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Preparation of Optically Active Six-Membered P-Heterocycles: A 3-Phosphabicyclo[3.1.0] hexane 3-oxide, a 1,2-Dihydrophosphinine 1-oxide, and a 1,2,3,6-Tetrahydrophosphinine 1-oxide

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ABSTRACT: *The earlier described a 3-methyl-1-phenyl-3-phospholene 1-oxide (**1**) → 6,6-dichloro-1-methyl-3-phenyl-3-phosphabicyclo[3.1.0]hexane 3-oxide (**2**) → 4-chloro-1-phenyl-1,2-dihydrophosphinine 1-oxide (**3**) → 4-chloro-5-methyl-1-phenyl-1,2,3,6-tetrahydrophosphinine 1-oxide (**4**) reaction sequence was investigated from the point of view of preparing optically active intermediates/products (**2–4**). In principle, both the resolution of the corresponding racemic products and the transformation of the optically active starting materials are suitable approaches for the preparation of optically active six-membered P-heterocycles (**2–4**). Racemization occurred during the dichlorocyclopropanation reaction of (S)-3-methyl-1-phenyl-3-phospholene 1-oxide ((S)-**1**), but the thermolytic ring opening of (−)-**2,** and the selective reduction of α,β-double bond of (−)-**3** did not cause the loss of optical activity. First in the literature, the resolution of a 3-phosphabicyclo[3.1.0]hexane 3-oxide (**2**) and a 1,2,3,6-tetrahydrophosphinine 1-oxide (**4**) was elaborated.* © 2013 Wiley Periodicals, Inc. Heteroatom Chem 24:179–186, 2013; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.21080

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INTRODUCTION

Optically active phosphine oxides form an important class within organophosphorous compounds, as they can be converted to the corresponding phosphines that can be ligands in transition metal complexes. Many optically active transition metal–phosphine complexes are used as catalysts in enantioselective homogeneous catalytic reactions, such as hydrogenation and hydroformylation [1–3].

As optically active P-chiral compounds cannot be found in the nature, the primary source of these compounds is asymmetric synthesis or resolution [4]. Several methods are reported for the resolution of P-chiral compounds based on the formation of diasteromeric salts, molecular and coordination complexes [5]. Chiral phosphonium salts can be resolved by diastereomeric salt formation with the silver salts of optically active acids [6]. The resolution of acyclic phosphine oxides and phosphinates can be accomplished by molecular complex formation with 1,1′-binaphthalene-2,2′-diol (BINOL) [7]. Several transition metal–chiral amine complexes were successfully used for the separation of the enantiomers of chiral phosphines [8].

In the literature, only a few examples can be found for the resolution of P-chiral phosphine oxides without acidic or basic character via diastereomer formation. These methods usually require the application of expensive resolving agents (e.g., BINOL)[7] or give the enantiomers in low enantiomeric excess (ee). Recently, our research group developed a resolution method for P-chiral cyclic phosphine oxides, namely aryl-, alkyl-, and alkoxy-3-methyl-3-phospholene 1-oxides, using cheap and easily available tartaric acid derivatives. Calcium hydrogen (−)-*O*,*O*′-dibezoyl-(2*R*,3*R*)-tartarate [Ca(H-DBTA)$_2$] (**5**) and calcium hydrogen (−)-*O*,*O*′-di-*p*-tolyl-(2*R*,3*R*)-tartarate [Ca(H-DPTTA)$_2$] (**6**) were used for the resolution of 3-phospholene oxides via diastereomeric coordination complex formation [9, 10]. The (4*R*,5*R*)-(−)-4,5-bis(diphenylhydroxymethyl)-2,2-dimethyldioxolane (TADDOL) (**7**) and (2*R*,3*R*)-(−)-α,α,α',α'-tetraphenyl-1,4-dioxaspiro [4.5] decan-2,3-dimethanol (spiro-TADDOL) (**8**) were also found suitable for the resolution of phospholene oxides based on diastereomeric molecular complex formation [11, 12]. The resolution of a 3:1 mixture of 3-methyl- and 5-methyl-4-chloro-1-phenyl-1,2-dihydrophosphinine 1-oxides (**3A** and **3B**) was also accomplished with (−)-spiro-TADDOL (**8**) [13]. To the best of our knowledge, these methods are the only examples in the literature for the resolution of P-chiral cyclic phosphine oxides with high ee and good yield. Moreover, the methods developed by us are not only efficient and practical in the sense of simplicity and low cost, but may also be of more general value. It seems to be probable that our procedure may also be suitable for the optical resolution of other phosphine oxides.

According to another synthesis strategy, (1*R*,2*S*,5*R*)-(−)-menthol and (*S*)-(−)-α-phenylethylamine were utilized as chiral building blocks to synthesize an optically active 3-phospholene 1-oxide, and a 3-phosphabicyclo[3.1.0]hexane 3-oxide [14].

Five-membered P-heterocycles are versatile starting materials for six-membered P-heterocycles, phosphinine derivatives. Dichlorocarbene addition on the double bond of 3-methyl-1-phenyl-3-phospholene 1-oxide (**1**) afforded 6,6-dichloro-1-methyl-3-phenyl-3-phosphabicyclo[3.1.0]hexane 3-oxide (**2**) in a diastereoselective manner [15]. Thermolytic opening of the cyclopropane ring of phosphabicyclohexane oxide **2** led to a 3:1 mixture of the double bond isomers of 4-chloro-1-phenyl-1,2-dihydrophosphinine 1-oxides (**3A** and **3B**) [15]. The 3-methyl-1,2-dihydrophosphinine 1-oxide **3A** may be converted to the corresponding 1,2,3,6-tetrahydrophosphinine 1-oxide (**4**) by selective reduction of the α,β-double bond by borane [16].

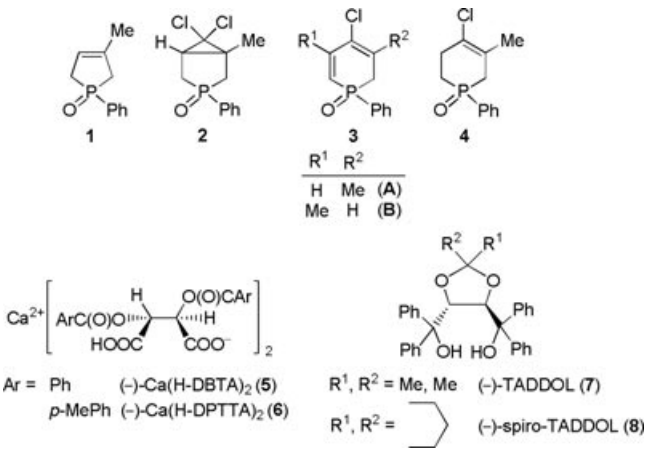


FIGURE 1 The P-heterocycles and resolving agents used in our study.

In this paper, strategies for the preparation of optically active six-membered P-heterocycles, such as a 3-phosphabicyclo[3.1.0]hexane 3-oxide (**2**), a 1,2-dihydrophosphinine 1-oxide (**3A** and **3B**), and a 1,2,3,6-tetrahydrophosphinine 1-oxide (**4**) are investigated. This work includes development of suitable resolution methods for these six-membered P-heterocycles (**2**–**4**) using [Ca(H-DBTA)$_2$] (**5**), (−)-[Ca(H-DPTTA)$_2$] (**6**), TADDOL (**7**), and spiro-TADDOL (**8**) as resolving agents (Fig. 1). The question was whether the resolution should be done in the starting material (**1**, **2**, **3**), or product (**2**, **3**, **4**) stage to obtain optically active **2**–**4**. It was also investigated, if the optical activity is preserved or racemization occurs during the individual steps of the **1** → **2** → **3** → **4** reaction sequence.

RESULTS AND DISCUSSION

First, we prepared the 1-phenyl-3-phospholene oxide dichlorocarbene adduct (**2**) having the dichlorocyclopropane ring and the P=O function in position trans in a racemic form as described earlier using chloroform and 50% sodium hydroxide under phase transfer catalytic conditions [15]. Then we tried to resolve the phosphabicyclo[3.1.0]hexane 3-oxide (**2**) so obtained. To the solution of calcium hydrogen (−)-*O*,*O*′-dibezoyl-(2*R*,3*R*)-tartarate [Ca(H-DBTA)$_2$] (**5**) in a 5:1 mixture of ethanol and water, 4 equivalents of racemic phosphabicyclo[3.1.0]hexane 3-oxide **2** was added. After crystallization at 26°C, the precipitate was filtered off to afford the corresponding complex Ca[(−)-**2**]$_2$-(H-DBTA)$_2$. The coordination complex was further purified by digestion: the crystalline complex was stirred in a 10:1 mixture of ethanol–water at room temperature. The complete dissolution of the crystals was not necessary; the digestion was found

TABLE 1 Preparation of Optically Active Six-Membered P-Heterocycles (**2**–**4**)

By optical resolution of the products

Entry	*Product*	*Resolving Agent*	*Solvent*	*Yield (%)*[a]	*Enantiomeric Excess (%)*[b]	*Specific Rotation*
1	**2**	(−)-Ca(H-DBTA)$_2$	EtOH/water	30	67	(−)
2	**2**	(−)-Ca(H-DPTTA)$_2$	EtOH/water	30	22	(+)
3	**2**	(−)-spiro-TADDOL	EtOAc/hexane	58	55	(+)
4	**3**	(−)-spiro-TADDOL	Acetone/hexane	39	87	(−)
5	**4**	(−)-Ca(H-DPTTA)$_2$	EtOH/water	28	99	(+)
6	**4**	(−)-TADDOL	EtOAc/hexane	21	65	(−)

Starting from optically active substrate

	Starting Material				*Product*			
Entry	*No.*	*Enantiomeric Excess (%)*[b]	*Specific Rotation*	*Synthetic Route*	*No.*	*Yield (%)*[a]	*Enantiomeric Excess (%)*[b]	*Specific Rotation*
7	**1**	93	(−)	**1**→**2** Method A	**2**	34	0	
8	**1**	93	(−)	**1**→**2** Method B	**2**	34	0	
9	**2**	67	(−)	**2**→**3**	**3**	20	67	(+)
10	**3**	87	(−)	**3**→**4**	**4**	20	87	(−)

[a]Yield of the enantiomers of the six-membered P-heterocycles (**2**–**4**) is based on the half of the racemate that is regarded to be 100% for each antipode.
[b]Enantiomeric excess was determined by chiral HPLC.

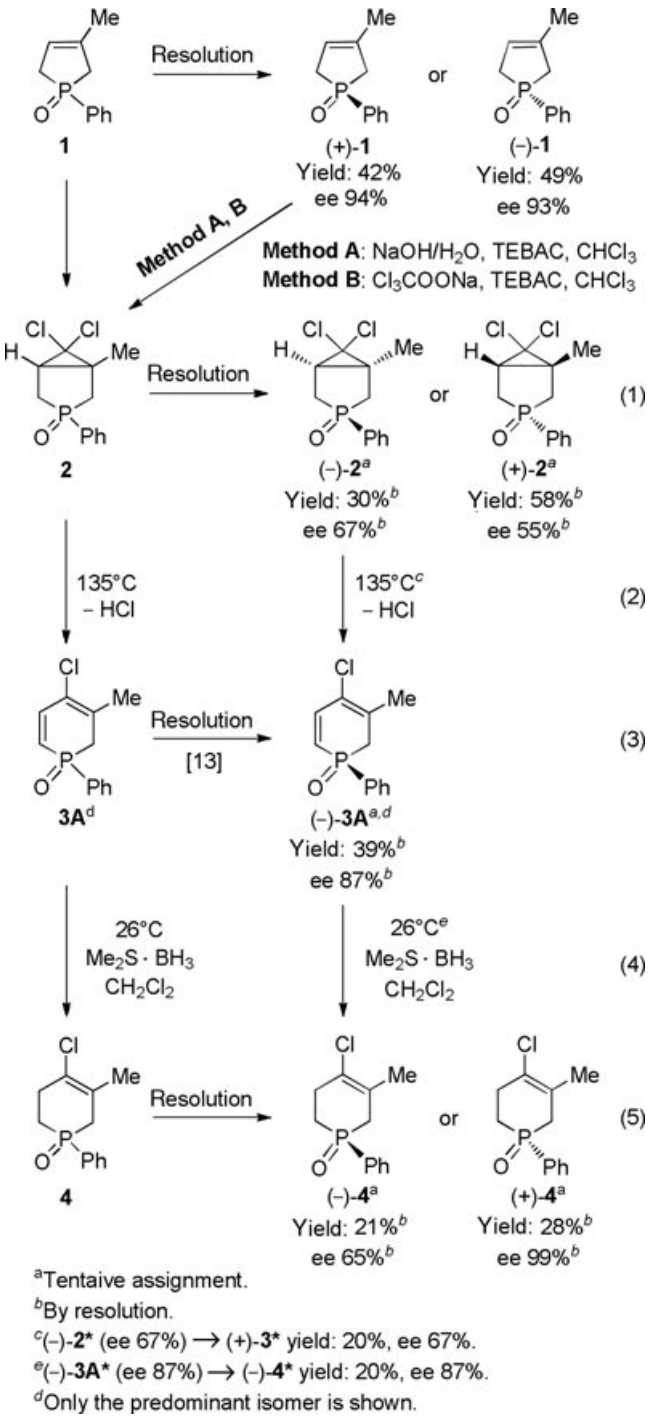
sufficient for the separation of the diastereomeric coordination complexes. The diastereomeric excess (de) of the Ca[(−)-**2**]$_2$(H-DBTA)$_2$ was 63% after first precipitation, and 67% after the digestion. The phenyl-phosphabicyclo[3.1.0]hexane oxide (−)-**2** was recovered by treating the chloroform solution of the complex with 10% aqueous ammonia to afford (−)-**2** with an ee of 67% in a yield of 30% (Scheme 1/(1); Table 1, entry 1). The resolution of racemic **2** was also accomplished with calcium hydrogen (−)-*O*,*O*′-di-*p*-tolyl-(2*R*,3*R*)-tartarate [Ca(H-DPTTA)$_2$] (**6**) according to the procedure described above, except that the resolving agent was prepared in situ by the reaction of DPTTA and half equivalent of CaO in a 10:1 mixture of ethanol and water. The decomplexation of the Ca[(+)-**2**]$_2$(H-DPTTA)$_2$ led to (+)-**2** with an ee of 22% in a yield of 30% (Table 1, entry 2). Interestingly, the (−)-Ca(H-DBTA)$_2$ (**5**) formed a coordination complex with enantiomer (−)-**2** whereas (−)-Ca-(H-DPTTA)$_2$ (**6**) preferred complex formation with the other antipode [(+)-**2**]. Hence, both antipodes of **2** could be prepared. The (−)-spiro-TADDOL (**8**) could also be applied successfully for the resolution of racemic **2**. During the resolution procedure, hexane was added to the solution of racemic **2** and half equivalent of (−)-spiro-TADDOL (**8**) in hot ethyl acetate, whereupon the molecular complex of [(+)-**2**](spiro-TADDOL) precipitated. Column chromatography of the complex afforded (+)-**2** with an ee of 55% and yield of 58% (Scheme 1/(1); Table 1, entry 3). The resolution of racemic **2** was also attempted with (−)-TADDOL (**7**), but in this case no crystalline molecular complex was formed.

Then we tried to convert the (*S*)-antipode of 3-phospholene oxide **1** to optically active **2** by dichlorocarbene addition. The dichlorocarbene was generated under phase transfer catalytic conditions from chloroform with aqueous sodium hydroxide (method A; Table 1, entry 7) or from sodium trichloroacetate (method B; Table 1, entry 8). As we observed, racemization occurred in both cases. It remains a question, if the racemization occurs in the starting material (**1**), or the product stage (**2**).

On the basis of the above experiences, resolution is the only way for the preparation of the optically active 6,6-dichloro-1-methyl-3-phenyl-3-phosphabicyclo[3.1.0]hexane 3-oxide (**2**), as the dichlorocarbane addition on the double bond of optically active 3-methyl-1-phenyl-3-phospholene 1-oxide (**1**) led to racemic 3-phosphabicyclo[3.1.0]-hexane oxide (**2**). The resolution methods developed were suitable for the preparation of both antipodes of phosphabicyclo[3.1.0] hexane oxide (**2**).

*Preparation of Optically Active 3-Methyl- and 5-Methyl-4-chloro-1-phenyl-1,2-dihydrophosphinine 1-oxides (***3A** *and* **3B***)*

First the title product (**3A** and **3B**) was prepared by resolution, then by the thermolysis of the optically active phospholene–dichlorocarbene adduct [(−)-**2**].



SCHEME 1 Preparation of optically active P-heterocycles.

The resolution of a 3:1 mixture of 3-methyl- and 5-methyl-4-chloro-1-phenyl-1,2-dihydrophosphinine 1-oxides (**3A** and **3B**) was accomplished as described earlier with 0.5 equivalent of (−)-spiro-TADDOL (**8**) affording (−)-**3A** and (−)-**3B** with an ee of 87% and yield of 39% (Scheme 1/(3); Table 1, entry 4). During the resolution, the ratio of the double bond isomers (**3A** and **3B**) did not change [13]. It was assumed that the sign of the rotation for the two isomers (**3A** and **3B**) is the same. The phenomenon that chiral phosphine oxides with similar P-neighborhood may have similar sign for the optical rotation is studied by us by quantum chemical calculations.

The thermolytic cyclopropane ring opening of the optically active (−)-6,6-dichloro-1-methyl-3-phenyl-3-phosphabicyclo[3.1.0]hexane 3-oxide [(−)-**2**] with an ee of 67% took place without racemization and afforded a 3:1 mixture of (+)-3-methyl and 5-methyl-4-chloro-1-phenyl-1,2-dihydrophosphinine 1-oxides ((+)-**3A** and (+)-**3B**) in 20% yield and with an ee of 67% for both double bond isomers (Scheme 1/(2); Table 1, entry 9).

Both the thermolysis of optically active phosphabicyclo[3.1.0]hexane 3-oxide **2**, and the resolution of 1-phenyl-1,2-dihydrophosphinine 1-oxides (**3A** and **3B**) were found suitable for the preparation of optically active dihydrophosphinine oxides **3A** and **3B**. Considering green chemical and environment friendly aspects, resolution in the starting material stage is preferable. However, resolution in the product stage provides 1-phenyl-1,2-dihydrophosphinine 1-oxides (**3A** and **3B**) in a higher ee.

*Preparation of Optically Active 4-Chloro-1-phenyl-5-methyl-1,2,3,6-tetrahydrophosphinine 1-Oxide (**4**)*

The resolution of racemic 1-phenyl-1,2,3,6-tetrahydrophosphinine 1-oxide (**4**) and the reduction of optically active **3A** were attempted to prepare the enantiomers of 1,2,3,6-tetrahydrophosphinine oxide **4**.

Racemic **4** was resolved with (−)-Ca(H-DPTTA)$_2$ (**6**) in a 10:1 mixture of ethanol–water as described earlier. The purification of the Ca[(+)-**4**]$_2$(H-DPTTA)$_2$ complex by two digestions in a 10:1 mixture of ethanol–water followed by decomposition of the diastereomer led to (+)-**4** with an ee of 99% and yield of 28% (Table 1, entry 5). The resolution of racemic **4** with half equivalent of (−)-TADDOL (**7**) in a 3:5 mixture of ethyl acetate and hexane led to (−)-**4** with an ee of 65% and yield of 21% after purification (Scheme 1/(5); Table 1, entry 6). The resolution with (−)-Ca(H-DBTA)$_2$ (**5**) and (−)-spiro-TADDOL (**8**) was not successful, as no crystalline complex was formed during the resolution attempt.

According to the other approach, the selective reduction of the α,β-double bond of a 3:1 mixture of (−)-3-methyl and 5-methyl-4-chloro-1-phenyl-1,2-dihydrophosphinine 1-oxides ((−)-**3A** and (−)-**3B**)

with an ee of 87% led to (−)-4-chloro-5-methyl-1-phenyl-1,2,3,6-tetrahydrophosphinine 1-oxide [(−)-**4**] with an ee of 87% and in a yield of 20% (Scheme 1/(4); Table 1, entry 10). In our previous studies, it was established that only the 4-chloro-3-methyl-1-phenyl-1,2-dihydrophosphinine 1-oxide (**3A**) isomer reacts in this reaction due to steric factors [15]. Hence, the other double bond isomer played no role in the reduction and was removed during the purification.

Both the resolution of racemic 1,2,3,6-tetrahydrophosphinine oxide **4** and the reduction of optically active 1,2-dihydrophosphinine oxide **3A** are suitable for the preparation of optically active tetrahydrophosphinine oxide **4**. It is favorable to accomplish the resolution in the starting material phase, as half of the borane reagent can be saved during the reduction.

CONCLUSIONS

In conclusion, first in the literature, the resolution of 6,6-dichloro-1-methyl-3-phenyl-3-phosphabicyclo-[3.1.0]hexane 3-oxide (**2**) and 4-chloro-5-methyl-1-phenyl-1,2,3,6-tetrahydrophosphinine 1-oxide (**4**) was accomplished by coordination and molecular complex formation using the easily available and relatively inexpensive calcium hydrogen (−)-*O*,*O*′-dibezoyl-(2*R*,3*R*)-tartarate [Ca(H-DBTA)$_2$] (**5**) and calcium hydrogen (−)-*O*,*O*′-di-*p*-tolyl-(2*R*,3*R*)-tartarate [Ca(H-DPTTA)$_2$] (**6**), or TADDOL derivatives (**7** and **8**), respectively. It was also proved that during the dichlorocarbene addition on the double bond of 3-methyl-1-phenyl-3-phospholene 1-oxide (**1**), racemization occurs, but the ring opening of 6,6-dichloro-1-methyl-3-phenyl-3-phosphabicyclo[3.1.0]hexane 3-oxide (**2**) and the selective reduction of the α,β-double bond of the 4-chloro-3-methyl-1-phenyl-1,2-dihydrophosphinine 1-oxide (**3A**) can be accomplished by preserving the configuration of the chiral P-centers. Overall, considering the principles of green chemistry, whenever it is possible, it is better to start the synthesis from the optically active starting materials.

EXPERIMENTAL

The ^{1}H and ^{31}P NMR spectra were recorded on a Bruker DRX-500 spectrometer operating at 500 and 202.4 MHz, respectively. Chemical shifts are downfield relative to TMS and 85% H_3PO_4.

The composition of the diastereomeric complexes was determined by ^{1}H NMR comparing the intensity of the signals belonging to the characteristic groups of the resolving agent and the enantiomers.

The ee of **1–4** was determined by chiral HPLC. The ee of **1** and **4** was determined using Kromasil® 5-Amycoat 250 × 4.6 mm ID, hexane/ethanol 85/15 as an eluent with a flow rate of 0.8 mL/min, T = 20°C, a UV detector α = 254 nm. Retention time: 11.4 min for (*R*)-**1** and 13.1 min for (*S*)-**1**; 15.8 min for (+)-**4** and 23.2 min for (−)-**4**. The ee of **2** was determined using Kromasil® 5-Amycoat 250 × 4.6 mm ID, hexane/ethanol 90/10 as an eluent with a flow rate of 1.0 mL/min, T = 20°C, the UV detector α = 254 nm. Retention time: 13.4 min for (−)-**2** and 15.6 min for (+)-**2**. The ee of **3** was determined using Daicel Chem. Ind. Chiralpack AD-H column 250 × 4.6 mm ID, using hexane/isopropanol 85/15 as the eluent with a flow rate of 0.8 mL/min, T = 20°C, the UV detector α = 254 nm. Retention time: 13.6 and 15.9 min for **3A**, 15.1 and 18.1 min for **3B**. Optical rotations were determined on a Perkin–Elmer 241 polarimeter.

Our methods for the resolution of optical isomers seem to be reproducible, and the deviation of the ee and yields are mostly within ±2.5% after repetitions.

The (4*R*,5*R*)-(−)-4,5-bis(diphenylhydroxymethyl)-2,2-dimethyldioxolane (**7**) [17], the (2*R*,3*R*)-(−)-$\alpha,\alpha,\alpha',\alpha'$-tetraphenyl-1,4-dioxaspiro [4.5] decan-2,3-dimethanol (**8**) [18], calcium hydrogen (−)-*O*,*O*′-dibezoyl-(2*R*,3*R*)-tartarate (**5**) [9], the racemic 3-methyl-1-phenyl-3-phospholene 1-oxide (**1**) [19], 6,6-dichloro-1-methyl-3-phenyl-3-phosphabicyclo[3.1.0]hexane 3-oxide (**2**) [20], 3-methyl- and 5-methyl-1-phenyl-4-chloro-1,2-dihydrophosphinine 1-oxide (**3A** and 3**B**) [21], and 4-chloro-5-methyl-1-phenyl-1,2,3,6-tetrahydrophosphinine 1-oxide (**4**) [16] were prepared as described earlier.

*Preparation of the Optically Active 3-Methyl-1-phenyl-3-phospholene 1-Oxide ((S)-**1**, (R)-**1**)*

The (*R*)- and (*S*)-enantiomers of 3-methyl-1-phenyl-3-phospholene 1-oxide (**1**) were prepared as described earlier by resolution with (−)-Ca(H-DBTA)$_2$ (**5**) and (−)-Ca(DPTTA)$_2$ (**6**), respectively [9]. Yield of (*R*)-**1**: 42%, ee: 94%; yield of (*S*)-**1**: 49%, ee: 93%.

*Preparation of 6,6-Dichloro-1-methyl-3-phenyl-3-phosphabicyclo[3.1.0]hexane 3-oxide (**2**) from 3-methyl-1-phenyl-3-phospholene-1-oxide (**1**)*

Method A. The solution of 3.9 g (96.4 mmol) of sodium hydroxide and 3.8 mL of water was added

dropwise to the solution of 0.65 g (3.4 mmol) of 3-methyl-1-phenyl-3-phospholene 1-oxide (**1**) and 0.16 g (0.68 mmol) of TEBAC in 6 mL of chloroform. The mixture was stirred for 3 h while the temperature rose to reflux. After filtration and separation of the two phases, the organic phase was made up to its original volume and 0.052 g (0.23 mmol) TEBAC was added. The treatment with aqueous sodium hydroxide was repeated, all together, three times. After separating the two phases, drying the organic phase and evaporating the solvent, the crude product was purified by column chromatography (silica gel, 3% methanol in chloroform) to give 0.38 g (41%) of product **2**. ^{31}P NMR ($CDCl_3$) δ: 76.0, (δ_P[20] 75.6).

Starting from optically active (*S*)-3-methyl-1-phenyl-3-phospholene 1-oxide ((*S*)-**1**) (ee: 93%), racemic 6,6-dichloro-1-methyl-3-phenyl-3-phosphabicyclo[3.1.0]hexane 3-oxide (**2**) was obtained in a yield of 34%. ^{31}P NMR ($CDCl_3$) δ: 75.7, (δ_P[20] 75.6).

Method B. The mixture of 0.20 g (1.0 mmol) of 3-methyl-1-phenyl-3-phospholene 1-oxide (**1**), 15.4 g (83.0 mmol) of sodium trichloroacetate, and 0.10 g (0.44 mmol) of TEBAC in 15 mL of chloroform was stirred at reflux for 4 days. After filtration, the solvent was evaporated and the crude product so obtained was purified by column chromatography (silica gel, 3% methanol in chloroform) (97:3) to give 0.097 g (yield: 34%) of **2**. ^{31}P NMR ($CDCl_3$) δ: 74.8, (δ_P[20] 75.6).

The reaction using (*S*)-3-methyl-1-phenyl-3-phospholene 1-oxide ((*S*)-**1**) (ee: 93%) led to racemic 6,6-dichloro-1-methyl-3-phenyl-3-phosphabicyclo[3.1.0]hexane 3-oxide (**2**) in a yield of 34%. ^{31}P NMR ($CDCl_3$) δ: 74.8, (δ_P[20] 75.6).

*Preparation of (+)-6,6-Dichloro-1-methyl-3-phenyl-3-phosphabicyclo[3.1.0]hexane 3-oxide [(+)-**2**] by Resolution with (−)-Ca(H-DBTA)$_2$ (**5**)*

To 0.12 g (0.15 mmol) of (−)-Ca(H-DBTA)$_2$ (**5**) in 0.35 mL of ethanol and 0.07 mL of water, 0.16 g (0.60 mmol) of racemic 6,6-dichloro-1-methyl-3-phenyl-3-phosphabicyclo[3.1.0]hexane 3-oxide (**2**) in 0.35 mL of ethanol was added. Immediately after the addition, colorless crystals appeared. After standing at room temperature for 24 h, the precipitate was filtered off to give 0.086 g (44%) of complex Ca[(−)-**2**]$_2$(H-DBTA)$_2$, de 63% (determined by HPLC). The complex was taken up in the mixture of 0.7 mL of ethanol and 0.07 mL of water, and the suspension was stirred for 8 h to give 0.065 g (33%) of complex Ca[(−)-**2**]$_2$(H-DBTA)$_2$ with a de of 67%. The (−)-6,6-dichloro-1-methyl-3-phenyl-3-phosphabicyclo[3.1.0]hexane 3-oxide [(−)-**2**] was recovered by treating the 2-mL chloroform solution of the complex Ca[(−)-**2**]$_2$(H-DBTA)$_2$ with 2 mL of 10% aqueous ammonia. The organic phase was washed with 0.5 mL of water, dried (Na_2SO_4), and concentrated to give 0.025 g (30%) of (−)-**2** with an ee of 67%. ^{31}P NMR ($CDCl_3$) δ: 76.0, (δ_P[20] 75.6); $[\alpha]^{25}_D = -9.7$ (c 0.9; $CHCl_3$).

*Preparation of (−)-6,6-Dichloro-1-methyl-3-phenyl-3-phosphabicyclo[3.1.0]hexane 3-oxide [(−)-**2**] by Resolution with (−)-Ca(H-DPTTA)$_2$ (**6**)*

To 0.034 g (0.09 mmol) of (−)-(*R*,*R*)-di-*p*-tolyltartaric acid monohydrate and 0.0025 g (0.045 mmol) of CaO in 0.11 mL of a 10:1 mixture of ethanol–water, 0.049 g (0.18 mmol) of racemic 6,6-dichloro-1-methyl-3-phenyl-3-phosphabicyclo[3.1.0]hexane 3-oxide (**2**) in 0.1 mL of ethanol was added. After standing at 26°C for 72 h, the crystals were filtered off to give 0.020 g (32%) of complex Ca[(+)-**2**]$_2$(H-DPTTA)$_2$ with a de of 22%. The (+)-6,6-dichloro-1-methyl-3-phenyl-3-phosphabicyclo[3.1.0]hexane 3-oxide [(+)-**2**] was recovered by treating the 2-mL chloroform solution of the complex with 1 mL of a 10% aqueous ammonia. The organic phase was washed with 0.5 mL of water, dried (Na_2SO_4), and concentrated to give 0.0073 g (30%) of (+)-**2** with an ee of 22%. ^{31}P NMR ($CDCl_3$) δ: 76.1, (δ_P[20] 75.6).

*Preparation of (+)-6,6-Dichloro-1-methyl-3-phenyl-3-phosphabicyclo[3.1.0]hexane 3-oxide [(+)-**2**] by Resolution with (−)-spiro-TADDOL (**8**)*

To 0.047 g (0.17 mmol) of racemic 6,6-dichloro-1-methyl-3-phenyl-3-phosphabicyclo[3.1.0]hexane 3-oxide (**2**) and 0.043 g (0.085 mmol) of (−)-spiro-TADDOL (**8**) in 0.1 mL of hot ethyl acetate, 0.90 mL of hexane was added. Immediately after the addition, colorless crystalline complex appeared. After 3 h, the crystals were separated by filtration to give 0.042 g (63%) of complex [(+)-**2**](spiro-TADDOL)] with a de of 55%. Column chromatography (silica gel, chloroform) of the complex regenerated 0.013 g (58%) of (+)-**2** with an ee of 55%. ^{31}P NMR ($CDCl_3$) δ: 75.8, (δ_P[20] 75.6).

*Preparation of (+)-3-Methyl- and 5-Methyl-4-chloro-1-phenyl-1,2-dihydrophosphinine 1-oxides [(+)-**3A** and (+)-**3B**] from (−)-6,6-Dichloro-1-methyl-3-phenyl-3-phosphabicyclo[3.1.0]hexane 3-oxide [(−)-**2**] by Thermolysis*

0.018 g (0.64 mmol) of (–)-6,6-dichloro-1-methyl-3-phenyl-3-phosphabicyclo[3.1.0]hexane 3-oxide [(−)-**2**] (ee 67%) was heated at 135°C until the evolution of hydrochloric acid ceased (ca. 2 min). The crude product was purified by column chromatography (silica gel, 3% methanol in chloroform) to give 0.0030 g (20%) of (+)-**3** as a 3:1 mixture of **3A** and **3B**; ee: 67% for both isomers. ^{31}P NMR ($CDCl_3$) δ: 16.1 (75%), 15.0 (25%), (δ_P[21] 16.1, 15.0). $[\alpha]^{25}_D$ = +5.5 [*c* 0.2; $CHCl_3$].

*Preparation of (−)-3-Methyl- and 5-Methyl-4-chloro-1-phenyl-1,2-dihydrophosphinine 1-oxides [(−)-**3A**, (−)-**3B**] by resolution with (−)-spiro-TADDOL (**8**)*

The enantiomers of (−)-3-methyl- and 5-methyl-4-chloro-1-phenyl-1,2-dihydrophosphinine 1-oxides [(−)-**3A** and (−)-**3B**] were prepared as described earlier, by resolution with (−)-spiro-TADDOL (**8**) [13]. The yield of (−)-**3**: 39% as a 3:1 mixture of **3A** and **3B**. The ee for **3A** and **3B** is 87%. ^{31}P NMR ($CDCl_3$) δ: 15.7 (75%), 14.6 (25%), (δ_P[21] 16.1, 15.0).

*Preparation of (+)-4-Chloro-5-methyl-1-phenyl-1,2,3,6-tetrahydrophosphinine 1-oxide [(+)-**4**] by Resolution with (−)-Ca(H-DPTTA)$_2$ (**6**)*

To 0.12 g (0.32 mmol) of (−)-(*R*,*R*)-di-*p*-tolyl-tartaric acid monohydrate and 0.0090 g (0.16 mmol) of CaO in 0.48 mL of 5:1 mixture of ethanol–water, 0.16 g (0.64 mmol) of racemic 4-chloro-5-methyl-1-phenyl-1,2,3,6-tetrahydrophosphinine 1-oxide (**4**) in 0.4 mL of ethanol was added. After standing at 26°C for 24 h, the crystals were filtered off to give 0.14 g (66%) of complex Ca[(+)-**4**]$_2$(H-DPTTA)$_2$ with a de of 86%. The complex was purified by two digestions, the crystals were taken up in 0.88 mL of a 10:1 mixture of ethanol and water, and the suspension was stirred for 24 h at 26°C to give 0.068 g (32%) of complex Ca[(+)-**4**]$_2$(H-DPTTA)$_2$ with a de of 99%. The (+)-4-chloro-5-methyl-1-phenyl-1,2,3,6-tetrahydrophosphinine-1-oxide [(+)-**4**] was recovered by treating the chloroform solution (2 mL) of the complex with 1 mL of 10% aqueous ammonia. The organic phase was washed with 0.5 mL of water, dried (Na_2SO_4), and concentrated to give 0.022 g (28%) of (+)-**4** with an ee of 99%. ^{31}P NMR ($CDCl_3$) δ: 27.9, (δ_P[16] 28.3); $[\alpha]^{25}_D$ = +19.7 (*c* 0.7; $CHCl_3$).

*Preparation of (–)-4-Chloro-5-methyl-1-phenyl-1,2,3,6-tetrahydrophosphinine 1-oxide [(–)-**4**] by resolution with (–)-TADDOL (**7**)*

To 0.054 g (0.22 mmol) of racemic 4-chloro-5-methyl-1-phenyl-1,2,3,6-tetrahydrophosphinine 1-oxide (**4**) and 0.052 g (0.11 mmol) of (–)-TADDOL (**7**) in 0.3 mL of hot ethyl acetate, 0.5 mL of hexane was added. Immediately after the addition, colorless crystalline complex appeared. After 4 h, the crystals were separated by filtration to give 0.042 g (67%) of complex [(–)-**4**]$_4$(TADDOL)$_3$] with a de of 38%. The complex was purified by recrystallization in 0.3 mL of ethyl acetate and 0.5 mL of hexane to afford 0.013 g (21%) of complex [(–)-**4**]$_4$(TADDOL)$_3$] with a de of 65%. ^{31}P NMR ($CDCl_3$) δ: 28.0, (δ_P[16] 28.3).

*Preparation of (–)-4-Chloro-5-methyl-1-phenyl-1,2,3,6-tetrahydrophosphinine 1-oxide [(–)-4] from (−)-4-Chloro-3-methyl-1-phenyl-1,2-dihydrophosphinine 1-oxide [(−)-**3A**]*

To the solution of 0.090 g (0.38 mmol) of 3:1 mixture of optically active (–)-3-methyl- and (–)-5-methyl-4-chloro-1-phenyl-1,2-dihydrophosphinine 1-oxide [(−)-**3A**, (−)-**3B**]* (ee 87% for both isomers) in 2 mL of dichloromethane, 0.28 mL (0.56 mmol) of 2 M borane-dimethyl sulfide in THF was added and the mixture was stirred at room temperature for 24 h. After the completion of the reaction, 1 mL of water was added and the mixture was stirred for 15 min. The white precipitate was filtered, the two phases were separated, and the organic phase was dried (Na_2SO_4). The crude product was purified by column chromatography (silica gel, 3% methanol in chloroform) to give 0.018 g (yield: 20%) of (–)-**4** with ee of 87%. ^{31}P NMR ($CDCl_3$) δ: 28.6, (δ_P[16] 28.3); $[\alpha]^{25}_D$ = –8.5 [*c* 0.6; $CHCl_3$]. *isomer **3B** did not take place in the reaction.

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