

RESEARCH ARTICLE

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Cite this: *Org. Chem. Front.*, 2022, **9**, 2797

Resolution of aryl-*H*-phosphinates applied in the synthesis of *P*-stereogenic compounds including a Brønsted acid NMR solvating agent†

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A library of racemic *H*-phosphinates incorporating a variety of alkoxy groups or substituted aryl groups was prepared. Starting with resolving agent screening, an efficient enantioseparation method was developed and optimized using (*R,R*)-(1-naphthyl)-spiro-TADDOL as the resolving agent. This method gave 12 out of 16 *H*-phosphinates with an ee of above 91%, and 9 of these derivatives were practically enantiopure (ee > 98%). Moreover, this resolution could be used on a gram-scale. The structures of the diastereomeric intermediates and the secondary interactions between them were investigated by single-crystal XRD, and the most important factors of enantiomeric recognition were established. (*R*)-1-Adamantyl phenyl-*H*-phosphinate was stereospecifically transformed into a few secondary and tertiary phosphine oxides. Moreover, two *P*-stereogenic Brønsted acids were prepared, and their applicability as chiral NMR solvating agents was assessed.

Received 13th February 2022,
Accepted 4th April 2022

DOI: 10.1039/d2qo00241h

rsc.li/frontiers-organic

Introduction

P-Stereogenic compounds represent an important class within organophosphorus chemistry. Originally, they were used as ligands of transition metal catalysts,¹ but in the past few decades their use in organocatalysis² and medicinal chemistry emerged significantly.³ The attention that *P*-chirogenic remdesivir just gained in COVID-19 treatment is a recent example of the latter fact.⁴ The most widely used strategies are the direct enantioseparation or asymmetric synthesis of target chiral organophosphorus compounds.^{1b,5} Additionally, stereoselective transformations of intermediates bearing a stable *P*-stereogenic center can also be used, and such a modular approach may give relatively diverse compounds from a given set of intermediates.⁶ As the stereochemical outcome of the reactions involving a *P*-stereogenic center is well documented and reviewed,⁷ the preparation of *P*-chirogenic intermediates

is of particular importance. From this perspective secondary phosphine oxides, phosphinates, and *H*-phosphinates (or their corresponding *P*-borane derivatives) can be regarded as ideal intermediates due to their bench and configurational stability. In this compound class, the chemistry of chiral secondary phosphine oxides received considerable attention in recent years,⁸ whereas the number of methods affording optically active *H*-phosphinates remained limited. However, *H*-phosphinates have higher synthetic potential, as they contain *P*-H and *P*-OR functional groups, both of which can be functionalized in a stereospecific manner by a variety of methods.⁹

Historically, the first *P*-stereogenic *H*-phosphinates were made available in optically active form *via* the formation and separation of covalent diastereomers using (–)-menthol as an affordable chiral auxiliary. The corresponding alkyl-*H*-phosphinates were the first few derivatives that could be prepared as a pure diastereomer.¹⁰ In the past decade, several improved procedures were published on the preparation and separation of menthyl aryl-*H*-phosphinates.^{9b,11} Han *et al.* optimized the synthesis and crystallization of this compound class,^{9b,11a,b} and they could solve the preparation issues caused by poor crystallinity of the racemate, which previously hindered the efficient preparation of pure diastereomers.¹² The key steps of these synthetic procedures were the formation and hydrolysis of the corresponding phosphonochloride [(-)-MentO]YPCl intermediate. Montchamp *et al.* prepared menthyl hydroxymethyl-*H*-phosphinate from hypophosphorous acid, paraformaldehyde

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†Electronic supplementary information (ESI) available: General methods and synthetic procedures; additional experimental data; X-ray data; ³¹P, ¹⁹F, ¹H and ¹³C NMR spectra; and HPLC traces. CCDC 2143598–2143607. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d2qo00241h>



hyde and (–)-menthol, the procedure of which avoided the use of the corresponding P-Cl intermediates. $[(-)\text{-MentO}](\text{HOCH}_2)_2\text{P}(\text{O})\text{H}$ could be transformed into a variety of *H*-phosphinates by P-C coupling and Corey–Kim oxidation (Fig. 1A).¹³

P-Stereogenic oxazaphospholidines, stereoselectively prepared from readily available amino-alcohols, became key intermediates for the preparation of various P-stereogenic compounds. The P-N bond can be selectively cleaved under hydrolytic conditions to afford *H*-phosphinate diastereomers, and the diastereomeric purity of these intermediates could be increased by recrystallization (Fig. 1B).¹⁴

Preparation of enantiomerically enriched $P^*(O)H$ compounds using kinetic resolution became a popular method in recent years. Generally, these procedures were optimized to give enantiopure tertiary phosphine oxides,¹⁵ but in a few instances, the remaining $>P(O)H$ starting materials were also obtained with high enantiomeric excess.¹⁶ Secondary phosphine oxides were the main starting materials in these reactions, but a few procedures are also known for *H*-phosphinates.¹⁷ In the latter instances, only one optically active *H*-phosphinate was isolated for mechanistic investigation, which leaves the scope of those procedures rather low (Fig. 1C).^{17a}

Phosphothionates might be regarded as acidic precursors of *H*-phosphinates, which can be resolved using commercially available chiral bases.¹⁸ Despite the fact that the majority of the resolution procedures focus on the enantioseparation of

the corresponding phosphothionates, a few studies demonstrated that desulfuration can be performed with RANEY®-nickel with the retention of the P-configuration to give optically active *H*-phosphinates (Fig. 1E).^{18c,19} This route towards enantiomerically enriched >P(O)H compounds is rather tedious, as it includes two additional steps besides the classical resolution, which increases the risk of partial racemization during the final desulfuration step.

There are only a few attempts towards the direct enantioseparation of P-stereogenic *H*-phosphinates. In 1970, Benschop described for the first time the partial resolution of *H*-phosphinates *via* inclusion complexation with cyclodextrins, but only low optical purities were obtained and the yields were not reported.²⁰ Toda tried to use BINOL for the enantioseparation of methyl or ethyl phenyl-*H*-phosphinate, but that attempt was rather unsuccessful, despite the fact that the same method gave good results for a few phosphinates and phosphine oxides (Fig. 1F).²¹ Leclaire, Giordano and co-workers used semi-preparative chiral HPLC to separate the enantiomers of various 1-adamantyl *H*-phosphinates (Fig. 1D). They also demonstrated that the adamantyl esters are less prone to racemization during the substitution reaction at the P-stereogenic center, which can be attributed to the increased steric hindrance of the adamantyloxy moiety.²²

This summary demonstrates that the literature lacks efficient separation methods to prepare P-stereogenic *H*-phosphinate enantiomers. Thus, the current paper aims at

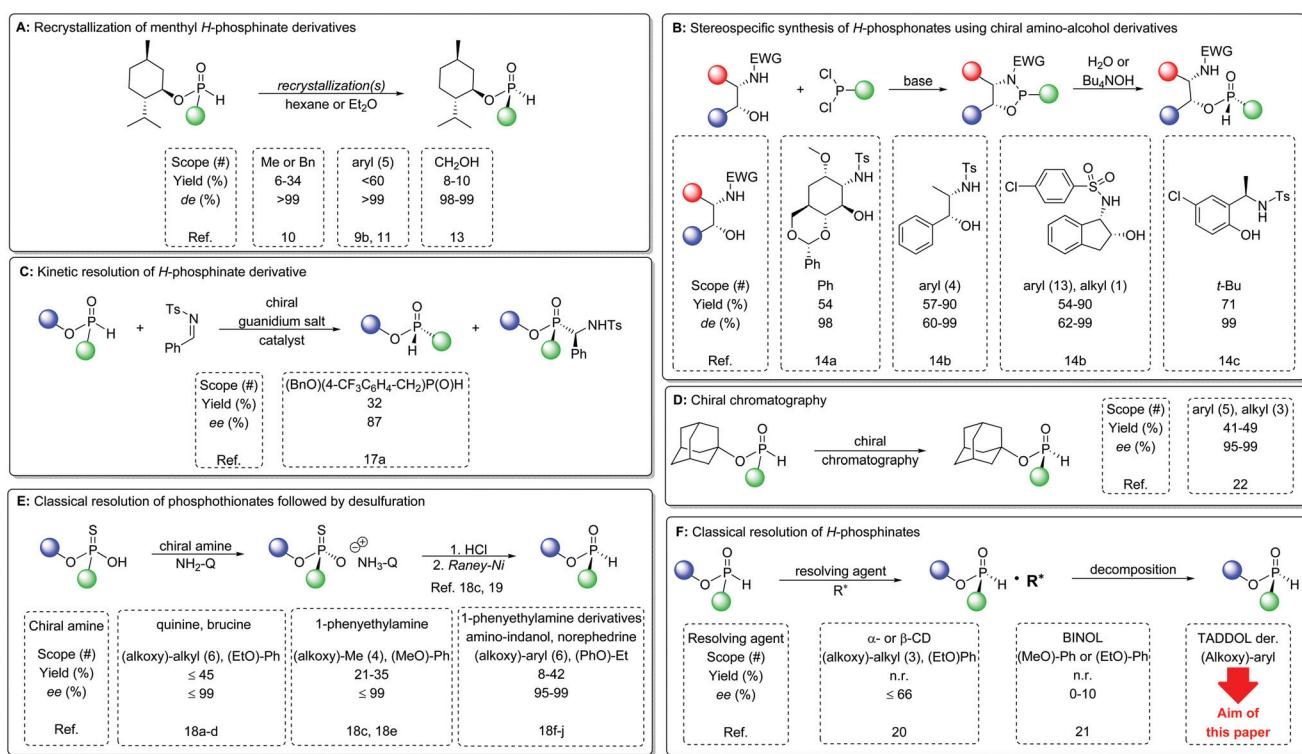


Fig. 1. Selected literature methods for the preparation of anti-thrombin B-stromogenic M_1 heparinins.

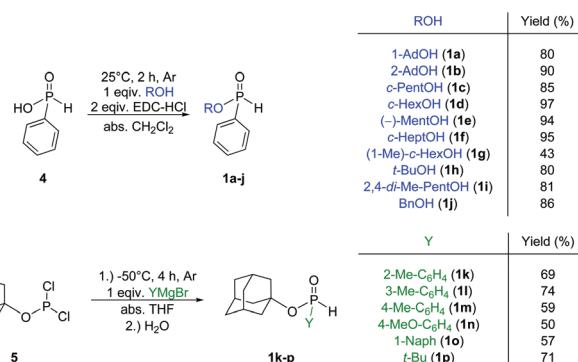
the development of such enantioseparation for this compound class (**1**). The synthesis of *H*-phosphinates incorporating a wide variety of sterically demanding alkoxy moieties, as well as various aryl groups, was planned (**1**). We intended to find the most suitable resolving agent class and crystallization conditions for *H*-phosphinates (**1**) in order to develop a robust resolution method for the target racemates. We wished to elucidate the structures of the diastereomeric associates by single crystal X-ray crystallography to study the intermolecular interactions and to determine the absolute P-configurations. In order to demonstrate the synthetic utility of *H*-phosphinates (**1**), stereoselective preparation of secondary and tertiary phosphine oxides (**3a–c**) as well as a few P-stereogenic Brønsted acids (**3e** and **3f**) was also planned, and the latter derivatives were tested as chiral NMR solvating agents (Fig. 2).

Results and discussion

In our study, sterically congested alcohols were used to prepare this *H*-phosphinate library (**1**), as previous research suggested that *H*-phosphinates prepared from aliphatic alcohols with low carbon chains are prone to racemization once they are resolved into their enantiomers.^{18c,22} Two different methods were used for the synthesis of racemic *H*-phosphinates (**1**). Phenyl-*H*-phosphinate esters (**1a–j**) were prepared from phenyl-*H*-phosphinic acid (**4**) and from the corresponding alcohol using EDC hydrochloride as the coupling agent. This synthetic strategy avoids the handling of organometallic and air-sensitive compounds, and it was used a few times for the synthesis of *P*-esters.²³ Recently, Montchamp *et al.* surveyed the different coupling agents for the synthesis of adamantyl *H*-phosphinate esters and found that T3P is an optimal choice.²⁴ In our study, 2 equiv. of EDC-HCl (without DMAP), and 1 equiv. of alcohol in abs. DCM gave the corresponding *H*-phosphinate esters (**1a–f** and **1h–j**) generally in yields of 80–97% after an extractive workup and purification by column chromatography. The only exception was 1-methyl-cyclohexyl phenyl *H*-phosphinate (**1g**) (yield = 43%) (Scheme 1).

For the synthesis of adamantyl aryl-*H*-phosphinates (**1k–p**), (1-AdO)PCl₂ (**5**) was prepared in the reaction of phosphorus trichloride and 1-adamantanol.²² This compound (**5**) was then reacted with 1 equiv. of the corresponding Grignard reagent to give *H*-phosphinates (**1k–p**) in yields of 50–74% after work-up and column chromatography (Scheme 1).

In order to find the most suitable resolution conditions, 1-adamantyl phenyl-*H*-phosphinate (**1a**) was chosen as the



Scheme 1 Preparation of racemic *H*-phosphinates (**1**).

model racemate from this *H*-phosphinate library (**1**), due to its high synthetic potential.²² First, a resolving agent study was conducted which included several resolving agents, successfully used for the enantioseparation of various P=O containing racemic compounds.^{1b,25} Using this resolving agent pool, TADDOL and spiro-TADDOL [(*R,R*)-**2a** and (*R,R*)-**2b**] showed the most promising preliminary results (see the ESI† for details). Thus, a series of TADDOL derivatives [(*R,R*)-**2a–g**] with various dioxolane scaffolds,²⁶ and different substituted aryl or naphthyl groups were tested for the enantioseparation of **1a**. Based on the results of the resolving agent study and our previous experience with this resolving agent class, a precipitation mediated resolution method was chosen using a mixture of toluene and hexane as the solvent. Only (*R,R*)-spiro-TADDOL [(*R,R*)-**2b**] and (*R,R*)-(1-naphthyl)-spiro-TADDOL [(*R,R*)-**2e**] gave crystalline diastereomeric complexes that could be purified further by additional recrystallization(s) to prepare (*R*)-1-adamantyl phenyl-*H*-phosphinate [(*R*)-**1a**] with an ee of above 95%. Using these two resolving agents, (*R,R*)-(1-naphthyl)-spiro-TADDOL [(*R,R*)-**2e**] gave a significantly better yield (72% vs. 38%) (see the ESI† for details). With the most suitable resolving agent [(*R,R*)-**2e**] in hand, solvent screening was performed and the solvents were selected based on our previous studies.²⁷ The results indicated that aromatic solvents in combination with hexane were the more suitable ones, and the best results were obtained in a mixture of toluene and hexane. It was also found that performing these resolutions according to the equivalent method is more beneficial than using a half equivalent of the resolving agent [(*R,R*)-**2e**]. It was also investigated whether the further purification of 1-adamantyl phenyl-*H*-phosphinate (**1a**) enantiomeric mixtures is feasible without any chiral additives utilizing only the SDE phenomenon (self-disproportion of enantiomers).²⁸ The results indicated that 1-adamantyl phenyl-*H*-phosphinate (**1a**) is a racemate-forming compound having a eutectic composition of *ca.* 30% (see the ESI† for details). This dataset also suggested that efficient further purification of samples having an initial ee of above 70% is less practical, as the ee increases marginally and a significant amount of **1a** is lost during the recrystallizations. In contrast, the recrystallization of the corresponding diastereo-

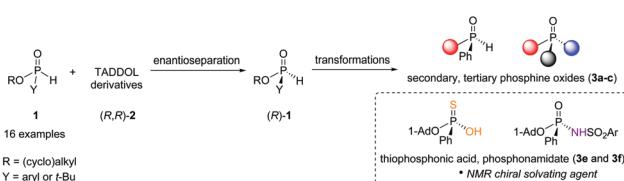


Fig. 2 Aims of this research project.



mer $[(R)\text{-1a}\cdot(R,R)\text{-2e}]$ from a mixture of toluene and hexane was a more efficient purification.

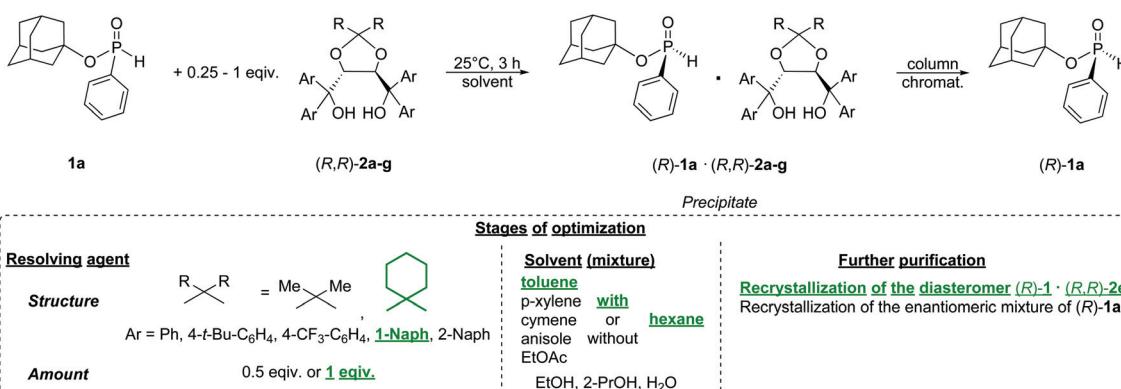
As a result of this set of experiments, a resolution method using one equivalent of (R,R) -(1-naphthyl)-spiro-TADDOL $[(R,R)\text{-2e}]$ in a mixture of toluene and hexane was developed, which afforded enantiopure (R) -1-adamantyl phenyl-*H*-phosphinate $[(R)\text{-1a}]$ in a yield of 74%, and only one recrystallization of the corresponding diastereomer was enough to achieve an ee of 99% (Scheme 2). The *H*-phosphinate $(R)\text{-1a}$ could be recovered from the diastereomer by column chromatography.

Under optimal conditions, this resolution method showed an excellent scope among phenyl-*H*-phosphinates (1) (Scheme 3). The 1- and 2-adamantyl, cyclopentyl-, cyclohexyl-, 1-methylcyclohexyl-, cycloheptyl-, *t*-butyl- and benzyl-esters $[(R)\text{-1a-d, 1f, 1h and 1j}]$ could be prepared in practically enantiopure form (ee = 96–99%). (R_P) -Menthyl phenyl-*H*-

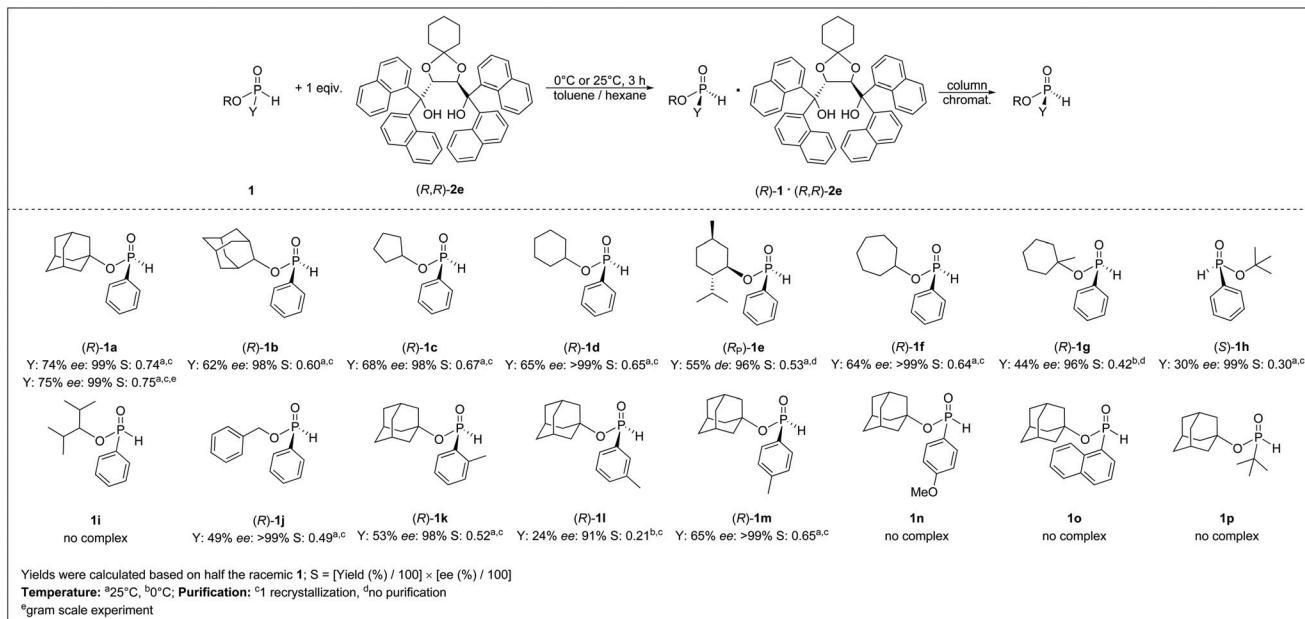
phosphinate $[(R_P)\text{-1e}]$ could also be prepared with a diastereomeric excess of 96%, demonstrating that our method can be an alternative preparation of this benchmark *H*-phosphinate diastereomer $[(R_P)\text{-1e}]$.

Using this resolution method, the crystallization issues of the corresponding diastereomeric mixtures $(1e)$ may be avoided. For most derivatives (1) , one purification was enough to increase the enantiomeric purity, and the yields were in the range of 55–74%; the three exceptions were 1-methylcyclohexyl, *t*-butyl and benzyl phenyl-*H*-phosphinates $[(R)\text{-1g, 1h and 1j}]$ (yield: 30–49%). In the selected *P*-ester scope $(1a-j)$, only 2,4-dimethylpentan-3-yl phenyl-*H*-phosphinate $(1i)$ could not be separated into its enantiomers, as no crystalline diastereomers were formed.

The scope of this resolution method seemed more limited among 1-adamantyl *H*-phosphinates containing different aryl



Scheme 2 Stages of optimization for the enantioseparation of 1-adamantyl phenyl-*H*-phosphinate (1a) with TADDOL-derivatives (R,R)-2a-g.



Scheme 3 Summary of the enantioseparation of *H*-phosphinates (1) with (R,R) -(1-naphthyl)-spiro-TADDOL $[(R,R)\text{-2e}]$ under optimized conditions.



groups or a *t*-butyl group (**1k–p**). This resolution method afforded *ortho*- and *para*-tolyl-derivatives [(*R*)-**1k** and (*R*)-**1m**] in enantiopure form (ee > 98%) in yields of 53% and 65%, respectively. Moreover, 1-adamantyl (3-methylphenyl)-*H*-phosphinate [(*R*)-**1l**] could also be prepared with good ee but in a low yield (ee: 91%, yield: 24%). On the other hand, the enantioseparation of 4-methoxyphenyl-, 1-naphthyl- and *t*-butyl derivatives (**1n–p**) was not successful, as no crystallization occurred in the presence of a resolving agent [(*R,R*)-**2e**]. For 1-adamantyl *t*-butyl-*H*-phosphinate (**1p**), the underlying cause might be the lack of π – π interactions between the *H*-phosphinate (**1p**) and resolving agent [(*R,R*)-**2e**] molecules (*vide infra*). This resolution method could be conveniently scaled up to a gram-scale level, and enantiopure (*R*)-1-adamantyl phenyl-*H*-phosphinate [(*R*)-**1a**] could be prepared from 4 grams of racemic **1a** in the same yield as in the case of small-scale experiments (Scheme 3).

Single crystal X-ray analysis verified that the ratio of **1** to (*R,R*)-**2e** is 1 : 1, and it is independent of the structure of the *H*-phosphinate (**1**). Moreover, the resolving agent generally preferred the (*R*) enantiomer of the corresponding *H*-phosphinate [(*R*)-**1a–g** and (*R*)-**1k–m**]. One may assume a similar mode of binding and secondary interactions between the resolving agent [(*R,R*)-**2e**] and the corresponding *H*-phosphinate [(*R*)-**1a–g** and (*R*)-**1k–m**], which was also confirmed by the X-ray analysis of diastereomeric intermediates (*vide infra*).

It is noteworthy that the corresponding diastereomers [**1**·(*R,R*)-**2e**] could be stored at room temperature in air for years without any decomposition of the corresponding *H*-phosphinate (**1**) or the deterioration of its enantiomeric excess. Additionally, 1-adamantyl, 2-adamantyl, cyclohexyl- and benzyl phenyl-*H*-phosphinates [(*R*)-**1a**, (*R*)-**1b**, (*R*)-**1d** or (*R*)-**1j**] were selected to test the configurational stability of the corresponding enantiomers (ee: 99%) by stirring the given toluene solutions either at 25 °C or at 110 °C under an inert atmosphere. The results showed that the ee value of the corresponding *H*-phosphinates [(*R*)-**1a**, (*R*)-**1b**, (*R*)-**1d** or (*R*)-**1j**] did not change at 25 °C in 3–8 days, whereas the enantiomeric purity of (*R*)-1-adamantyl and (*R*)-2-adamantyl phenyl-*H*-phosphinate [(*R*)-**1a** and (*R*)-**1b**] decreased only to 96% or 93%, respectively, after 3 days of reflux, which is another indication of the excellent configurational stability of the adamantyl *H*-phosphinates [(*R*)-**1a** and (*R*)-**1b**] as was originally proposed by Leclaire, Giordano and co-workers (see the ESI† for additional details).²²

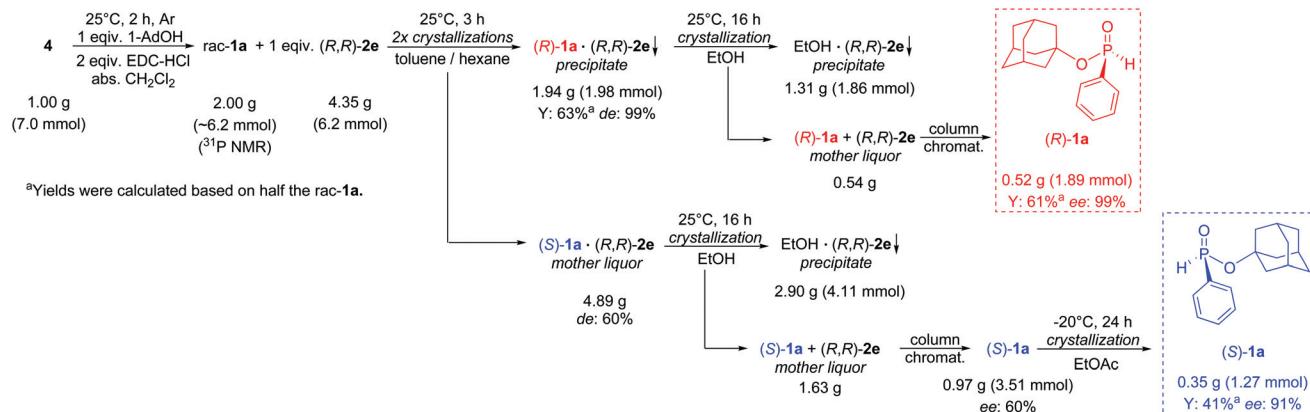
Besides the scalability, we intended to demonstrate the robustness of the resolution method, and to develop a complete preparation and enantioseparation procedure for **1a** in which the purification steps are simplified. The racemic 1-adamantyl phenyl-*H*-phosphinate (**1a**) was synthesized from 1.0 g of phenyl-*H*-phosphinic acid (**4**) using EDC-HCl. This crude product (with a purity of *ca.* 85%) was transferred to the enantioseparation step without any additional purification. Our optical resolution of **1a** was proved to be robust enough to give enantiopure (*R*)-1-adamantyl phenyl-*H*-phosphinate [(*R*)-**1a**]. Similarly to the small-scale experiments, one crystallization

and an additional recrystallization of the corresponding diastereomer [(*R*)-**1a**·(*R,R*)-**2e**] were also sufficient using crude *H*-phosphinate (**1a**), but the yield was somewhat lower than the one obtained with the purified starting material (**1a**) (74% *vs.* 63%), which might be attributed to the impurities originating from EDC-coupling. The chromatographic isolation of optically active *H*-phosphinates (**1**) from the corresponding diastereomers was tedious on a larger scale due to the significant (molecular) weight difference of **1** and the resolving agent [(*R,R*)-**2e**]. It was observed during the optimization of the resolution that (*R,R*)-(1-naphthyl)-spiro-TADDOL [(*R,R*)-**2e**] forms a stable complex with ethanol (see the ESI† for additional details of decomposition). Utilizing this phenomenon, the (*R*)-**1a**·(*R,R*)-**2e** diastereomeric complex was treated with hot ethanol, and the majority of the resolving agent [(*R,R*)-**2e**] was recovered as its crystalline ethanol complex leaving only a minor amount of [(*R,R*)-**2e**] besides the (*R*)-1-adamantyl phenyl-*H*-phosphinate [(*R*)-**1a**]. Another portion of the resolving agent [(*R,R*)-**2e**] also could be recycled from the mother liquor of the resolution using a similar ethanolic decomposition. From the two residual mixtures containing (*R,R*)-**2e** and (*R*)/(*S*)-**1a**, the enantiopure (*R*)-1-adamantyl phenyl-*H*-phosphinate [(*R*)-**1a**] (ee: 99%, Y: 61%) and the corresponding (*S*) enantiomer [(*S*)-**1a**] with an ee of 60% were isolated by column chromatography. The purity of the enantiomeric mixture containing (*S*)-**1a** in excess was increased by a simple recrystallization from ethyl acetate utilizing the SDE phenomenon, and in this manner (*S*)-1-adamantyl phenyl-*H*-phosphinate [(*S*)-**1a**] could be obtained with an ee of 91% and in a yield of 41% without using the antipode of the resolving agent [(*S,S*)-**2e**] (Scheme 4).

It is worth mentioning that the final column chromatographic separation of the (*R*)-**1a** and (*R,R*)-(1-naphthyl)-spiro-TADDOL [(*R,R*)-**2e**] mixtures was performed by a simplified DCM to DCM–MeOH gradient elution. Our previous study also demonstrated that organic solvent nanofiltration may be an alternative to column chromatography during the isolation of optically active products and the recovery of the resolving agent.^{27a}

X-Ray quality crystals could be prepared from the diastereomeric intermediates of all successful resolutions, and the two exceptions were (*R*)-**1g**·(*R,R*)-**2e** and (*R*)-**1l**·(*R,R*)-**2e** diastereomers. These measurements allowed the unambiguous assignment of absolute P-configurations and the study of non-bonding interactions responsible for enantiomeric recognition within this wide scope of *H*-phosphinates (**1a–h** and **1j–m**). All of the 10 diastereomeric complexes crystallized in the orthorhombic crystal system space group of $P2_12_12_1$. The unit cell parameters are isostructural, except for the (*R_P*)-**1e**·(*R,R*)-**2e** and (*S*)-**1h**·(*R,R*)-**2e** structures where the *b* and *c* unit cell parameters are smaller. The contents of the asymmetric unit (*Z'*) are the (*R,R*)-(1-naphthyl)-spiro-TADDOL [(*R,R*)-**2e**] host molecule with a known absolute configuration and the corresponding optically active *H*-phosphinate guest molecules [(*R*)-**1a–f**, (*S*)-**1h**, (*R*)-**1j**, (*R*)-**1k** and (*R*)-**1m**]. Moreover, a toluene solvent molecule is also incorporated into the asymmetric unit





Scheme 4 Gram scale preparation of (R)- and (S)-1-adamantyl phenyl-H-phosphinate [(R)- and (S)-1a] using a simplified preparation and enantioseparation procedure.

in all but two instances $[(R_P)\mathbf{1e}\cdot(R,R)\mathbf{2e}]$ and $[(S)\mathbf{1h}\cdot(R,R)\mathbf{2e}]$, which is in accordance with the experimental observation that aromatic solvents, especially toluene, gave the best enantioseparation results.

It is worth mentioning that the disordered regions of toluene and alkoxy-groups can be observed in most crystal structures. The diastereomeric complex $(R)\mathbf{1m}\cdot(R,R)\mathbf{2e}$ was selected to illustrate the non-bonding interactions responsible for enantiomeric recognition, and these interactions were similar regardless of the structure of the H-phosphinate (1) (*vide infra*). In this crystal structure, only half of the toluene solvent was refinable in the solvent cavity due to the above-mentioned disorder phenomenon. No other cavity is observed in the crystal lattices, which is indicated by a KPI packing index of 68.8, and a density of 1.270 g cm^{-3} . (R,R) -(1-Naphthyl)-spiro-TADDOL $[(R,R)\mathbf{2e}]$ and 1-adamantyl (4-methylphenyl)-H-phosphinate $[(R)\mathbf{1m}]$ are associated with many weak secondary intermolecular connections, and DFT calculations were used to reveal the main contacts within the neighboring molecules (calculated using CrystalExplorer with B3LYP/6-31G(d,p); see the ESI† for details). The main H-phosphinate $[(R)\mathbf{1m}]$ and (R,R) -(1-naphthyl)-spiro-TADDOL $[(R,R)\mathbf{2e}]$ dimer molecules have the strongest interaction based on Coulomb interactions with a hydrogen bond system between the $((1\text{-naphthyl})\text{-spiro-TADDOL})\text{O1-H1}\cdots((1\text{-naphthyl})\text{-spiro-TADDOL})\text{O2-H2}\cdots\text{O5(P(1-AdO)(4-Me-C}_6\text{H}_4)}$ atoms (distances are $2.66(1)\text{ \AA}$ and $2.65(1)\text{ \AA}$, respectively). Moreover, a parallel $\pi\cdots\pi$ interaction is also present between the 1-naphthyl ring of $(R,R)\mathbf{2e}$ and the 4-methylphenyl moiety of the H-phosphinate $[(R)\mathbf{1m}]$ and the corresponding $\pi\cdots\pi$ centroid distance is $3.89(1)\text{ \AA}$ (Fig. 3a). Two other (R,R) -(1-naphthyl)-spiro-TADDOL $[(R,R)\mathbf{2e}]$ molecules connect to the same H-phosphinate $[(R)\mathbf{1m}]$ with strong dispersion intermolecular interactions: T-shape $\pi\cdots\pi$, $\text{PH}\cdots\pi$ and $\text{CH}\cdots\pi$ interactions (Fig. 3b). The bulky alkoxy group fills the cavities, and toluene also fits into the remaining space, which stabilizes the crystal structure. There are a few weaker interactions that can be associated with the contacts of the adamantyloxy group

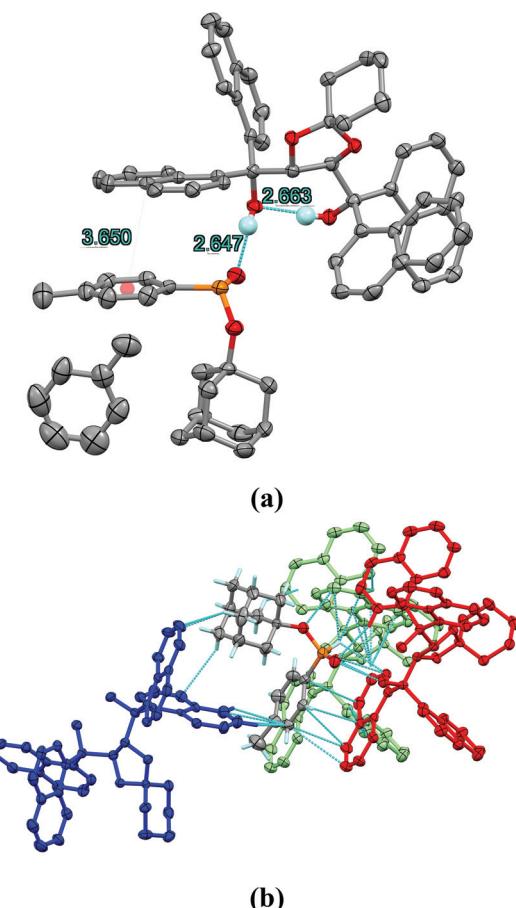


Fig. 3 (a) The main interactions within the (R,R) -(1-naphthyl)-spiro-TADDOL $[(R,R)\mathbf{2e}]$ and the 1-adamantyl (4-methylphenyl)-H-phosphinate $[(R)\mathbf{1m}]$. (b) DFT calculated weaker interactions of $(R)\mathbf{1m}$ with the neighboring $(R,R)\mathbf{2e}$ molecules.

of the H-phosphinates $[(R)\mathbf{1m}]$, the space-filling solvent and the resolving agent $[(R,R)\mathbf{2e}]$.

This overall filled chiral environment might be the underlying reason why the (R) enantiomer of the corresponding



H-phosphinates [(*R*)-**1a–f**, (*R*)-**1j**, (*R*)-**1k** and (*R*)-**1m**] could be prepared in most of the instances. The above-mentioned interaction pattern also suggests that different aromatic substituents of the *H*-phosphinate (**1**) may hinder the tight $\pi\cdots\pi$ interactions between the host and guest molecules [**1** and (*R,R*)-**2e**], which consequently leads to a destabilized crystal structure. This may explain the lower scope of this resolution method towards (substituted) aryl- and *t*-butyl-substituted adamantyl *H*-phosphinates (**1n–p**).

These non-bonding interactions were also characteristic of the crystal structure of the diastereomeric complexes incorporating other *H*-phosphinates [(*R*)-**1a–f**, (*R*)-**1j** and (*R*)-**1k**]. Fig. 4 shows the a sole (*R*)-**1m**·(*R,R*)-**2e** dimer (Fig. 4a) and its overlay with the other diastereomers incorporating the corresponding (*R*)-*H*-phosphinate enantiomers [(*R*)-**1a–f**, (*R*)-**1j** and (*R*)-**1k**] (Fig. 4b).

The overlaid structures indicate similar positions in the crystal lattices, and thus similar spatial arrangements and main secondary intermolecular connections between the host

[(*R,R*)-**2e**] and guest molecules (**1**), which serves as an explanation for why the range of *H*-phosphinates (**1**) could be resolved effectively by this enantioseparation method despite the structural variety of the alkoxy moiety.

In order to demonstrate the synthetic utility of (*R*)-1-adamantyl phenyl-*H*-phosphinate [(*R*)-**1a**], a few stereoselective transformations were performed to obtain a variety of valuable *P*-stereogenic products (**3**). (*R*)-(1-AdO)PhP(O)H [(*R*)-**1a**] was first reacted with (2-methoxyphenyl)lithium to give (*R*)-(2-methoxyphenyl)-phenylphosphine oxide [(*R*)-**3a**], which indicated that the *H*-phosphinate (*R*)-**1a** can also be substituted with aromatic moieties in excellent yield (89%) and without significant erosion of enantiomeric purity (ee: 95%) (Scheme 5A). It is noteworthy that (2-methoxyphenyl)lithium was prepared by the direct ortholithiation of anisole using *n*-BuLi and TMEDA. A halogen lithium exchange by means of *n*-BuLi was not feasible for the preparation of the corresponding aryl-lithium,²⁹ as the bromobutane by-product would have caused a side reaction *via* the formation of the corresponding tertiary phosphine oxides (*vide infra*).

In a separate attempt, the anionic intermediate formed in the reaction of (*R*)-1-adamantyl phenyl-*H*-phosphinate [(*R*)-**1a**] and (2-methoxyphenyl)lithium was quenched with iodomethane to give (*R*)-PAMP-oxide [(*R*)-**3b**] (Scheme 5B). The initial enantiomeric excess of (*R*)-**3b** (ee: 93%) was increased to an ee of 97% by the recrystallization of the corresponding enantiomeric mixture. Then, the phenyl ring was selectively saturated by heterogeneous catalytic hydrogenation to prepare (*R*)-CAMP-oxide [(*R*)-**3c**] (yield: 80%, ee: 96%) as another well-known *P*-stereogenic compound (Scheme 5C).

The (*R*)-(1-AdO)PhP(O)H [(*R*)-**1a**] was converted under Atherton-Todd conditions to the corresponding *P*-chloride which immediately reacted with NH₄OH to give (*R*)-1-adamantyl phenylphosphonamide [(*R*)-**3d**] (Scheme 5D). It was assumed that the sequence of these two transformations involves an inversion of the *P*-configuration.³⁰ The corresponding sulfonamide [(*R*)-**3e**] was also prepared in the reaction of (*R*)-**3d** and 2,4,6-triisopropylbenzenesulfonyl chloride (Scheme 5E).

Moreover, the *H*-phosphinate (*R*)-**1a** was also reacted with elemental sulfur in the presence of triethylamine to prepare the corresponding thiophosphonic acid [(*S*)-**3f**] with the retention of the configuration (Scheme 5F).^{11b}

As the last step, we sought the applications of the compounds prepared in this study. (*S*)-(1-Adamantyl)-phenylthiophosphonic acid [(*S*)-**3f**] seemed like a promising NMR chiral solvating agent (CSA), as it is a structural analogue of (*R*)-*t*-butyl-phenylthiophosphinic acid,³¹ and a few chiral phosphonothioic acids are known to behave as CSAs, as well.^{18d,32} The optimization of the NMR parameters was performed with 1-(1-naphthyl)ethylamine (**6**) as the racemate, and using 1–1.5 equiv. of (*S*)-**3f** in CDCl₃ with a final concentration of 25 mM gave the best peak separation. The ³¹P NMR signals of the (*S*)-**3f**·**6** intermediates coalesced into one peak making enantiomeric purity determination impossible. On the other hand, ¹H NMR could be used to differentiate between the given

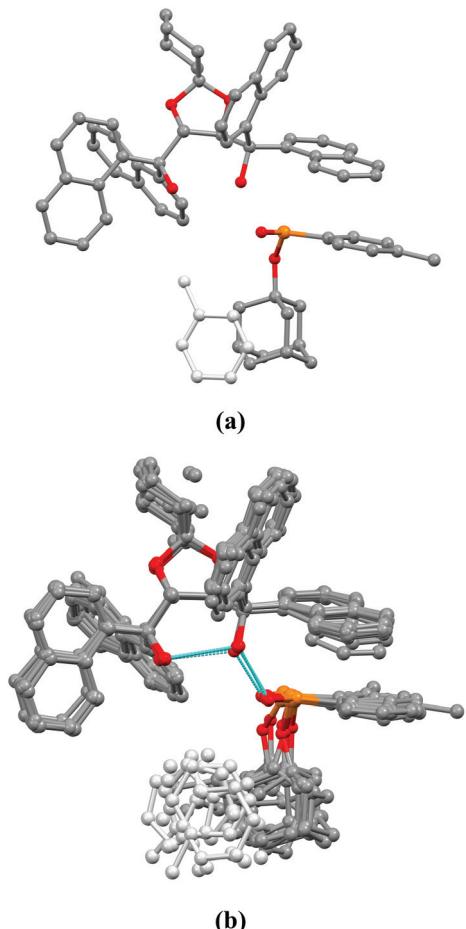
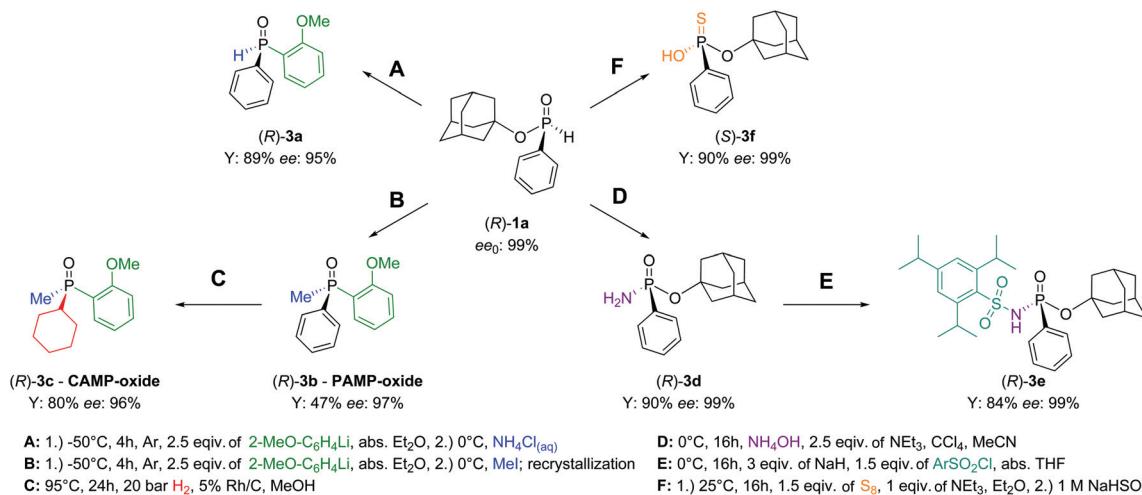


Fig. 4 (a) Asymmetric unit of the diastereomer incorporating 1-adamantyl (4-methylphenyl)-*H*-phosphinate [(*R*)-**1m**] and (*R,R*)-(1-naphthyl)-spiro-TADDOL [(*R,R*)-**2e**]. (b) Overlaid structures of the diastereomeric complexes [(*R*)-**1**-(*R,R*)-**2e**] except the structure of [(*S*)-**1h**-(*R,R*)-**2e**]. The toluene atoms are shown in front, white-coloured. Hydrogens are omitted for clarity.





Scheme 5 Stereospecific synthesis of various P-stereogenic compounds (3a-f) from (R)-1-adamantyl phenyl-H-phosphinate [(R)-1a].

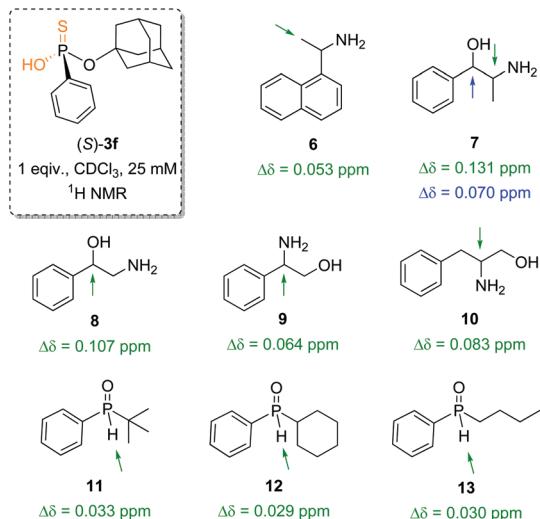


Fig. 5 Utilization of (S)-(1-adamantyl)-phenylthiophosphonic acid [(S)-3f] as a NMR chiral solvating agent.

signals. (S)-(1-Adamantyl)-phenylthiophosphonic acid [(S)-3f] as a CSA showed a good scope among chiral amino-alcohols (**7-10**) and secondary phosphine oxides (**11-13**) differentiating the $>\text{CH(OH)}$, $>\text{CH(NH}_2$) or P-H protons, respectively (Fig. 5). Among the chiral amines, 1-(1-naphthyl)ethylamine (**6**) was the only derivative that could be analyzed.

Conclusions

In this paper, the enantioseparation of P-stereogenic H-phosphinates (**1**) was demonstrated. Altogether 16 examples of H-phosphinates (**1**) with structurally different alkoxy groups or substituted aryl groups were prepared in racemic form by two methods. A resolution method was then developed, and the crystallization conditions were investigated. Under opti-

mized conditions, (R,R)-(1-naphthyl)-spiro-TADDOL [(R,R)-2e] was found to be the most suitable resolving agent affording 12 out of 16 examples with an ee above 91%, and 9 of these derivatives were obtained in practically enantiopure form (ee > 98%). The enantioseparation method developed showed a good scope for the preparation of phenyl-H-phosphinates incorporating various alkoxy-groups (**1a-j**). The scalability of the resolution method was demonstrated. It was also found that crude H-phosphinates (**1**) can also be used as starting racemates, which does not influence the overall efficiency of the resolution method significantly. Moreover, the decomposition of the diastereomeric intermediates can also be simplified by precipitating most of the (R,R)-(1-naphthyl)-spiro-TADDOL [(R,R)-2e] as an ethanol complex. The SDE phenomenon in the case of 1-adamantyl phenyl-H-phosphinate (**1a**) and the thermal stability of a few selected H-phosphinates were also assessed (**1a**, **1b**, **1d** and **1j**). Single crystal XRD allowed us to determine the absolute P-configurations of most of the H-phosphinates, and the most important non-bonding interactions responsible for the enantiomeric recognition. The crystal structures showed similarities, which explained well the experimental findings regarding the H-phosphinate scope (**1**) and the role of the aromatic solvents.

A few stereoselective transformations of (R)-1-adamantyl phenyl-H-phosphinate [(R)-1a] were also elaborated. Using 2-methoxyphenyl-lithium, the nucleophilic substitution of the adamantyloxy group was facilitated to prepare (2-methoxyphenyl)-phenylphosphine oxide [(R)-3a] and PAMP-oxide [(R)-3b]. The latter derivative was also transformed into CAMP-oxide [(R)-3c]. (R)-N-(1-Adamantyl-phenylphosphonyl)-2,4,6-triisopropylbenzenesulfonamide [(R)-3e] and (S)-(1-adamantyl)-phenylthiophosphonic acid [(S)-3f] were also prepared in a stereoselective manner from H-phosphinate [(R)-1a]. (S)-(1-Adamantyl)-phenylthiophosphonic acid [(S)-3f] was applicable as an NMR solvating agent for chiral amino-alcohols (**7-10**) and secondary phosphine oxides (**11-13**).

Author contributions

Conceptualization: B. V. and P. B.; investigation: B. V., D. V., H. P., L. B., J. P., T. H., B. M., L. H., and P. B.; formal analysis: B. V., T. H., B. M., and P. B.; data curation: B. V. and P. B.; visualization: B. V. and T. H.; supervision: P. B.; resources: P. B.; validation: P. B.; funding acquisition: B. V. and P. B.; writing—original draft preparation: B. V. and T. H.; and writing—review and editing: E. F., G. K., and P. B.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

B. V. acknowledges the financial support from the New National Excellence Program of the Ministry of Human Capacities (ÚNKP-21-3-II-BME-299). T.H. is grateful for the support from the National Research, Development and Innovation Office-NKFIH (Grant No. OTKA PD 128504).

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