar acids (*S*)-**4a**−**e** were not isolated but directly esterified with CH_2N_2 to the corresponding methyl esters (*S*)-**5a**−**e**, which could be easily purified by flash column chromatography on silica gel (*n*-hepane/isopropyl alcohol 9:1).

The possibility of performing the addition of a phosphorus compound, containing a labile P−H bond, to double and triple bonds using a solid base was first shown by Koenig and co-workers,[13] who used an Al_2O_3/KOH system in the Pudovik reaction of various secondary phosphines and phosphites.

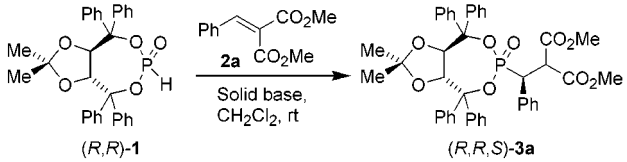
In recent years other research groups were also involved in the study of C−C bond formation via Michael addition using MgO[14] or Mg−Al−O-*t*-Bu hydrotalcite[15] as solid base catalysts.[16] In the latter case the activity of the solid base catalyst was shown to be strongly dependent on the preparation method of the oxide and the pretreatment temperature.

As heterogeneous reactions can be performed under particularly mild conditions, we decided to develop a new solid base for the asymmetric conjugate addition of phosphorus nucloephiles to α,*β*-unsaturated malonates.

Metal oxides can activate P(O)H groups so that deprotonation of the P−H bond occurs in the presence of weaker bases than organolithium reagents such as, for example, KOH.

In our study we first examined the effect of different metal oxides as solid supports for KOH on the stereoselectivity of the Michael addition of (*R*,*R*)-**1** to malonate **2a** (Scheme 2).

Scheme 2. Case Study for the Screening of the Solid Base



The solid bases for the initial screening were prepared by dissolving KOH in methanol and adding the solution to a stirred suspension of the desired metal oxide in methanol. The solvent was then removed under reduced pressure, and the residue dried under vacuum at room temperature. A 1:5 ratio of phosphite/solid support and a 1:1.7 molar ratio of phosphite/base were initially used.

Formation of the phosphonate **3a** could be observed in all cases with a diastereoselectivity depending on the metal oxide. The best value was achieved in the case of Fe_2O_3 (Table 1).

The presence of the solid support appeared to be essential for the activation of the P−H bond toward deprotonation. No reaction could be observed when only KOH in the absence of metal oxide was used.

The solvent effect was also studied, and among those examined, CH_2Cl_2 led to the best diastereoselectivity com-

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Table 1. Screening of Different Solid Bases for the Michael Addition of Phosphite (*R*,*R*)-**1** to Malonate **2a** to Form the Adduct **3a** (Scheme 2)

entry[a]	solid base	yield [%][b]	de [%][c]
1	Al_2O_3/KOH	88	65
2	ZnO/KOH	81	43
3	Cu_2O/KOH	77	41
4	MnO_2/KOH	72	58
5	Fe_2O_3/KOH	85	77
6	MgO/KOH	85	67

[a] All reaction were carried out in CH_2Cl_2 (1 mL/mmol) at room temperature. [b] Yields of isolated products. [c] Determined via ^{31}P NMR spectroscopy of the crude product.

pared to oxygen-containing solvents such as methanol, acetone, THF, diethyl ether, or dimethoxyethane.

The diastereoselectivity was also strongly dependent on the molar ratio of base adsorbed on the solid support, and the best results could be obtained in the case of a 1:2.5 molar ratio phosphite/KOH.

As already mentioned pretreatment of the solid base plays a crucial role on its activity. The most effective system was obtained by drying the solid base under high vacuum for 72 h at 140 °C and performing the addition reaction in the presence of small amounts of water.

Curiously, in the presence of water the diastereoselectivity of the addition proved to be time dependent, increasing with longer reaction times.

The inexpensive and readily accessible Fe_2O_3/KOH system could be now applied under optimized conditions[17] to the conjugate addition of (*R*,*R*)-**1** to variously substituted aromatic α,β-unsaturated malonates **2**. Optically active β-substituted β-phosphono malonates **3a**−**e** could thus be obtained in good chemical yields (61−75%) and high de (82−94%) (Table 2).

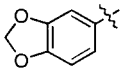
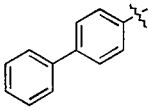
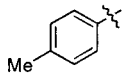
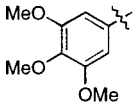
Aliphatic substituents were also employed (cyclohexyl, isopropyl), and they showed even higher reactivity leading to improved yields (85−87%) but only unsatisfactory de values (15−30%).

Separation of small quantities of minor diastereoisomer in the addition products **3a**−**e** could be achieved by HPLC or recrystallization to obtain optically pure compounds.

The absolute configuration of the new stereogenic center generated by the conjugate addition was unambiguously established as *S* by X-ray crystallography of **3e**.[18]

The cleavage of the chiral auxiliary under nonracemizing conditions in the final step led to the title products (*S*)-**5a**−**e** in good yields (Table 3).

Table 2. Michael Addition of Phosphite (*R*,*R*)-**1** to α,β-Unsaturated Malonates **2a**−**e** (Scheme 1)

entry	R	product	reaction time (h)	yield [%][a]	de [%][b]
1		**3a**	4	64	86 (>99)
2		**3b**	18	67	91 (>99)
3		**3c**	4	63	94 (>99)
4		**3d**	3	75	82 (>99)
5		**3e**	4	61	89 (>99)

[a] Yields of isolated products. [b] Determined via ^{31}P NMR spectroscopy of the crude product. Values in parentheses after chromatographic epimer separation (Merck Fertigsäule LiChrosorb, pentane/diethyl ether).

Table 3. Cleavage of TADDOL Auxiliary to Yield β-Phosphono Malonates (*S*)-**5a**−**e**

entry	product	yield [%][a]	ee [%][b]	δ^{31}P [ppm]
1	**5a**	72	84	27.8
2	**5b**	86	92	27.9
3	**5c**	77	94	27.8
4	**5d**	74	84	28.0
5	**5e**	82	90	27.8

[a] Yields of isolated products. [b] Determined via HPLC over chiral stationary phase (Daicel OD, Daicel AD, *n*-heptane/isopropyl alcohol, 9:1).

In summary, we have succeeded in developing a general and efficient asymmetric synthesis of β-substituted β-phosphono malonates in good yields and very good enantiomeric excesses via a Fe_2O_3-mediated P−C bond forming Michael addition under mild conditions. The title compounds are of chemical and medicinal interest.

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(17) **General procedure** for the phospha-Michael addition to α,β-unsaturated malonates. Phosphite (*R*,*R*)-**1** (1 mmol), malonate **2** (1 mmol), and solid base (2.7 g, containing 2.5 mmol KOH) were stirred together in a minimum quantity of CH_2Cl_2 (1 mL), containing 5 mmol of water. The solid base was then filtered off and washed with CH_2Cl_2, and the solvent was evaporated under reduced pressure to give colorless solids, which were purified by flash chromatography on silica gel (pentane/diethyl ether).

(18) Details of the X-ray structure analysis will be described in a full paper.