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AN EFFICIENT SYNTHESIS OF CHIRAL, NONRACEMIC ISOPROPYL ALKENYLMETHYLPHOSPHINATES VIA PALLADIUM ROUTE

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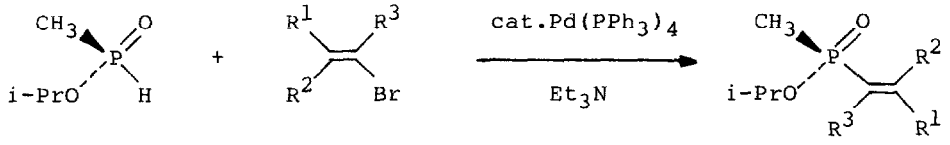
Summary: Enantiomerically pure (S)- and (R)-isopropyl alkenylmethylphosphinates were obtained from the reaction of (R)- and (S)-isopropyl methylphosphinates, respectively, with alkenyl bromides via palladium-catalyzed formation of carbon-phosphorus bond.

Optically active alkenylalkylphosphinates are largely unknown[1], although their racemates are useful intermediates for the synthesis of herbicides[2]. Recently, we have studied the stereochemistry at the phosphorus atom during palladium-catalyzed formation of carbon-phosphorus bonds and found that optically active (R)-(+)-isopropyl methylphosphinate (**1a**) underwent the reaction with bromobenzene in the presence of triethylamine to afford (S)-(-)-isopropyl methylphenylphosphinate with complete retention of configuration at the chiral phosphorus center[3]. As a consequence, a novel route to optically active isopropyl arylmethylphosphinates has been developed thereafter[4]. Herein, we wish to report the synthesis of both the (S)- and (R)- enantiomers of a series of hitherto unknown chiral isopropyl alkenylmethylphosphinates in high enantiomeric purity via this palladium route (see Scheme).

The starting materials, optically active (R)-(+)- and (S)-(-)-isopropyl methylphosphinates (**1a** and **1b**, respectively, e.e. >97%) were prepared according to a known procedure[5] from the corresponding optically active O-isopropyl methylphosphonothioic acid[6], which was easily obtainable in enantiomerically pure form. In a typical experiment of the phosphinylation reactions, a mixture of (R)-(+)-isopropyl methylphosphinate (**1a**), $[\alpha]_D$ +32.3°, e.e. >97% (0.5 mmol), (E)-β-bromostyrene (0.55 mmol), $Pd(PPh_3)_4$ (0.04 mmol) and Et_3N (0.4 ml) was placed in a thick-wall tube. The tube was flushed with nitrogen, capped and

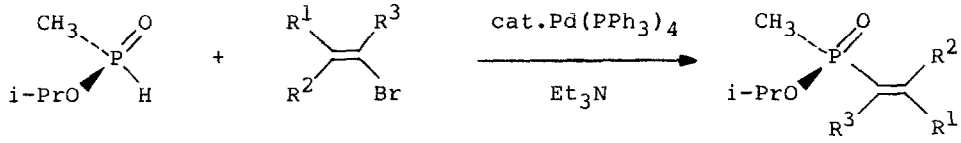
heated in an oil bath at 90°C for 3h. Ethyl acetate was added and then filtered. The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate-methanol (10:1,v/v). The product was further purified by short-path distillation to give (S)-(-)-isopropyl methyl[(E)-β-styryl]phosphinate (**3ac**), b.p. 100°C/0.1mm, 98% yield, $[\alpha]_D$ -60.7° (c, 0.53, benzene), e.e.>97%.



(R)-(+)
1a, e.e.>97%[7]

2a, $R^1=R^2=R^3=H$
b, $R^1=R^2=H$, $R^3=Me$
c, $R^1=Ph$, $R^2=R^3=H$

(S)
3aa, 3ab, 3ac, e.e.>97%



(S)-(-)
1b, e.e.>97%[8]

2b, $R^1=R^2=H$, $R^3=Me$
c, $R^1=Ph$, $R^2=R^3=H$
d, $R^2=Ph$, $R^1=R^3=H$

(R)
3bb, 3bc, 3bd, e.e.>97%

Scheme

The results are summarized in the Table. Thus, enantiomerically pure isopropyl alkenylmethylphosphinates could be readily synthesized via this palladium route in good yields. The (S) configuration of **3ac** was assigned by comparison of the optical rotation with an authentic sample of (S)-(-)-isopropyl methyl[(E)-β-styryl]phosphinate prepared by the reaction of (S)-(-) S-methyl O-isopropyl methylphosphonothioate (**4**) with (E)-β-styrylmagnesium bromide at low temperature[9]; the reaction of **4** with phenylmagnesium bromide to give (S)-(-)-isopropyl methylphenylphosphinate with retention of configuration at the phosphorus atom was known[9]. Thus, the stereochemical outcome of the present reaction further supports the notion that palladium-catalyzed formation of carbon-phosphorus bond proceeds with complete retention of configuration[3]. The configurations of compounds **3aa, 3ab, 3bb, 3bc, 3bd** were assigned by deduction.

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

Product No.	alkenyl moiety R^1	R^2	R^3	b.p.[c)] °C/mm	Yield %	$[\alpha]_D$ in benzene	Chirality at P	%e.e.[d)]
3aa	H	H	H	75/2	64	-17.2°(c, 0.57)	S	>97
3ab	H	H	Me	90/5	71	-26.0°(c, 0.78)	S	>97
3ac	Ph	H	H	100/0.1	98	-60.7°(c, 0.53)	S	>97
3bb	H	H	Me	90/5	71	+26.1°(c, 0.46)	R	>97
3bc	Ph	H	H	100/0.1	98	+60.3°(c, 0.36)	R	>97
3bd	H	Ph	H	100/0.1	98	-43.8°(c, 0.26)	R	>97

a) Reaction conditions: **1a** or **1b** (0.5 mmol), alkenyl bromide (0.55 mmol), $Pd(PPh_3)_4$ (0.04 mmol) and Et_3N (0.4 ml), heated at 90°C for 0.5-3.5 h (for **3ab, 3bb**, 0.5 h; for **3ac, 3bc, 3bd**, 3 h; for **3aa**, 3.5 h).

b) All these compounds have been fully characterized spectrally(IR, ^{1}H-NMR, MS) and elemental composition determined by HRMS. In the case of **3ac, 3bc,** and **3bd**, no contamination of the other geometric isomer was observed[10].

c) Short-path distillation, bath temperature given.

d) Determined by 200 MHz ^{1}H-NMR ($CDCl_3$) in the presence of an equivalent amount of (+)-t-Bu(Ph)P(S)OH[11]. No contamination of the other enantiomer was observed in each case.

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References and Notes

1) R. Bodalski, T. Michalski, J. Monkiewiez and K. M. Pietrusiewiez, ACS Symp. Ser., No. **171**, p. 242 (1981).

2) See, for example: Belgian Patent 854753 (1977), Hoechst A.-G., C.A., **89**, 141899 (1978); N. Minowa, M. Hirayama and S. Fukutsu, Bull. Chem. Soc. Jpn., **60**, 1761 (1987).

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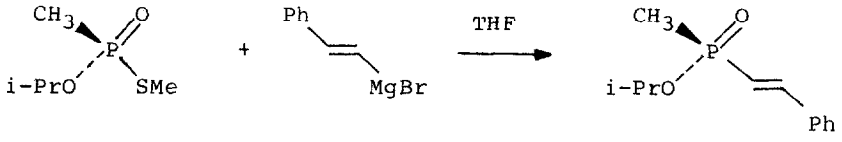
5) L. J. Szafraniec, L. L. Szafraniec and H. S. Aaron, J. Org. Chem., **47**, 1936 (1982).

6) M. Moriyama and W. G. Bentrude, J. Am. Chem. Soc., **105**, 4727 (1983).

7) $[\alpha]_D$ +32.3°(c, 3.13, EtOH), 53% yield from (S)-(-)-MeP(O)(i-PrO)SH of 100% O.P. by desulfurization, Szafraniec et al.[5] reported $[\alpha]_D$ +32.25° (EtOH), 100% O.P..

8) $[\alpha]_D$ -31.2°(c, 1.84, EtOH), 63% yield from (R)-(+)-MeP(O)(i-PrO)SH of 100% O.P. by desulfurization, Szafraniec et al.[5] reported $[\alpha]_D$ -31.17° (EtOH).

9)



4, (S)
$[\alpha]_D$ -77.5° (C_6H_6),
O.P. 88.4% [Lit.[8] $[\alpha]_D$ -86.8° (C_6H_6), O.P. 99%]

(S)
$[\alpha]_D$ -53.15° (C_6H_6)

The reaction of **4** with PhMgBr gave (S)-(-)-isopropyl methylphenylphosphinate; see G. R. Van Den Berg, D. H. T. M. Platenberg and H. P. Benshop, Rec. Trav. Chim. Pays-Bas, **91**, 929 (1972).

10) Retention of configuration at the double bond was also observed in palladium-catalyzed synthesis of racemic alkenylmethyl- and alkenylphenylphosphinates; see Yuanyao Xu and Zhong Li, Synthesis, 240 (1986).

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