Received: 3 November 2017 | Revised: 6 December 2017 | Accepted: 8 December 2017

DOI: 10.1002/chir.22816

REGULAR ARTICLE

WILEY

The resolution of acyclic *P*-stereogenic phosphine oxides via the formation of diastereomeric complexes: A case study on ethyl-(2-methylphenyl)-phenylphosphine oxide

Péter Bagi[1] | Bence Varga[1] | András Szilágyi[2] | Konstantin Karaghiosoff[3] | Mátyás Czugler[1] | Elemér Fogassy[1] | György Keglevich[1]

[1]Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, Budapest, Hungary

[2]Department of Physical Chemistry and Material Science, Budapest University of Technology and Economics, Budapest, Hungary

[3]Department Chemie und Biochemie, Ludwig-Maximilians-Universität München, Munich, Germany

Correspondence
Péter Bagi, Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, Műegyetem rkp. 3., H-1111 Budapest, Hungary.
Email: pbagi@mail.bme.hu

Funding information
New National Excellence Program of the Ministry of Human Capacities, Grant/Award Number: ÚNKP-17-4-I-BME-102; National Research, Development and Innovation Office—NKFIH, Grant/Award Number: OTKA PD 116096

Abstract

As an example of acyclic *P*-chiral phosphine oxides, the resolution of ethyl-(2-methylphenyl)-phenylphosphine oxide was elaborated with TADDOL derivatives, or with calcium salts of the tartaric acid derivatives. Besides the study on the resolving agents, several purification methods were developed in order to prepare enantiopure ethyl-(2-methylphenyl)-phenylphosphine oxide. It was found that the title phosphine oxide is a racemic crystal-forming compound, and the recrystallization of the enantiomeric mixtures could be used for the preparation of pure enantiomers. According to our best method, the (*R*)-ethyl-(2-methylphenyl)-phenylphosphine oxide could be obtained with an enantiomeric excess of 99% and in a yield of 47%. Complete racemization of the enantiomerically enriched phosphine oxide could be accomplished via the formation of a chlorophosphonium salt. Characterization of the crystal structures of the enantiopure phosphine oxide was complemented with that of the diastereomeric intermediate. X-ray analysis revealed the main nonbonding interactions responsible for enantiomeric recognition.

KEYWORDS

acyclic phosphine oxide, enantiomeric enrichment, optical resolution, *P*-stereogenic center, X-ray structure

1 | INTRODUCTION

Since their first appearance, *P*-stereogenic ligands form an important class of compounds used in asymmetric catalysis,[1,2] and there is still a continuing interest for novel synthetic methods, which can be applied for the preparation of optically active *P*-chiral derivatives.

The synthesis of optically active *P*-chiral compounds generally involves the preparation of the corresponding phosphine boranes or phosphine oxides, as they are regarded as bench stable precursors of phosphines.[3,4] Moreover, a number of deoxygenation or deboronation protocols were developed for the preparation of the corresponding P(III) compounds, and the stereochemical outcome of those reactions was also studied in detail.[5,6]

Enantioselective synthesis is one of the main sources for optically active organophosphorus compounds.[7-9] In those reactions, (−)-menthol and (−)-ephedrine are frequently used chiral templates,[6,10-17] but other synthetic derivatives were also used.[18-21] Enantioselective synthesis affords enantiomerically enriched or enantiopure compounds. However, in this case, the purification of the enantiomeric mixtures should be an integral part of

these procedures. The self-disproportion of enantiomeric mixtures via achiral chromatography or sublimation is receiving more and more attention,[22-26] but the first example of this phenomenon in the sphere of *P*-stereogenic compounds is yet to be published.

The other main approach for the preparation of optically active *P*-chiral compounds involves the separation of racemic mixtures. One elegant possibility is preparative chromatography on a chiral stationary phase.[27] This approach was used for the preparation of a few enantiopure *P*-chiral phosphine oxides on a multigram scale.[28-33] Moreover, the costs of such separations may be decreased by using a supercritical fluid as the mobile phase, which complements the time efficiency of chromatographic separations with cost efficiency.[34] Optical resolution via the formation of diastereomers is the most common way for the separation of racemic mixtures into enantiomers. Many methods based on the formation of covalent diastereomers, diastereomeric salts, or diastereomeric complexes were elaborated for *P*-chiral phosphine oxides.[3,4,35-39] In a few cases, dynamic resolutions were also developed. These methods involved in situ racemization of the phosphine oxide or its derivative under the resolution conditions. In this manner, the total amount of the racemic starting material may be converted into a single enantiomer.[40-44] However, many enantioseparation methods developed for chiral phosphine oxides comprise classical resolutions. Although a number of methods were elaborated over the decades, most of these resolutions were individual examples, and a generally applicable resolving agent for a wide variety of phosphine oxides is still to be found.[3,4] *O*,*O*′-dibenzoyl-tartaric acid was one of the most commonly applied resolving agents, but the main scope of substrates comprised a few *P*-chiral bis(phosphine oxides),[30,45-47] and species bearing an axially dissymmetric element.[48-53] Moreover, this resolving agent could also be used for the enantioseparation of *tert*-butyl-phenylphosphine oxide.[44,54] Our research group found that TADDOL derivatives and the Ca^{2+} salts of tartaric acid derivatives were suitable resolving agents to separate the enantiomers of several 5- and 6-membered *P*-heterocyclic phosphine oxides having various substitution patterns.[55-65]

The aim of this study is to demonstrate that our resolution methods can be applied to a wider substrate scope. Herein, we report the resolution of ethyl-(2-methylphenyl)-phenylphosphine oxide and the purification strategies for the corresponding enantiomeric mixtures, as a detailed example for the preparation of optically active acyclic diaryl-alkylphosphine oxides. Moreover, the structures of the optically active phosphine oxide prepared and one of its diastereomeric intermediate were also elucidated by X-ray crystallography.

2 | MATERIALS AND METHODS

2.1 | General (instruments)

The ^{31}P, ^{13}C, and ^{1}H NMR spectra were taken on a Bruker AV-300 or DRX-500 spectrometer operating at 121.5, 75.5, and 300 or 202.4, 125.7, and 500 MHz, respectively. Coupling constants are expressed in hertz.

The exact mass measurements were performed using a Q-TOF Premier mass spectrometer in positive electrospray mode.

The enantiomeric excess (*ee*) values were determined by chiral high-performance liquid chromatography (HPLC) on a PerkinElmer Series 200 instrument equipped with chiral HPLC using Kromasil 5-Amycoat column (250 × 4.6-mm ID, hexane/ethanol 85/15 as an eluent with a flow rate of 0.8 mL/min, $T = 20°C$, UV detector $\alpha = 254$ nm). Retention times: 8.4 minutes for (*S*)-**3** and 12.6 minutes for (*R*)-**3**.

Optical rotations were determined on a PerkinElmer 241 polarimeter.

Differential scanning calorimetry (DSC) curves were recorded by using a PYRIS Diamond Differential Scanning Calorimeter (PerkinElmer). The measurements were performed on ~10-mg samples in N_2 atmosphere with a heating rate of 10°C/min between 30°C and 200°C. The temperatures at the minimum of the endotherms were referred to as the melting points of the enantiomeric mixtures.

Melting points were determined in capillary tubes by using a Gallenkamp melting point apparatus.

The microwave reaction was conducted in a 300 W CEM Discover focused microwave reactor equipped with a pressure controller using 20 to 30 W irradiation under isothermal conditions.

The (−)-(4*R*,5*R*)-4,5-bis(diphenylhydroxymethyl)-2,2-dimethyldioxolane [(−)-**4**], (−)-(2*R*,3*R*)-*α*,*α*,*α*′,*α*′-tetraphenyl-1,4-dioxaspiro[4.5]decan-2,3-dimethanol [(−)-**5**] were synthesized as described earlier.[66] The (−)-*O*,*O*′-dibenzoyl- and (−)-*O*,*O*′-di-*p*-toluoyl-(2*R*,3*R*)-tartaric acid were purchased from Sigma Aldrich.

2.2 | The preparation of ethyl-(2-methylphenyl)-phenylphosphine oxide (3)

To the solution of 9.0 g (46 mmol) phenylphosphonic dichloride (**1**) in 75 mL of diethyl ether was added dropwise 51 mmol of 2-methylphenylmagnesium bromide in 35 mL of diethyl ether [prepared from 1.3 g (53 mmol) of magnesium and 6.1 mL (51 mmol) of 2-bromotoluene] over 30 minutes at −78°C. After the addition, the reaction mixture was allowed to warm slowly to 26°C, and the mixture was stirred further for 1 hour. Then, the reaction mixture was cooled to −78°C, and 58 mmol of

TABLE 1 Resolution of ethyl-(2-methylphenyl)-phenylphosphine oxide (**3**) with TADDOL derivatives (−)-**4** and (−)-**5**

Entry	Resolving Agent	Eq.	Solvents[a]	Diastereomer complex[b]	Yield[c,f] (%)	*ee*[d,f] (%)	S[e,f] (−)	Abs. Config.[g]
1	TADDOL	0.5	2 × EtOAc/10 × hexane	(**3**)·(TADDOL)	(103) **74**	(4) **3**	(0.04) **0.02**	(*S*)
2	spiro-TADDOL	0.5	2 × EtOAc/10 × hexane	(**3**)·(spiro-TADDOL)	(86) **35**	(6) **66**	(0.05) **0.23**	(*R*)
3	spiro-TADDOL	0.5	4 × iPrOH	(**3**)·(spiro-TADDOL)	(117) **43**	(19) **89**	(0.22) **0.38**	(*R*)
4	spiro-TADDOL	1	4 × iPrOH	(**3**)·(spiro-TADDOL)	(148) **42**	(11) **90**	(0.17) **0.38**	(*R*)

Abbreviation: *ee*, enantiomeric excess.

[a]Mixture of solvents for the crystallization and recrystallizations [milliliter of solvent/g of resolving agent].

[b]The ratio of (**3**) and the resolving agent was determined by ^{1}H NMR.

[c]The yield of the diastereomer was calculated based on the half of the racemate (**3**) that is regarded to be 100% for each antipode.

[d]Determined by chiral HPLC.

[e]Resolving capability, also known as the Fogassy parameter [S = (Yield/100) × (*ee*/100)].[67]

[f]The results obtained after the first crystallization are shown in parentheses, while the results obtained after 2 recrystallizations are shown in boldface.

[g]The absolute configuration of (**3**) was determined by X-ray analysis (vide infra).

ethylmagnesium bromide in 50 mL of diethyl ether [prepared from 1.5 g (60 mmol) of magnesium and 4.3 mL (58 mmol) of bromoethane] was added dropwise over 30 minutes. Then, the reaction mixture was allowed to warm to 26°C, and the mixture was stirred overnight. The reaction was then quenched with 80 mL of saturated NH_4Cl solution at 0°C. The 2 phases were separated, the aqueous layer was extracted with diethyl ether. The organic layers were washed with brine, and then dried (Na_2SO_4). The crude product obtained after evaporating the solvent was purified by column chromatography (silica gel, 5% methanol in ethyl acetate) to give 5.5 g (49%) of ethyl-(2-methylphenyl)-phenylphosphine oxide (**3**) as a white solid. Mp 87–88 °C; ^{31}P NMR (121.5 Hz, $CDCl_3$, δ): 36.2 (δ_{lit} 35.5)[42]; ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.67–7.60 (m, 3H, Ar-H), 7.50–7.39 (m, 4H, Ar-H), 7.30–7.26 (m, 1H, Ar-H), 7.22–7.20 (m, 1H, Ar-H), 2.43–2.19 (m, 5H, CH_2CH_3 and Ar-CH_3), 1.19 (dt, J = 16.9 and 7.6, 3H, CH_2-CH_3); ^{13}C NMR (125.7 Hz, $CDCl_3$, δ): 142.7 ($^2J_{P\text{-}C}$ = 7.6, C_2'), 133.7 ($^1J_{P\text{-}C}$ = 96.5, C_1), 132.1 ($^3J_{P\text{-}C}$ = 10.2, C_3'), 132.0 ($^4J_{P\text{-}C}$ = 2.6, C_4'), 131.6 ($^2J_{P\text{-}C}$ = 11.1, C_6'), 131.5 ($^4J_{P\text{-}C}$ = 3.1, C_4), 130.9 ($^2J_{P\text{-}C}$ = 9.5, C_2), 130.2 ($^1J_{P\text{-}C}$ = not visible, C_1'), 128.6 ($^3J_{P\text{-}C}$ = 11.6, C_3), 125.5 ($^3J_{P\text{-}C}$ = 11.8, C_5'), 22.7 ($^1J_{P\text{-}C}$ = 73.4, CH_2), 21.5 ($^2J_{P\text{-}C}$ = 4.3, Ar-CH_3), 5.8 ($^2J_{P\text{-}C}$ = 4.9, CH_2CH_3); HRMS (ESI, m/z): $[M + H]^+$ calcd for $C_{15}H_{17}OP$ 245.1090; found, 245.1085.

2.3 | Resolution of ethyl-(2-methylphenyl)-phenylphosphine oxide (3) with spiro-TADDOL [(−)-5] (Representative Procedure I)

In 0.31 mL of hot ethyl acetate were dissolved 0.15 g (0.61 mmol) of racemic ethyl-(2-methylphenyl)-phenylphosphine oxide (**3**) and 0.16 g (0.31 mmol) of spiro-TADDOL [(−)-**5**], and then, 1.6 mL of hexane was added. Colorless crystalline diastereomeric complex of (*R*)-**3**·(spiro-TADDOL) appeared immediately. After standing at 26°C for 3 hours, the crystals were separated by filtration to give 0.20 g (86%) of (*R*)-**3**·(spiro-TADDOL) with a diastereomeric excess (*de*) of 6%. The diastereomeric complex (*R*)-**3**·(spiro-TADDOL) was purified further by 2 recrystallizations from a mixture of 0.31 mL of ethyl acetate and 1.6 mL of hexane to afford 0.081 g (35%) of the complex (*R*)-**3**·(spiro-TADDOL) with a *de* of 66% (Table 1, entry 2). The ethyl-(2-methylphenyl)-phenylphosphine oxide [(*R*)-**3**] was recovered from the diastereomer by column chromatography (silica gel, dichloromethane-methanol 97:3) to give 0.023 g (31%) of phosphine oxide (*R*)-**3** with an *ee* of 66%. The resolution of racemic ethyl-(2-methylphenyl)-phenylphosphine oxide (**3**) was also elaborated with spiro-TADDOL [(−)-**5**] using isopropyl alcohol. According to this variation, the mixture of the racemic compound (**3**) and spiro-TADDOL [(−)-**5**] was dissolved in hot isopropyl alcohol, and the corresponding diastereomeric complex (*R*)-**3**·(spiro-TADDOL) precipitated on cooling the mixture to 26°C (Table 1, entries 3 and 4). Resolution of racemic ethyl-(2-methylphenyl)-phenylphosphine oxide (**3**) was also accomplished with TADDOL [(−)-**5**] according to the Representative Procedure I. (Table 1, entry 1). Mp of (*R*)-**3**·(spiro-TADDOL) (de: 89%): 155°C to 157°C.

2.4 | Resolution of ethyl-(2-methylphenyl)-phenylphosphine oxide (3) with calcium hydrogen O,O′-dibenzoyl-(2R,3R)-tartrate [(−)-6] (Representative Procedure II)

To 0.23 g (0.61 mmol) of DBTA·H_2O in a mixture of 0.74 mL of ethanol and 0.075 mL of water was added 0.017 g (0.31 mmol) of CaO, and the mixture was heated

TABLE 2 Resolution of ethyl-(2-methylphenyl)-phenylphosphine oxide (**3**) with $Ca(H\text{-}DBTA)_2$ or $Ca(H\text{-}DPTTA)_2$ [(−)-**6** or (−)-**7**]

Entry	Resolving Agent	Eq.	Solvents[a]	Diastereomer Complex[b]	Yield[c,f] (%)	*ee*[d,f] (%)	S[e,f] (−)	Abs. Config.[g]
1	$Ca(H—DBTA)_2$	0.25	3 × EtOAc/3 × EtOH/ 10%H_2O	$Ca(\mathbf{3})_2(H—DBTA)_2$	(61) **25**	(61) **94**	(0.37) **0.23**	(*R*)
2	$Ca(H—DBTA)_2$	0.5	3 × EtOAc/3 × EtOH/ 10%H_2O	$Ca(\mathbf{3})_2(H—DBTA)_2$	(79) **14**	(82) **87**	(0.64) **0.12**	(*R*)
3	$Ca(H—DBTA)_2$	0.5	3 × MeCN/3 × EtOH/ 10%H_2O	$Ca(\mathbf{3})(H—DBTA)_2$	(57) **15**	(64) **94**	(0.36) **0.14**	(*R*)
4	$Ca(H—DPTTA)_2$	0.25	3 × EtOAc/3 × EtOH/ 10%H_2O	$Ca(\mathbf{3})_2(H—DPTTA)_2$	(63) **18**	(58) **82**	(0.36) **0.15**	(*R*)
5	$Ca(H—DPTTA)_2$	0.5	3 × EtOAc/3 × EtOH/ 10%H_2O	$Ca_3(\mathbf{3})_4(H—DPTTA)_6$	(59) **8**	(69) **83**	(0.41) **0.07**	(*R*)
6	$Ca(H—DPTTA)_2$	0.5	3 × MeCN/3 × EtOH/ 10%H_2O	$Ca(\mathbf{3})_2(H—DPTTA)_2$	(76) **14**	(76) **88**	(0.54) **0.13**	(*R*)

Abbreviation: *ee*, enantiomeric excess.

See Table 1 for footnotes.

at the boiling point until it became clear. To the solution of the in situ formed resolving agent $Ca(H\text{-}DBTA)_2$ [(−)-**6**] was then added 0.15 g (0.61 mmol) of racemic ethyl-(2-methylphenyl)-phenylphosphine oxide (**3**) in 0.74 mL of ethyl acetate. After the addition, the solution was allowed to cool down to 26°C, whereupon colorless crystals appeared. After standing at 26°C for 24 hours, the crystals were filtered off to give 0.15 g (79%) of $Ca[(R)\text{-}\mathbf{3})_2(H\text{-}DBTA)_2]$ with a de of 82% (Scheme 4, I). The diastereomeric complex was purified further by stirring the diastereomer in a mixture of 0.74 mL of ethanol and 0.74 mL of ethyl acetate at 26°C for 24 hours to give 0.096 g (50%) $Ca[(R)\text{-}\mathbf{3})_2(H\text{-}DBTA)_2]$ with a *de* of 86% (Scheme 4, II). The diastereomer was purified again as described above to afford 0.027 g (14%) $Ca[(R)\text{-}\mathbf{3})_2(H\text{-}DBTA)_2]$ with a *de* of 87% (Table 2, entry 2). The (*R*)-ethyl-(2-methylphenyl)-phenylphosphine oxide [(*R*)-**3**] was recovered from the diastereomer by treating the 2 mL dichloromethane suspension of $Ca[(R)\text{-}\mathbf{3})_2(H\text{-}DBTA)_2]$ with 2 mL of 10% aqueous ammonia. The organic layer was washed with 0.5 mL of water, dried (Na_2SO_4), and concentrated to give 0.008 g (11%) of (*R*)-ethyl-(2-methylphenyl)-phenylphosphine oxide [(*R*)-**3**] with an *ee* of 87% (Scheme 4, III). All resolution experiments of ethyl-(2-methylphenyl)-phenylphosphine oxide (**3**) with $Ca(H—DBTA)_2$ and $Ca(H—DPTTA)_2$ [(−)-**6** and (−)-**7**] were performed according to Representative Procedure II. The conditions and the results are shown in Table 2.

2.5 | Preparation and recrystallization of the enantiomeric mixtures of ethyl-(2-methylphenyl)-phenylphosphine oxide (3)

Racemic and enantiopure (*R*)-ethyl-(2-methylphenyl)-phenylphosphine oxide [**3** and (*R*)-**3**] were mixed to provide a total amount of 0.10 g of the given enantiomeric mixture. The exact enantiomeric composition of that given enantiomeric mixture was determined by HPLC. In 0.15 mL of diethyl ether was dissolved 0.015 g (0.041 mmol) of the corresponding enantiomeric mixture of (*R*)-ethyl-(2-methylphenyl)-phenylphosphine oxide [(*R*)-**3**]. The crystals that appeared on cooling the solution to 26°C were collected by filtration after 15 minutes of crystallization. Results: ee_0: 23%: *ee*: 3% and yield: 57%; results: ee_0: 41%: *ee*: 6% and yield: 41%; results: ee_0: 58%: *ee*: 61% and yield: 41%; results: ee_0: 82%: *ee*: 97% and yield: 46% (Figure 1B).

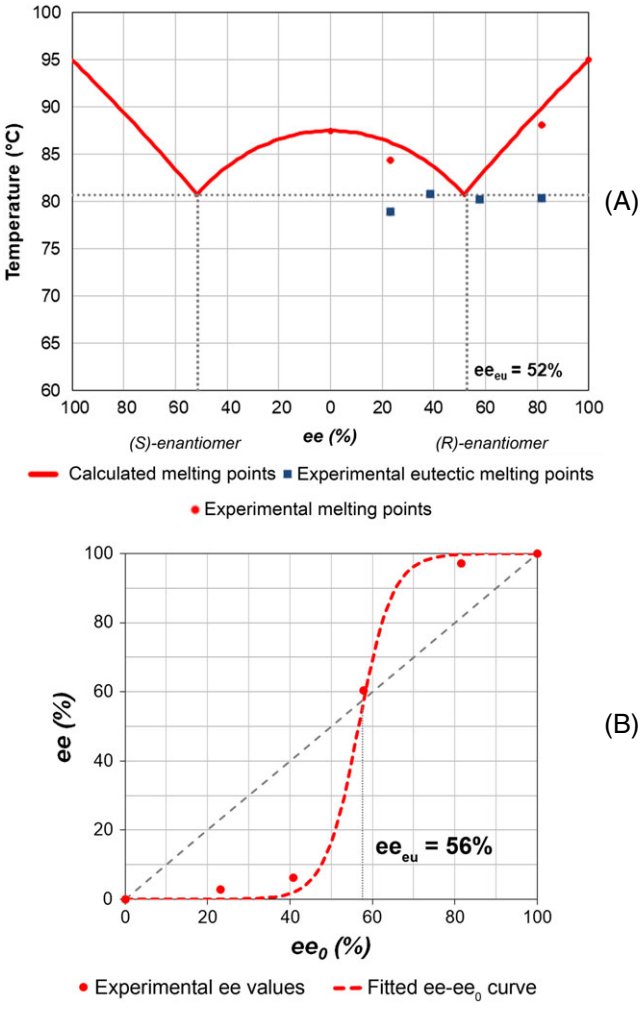


FIGURE 1 A, The binary melting point and B, the ee_0-*ee* diagram for ethyl-(2-methylphenyl)-phenylphosphine oxide (**3**)

2.6 | Comparative study on the purification of non-racemic mixtures of ethyl-(2-methylphenyl)-phenylphosphine oxide (3)

2.6.1 | Repeated resolution according to the half-equivalent method

To obtain 0.16 g (71%) (*R*)-ethyl-(2-methylphenyl)-phenylphosphine oxide [(*R*)-**3**] with an *ee* of 82% (Scheme 4, IV), 0.45 g of Ca(*R*)-**3**$_2$(H-DBTA)$_2$ (yield: 79%, *de*: 82%) prepared from 0.45 g (1.8 mmol) of racemic ethyl-(2-methylphenyl)-phenylphosphine oxide (**3**), 0.69 g (1.8 mmol) of DBTA·H_2O, and 0.051 g (0.92 mmol) of CaO as described in the Representative Procedure II was decomposed by extraction with dichloromethane and 10% aqueous ammonia. The enantiomeric mixture so obtained was resolved with 0.22 g (0.59 mmol) of DBTA·H_2O and 0.017 g (0.30 mmol) of CaO in a mixture of 0.72 mL of ethyl acetate, 0.72 mL of ethanol, and 0.07 mL of water according to Representative Procedure II. After the decomposition of Ca[(*R*)-**3**$_2$(H-DBTA)$_2$] diastereomer (Scheme 4, V), 0.084 g (38%) of (*R*)-ethyl-(2-methylphenyl)-phenylphosphine oxide [(*R*)-**3**] was obtained with an *ee* of 96%.

2.6.2 | Repeated resolution according to the equivalent method

(*R*)-ethyl-(2-methylphenyl)-phenylphosphine oxide [(*R*)-**3**] (0.16 g, *ee*: 82%) prepared as described in Section 2.6.1 was resolved with 0.25 g (0.65 mmol) of DBTA·H_2O and 0.018 g (0.33 mmol) of CaO in a mixture of 0.79 mL of ethyl acetate, 0.79 mL of ethanol and 0.08 mL of water according to Representative Procedure II. After the decomposition of Ca[(*R*)-**3**$_2$(H-DBTA)$_2$] diastereomer, 0.093 g (42%) of (*R*)-ethyl-(2-methylphenyl)-phenylphosphine oxide [(*R*)-**3**] was obtained with an *ee* of 96% (Scheme 4, VI). Mp of Ca[(*R*)-**3**$_2$(H-DBTA)$_2$] (*de*: 96%): 169°C to 170°C.

2.6.3 | Recrystallization of the enantiomeric mixture of (*R*)-ethyl-(2-methylphenyl)-phenylphosphine oxide [(*R*)-3]

(*R*)-ethyl-(2-methylphenyl)-phenylphosphine oxide [(*R*)-**3**] (0.16 g, *ee*: 82%) prepared as described in Section 2.6.1 was recrystallized from 0.40 mL of diethyl ether to give 0.13 g (57 %) (*R*)-ethyl-(2-methylphenyl)-phenylphosphine oxide [(*R*)-**3**] with an ee of 96%. Another recrystallization of this enantiomeric mixture from 0.40 mL of diethyl ether afforded 0.10 g (47%) enantiopure (*R*)-ethyl-(2-methylphenyl)-phenylphosphine oxide [(*R*)-**3**] (*ee* > 99%) (Scheme 4, VII) $[\alpha]_D^{25} = [\alpha]_D^{25} + 32.6$ (c = 1.2 in $CHCl_3$). Mp 94°C to 95°C.

2.6.4 | Racemization of (*R*)-ethyl-(2-methylphenyl)-phenylphosphine oxide [(*R*)-3] via chlorophosphonium salt (8)

To the solution of 0.10 g (0.42 mmol) (*R*)-ethyl-(2-methylphenyl)-phenylphosphine oxide [(*R*)-**3**] (*ee*: 99%) in 2 mL of dry dichloromethane was added dropwise 0.053 mL (0.62 mmol) of oxalyl chloride at 0°C over 10 minutes. The mixture was then allowed to warm to 26°C, and it was stirred under a nitrogen atmosphere for 2 hours. The solvent and the excess of the reagent was removed under reduced pressure. The chlorophosphonium salt so obtained was dissolved in 2 mL of dichloromethane. The mixture was cooled to 0°C, and 0.5 mL of water was added to the reaction mixture over 10 minutes. The emulsion was stirred for 2 hours at 0°C. The 2 phases were separated, and the aqueous layer was extracted with dichloromethane. The organic layers were combined, and the resulting solution was dried (Na_2SO_4); the solvent was evaporated, and the crude product was passed through a silica gel column (5% methanol in dichloromethane) to afford 0.082 g (80%) of racemic ethyl-(2-methylphenyl)-phenylphosphine oxide (**3**).

2.7 | X-ray measurements (general)

Intensity data were collected for the crystals of racemic and the enantiopure (*R*)-ethyl-(2-methylphenyl)-phenylphosphine oxide [**3** and (*R*)-**3**] on an Xcalibur, Sapphire3 diffractometer (graphite monochromator; Mo-Kα radiation, λ = 0.71069 Å) at 123(2)K. The data collection was performed for the 1:1 molecular complex of (*R*)-**3**: spiro-TADDOL on a D8 Venture diffractometer (Mo-*K*α radiation, λ = 0.71069 Å) at 100 (2)K. All crystals were mounted on glass fibers. Multiscan absorption corrections were applied to the data in all cases. All initial structure models were obtained by direct methods and subsequent difference syntheses.[68] Models were then refined by full-matrix least squares procedures[69] using anisotropic displacement parameters for all non-*H* atoms. The standard treatment for hydrogen atomic positions was calculations from assumed geometries, unless indicated otherwise. Hydrogen atoms were included in structure factor calculations, but they were not refined, unless noted. The isotropic displacement parameters of the hydrogen atoms were approximated from the U(eq) value of the atom they were bonded.

Geometry calculations and validations were done.[70] Part of the drawings used in this work were made by the perusal of DIAMOND[71] and MERCURY.[72]

Final crystal structure model data are deposited with the Cambridge Crystallographic Data Centre under CCDC 1572195–1572197 and can be obtained free of charge upon contacting.

3 | RESULTS AND DISCUSSION

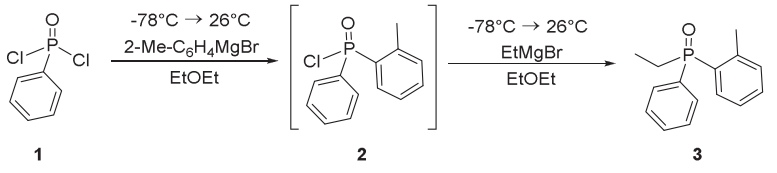
3.1 | Preparation of racemic ethyl-(2-methylphenyl)-phenylphosphine oxide (3)

The ethyl-(2-methylphenyl)-phenylphosphine oxide (**3**) was chosen as an air stable model compound having a diaryl-alkyl substitution pattern, as this organophosphorus compound (**3**) shows structural similarity to a few P(III) ligands used in asymmetric syntheses.[9,73] The title compound (**3**) was prepared by reacting phenylphosphonic dichloride (**1**) with 2-methylphenyl-magnesium bromide. The phosphinic chloride intermediate (**2**) was reacted further without isolation with ethyl-magnesium bromide to afford ethyl-(2-methylphenyl)-phenylphosphine oxide (**3**) in a yield of 49% after the work-up and purification by column chromatography (Scheme 1).

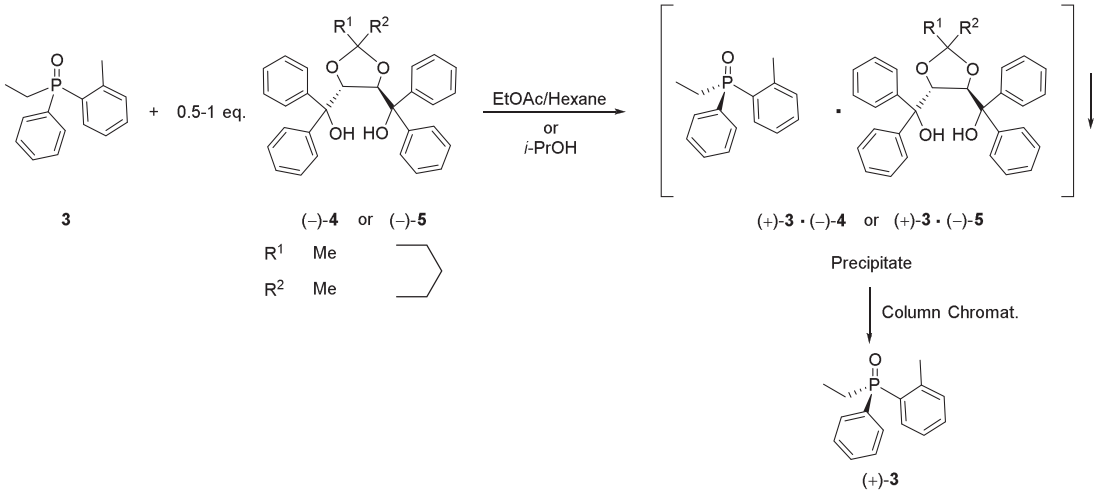
3.2 | Resolution of ethyl-(2-methylphenyl)-phenylphosphine oxide (3) with TADDOL derivatives (−)-4 and (−)-5

The resolution of ethyl-(2-methylphenyl)-phenylphosphine oxide (**3**) was first attempted with TADDOL derivatives (−)-**4** and (−)-**5**. The phosphine oxide (**3**) and the corresponding TADDOL derivative (−)-**4** or (−)-**5** were dissolved in boiling ethyl acetate. The precipitation of the diastereomeric complexes having the composition of (**3**)·(TADDOL) or (**3**)·(spiro-TADDOL) was observed upon the addition of hexane to the solution. The crystalline diastereomers were separated by filtration after 3 hours, and they were purified further by 2 recrystallizations. The optically active ethyl-(2-methylphenyl)-phenylphosphine oxide [(*R*)-**3** or (*S*)-**3**] could be liberated from the corresponding diastereomer by column chromatography (Scheme 2). The composition of the diastereomers was determined by ^{1}H NMR, whereas the *ee* values of the ethyl-(2-methylphenyl)-phenylphosphine oxide (**3**) were monitored by HPLC using a chiral stationary phase. The results were collected in Table 1.

Despite our previous success,[65] TADDOL [(−)-**4**] was not a suitable resolving agent for the enantioseparation of the ethyl-(2-methylphenyl)-phenylphosphine oxide (**3**) as the overall efficiency for the resolution of phosphine oxide (**3**) remained low and the maximal *ee* was only 3% (Table 1, entry 1). Although our initial



SCHEME 1 Synthesis of racemic ethyl-(2-methylphenyl)-phenylphosphine oxide (**3**)



SCHEME 2 General resolution procedure for racemic ethyl-(2-methylphenyl)-phenylphosphine oxide (**3**) using TADDOL derivatives (−)-**4** and (−)-**5**

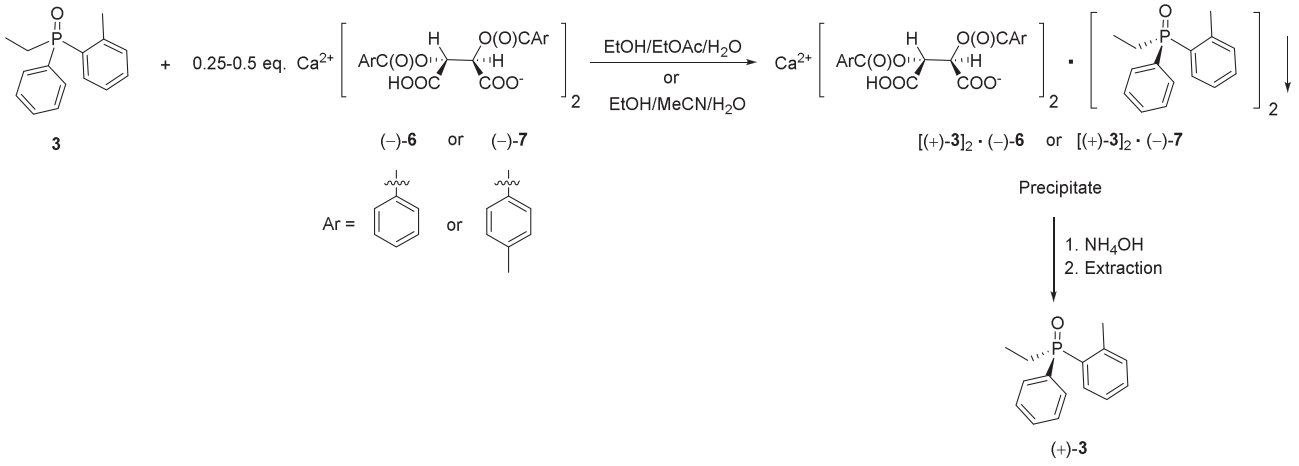
experiments with TADDOL [(−)-**4**] remained unsuccessful, the resolution of ethyl-(2-methylphenyl)-phenylphosphine oxide (**3**) was also attempted with spiro-TADDOL [(−)-**5**], which is the structural analogue of TADDOL [(−)-**4**]. Applying half equivalent of spiro-TADDOL [(−)-**5**] in the mixture of ethyl acetate and hexane, the (*R*)-ethyl-(2-methylphenyl)-phenylphosphine oxide [(*R*)-**3**] could be obtained in an *ee* of 66% after purification and decomposition of the corresponding diastereomer (Table 1, entry 2).

Previously, we found that alcohols may also be suitable solvents for resolutions with TADDOL-derivatives (−)-**4** or (−)-**5**, especially in the case of spiro-TADDOL [(−)-**5**].[65] Thus, the resolution of racemic phosphine oxide (**3**) was also accomplished with 0.5 equivalents or 1 equivalent of spiro-TADDOL [(−)-**5**] in isopropyl alcohol. These experiments led to the best results (*ee*: 89%, S = 0.38 and *ee*: 90%, S = 0.38) (Table 1, entries 5 and 6). Interestingly, the results obtained with the half equivalent or the equivalent method showed parity.

3.3 | Resolution of ethyl-(2-methylphenyl)-phenylphosphine oxide (3) with calcium salts of the (−)-*O*,*O*′-dibenzoyl- or (−)-*O*,*O*′-di-*P*-toluoyl-(2*R*,3*R*)-tartaric acids (−)-4 or (−)-5

The TADDOL derivatives (−)-**4** or (−)-**5** were promising resolving agents, as the (*R*)-ethyl-(2-methylphenyl)-phenylphosphine oxide [(*R*)-**3**] could be prepared with an *ee* of 90%, but the overall efficiency of that resolution experiment was moderate (S = 0.38) (Table 1, entry 4). As the next step of this study, we turned our attention to the application of the acidic calcium salts of the (−)-*O*,*O*′-dibenzoyl- or (−)-*O*,*O*′-di-*p*-toluoyl-(2*R*,3*R*)-tartaric acid [Ca(H-DBTA)$_2$ or Ca(H-DPTTA)$_2$; (−)-**6** or (−)-**7**] for the resolution of the title phosphine oxide (**3**). Both resolving agents were prepared in situ by the reaction of (−)-*O*,*O*′-dibenzoyl- or (−)-*O*,*O*′-di-*p*-toluoyl-(2*R*,3*R*)-tartaric acid with CaO in a boiling mixture of ethanol and water. To this solution was added ethyl-(2-methylphenyl)-phenylphosphine oxide (**3**) in ethyl acetate or in acetonitrile. The corresponding diastereomers precipitated from the solution on cooling. After 24 hours, the crystals were collected by filtration, and then they were purified further by stirring the solid diastereomer in the corresponding solvent mixture. The enantiomeric mixture of the phosphine oxide (**3**) could be liberated by adding aqueous NH_4OH to the diastereomeric mixture followed by extraction with dichloromethane (Scheme 3). The composition of the diastereomers was analyzed by ^{1}H NMR. The enantiomeric purity was monitored by chiral HPLC. The results are summarized in Table 2.

The resolution of ethyl-(2-methylphenyl)-phenylphosphine oxide (**3**) was first attempted with 0.25 or 0.5 equivalent of Ca(H-DBTA)$_2$ [(−)-**6**] in a mixture of ethyl acetate, ethanol, and water (Table 2, entries 1 and 2). In these experiments, coordination complexes with a composition of Ca(**3**)$_2$(H-DBTA)$_2$ were formed. In this manner, resolutions were conducted according to the half equivalent or the equivalent method, respectively (Table 2, entries 1 or 2). The results obtained after the first crystallization were promising, as the *ee* of (*R*)-**3** was 61%, and the resolving capability was 0.37, when 0.25 equivalents of the resolving agent [(−)-**6**] were applied (Table 2, entry 1). When both enantiomers were converted to the corresponding diastereomer (ie, the resolution was conducted according to the equivalent method), the enantiomeric purity (*ee*) and the overall efficiency values increased to 82% and 0.64, respectively (Table 2, entry 2). After recrystallizations, the purity of the diastereomers obtained in these 2 experiments increased to 94% or 87%, respectively,



SCHEME 3 General resolution procedure for racemic ethyl-(2-methylphenyl)-phenylphosphine oxide (**3**) using Ca(H-DBTA)$_2$ or Ca(H-DPTTA)$_2$ [(−)-**6** or (−)-**7**]

but the resolving capability values decreased significantly to 0.23 or 0.12, respectively (Table 2, entries 1 and 2), which in fact is the consequence of the low yields (25% or 14%, respectively) caused by the inefficient purification.

The enantioseparation of the title phosphine oxide (**3**) was also attempted with Ca(H-DBTA)$_2$ [(−)-**6**] in a mixture of acetonitrile, ethanol, and water. However, this change in the solvent mixture did not have a positive impact on the results, as the enantiomeric excess values showed parity, but the overall efficiency decreased (*ee*: 94%, S = 0.14) (Table 2, entry 3). The resolution of ethyl-(2-methylphenyl)-phenylphosphine oxide (**3**) was also attempted with Ca(H-DPTTA)$_2$ [(−)-**7**] using similar molar ratios and solvents, as in the case of Ca(H-DBTA)$_2$ [(−)-**6**]. Probably, as a consequence of the structural similarity of the 2 resolving agents [(−)-**6** and (−)-**7**], the purity of the enantiomeric mixtures, as well as the overall resolution efficiency could not be improved further with Ca(H-DPTTA)$_2$ [(−)-**7**], as the *ee* values fell in the range of 82% to 88%, and the resolving capability values were between 0.07 and 0.15 after purification (Table 2, entries 4-6).

3.4 | Purification of the enantiomeric mixture of (*R*)-ethyl-(2-methylphenyl)-phenylphosphine oxide [(*R*)-3]

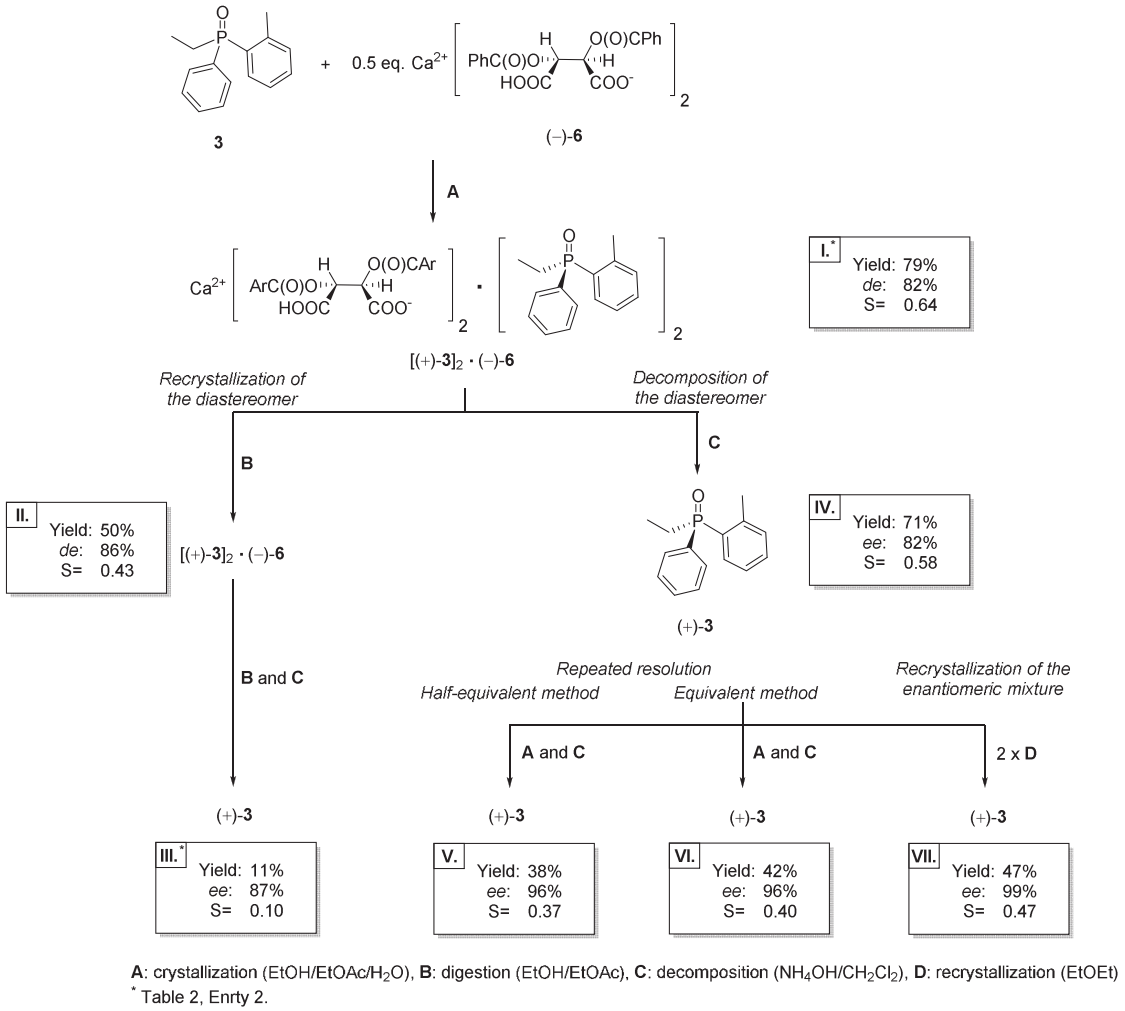
Considering all of the results discussed in the previous sections, we found that efficient enantiomeric separation could be accomplished with Ca(H-DBTA)$_2$ [(−)-**6**], but pure enantiomers could not be obtained by the recrystallizations of the corresponding diastereomers. Thus, other purification strategies[74,75] (eg, repeated resolution or purification of enantiomeric mixtures) were evaluated to prepare enantiopure (*R*)-ethyl-(2-methylphenyl)-phenylphosphine oxide [(*R*)-**3**]. In our opinion, these approaches are less discussed in the sphere of *P*-stereogenic organophosphorus compounds.

First, the solid state behavior of the enantiomeric mixtures of ethyl-(2-methylphenyl)-phenylphosphine oxide (**3**) was investigated, as this information is essential to design a proper purification method.[75-77] Binary melting point diagrams can be used to determine whether a given enantiomeric mixture forms a conglomerate, racemic crystals, or solid solution. Differential scanning calorimetry measurements of the racemic compound and the pure enantiomer were accomplished to determine the corresponding melting point and heat of fusion values (See Supporting Information), and the binary melting point diagram was constructed using the simplified Schröder-van Laar and Prigogine-Defay equations.[76,77] The results indicated that the ethyl-(2-methylphenyl)-phenylphosphine oxide (**3**) is a racemic crystal-forming compound having a eutectic composition (ee_{eu}) of 52% (Figure 1a).

To verify the accuracy of the calculated melting point diagram, enantiomeric mixtures having the *ee* values of approximately 20% to 40% to 60% to 80% were prepared, and these samples were also subjected to DSC analysis (See Supporting Information). The experimental melting points of the enantiomeric mixtures showed good agreement with the calculated values (Figure 1A).

Beside the ternary solubility diagrams, the ee_0-*ee* diagram is a simple model to predict how a given enantiomeric mixture behaves during crystallization.[75] Thus, the behavior of the enantiomeric mixtures of phosphine oxide (**3**) was also elucidated by an ee_0-*ee* diagram. Separate samples of enantiomeric mixtures prepared for DSC measurements were recrystallized from diethyl ether. The ee_0-*ee* diagram (Figure 1B), which was constructed by plotting the enantiomeric excess after the recrystallization (*ee*) against the initial enantiomeric purity (ee_0) confirms that the ethyl-(2-methylphenyl)-phenylphosphine oxide (**3**) is a racemic crystal-forming compound, and the eutectic composition determined by these recrystallization experiments (ee_{eu}: 56%) is also in good agreement with the value suggested by the DSC measurements (ee_{eu}: 52%).

Having all these results in hand, we wished to find the most suitable method for the preparation of pure enantiomers. In the study of the resolving agents, the stirring of the solid diastereomers in a given solvent mixture was the purification method used. However, the purity of the diasteremeric mixtures could only be improved by losing a large amount of diastereomers during the purification, which resulted in low yields, and consequently low efficiency values (*S*). Besides the purification of diastereomers used earlier (Table 2, entry 2), the repeated resolution according to the half equivalent or the equivalent method, or the recrystallization of the enantiomeric mixtures was also considered as an option. The results are summarized in Scheme 4. For comparable results, a diastereomeric mixture obtained by the resolution with Ca(H-DBTA)$_2$ according to the optimum conditions was considered as the starting material (Table 2, entry 2). Scheme 4 also illustrates the results shown in Table 2, entry 2, and the corresponding enantiomeric mixture of (*R*)-**3** could be obtained in a yield of 11% and with an *ee* of 87% after decomposition of the diastereomer (Scheme 4, III). In a separate experiment, the diastereomeric mixture obtained after the first crystallization (Scheme 4, I) was decomposed by extraction to obtain the enantiomeric mixture of (*R*)-ethyl-(2-methylphenyl)-phenylphosphine oxide [(*R*)-**3**] in a yield of 71% and with an *ee* of 82% (Scheme 4, IV). The purification of this enantiomeric mixture was attempted by repeated resolution according to the half equivalent or the equivalent method



SCHEME 4 The purification procedure for the enantiomeric mixture of (*R*)-ethyl-(2-methylphenyl)-phenylphosphine oxide [(*R*)-**3**]

(Scheme 4, V or VI). The enantiomeric purity obtained after the crystallization and decomposition of the diastereomer was improved to 96% in both instances, but the yields were moderate 38% or 42%, respectively (Scheme 4, V or VI). Finally, the enantiomeric mixture was purified without any chiral auxiliary, by a simple recrystallization in diethyl ether. In this manner, enantiopure (*R*)-ethyl-(2-methylphenyl)-phenylphosphine oxide [(*R*)-**3**] (*ee* > 99%) could be obtained in a yield of 47% (Scheme 4, VII). To the best of our knowledge, despite the simplicity of this method, only a few examples can be found in the literature, when the recrystallization of the enantiomeric mixtures was suitable for the preparation of enantiopure *P*-stereogenic organophosphorus compounds.[21,44,78,79]

3.5 | Racemization of optically active ethyl-(2-methylphenyl)-phenylphosphine oxide (3)

After a thorough investigation of the resolution of ethyl-(2-methylphenyl)-phenylphosphine oxide (**3**), the racemization of phosphine oxide (**3**) was investigated as the last step of this study. The racemic phosphine oxide (**3**) so obtained from the undesired enantiomer could be used as starting material in subsequent optimized resolution experiments, and hence, it may increase the overall yield of a given resolution protocol.

In this study, the enantiopure (*R*)-ethyl-(2-methylphenyl)-phenylphosphine oxide [(*R*)-**3**] was considered as the model compound.

First, the racemization of the enantiopure phosphine oxide [(*R*)-**3**] was attempted under thermal or microwave conditions in a dimethylformamide solution or as a melt. However, these racemization attempts were inefficient, as enantiomeric mixtures of phosphine oxide (**3**) having an *ee* of 95% could be obtained upon heating for extended time (See Supporting Information). Recently, Gilheany et al demonstrated that chlorophosphonium salts that can be prepared from phosphines or phosphine oxides in a single quantitative reaction step, racemize spontaneously, even at a low temperature.[80] The racemization of *P*-stereogenic phosphine oxides via chlorophosphonium

salt intermediates has already been used to epimerize the undesired enantiomer obtained from a resolution process.[81] Thus, the (*R*)-ethyl-(2-methylphenyl)-phenylphosphine oxide [(*R*)-**3**] was reacted with oxalyl-chloride at 0°C (Scheme 5), and then the chlorophosphonium salt (**8**) so obtained was hydrolized to afford racemic ethyl-(2-methylphenyl)-phenylphosphine oxide (**3**) in a yield of 80%.

3.6 | Single crystal X-ray analysis of the racemic and enantiopure ethyl-(2-methylphenyl)-phenylphosphine oxide [3 and (*R*)-3], as well as the (*R*)-3-spiro-TADDOL 1:1 complex

X-ray quality crystals could be grown from racemic and enantiopure ethyl-(2-methylphenyl)-phenylphosphine oxide [**3** and (*R*)-**3**], as well as a diastereomeric complex having the composition of (**3**)·(spiro-TADDOL). The crystallographic measurements enabled us to assign the (*R*) absolute configuration to the (+)-ethyl-(2-methylphenyl)-phenylphosphine oxide [(+)-**3**]. Crystal structure models of both the racemic **3** (Figure S1) and the enantiopure (*R*)-**3** (Figure S2) show practically identical shape and conformation of the 2 independent molecular structures (Figure S3).

The crystal structure of the (*R*)-**3**-spiro-TADDOL complex corroborates a 1:1 composition of the acyclic phosphine oxide with the spiro-TADDOL host molecule (Figure 2).

The comparison of the 2 (*R*)-**3** molecules observed in the enantiopure phosphine oxide crystal and the one in the 1:1 assembly with the spiro-TADDOL [(−)-**5**] host shows only 1 marked difference (See Figure S4). Methyl termini of the ethyl group is placed in an alternative gauche position. Otherwise, the atomic positions more or less coincide with the *o*-methyl group exhibiting the largest (approximately 0.6 Å) deviation. As this value is below the experimental resolution, one may practically take all atomic positions alike less the quoted methyl termini.

The asymmetric unit drawing also shows the characteristic intramolecular OH ... O hydrogen bridge linking the 2 —OH functions. The only free —OH acts as donor to the O═P group, thus providing a basis for the host-guest assembly. This classical *H*-bonding scheme is

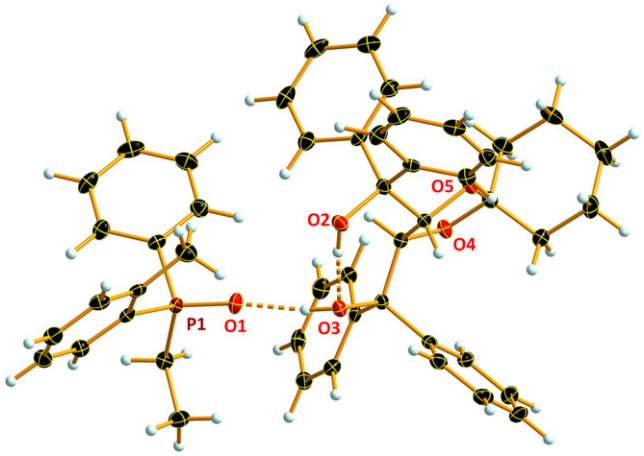


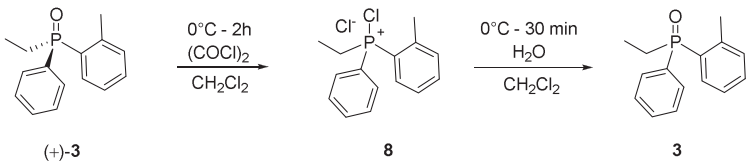
FIGURE 2 Asymmetric unit structure of the (*R*)-**3**-spiro-TADDOL 1:1 complex in the crystal. Non-*H* atoms are shown in 50% probability of atomic displacement values

complemented then by 4 short C—H ... O contacts (Table 3).

As an attempt to assess the relative interaction strengths in the crystal, intermolecular potentials were calculated,[82,83] of which only the top 5 are shown (Table 4). These identify that the principal interaction is indeed between the —OH acting as donor to the O═P group of the target phosphine oxide (**3**). As these values do not contain any error estimates, one can assume that they are merely approximating the reality, and thus, serve only as a guide. Nevertheless, as Figure S5 indicates, these comply with the shortest interactions listed above, and support their interpretation as the structure directing ones. The calculated density of the complex

TABLE 3 Selected O—H ... O and C—H ... O short contact dimensions (in Å and in °) with their standard deviations (σ) in parentheses in the crystal structure of the (*R*)-**3**-spiro-TADDOL 1:1 complex

Short Contacts	Length, Å	Length, Å	Length, Å	Angle, °
O2—H2 ... O3	0.91(3)	1.80(3)	2.706(2)	176(2)
O3—H3 ... $O1_{(x,y,z+1)}$	0.91(3)	1.74(3)	2.633(2)	167(3)
C27—H27 ... O4	0.92(1)	2.41(1)	2.964(2)	119(1)
C33—H33 ... O3	0.96(2)	2.41(1)	2.749(2)	100(1)
C43—H43 ... O2	0.95(1)	2.48(1)	2.808(2)	101(1)
C45—H45 ... O5	0.99(2)	2.37(1)	2.914(2)	114(1)



SCHEME 5 The racemization of (*R*)-ethyl-(2-methylphenyl)-phenylphosphine oxide [(*R*)-**3**] via chlorphosphonium salt (**8**)

TABLE 4 Calculated intermolecular potentials (packing energy) rounded to integer numbers

Mol 1	Mol 2	Distance	Energy, kJ/mol
0	1	7.13249	−56
2	3	7.13249	−56
0	4	8.621	−39
0	5	8.621	−39
0	6	8.91578	−36

(1.24 Mg/m^3) gets closer to that of the racemic crystal, yet another indication of the importance of attractive interactions.

4 | CONCLUSIONS

In summary, a detailed study was conducted to investigate all main aspects of the resolution procedures of acyclic diaryl-alkylphosphine oxides. The ethyl-(2-methylphenyl)-phenylphosphine oxide (**3**) was considered as the model compound, and the resolution of phosphine oxide (**3**) was elaborated with TADDOL derivatives [(−)-**4** or (−)-**5**] and the acidic calcium salt of the (−)-*O*,*O*′-dibenzoyl- or (−)-*O*,*O*′-di-*p*-toluoyl-(2*R*,3*R*)-tartaric acid [(−)-**6** or (−)-**7**]. Both resolving agent classes were applicable for the enantiomeric separation of phosphine oxide (**3**), and the best results could be obtained using $Ca(H\text{-}DBTA)_2$ (−)-**6**. The purification strategies of the enantiomerically enriched phosphine oxide (**3**) were investigated in detail. We found that enantiopure (*R*)-ethyl-(2-methylphenyl)-phenylphosphine oxide [(*R*)-**3**] could be prepared by resolution with $Ca(H\text{-}DBTA)_2$ [(−)-**6**] followed by recrystallization of the partially enantioenriched phosphine oxide (**3**). An efficient racemization of ethyl-(2-methylphenyl)-phenylphosphine oxide (**3**) enantiomers via the formation of chlorophosphonium salt (**8**) was also elaborated. In this manner, the undesired enantiomer of the phosphine oxide (**3**) may be converted into racemic **3** that can be used in subsequent resolution experiments as a starting material. Single crystal X-ray analysis of the 1:1 diastereomeric coordination complex (*R*)-**3** : spiro-TADDOL point to the fact that the principal molecular recognition events are affected by the ─OH group acting as donor to the O═P group of the target phosphine oxide (**3**).

This study is the first example for the application of TADDOL derivatives [(−)-**4** or (−)-**5**] and the calcium salts of tartaric acid derivatives [(−)-**6** or (−)-**7**] for the resolution of an acyclic phosphine oxide. Our experience indicates that these enantiomeric separation methods may have a more general value during classical resolution of *P*-stereogenic phosphine oxides. Moreover, we also demonstrated that the enantiomeric mixtures of *P*-chiral phosphine oxides can be purified efficiently by a simple recrystallization, which method is rarely used in the sphere of *P*-chiral compounds. This approach requires the knowledge of the solid state behavior of the particular chiral compound. However, this rather simple purification can serve as a supplementary method to purify non-racemic mixtures of phosphine oxides obtained by inefficient resolution methods or asymmetric syntheses.

ACKNOWLEDGMENTS

This work was supported by the National Research, Development and Innovation Office—NKFIH (Grant No. OTKA PD 116096). PB thanks the financial support of the ÚNKP-17-4-I-BME-102 New National Excellence Program of the Ministry of Human Capacities.

ORCID

Péter Bagi http://orcid.org/0000-0002-9043-6435

REFERENCES

1. Börner A (Ed). *Phosphorus Ligands in Asymmetric Catalysis*. Weinheim: Wiley-VCH; 2008.
2. Ojima I (Ed). *Catalytic Asymmetric Synthesis*. Weinheim: Wiley-VCH; 2010.
3. Pietrusiewicz KM, Zablocka M. Preparation of Scalemic P-Chiral Phosphines and Their Derivatives. *Chem Rev*. 1994;94:1375-1411.
4. Grabulosa A. P-*Stereogenic Ligands in Enantioselective Catalysis*. Cambridge: The Royal Society of Chemistry; 2010.
5. Herault D, Nguyen DH, Nuel D, Buono G. Reduction of secondary and tertiary phosphine oxides to phosphines. *Chem Soc Rev*. 2015;44:2508-2528.
6. Chaux F, Frynas S, Laureano H, et al. Enantiodivergent synthesis of P-chirogenic phosphines. *C R Chim*. 2010;13:1213-1226.
7. Grabulosa A, Granell J, Muller G. Preparation of optically pure *P*-stereogenic trivalent phosphorus compounds. *Coord Chem Rev*. 2007;251:25-90.
8. Kolodiazhnyi OI, Kukhar VP, Kolodiazhna AO. Asymmetric catalysis as a method for the synthesis of chiral organophosphorus compounds. *Tetrahedron: Asymmetry*. 2014;25:865-922.
9. Dutartre M, Bayardon J, Jugé S. Applications and stereoselective syntheses of P-chirogenic phosphorus compounds. *Chem Soc Rev*. 2016;45:5771-5794.
10. Korpiun O, Lewis RA, Chickos J, Mislow K. Synthesis and absolute configuration of optically active phosphine oxides and phosphinates. *J Am Chem Soc*. 1968;90:4842-4846.
11. Gatineau D, Giordano L, Buono G. Bulky, optically active P-stereogenic phosphine–boranes from pure H-menthylphosphinates. *J Am Chem Soc*. 2011;133:10728-10731.

12. Berger O, Montchamp JL. A general strategy for the synthesis of P-stereogenic compounds. *Angew Chem Int Ed*. 2013;52:11377-11380.

13. Wang WM, Liu LJ, Zhao CQ, Han LB. Diastereoselective hydrolysis of asymmetric P-Cl species and synthesis of optically pure (RP)-(−)-menthyl H-phenylphosphinate. *Eur J Org Chem*. 2015;2015:2342-2345.

14. Berger O, Montchamp JL. General synthesis of P-stereogenic compounds: the menthyl phosphinate approach. *Org Biomol Chem*. 2016;1:7552-7562.

15. Jugé S, Genet JP. Asymmetric synthesis of phosphinates, phosphine oxides and phosphines by Michaelis Arbuzov rearrangement of chiral oxazaphospholidine. *Tetrahedron Lett*. 1989;30:2783-2786.

16. Jugé S, Stephan M, Laffitte JA, Genet JP. Efficient asymmetric synthesis of optically pure tertiary mono and diphosphine ligands. *Tetrahedron Lett*. 1990;31:6357-6360.

17. Carey JV, Barker MD, Brown JM, Russell MJH. Preparation of enantiomerically pure phosphine oxides by nucleophilic displacement chemistry using oxazaphospholidines. *J Chem Soc Perkin Trans 1*. 1993;7:831-839.

18. Oliana M, King F, Horton PN, Hursthouse MB, Hii KK. Practical synthesis of chiral vinylphosphine oxides by direct nucleophilic substitution. Stereodivergent synthesis of aminophosphine ligands. *J Org Chem*. 2006;71:2472-2479.

19. Copey L, Jean-Gérard L, Andrioletti B, Framery E. Synthesis of P-stereogenic secondary phosphine oxides using α-d-glucosamine as a chiral precursor. *Tetrahedron Lett*. 2016;57:543-545.

20. Han ZS, Goyal N, Herbage MA, et al. Efficient asymmetric synthesis of P-chiral phosphine oxides via properly designed and activated benzoxazaphosphinine-2-oxide agents. *J Am Chem Soc*. 2013;135:2474-2477.

21. Han ZS, Wu H, Xu Y, et al. General and stereoselective method for the synthesis of sterically congested and structurally diverse P-stereogenic secondary phosphine oxides. *Org Lett*. 2017;19:1796-1799.

22. Soloshonok V, Roussel C, Kitagawa O, Sorochinsky A. Self-disproportionation of enantiomers via achiral chromatography: a warning and an extra dimension in optical purifications. *Chem Soc Rev*. 2012;41:4180-4188.

23. Soloshonok V, Klika K. Terminology related to the phenomenon 'self-disproportionation of enantiomers' (SDE). *Helv Chim Acta*. 2014;97:1583-1589.

24. Wzorek A, Klika KD, Drabowicz J, Sato A, Aceña JL, Soloshonok V. The self-disproportionation of the enantiomers (SDE) of methyl n-pentyl sulfoxide via achiral, gravity-driven column chromatography: a case study. *Org Biomol Chem*. 2014;12:4738-4746.

25. Suzuki Y, Han J, Kitagawa O, Aceña JL, Klika KD, Soloshonok VA. comprehensive examination of the self-disproportionation of enantiomers (SDE) of chiral amides via achiral, laboratory-routine, gravity-driven column chromatography. *RSC Adv*. 2015;5:2988-2993.

26. Soloshonok V, Wzorek A, Klika KD. A question of policy: should tests for the self-disproportionation of enantiomers (SDE) be mandatory for reports involving scalemates? *Tetrahedron: Asymmetry*. 2017;28:1430-1434.

27. Cox GB (Ed). *Preparative Enantioselective Chromatography*. Oxford: Blackwell Publishing; 2005.

28. Jiang X, Minnaard AJ, Hessen B, et al. Application of monodentate secondary phosphine oxides, a new class of chiral ligands, in Ir(I)-catalyzed asymmetric imine hydrogenation. *Org Lett*. 2003;5:1503-1506.

29. Jiang X, van den Berg M, Minnaard AJ, Feringa BL, de Vries JG. The application of monodentate secondary phosphine oxide ligands in rhodium- and iridium-catalyzed asymmetric hydrogenation. *Tetrahedron: Asymmetry*. 2004;15:2223-2229.

30. Imamoto T, Crépy KV, Katagiri K. Optically active 1,1′-di-tert-butyl-2,2′-dibenzophosphetenyl: a highly strained P-stereogenic diphosphine ligand. *Tetrahedron: Asymmetry*. 2004;15:2213-2218.

31. Bigeault J, Giordano L, Buono G. [2+1] Cycloadditions of terminal alkynes to norbornene derivatives catalyzed by palladium complexes with phosphinous acid ligands. *Angew Chem Int Ed*. 2005;44:4753-4757.

32. Widhalm M, Brecker L, Mereiter K. Rigid P-chiral mono and diphosphines. Configurative stability and P-inversion barrier. *Tetrahedron: Asymmetry*. 2006;17:1355-1369.

33. Gatineau D, Nguyen DH, Hérault D, et al. H-adamantylphosphinates as universal precursors of P-stereogenic compounds. *J Org Chem*. 2015;80:4132-4141.

34. Leek H, Thunberg L, Jonson AC, Öhlén K, Klarqvist M. Strategy for large-scale isolation of enantiomers in drug discovery. *Drug Discov Today*. 2017;22:133-139.

35. Tang W, Qu B, Capacci AG, et al. Novel, tunable, and efficient chiral bisdihydrobenzooxaphosphole ligands for asymmetric hydrogenation. *Org Lett*. 2010;12:176-179.

36. Andersen NG, Ramsden PD, Che D, Parvez M, Keay BA. A novel resolution procedure for the preparation of P-stereogenic phosphine oxides. *Org Lett*. 1999;1:2009-2011.

37. Dziuba K, Flis A, Szmigielska A, Pietrusiewicz KM. Efficient oxidative resolution of a P-stereogenic triarylphosphine and asymmetric synthesis of a P-stereogenic atropoisomeric biphenyl diphosphine dioxide. *Tetrahedron: Asymmetry*. 2010;21:1401-1405.

38. Toda F, Mori K, Zafra S, Goldberg I. Optical resolution of phosphinates and phosphine oxides by complex formation with optically active 2,2′-dihydroxy-1,1′-binaphthyl and crystallographic study of two diastereomeric complexes with (CH3)(C6H5)(OCH3)PO. *J Org Chem*. 1988;53:308-312.

39. Drabowicz J, Łyżwa P, Omelańczuk J, Pietrusiewicz KM, Mikołajczyk M. New procedures for the resolution of chiral tert-butylphenylphosphine oxide and some of its reactions. *Tetrahedron: Asymmetry*. 1999;10:2757-2763.

40. Bergin E, O'Connor CT, Robinson SB, McGarrigle EM, O'Mahony CP, Gilheany DG. Synthesis of P-stereogenic phosphorus compounds. Asymmetric oxidation of phosphines under Appel conditions. *J Am Chem Soc*. 2007;129:9566-9567.

41. Rajendran KV, Gilheany DG. Identification of a key intermediate in the asymmetric Appel process: one pot stereoselective

synthesis of P-stereogenic phosphines and phosphine boranes from racemic phosphine oxides. *Chem Commun*. 2012;48:10040-10042.

42. Nikitin K, Rajendran KV, Müller-Bunz H, Gilheany DG. Turning regioselectivity into stereoselectivity: efficient dual resolution of P-stereogenic phosphine oxides through bifurcation of the reaction pathway of a common intermediate. *Angew Chem Int Ed*. 2014;53:1906-1909.
43. Rajendran KV, Nikitin KV, Gilheany DG. Hammond postulate mirroring enables enantiomeric enrichment of phosphorus compounds via two thermodynamically interconnected sequential stereoselective processes. *J Am Chem Soc*. 2015;137:9375-9381.
44. Kortmann FA, Chang MC, Otten E, Couzijn EPA, Lutz M, Minnaard AJ. Consecutive dynamic resolutions of phosphine oxides. *Chem Sci*. 2014;5:1322-1327.
45. Miura T, Imamoto T. Enantiomerically pure 1,2-bis(isopropylmethylphosphino)benzene and its use in highly enantioselective Rh-catalyzed asymmetric hydrogenation. *Tetrahedron Lett*. 1999;40:4833-4836.
46. Omelańczuk J, Karaçar A, Freytag M, et al. Chiral 1,8-bis(tert-butylphenylphosphino)naphthalene oxides and sulfides: resolution and structures. *Inorg Chim Acta*. 2003;350:583-591.
47. Liu D, Gao W, Wang C, Zhang X. Practical synthesis of enantiopure γ-amino alcohols by rhodium-catalyzed asymmetric hydrogenation of β-secondary-amino ketones. *Angew Chem Int Ed*. 2005;44:1687-1689.
48. Takaya H, Mashima K, Koyano K, et al. Practical synthesis of (R)- or (S)-2,2′-bis(diarylphosphino)-1,1′-binaphthyls (BINAPs). *J Org Chem*. 1986;51:629-635.
49. Minami T, Okada Y, Nomura R, Hirota S, Nagahara Y, Fukuyama K. Synthesis and resolution of a new type of chiral bisphosphine ligand, trans-bis-1,2-(diphenylphosphino) cyclobutane, and asymmetric hydrogenation using its rhodium complex. *Chem Lett*. 1986;4:613-616.
50. Benincori T, Gladiali S, Rizzo S, Sannicolo FA. New modular class of easily accessible, inexpensive, and efficient chiral diphosphine ligands for homogeneous stereoselective catalysis. *J Org Chem*. 2001;66:5940-5942.
51. Tang W, Chi Y, Zhang X. An ortho-substituted BIPHEP ligand and its applications in Rh-catalyzed hydrogenation of cyclic enamides. *Org Lett*. 2002;4:1695-1698.
52. de Paule SD, Jeulin S, Ratovelomanana-Vidal V, Genêt JP, Champion N, Dellis P. Synthesis and molecular modeling studies of SYNPHOS, a new, efficient diphosphane ligand for ruthenium-catalyzed asymmetric hydrogenation. *Eur J Org Chem*. 2003;2003:1931-1941.
53. Rankic DA, Parvez M, Keay BA. 3,3′-Substituted BINAP derivatives containing C-bound substituents: applications in asymmetric hydrogenation reactions. *Tetrahedron: Asymmetry*. 2012;23:754-763.
54. Holt J, Maj AM, Schudde EP, et al. On the resolution of secondary phosphine oxides via diastereomeric complex formation: the case of tert-butylphenylphosphine oxide. *Synthesis*. 2009;2009:2061-2065.
55. Novák T, Schindler J, Ujj V, Czugler M, Fogassy E, Keglevich G. Resolution of 3-methyl-3-phospholene 1-oxides by molecular complex formation with TADDOL derivatives. *Tetrahedron: Asymmetry*. 2006;17:2599-2602.
56. Novák T, Ujj V, Schindler J, et al. Resolution of 1-substituted-3-methyl-3-phospholene 1-oxides by molecular complex formation with TADDOL derivatives. *Tetrahedron: Asymmetry*. 2007;18:2965-2972.
57. Ujj V, Schindler J, Novák T, Czugler M, Fogassy E, Keglevich G. Coordinative resolution of 1-phenyl- and 1-naphthyl-3-methyl-3-phospholene 1-oxides with calcium hydrogen O,O′-dibenzoyl-(2*R*,3*R*)-tartrate or calcium hydrogen O,O′-di-p-toluyl-(2*R*,3*R*)-tartrate. *Tetrahedron: Asymmetry*. 2008;19:1973-1977.
58. Ujj V, Bagi P, Schindler J, Madarász J, Fogassy E, Keglevich G. A practical and efficient method for the resolution of 3-phospholene 1-oxides via coordination complex formation. *Chirality*. 2010;22:699-705.
59. Bagi P, Laki A, Keglevich G. 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. *Heteroat Chem*. 2013;24:179-186.
60. Bagi P, Kállay M, Hessz D, et al. Resolution of 1-n-propoxy-3-methyl-3-phospholene 1-oxide by diastereomeric complex formation using TADDOL derivatives and calcium salts of O,O′-dibenzoyl-(2*R*,3*R*)- or O,O′-di-p-toluoyl-(2*R*,3*R*)-tartaric acid. *Tetrahedron: Asymmetry*. 2014;25:318-326.
61. Bagi P, Fekete A, Kállay M, et al. Resolution of 1-n-butyl-3-methyl-3-phospholene 1-oxide with TADDOL derivatives and calcium salts of O,O′-dibenzoyl-(2*R*,3*R*)- or O,O′-di-p-toluoyl-(2*R*,3*R*)-tartaric acid. *Chirality*. 2014;26:174-182.
62. Bagi P, Fekete A, Kállay M, et al. A case study on the resolution of the 1-*i*-butyl-3-methyl-3-phospholene 1-oxide via diastereomeric complex formation using TADDOL derivatives and via diastereomeric coordination complexes formed from the calcium salts of O, O′-diaroyl-(2*R*,3*R*)-tartarates. *Heteroat Chem*. 2015;26:79-90.
63. Bagi P, Juhász K, Timári I, et al. A study on the optical resolution of 1-isopropyl-3-methyl-3-phospholene 1-oxide and its use in the synthesis of borane and platinum complexes. *J Organomet Chem*. 2015;797:140-152.
64. Bagi P, Karaghiosoff K, Czugler M, et al. Synthesis, characterization, and application of platinum(II) complexes incorporating racemic and optically active 4-chloro-5-methyl-1-phenyl-1,2,3,6-tetrahydrophosphinine ligand. *Heteroat Chem*. 2016;27:91-101.
65. Bagi P, Ujj V, Czugler M, Fogassy E, Keglevich G. Resolution of P-stereogenic P-heterocycles via the formation of diastereomeric molecular and coordination complexes (a review). *Dalton Trans*. 2016;45:1823-1842.
66. Beck AK, Bastani B, Plattner DA, et al. Large-scale preparation of α, α, α′, α′-tetraaryl-1,3-dioxolane-4,5-dimethanols (TADDOL)—versatile auxiliaries for EPC synthesis and its solid-state structure. *Chimia*. 1991;45:238-244.
67. Sheldon RA. *Chirotechnology: Industrial Synthesis of Optically Active Compounds*. New York: Marcel Dekker; 1993.
68. Sheldrick GM. A short history of SHELX. *Acta Cryst. A*. 2008;64:112-122.
69. Sheldrick GM. Crystal structure refinement with SHELXL. *Acta Cryst C*. 2015;71:3-8.

70. Spek AL. Structure validation in chemical crystallography. *Acta Cryst D*. 2009;65:148-155.

71. Pennington WT. DIAMOND—visual crystal structure information system. *J Appl Cryst*. 1999;32:1028-1029.

72. Macrae CF, Bruno IJ, Chisholm JA, et al. 2.0—new features for the visualization and investigation of crystal structures. *J Appl Cryst*. 2008;41:466-470.

73. Lagasse F, Kagan HB. Chiral monophosphines as ligands for asymmetric organometallic catalysis. *Chem Pharm Bull*. 2000;48:315-324.

74. Faigl F, Fogassy E, Nógrádi M, Pálovics E, Schindler J. Strategies in optical resolution: a practical guide. *Tetrahedron: Asymmetry*. 2008;19:519-536.

75. Faigl F, Fogassy E, Nógrádi M, Pálovics E, Schindler J. Separation of non-racemic mixtures of enantiomers: an essential part of optical resolution. *Org Biomol Chem*. 2010;8:947-959.

76. Lorenz H, Seidel-Morgenstern A. Binary and ternary phase diagrams of two enantiomers in solvent systems. *Thermochim Acta*. 2002;382:129-142.

77. Lorenz H, Seidel-Morgenstern A. Processes to separate enantiomers. *Angew Chem Int Ed*. 2014;53:1218-1250.

78. Serreqi AN, Kazlauskas RJ. Kinetic resolution of phosphines and phosphine oxides with phosphorus stereocenters by hydrolases. *J Org Chem*. 1994;59:7609-7615.

79. Leyris A, Nuel D, Giordano L, Achard M, Buono G. Enantioselective synthesis of both enantiomers of tert-butylphenylphosphine oxide from (S)-prolinol. *Tetrahedron Lett*. 2005;46:8677-8680.

80. Jennings EV, Nikitin K, Ortin Y, Gilheany DG. Degenerate nucleophilic substitution in phosphonium salts. *J Am Chem Soc*. 2014;136:16217-16226.

81. Li G, Wang X, Zhang Y, et al. Synthesis of P-chiral dihydrobenzooxaphosphole core for BI ligands in asymmetric transformations. *J Org Chem*. 2017;82:5456-5460.

82. Gavezzotti A. Are crystal structures predictable? *Acc Chem Res*. 1994;27:309-314.

83. Gavezzotti A, Filippini G. Geometry of the intermolecular X-H. cntdot..cntdot..cntdot.Y (X, Y = N, O) hydrogen bond and the calibration of empirical hydrogen-bond potentials. *J Phys Chem*. 1994;98:4831-4837.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Bagi P, Varga B, Szilágyi A, et al. The resolution of acyclic *P*-stereogenic phosphine oxides via the formation of diastereomeric complexes: A case study on ethyl-(2-methylphenyl)-phenylphosphine oxide. *Chirality*. 2018;30:509–522. https://doi.org/10.1002/chir.22816