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PALLADIUM-CATALYZED SYNTHESIS OF CHIRAL, NONRACEMIC ISOPROPYL ARYLMETHYLPHOSPHINATES

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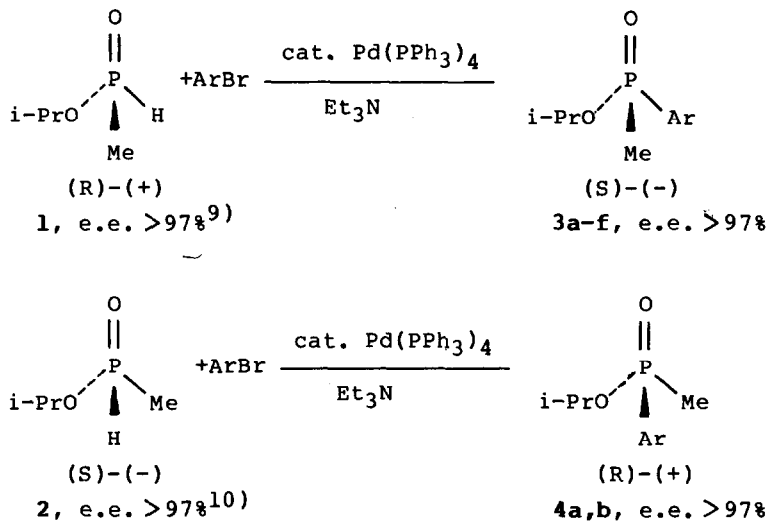
Summary: An efficient, new synthesis of enantiomerically pure functionalized isopropyl arylmethylphosphinates via palladium-catalyzed formation of C-P bond is presented.

Optically active phosphinate esters with chirality residing at phosphorus are important intermediates for synthesizing other classes of chiral phosphorus compounds such as phosphine oxides[1,2] and phosphines[3], phosphoramidates[4] and phosphinothioates[5]. However, only few methods have been reported for their preparations. The classical method based on menthyl alkylarylphosphinates required very time-consuming recrystallizations of the phosphinate which then was not always optically pure and was obtained in low yields[1]. In addition, the steric bulk of the menthyl ligand hindered transformations which involved a nucleophilic displacement[2]. Also, with the menthyl methylphosphinate, which was widely used for the preparation of optically active tertiary phosphine oxides, only the (S)p diastereomer was obtained in high purity[1]. Reaction of optically active O-isopropyl S-alkyl methylphosphonothioates with Grignard reagents led to the displacement of S-alkyl group with either retention or inversion of configuration at the chiral phosphorus center, depending on the R group of the S-alkyl moiety, however, it was not easy to control the extent of displacement in this reaction, so usually not only the desired monosubstituted product but also the disubstituted product, tertiary phosphine oxide, was formed[6,7].

Our recent finding[8] that optically active (R)-(+)-monoisopropyl methanephosphonite(1) underwent palladium-catalyzed reaction with bromobenzene in the presence of triethylamine to afford (S)-(-)-isopropyl methylphenylphosphinate (**3a**) with complete retention of configuration suggested that this reaction might be developed into a useful, efficient method for synthesizing optically active isopropyl arylmethylphosphinates. Herein, we wish to report the

synthesis of both the (S)- and (R)-enantiomers of a series of hitherto unknown chiral isopropyl arylmethylphosphinates(**3b-f** and **4a,b**) in high enantiomeric purity via this palladium route.



The starting material, optically active (R)-(+)- or (S)-(-)-monoisopropyl methanephosphonite(**1** or **2**, respectively, e.e. >97%) was prepared according to a known procedure by stereospecific Raney-Ni desulfurization[11] of the corresponding optically active O-isopropyl methylphosphonothioic acid[7], which was easily obtainable in enantiomerically pure form. The values of enantiomeric excess of both the products(**3** and **4**) and their precursors(**1** and **2**) were determined by 200 MHz ^{1}H NMR in the presence of an optically active phosphinothioic acid, (S)-(+)-t-Bu(Ph)P(S)OH, which served as the chiral shift reagent[12]. The configurations of **3b-f** and **4a,b** were assigned by deduction on the basis of the stereochemical outcome turned out in the conversion of **1** to **3a**[8](vide supra).

In a typical experiment, a mixture of (R)-(+)-monoisopropyl methanephosphonite(**1**), $[\alpha]_D$ +32.3°, e.e. >97% (3mmol), bromobenzene (3mmol), $Pd(PPh_3)_4$ (0.15mmol) and Et_3N (1ml) was placed in a thick-wall tube. The tube was flushed with nitrogen, capped, and heated in an oil bath at 90°C for 1 h. Ethyl acetate was added and then filtered. The filtrate was concentrated on a rotary evaporator and the residue was purified by column chromatography on silica gel, eluting with petroleum ether(60-90°)/ethyl acetate. The product was further purified by distillation to give (S)-(-)-isopropyl methylphenylphosphinate(**3a**)[13], b.p. 80°/0.05mm, 90% yield, $[\alpha]_D$ -50.8°, e.e. >97%.

The results are summarized in the Table. Enantiomerically pure isopropyl methylarylphosphinates with either electron-donating or electron-withdrawing substituent in the benzene ring, which are not easily accessible otherwise, could be readily synthesized via this palladium route in excellent yields. Moreover, both the (R)- and (S)-enantiomers are obtainable. Thus, the present method provides a facile and versatile synthesis of functionalized chiral, nonracemic isopropyl arylmethylphosphinates in high enantiomeric purity. This methodology might be also applicable to the synthesis of other optically active phosphinates.

Table. Optically active isopropyl arylmethylphosphinates prepared[a) b)]

Product No.	Ar	m.p.(°C) or b.p.(°C/mm)	Yield (%)	Chirality at P	$[\alpha]_D$[c)]	%e.e.[d)]
3a	C_6H_5	80/0.05	90	S	-50.8°(c, 1.55)[e)]	>97
3b	4-$CH_3C_6H_4$	40-42	86	S	-37.8°(c, 1.59)	>97
3c	4-$CH_3OC_6H_4$	53-55	79	S	-54.5°(c, 1.36)	>97
3d	4-$NO_2C_6H_4$	97-98.5	95	S	-40.9°(c, 1.27)	>97
3e	β-naphthyl	94-95	90	S	-56.9°(c, 1.30)	>97
3f	4-C_6H_5-C_6H_4	73-74	90	S	-53.8°(c, 1.53)	>97
4a	4-NO_2-C_6H_4	97-98	95	R	+41.1°(c, 1.45)	>97
4b	β-naphthyl	94-95	91	R	+56.5°(c, 1.61)	>97

a) Reaction conditions: **1** or **2** (3mmol), aryl bromide (3mmol), $Pd(PPh_3)_4$ (0.15mmol) and Et_3N (1ml) [when the aryl bromide used was a solid, 1 ml of toluene was added as solvent] heated at 90°C for 1-2 h(for **3a**, **3d**, **3e**, **4a**, **4b**, 1 h; for **3f**, 1.5 h; for **3b**, **3c**, 2 h).

b) All these compounds have been fully characterized spectrally (IR, ^1H NMR, MS) and elemental composition determined by combustion analysis.

c) Measurements were carried out in benzene.

d) Determined by 200 MHz ^1H NMR ($CDCl_3$) in the presence of an equivalent amount of (+)-t-Bu(Ph)P(S)OH. No contamination of the other enantiomer was observed in each case.

e) Lit.[7)], (R)-(+), $[\alpha]_D^{25}$ +35.7°, 66% o.p. .

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9) $[\alpha]_D$ +32.3° (c, 3.13, EtOH), 53% yield from (S)-(-)-$CH_3P(O)(i\text{-}PrO)SH$ of 100% o.p. by desulfurization, lit.[11] reported $[\alpha]_D$ +32.25° (EtOH), 100% o.p..
10) $[\alpha]_D$ -31.2° (c, 1.84, EtOH), 63% yield from (R)-(+)-$CH_3P(O)(i\text{-}PrO)SH$ of 100% o.p. by desulfurization, lit.[11] reported $[\alpha]_D^{12}$ -31.17° (EtOH),.
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13) **3a** has been converted to (R)-(+)-methylphenyl-n-propylphosphine oxide on treatment with n-propylmagnesium bromide in refluxing benzene according to a known procedure[14] in 65% yield, $[\alpha]_D^{20}$ +19.1° (c, 2,23, MeOH), lit.[15] reported $[\alpha]_D$ +19.6° (MeOH).
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