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Graphical Abstract

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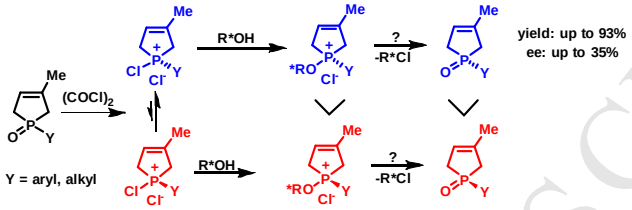

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Dynamic kinetic resolution of 1-substituted-3-methyl-3-phospholene oxides via the formation of diastereomeric alkoxyphospholenium salts

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ABSTRACT

A dynamic kinetic resolution method based on the formation of covalent diastereomeric intermediates was elaborated for the preparation of enantiomerically enriched 1-substituted-3-methyl-3-phospholene oxides. The 3-phospholene oxides were first converted to the corresponding chloro-3-phospholenium chlorides. The dynamic interconversion between the enantiomers of the chlorophospholenium salts was verified experimentally, as it is the key step for a dynamic resolution. The cyclic chlorophospholenium salts were reacted with a chiral auxiliary bearing a hydroxy function to form the corresponding diastereomeric alkoxyphospholenium salts in unequal amounts. The diastereomeric species then rearranged into the corresponding optically active 3-phospholene oxides upon heating. After a screening of chiral auxiliaries and the optimization of the reaction conditions, several scalemic 1-aryl- or 1-alkyl-3-methyl-3-phospholene oxides were prepared in excellent yields and with ee-s up to 35%. The key steps of this resolution were investigated by quantum chemical calculations to get some insights into the factors responsible for the stereoselection.

1. Introduction

Among organophosphorus compounds, even the *P*-stereogenic and the *P*-heterocyclic derivatives form important groups.[1,2] *P*-chirogenic heterocycles are of special interest that is underlined by the application of *P*-stereogenic heterocyclic ligands in transition metal complexes used in catalytic reactions.[3–6] Moreover, a few biologically active derivatives belonging to this group are also known.[7,8] Hence, the need for cyclic *P*-chirogenic compounds and procedures leading to them is justified.

In the past decade, there has been an increasing interest for developing novel procedures for optically active *P*-stereogenic compounds.[9] The most desired approaches are stereospecific syntheses, in which only one enantiomer is formed with high stereoselectivity and in good yield. Generally, these procedures are based on the application of heterobifunctional auxiliaries (e.g. chiral aminoalcohols) to give cyclic organophosphorus intermediates with high diastereoselectivity. The *P*-*O* and the *P*-*N* bonds of these diastereomeric intermediates can be stereoselectively substituted by organometallic reagents to give enantiopure phosphine oxides (Scheme 1/a).[10–16] Other strategies utilize monofunctional auxiliaries (e.g. chiral alcohols or amines) to form the corresponding diastereomeric esters or amides as key intermediates, which step is followed by a nucleophilic displacement (Scheme 1/b).[17,18] In many instances, the two diastereomers are formed in equal amounts, but there are also a few examples for diastereoselective procedures.[19–23]

For *P*-stereogenic phosphine oxides, classical resolution procedures based on the formation and separation of diastereomeric species still represent a simple, scalable and robust approach (Scheme 1/c).[24] However, the theoretical yield of a classical resolution procedure is limited to 50%, since the racemic starting material is a 1:1 mixture of the two antipodes. In order to overcome this key difficulty of classical resolutions, a few dynamic resolution procedures were developed, which allow an interconversion between the enantiomers under the reaction conditions. As the configurational stability of phosphine oxides is high, the formation of stereolabile *P*-stereogenic species is the key step for a dynamic resolution process.[25] *Gilheany* and co-workers found that chlorophosphonium salts meet this criterion, and these species were utilized in dynamic kinetic

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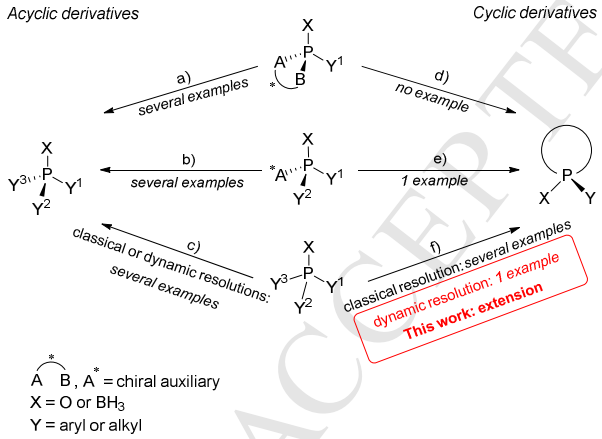
resolutions to prepare optically active diaryl-alkylphosphine oxides via the Appel process.[26–28]

Most of the above mentioned strategies, especially the stereoselective ones, are mainly applicable for acyclic phosphine oxides. In contrast, the number of methods for the preparation of optically active *P*-stereogenic cyclic phosphine oxides is limited. Stereoselective methodologies based on subsequent *P-O* or *P-N* bond cleavage could not be used for cyclic derivatives due to synthetic reasons (Scheme 1/d). Although, the applicability of monofunctional chiral auxiliaries, such as (–)-menthol or (–)-1-phenylethylamine have already been tested for 3-phospholene oxides, but these syntheses were not diastereoselective, and the corresponding diastereomers could not be separated under achiral conditions (Scheme 1/e).[29]

The resolution of the racemic compounds is the most frequently used method for the preparation of cyclic phosphine oxides. In the past few years, our research group has developed classical resolution procedures for the preparation of a wide variety of optically active cyclic phosphine oxides with TADDOL and tartaric acid derivatives as the resolving agents.[30] Furthermore, it should be noted, that the applicability of these methods are not limited to cyclic phosphine oxides (Scheme 1/f).[31] Although those procedures afforded the corresponding enantiomers in high purity, several recrystallizations were necessary, which led to moderate or low yields.

These disadvantages prompted us to elaborate a dynamic kinetic resolution method for 3-phospholene oxides that are representative members within heterocyclic organophosphorus compounds. As the dynamic resolution of the heterocyclic dihydrobenzophosphole oxide was accomplished under asymmetric Appel conditions,[32] we thought that this process might be applicable for other heterocyclic derivatives, as well. Herein, we report the dynamic kinetic resolution of 3-phospholene oxides via the formation of alkoxyphospholenium salts as covalent diastereomeric intermediates.

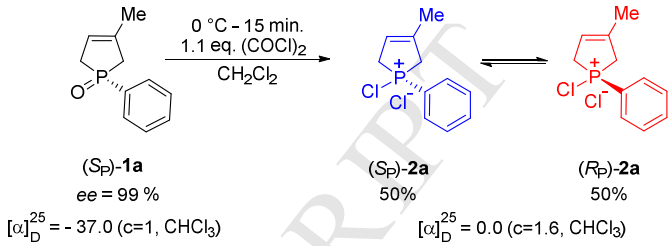


Scheme 1. General strategies for the preparation of acyclic and cyclic *P*-stereogenic organophosphorus compounds.

2. Results and Discussion

2.1. Racemization of chloro-3-phospholenium chlorides (2)

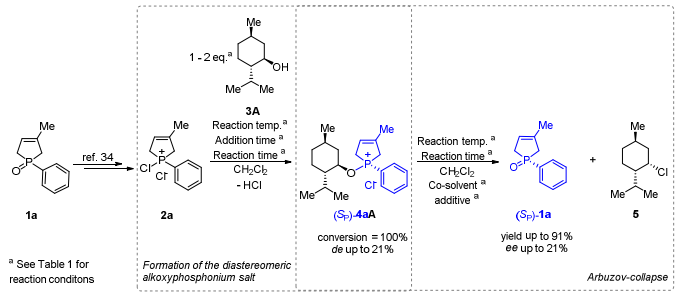
At first, the racemization of the enantiomerically pure 1-phenyl-3-methyl-3-phospholene oxide (**1a**) via its chloro-3-phospholenium salt (**2**) was studied, as it is the crucial step of the dynamic resolution. The enantiomerically pure (*S*)-phospholene oxide [(S_P)-**1a**, (ee > 99%] was prepared by one of our earlier methods.[30,33] The synthesis of cyclic chlorophosphonium salts (**2**) by reaction of the 1-substituted-3-methyl-3-phospholene oxides (**1**) and oxalyl chloride was the subject of our earlier study.[34] According to this, the (*S*)-phenyl-3-methyl-3-phospholene oxide [(S_P)-**1a**] was reacted with oxalyl chloride at 0°C for 15 min. The solvent and the excess of the reagent were then removed under reduced pressure to afford the corresponding chloro-3-phospholenium salt (**2a**) in quantitative yield. The specific rotation of the cyclic chlorophosphonium salt (**2a**) was zero, which referred to a rapid dynamic interconversion between the enantiomeric chlorophospholenium species [(S_P)- and (R_P)-**2a**] resulting in eventually racemic **2a** (Scheme 2).



Scheme 2. Racemization of 1-chloro-3-methyl-1-phenyl-3-phospholenium chloride (**2a**).

2.2. Optimization of the reaction conditions for the dynamic kinetic resolution of 1-phenyl-3-methyl-3-phospholene oxide (1a) using (–)-menthol (3A) as the chiral auxiliary

In the next step, we utilized the chlorophospholenium chlorides (**2**) in a dynamic resolution procedure based on the formation of alkoxyphospholenium salts (**4**) as covalent diastereomeric intermediates to prepare enantiomerically enriched 1-substituted-3-methyl-3-phospholene oxides (**1**). The resolution procedure comprises two steps. First, the corresponding chlorophospholenium salt (**2**) reacts with a chiral alcohol (**3**) to form the corresponding alkoxyphospholenium salts (**4**). Then, these diastereomeric species (**4**) are rearranged into the enantiomerically enriched 3-phospholene oxide (**1**) by *Arbuzov* fission. The 1-chloro-3-methyl-1-phenyl-3-phospholenium chloride (**2a**) and the inexpensive and commercially available (–)-menthol (**3A**) were applied as model compounds in our initial investigations (Scheme 3).



Scheme 3. Optimization of the dynamic kinetic resolution of 1-phenyl-3-methyl-3-phospholene oxide (**1a**) using (–)-menthol (**3A**) as the chiral auxiliary.

As the chloro-3-phospholenium salts (**2**) are moisture sensitive species, they were always prepared freshly according to the method described by us.[34] The solution of 1.5 eq. of (–)-menthol (**3A**) was added to the dichloromethane solution of the chlorophospholenium salt (**2a**). In our first attempt, the reaction temperature was 0 °C, to avoid the rearrangement of the alkoxyphosphonium salts.[27,28] After 2 h, an aliquot part of the reaction mixture was analyzed by ^{31}P NMR that confirmed the formation of the diastereomeric alkoxyphosphonium salts (**4aA**). The *P* atom of the 1-chloro-3-methyl-1-phenyl-3-phospholenium

Table 1. Optimization of the dynamic kinetic resolution of 1-phenyl-3-methyl-3-phospholene oxide (**1a**) using (–)-menthol (**3A**) as the chiral auxiliary.

Formation of the diastereomeric alkoxyphosphonium salts (**4aA**)						*Arbuzov* collapse of (**4aA**)				
Entry	Eq. of **3A**	Reaction temp (°C)	Addition time (min)	Reaction time (h)	*de* (%)[a]	Reaction temp (°C)	Reaction time (h)	Co-solvent Additive	Yield (%)[b]	*ee* (%)[c,d]
1	1.5	0	10	2	5	26	24	-	87	3
2	1.5	-78	10	2	21	26	24	-	90	16
3	1.5	-78	270	2	20	-	-	-	-	-
4	1.5	-78	10	0.25	20	-	-	-	-	-
5	1.5	-78	10	0.5	20	-	-	-	-	-
6	1.5	-78	10	1	21	-	-	-	-	-
7	1.5	-78	10	3	20	-	-	-	-	-
8	1	-78	10	2	21	-	-	-	-	-
9	2	-78	10	2	21	-	-	-	-	-
10	1.5	-78	10	2	21	60	2	toluene	90	9
11	1.5	-78	10	2	21	60	2	toluene pyridine	91	21

[a] The *de* of (S_P)-(**4aA**) was determined by ^{31}P NMR. The conversion of **2a** was 100%.
[b] The yield of the scalemic phospholene oxide **1a** was calculated based on the full amount of the racemate (**1a**).
[c] The *ee* of (S_P)-**1a** was determined by HPLC using chiral stationary phase.
[d] The (S_P)-1-phenyl-3-methyl-3-phospholene oxide [(S_P)-**1a**] was prepared.

chloride (**2a**) appeared at δ_P 92.7. After the addition of (–)-menthol (**3A**), the starting material (**2a**) was fully consumed, and the ^{31}P NMR spectrum showed full conversion to the corresponding diastereomeric species (S_P)- and (R_P)-(**4aA**) having δ_P 98.8 and 98.9, respectively. The covalent diastereomers (**4aA**) were present in unequal amounts with a *de* of 5%. Then, the solution of the diastereomeric mixture of alkoxyphosphonium salts (**4aA**) was stirred at ambient temperature. The *Arbuzov* collapse was rather slow, and after 24 h, the scalemic (S_P)-phenyl-3-methyl-3-phosphole oxide [(S_P)-**1a**] was prepared in a yield of 87% and with an *ee* of 3% (Table 1, Entry 1). The neomenthyl chloride (**5**) formed as the byproduct was removed by column chromatography.

In our initial attempt, the diastereoselectivity of the alkoxyphosphonium salt (**4aA**) formation step was low. Literature data confirmed that the diastereoselectivity of this step has a decisive role on the overall success of this reaction sequence.[28] Thus, we attempted the optimization of the key-step of the reaction sequence shown in Scheme 3. The results are shown in Table 1. First, the temperature was lowered to -78 °C. After 2 h of reaction time, the ^{31}P NMR analysis showed full conversion to the corresponding diastereomeric species (**4aA**), and the diastereomeric excess of the covalent diastereomeric species [(S_P)- and (R_P)-(**4aA**)] increased to 21% (Table 1, Entry 2). The fact that the alkoxyphosphonium salts (**4aA**) were formed in full conversion in a ratio of *ca.* 6:4 was the proof of concept that this dynamic resolution process may be feasible for cyclic phosphine oxides (**2**). As the next step, it was investigated, whether the addition time of the chiral auxiliary (**3A**), or the reaction time influences the diastereoselectivity. In our first few attempts, the solution of (–)-menthol (**3A**) was added dropwise over 10 min at -78°C (Table 1, Entry 2). The extension of the addition time to 270 min by using a syringe pump did not have a significant impact on the diastereoselectivity, as the *de* value of (**4aA**) showed parity with the previous attempt (*de*: 21% vs. 20%; Table 1, Entry 2 vs. Entry 3). The effect of the reaction time was also investigated. After adding the solution of (–)-menthol (**3A**) to the chlorophospholenium salt (**2a**) over 10 min, the reaction mixture was allowed to react at -78 °C for 3 h. ^{31}P NMR analysis of the samples taken after 15 min, 30 min, 1 h and 3 h revealed that the diastereomeric purity was practically constant over time (*de*: 20-21%; Table 1, Entries 4-7). These experiments may indicate, that the ratio of the diastereomeric species [(S_P)- and (R_P)-(**4aA**)] is set at the beginning of the reaction, and there is no interconversion between the diastereomers [(S_P)- and (R_P)-(**4aA**)]. In the last part of the investigation of the reaction parameters, the amount of (–)-menthol (**3A**) was changed in the range of 1-2 equivalents. The results showed parity in this set of experiments, suggesting that there was no point in using more chiral auxiliary (**3**) than the stoichiometric amount (compare Table 1, Entries 2, 8 and 9). In the first reaction step, dichloromethane was the solvent of our choice. Due to the reactivity of the chloro-3-phospholenium salts (**2**), solvents with nucleophilic heteroatoms could not be used. Aprotic, aliphatic or aromatic solvents and ethers could not be considered either due to the low solubility of the chloro-3-phospholenium salts (**2**).

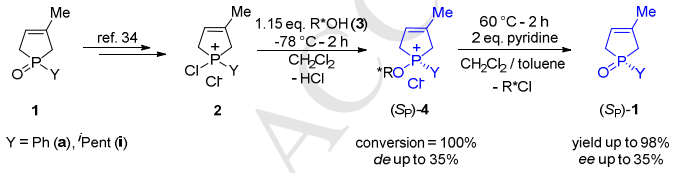
In the next step, the reaction conditions of the *Arbuzov* collapse were optimized. In our initial attempts, the solution of diastereomeric mixture of the alkoxyphosphonium salts (**4aA**) was stirred at 26°C. However, at this attempt, the *Arbuzov* collapse of the alkoxyphosphonium salts (**4aA**) was rather slow, as a reaction time of 24 h was necessary for full conversion. Moreover, the *ee* of the (*S*)-1-phenyl-3-phospholene oxide [(S_P)-**1a**] was lower than the *de* of the diastereomeric species [(S_P)-(**4aA**)] indicating the loss of chiral information during the *Arbuzov* collapse (Table 1, Entries 1 and 2). By adding a small amount of toluene as a co-solvent to the dichloromethane solution, the second reaction step could be performed at 60°C, at which temperature the alkoxyphosphonium salts (**4aA**) were fully converted to a scalemic 1-phenyl-3-methyl-3-phospholene oxide [(S_P)-**1a**] in 2 h. However, the "erosion" of stereoselectivity was more pronounced at this temperature as the (S_p)-1-phenyl-3-phospholene oxide [(S_P)-**1a**] was isolated with an *ee* of 9% (Table 1, Entry 10). During the formation of alkoxyphosphonium salts (**4aA**), one equivalent of hydrogen chloride is the byproduct.

It was assumed, that HCl is the reason for the decrease in the *ee* of the (S_P)-phenyl-3-phospholene oxide [(S_P)-**1a**].[27,35,36] By adding an acid scavenger, such as pyridine to the reaction mixture, the *ee* of the phenyl-3-phospholene oxide [(S_P)-**1a**] showed parity with the *de* of the diastereomeric intermediate [(S_P)-(**4aA**)] meaning that the diastereoselectivity of the first reaction step can be preserved (Table 1, Entry 11).

In this series of experiments, we could not determine the absolute configuration of the diastereomeric intermediate (**4aA**) by crystallographic or spectroscopic methods. The *Arbuzov* collapse of alkoxyphosphonium salts proceeds with retention of configuration,[28] which may suggest that the diastereomeric intermediate (S_P)-**4aA** was formed in excess, as the (*S*)-phenyl-3-phospholene oxide [(S_P)-**1a**] was prepared in a maximal *ee* of 21%.

2.3. Optimization of the chiral auxiliaries (3) for the dynamic kinetic resolution of 1-substituted-3-methyl-3-phospholene oxides (1).

One major conclusion of the parameter optimization study was that the *de* of the alkoxyphosphonium salts (**4**) could not be increased above a certain extent (21%) by changing the reaction conditions. These results suggested that the diastereoselectivity of this reaction step might only be increased by using a different chiral auxiliary.[28] Thus, other commercially available chiral auxiliaries bearing a hydroxyl group were also tested to evaluate their suitability for this dynamic resolution. The list of chiral auxiliaries included various alcohols, diols, esters of hydroxy acids, as well as a few amino alcohols (See Supporting Information for the complete list of chiral auxiliaries). For these experiments, the 1-phenyl-3-methyl-3-phospholene oxide (**1a**) and the 1-isopentyl-3-methyl-3-phospholene oxide (**1i**) with a sterically demanding *P*-substituent were considered as model compounds, and the reaction conditions were set according to the parameter optimization study. The chloro-3-phospholenium salts (**2a** and **2i**) were always prepared before the experiment,[34] the chiral auxiliary (**3**) was used in a slight excess (1.15 eq.), and it was reacted with the chlorophospholenium salt (**2a** or **2i**) at -78°C for 2 h to ensure the full conversion to the corresponding alkoxy-phosphonium salts (**4**). The *de* of the diastereomeric intermediate (**4**) was determined by ^{31}P NMR, followed by the *Arbuzov* collapse of the alkoxyphospholenium salt **4** at 60°C in a mixture of dichloromethane and toluene using pyridine as the acid scavenger (Scheme 4). Table 2 contains the best results (See Supporting Information for the complete list of chiral auxiliaries, as well as for the results).



Scheme 4. Optimization of the chiral auxiliaries (**3**) the dynamic kinetic resolution of 1-phenyl- and 1-isopentyl-3-methyl-3-phospholene oxides (**1a** and **1i**).

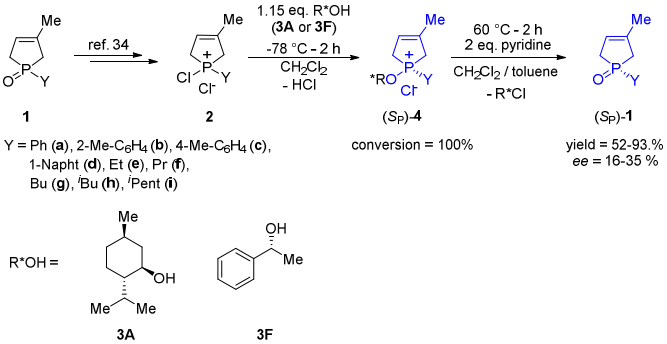
In all experiments, ^{31}P NMR analysis revealed that the chlorophospholenium salts (**2a** or **2i**) were fully converted to the corresponding alkoxyphospholenium species (**4**). In a few instances, the ^{31}P NMR signals of the diastereomeric intermediates (**4**) coalesced into a single unresolved peak making the determination of the *de* impossible. However, the other experimental results suggested that in these instances the diasteromeric purity of the alkoxyphospholenium salt **4** was also equal to the final enantiomeric purity of the scalemic mixture of the phospholene oxide [(S_P)- or (R_P)-**1**].

Besides (–)-menthol (**3A**), (+)-1-phenylethanol (**3F**) and (–)-benzyl mandelate (**3L**) were also suitable auxiliaries for the dynamic resolution of the phenyl-3-phospholene oxide (**1a**), but these results showed parity, as the *ee* of phospholene oxide **1a** was in the range of 21-23%, and the yields were above 90% (Table 2, Entries 1, 4 and 7). Applying other chiral auxiliaries, *ee* values up to 13% could be obtained, and the yields were moderate. Diols were not suitable agents, as the phenyl-phospholene oxide (**1a**) was prepared as a racemate. Moreover, when amino alcohols were tested, a complex diastereomeric mixture was obtained, which indicated a competition between the hydroxy and the amino functional groups (See Supporting Information for the details).

Considering the dynamic resolution of 1-isopentyl-3-methyl-3-phospholene oxides (**1i**), the application of chiral auxiliaries incorporating a benzyl alcoholic moiety (**3F**, **3G** and **3L**) was the most beneficial (Table 2, Entries 12, 13 and 15). From this class of compounds, the best enantiomeric excess value (*ee*: 35%) could be obtained with (+)-1-phenylethanol (**3F**). Contrary to the aryl model compound (**1a**), (–)-menthol (**3A**) was not suitable as an auxiliary for the isopentyl derivative (**1i**), as the (*S*) enantiomer [(S_P)-**1i**] could be prepared with only an ee of 7% (Table 2, Entry 9).

2.4. Dynamic kinetic resolution of 1-substituted-3-methyl-3-phospholene oxides (1) via the formation of diastereomeric alkoxyphosphonium salts (4)

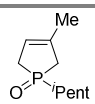
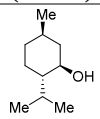
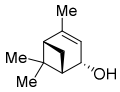
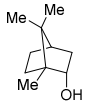
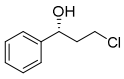
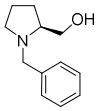
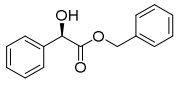
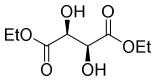
After setting the optimal reaction parameters and finding the most suitable chiral auxiliary, this dynamic resolution procedure was extended to other aryl- and alkyl-3-methyl-3-phospholene oxides (**1b-h**). Considering the optimization study, (–)-menthol (**3A**), (+)-1-phenylethanol (**3F**) showed comparable results, but the opposite enantiomers of phenyl-phospholene oxide (**1a**) could be prepared with the two auxiliaries. Thus, the aryl derivatives (**1b-d**) were resolved with both auxiliaries (**3A** and **3F**), whereas the alkyl derivatives (**1e-i**) were reacted only with (+)-1-phenylethanol (**3F**) (Scheme 5). The results are summarized in Table 3.



Scheme 5. Dynamic kinetic resolution of 1-substituted-3-methyl-3-phospholene oxides (**1**) via the formation of diastereomeric alkoxyphosphonium salts (**4**).

The dynamic resolution procedure based on the formation of diastereomeric alkoxyphosphonium salts (**4**) could be successfully extended to a variety of aryl- and alkyl-3-methyl-3-phospholene oxides (**1a-i**), and the scalemic mixtures of phosphine oxide **1** could be prepared in an *ee* of 16-35%. Both enantiomers of the aryl-3-methyl-3-phospholene oxides (**1a-d**) could be obtained with (–)-menthol (**3A**) or (+)-1-phenylethanol (**3F**), and the *ee* values were in the range of 16-24%.

Table 2. Evaluation of chiral auxiliaries (**3**) for the dynamic kinetic resolution of 1-phenyl- and 1-isopentyl-3-methyl-3-phospholene oxides (**1a** and **1i**).

	 **1a**				 **1i**			
Chiral auxiliary (R*OH)	Entry	*de* (%)[a]	*ee* (%)[b] (Abs. config.)	Yield (%)[c]	Entry	*de* (%)[a]	*ee* (%)[b] (Abs. config.)	Yield (%)[c]
 **3A**	1[d]	21	21 (*S*)	91	9	7	7 (*S*)	90
 **3B**	2	n. d.	10 (*S*)	40	10	n. d.	rac.	34
 **3D**	3	10	10 (*S*)	71	11	14	13 (*S*)	55
 **3F**	4	n.d.	21 (*R*)	92	12	n.d.	35 (*R*)	74
 **3G**	5	n. d.	rac.	89	13	n.d.	27 (*R*)	58
 **3J**	6	n. d.	9 (*R*)	42	14	7	5 (*R*)	85
 **3L**	7	n. d.	21 (*R*)	98	15	24	23 (*R*)	97
 **3N**	8	12	13 (*S*)	96	16	9	8 (*S*)	85

[a] The *de* of the diastereomers (**4a** or **4i**) was determined by ^{31}P NMR. The conversion of **2a** or **2i** was 100%.
[b] The *ee* of **1a** or **1i** was determined by HPLC using chiral stationary phase.
[c] The yield of the scalemic phospholene oxide **1a** or **1i** was calculated based on the full amount of the racemate.
[d] Table 1, Entry 11.

The alkyl-3-phospholene oxides (**1e-1i**) were obtained in slightly higher *ee* values (27-35%). For most 3-phospholene oxides (**1a**, **1c**, **1d** and **1f-h**), the yields were in the range of 83-93%. It is noteworthy that in this dynamic procedure, the full amount of the racemate (**1**) can be converted to enantiomerically enriched 3-phospholene oxide (**1**), contrary to the case of classical resolutions, when the theoretical yield is limited to the half amount of the racemic compound.[30]

The practical importance of our method lies in the fact that it may be coupled with the synthesis of 3-phospholene derivatives (**1**). The *McCormack* cycloaddition, a widely used method for the synthesis of the five-membered organophosphorus core, produces halophospholenium salts (**2**), which are the key intermediates of this dynamic resolution method. In this manner, enantiomerically enriched 3-phospholene oxides (**1**) can be prepared, and these enantiomeric mixtures can be purified further even under achiral conditions to give enantiopure 3-phospholene oxides (**1**).[31]

Table 3. Dynamic kinetic resolution of 1-substituted-3-methyl-3-phospholene oxides (**1**) with (–)-menthol (**3A**) or (+)-1-phenylethanol (**3F**) via the formation of diastereomeric alkoxyphosphonium salts (**4**).

Entry	Y	Chiral auxiliary (R*OH)	ee (%)[a] (Abs. config.)	Yield (%)[b]
1[c]	Ph (**1a**)	**3A**	21 (*S*)	91
2[d]	Ph (**1a**)	**3F**	21 (*R*)	92
3	2-Me-C_6H_4 (**1b**)	**3A**	19 (*S*)	57
4	2-Me-C_6H_4 (**1b**)	**3F**	24 (*R*)	52
5	4-Me-C_6H_4 (**1c**)	**3A**	18 (*S*)	83
6	4-Me-C_6H_4 (**1c**)	**3F**	16 (*R*)	85
7	1-Napht (**1d**)	**3A**	20 (*S*)	92
8	1-Napht (**1d**)	**3F**	22 (*R*)	83
9	Et (**1e**)	**3F**	33 (*R*)	65
10	Pr (**1f**)	**3F**	33 (*R*)	92
11	Bu (**1g**)	**3F**	33 (*R*)	83
12	^{i}Bu (**1h**)	**3F**	28 (*R*)	93
13[e]	^{i}Pent (**1i**)	**3F**	35 (*R*)	74

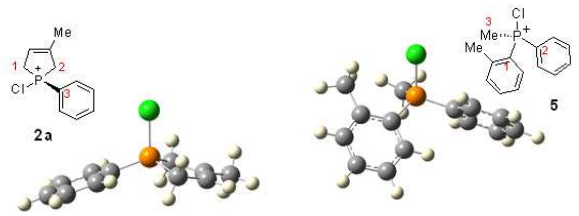
[a] The *ee* of **1** was determined by HPLC using chiral stationary phase.
[b] The yield of the scalemic phospholene oxide **1** was calculated based on the full amount of the racemate.
[c] Table 1, Entry 11.
[d] Table 2, Entry 4.
[e] Table 2, Entry 12.

2.5. Theoretical calculations

The fact that the enantiomeric excess of the optically active 3-phospholene oxides (**1**) did not exceed an ee of 35% encouraged us to investigate this dynamic resolution process computationally to get some insights into the factors responsible for the stereoselection. In our calculations, the chloro- and menthyloxyphospholenium salts (**2a** and **4aA**; *de*: 21%) derived from 1-phenyl-3-methyl-3-phospholene oxide (**1a**) were studied. For comparison, the corresponding chloro- and menthyloxyphosphonium species (**5** and **6**) derived from methyl-(2-methylphenyl)-phenylphosphine oxide were also included in our calculations, as the diastereomers of this acyclic derivative could be prepared in high diastereoselctivity (*de*: 87%) with a dynamic resolution method.[27] One of our goals was the investigation of the racemization process of the cyclic chlorophosphonium species (**2**), and the comparison of these results with those obtained for acyclic derivatives (**5**). Moreover, we wished to analyze computationally the formation of the diastereomers of the acylic or cyclic alkoxyphosphonium salts (**4a** and **6**) in order to explain the difference in the experimental diastereoselectivity values.

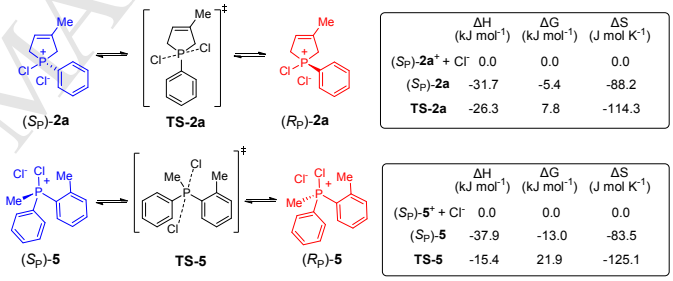
First, geometry optimization was performed on the cyclic and acyclic halophosphonium cations (**2a** and **5**), and the bond angles around the phosphorus atom were analyzed (Table 4). It was found that in the case of acyclic chlorophosphonium cation (**5**), the geometry of the molecule is rather tetrahedral, while this geometry is more distorted, resembling to a pyramidal structure for the cyclic derivative (**2a**). One might see that chlorophospholenium salt (**2a**) has a side more open for nucleophilic attack than the acyclic derivative (**5**), which is sterically more closed from all sides due to the spherical geometry. Therefore, even the geometric data indicate that cyclic chlorophospholenium salt (**2**) might be more reactive in substitution reactions that is disadvantageous in the case of a diastereoselective transformation.

Table 4. Calculated bond angles (°) for cyclic and acyclic halophosphonium cations (**2a** and **5**).



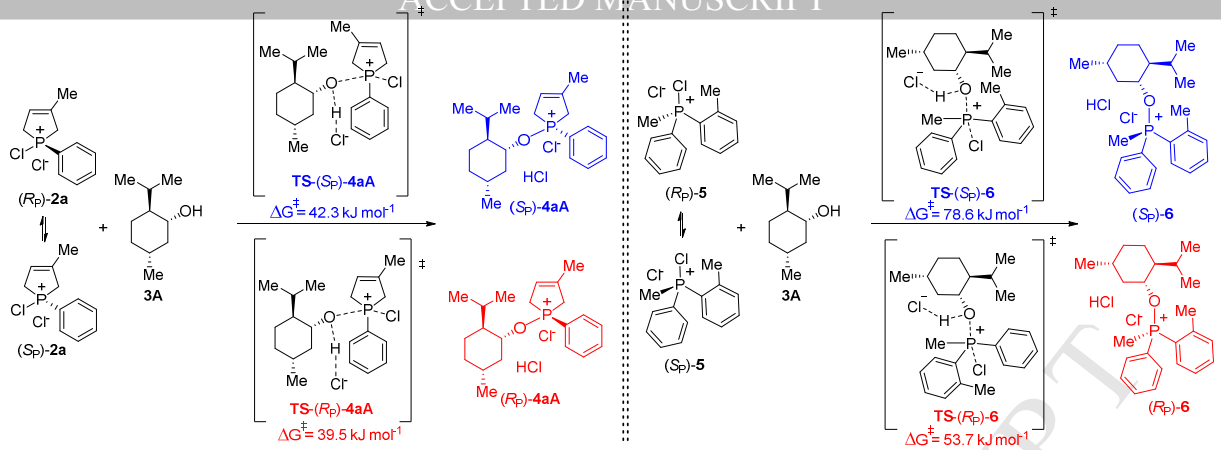
C_1-P-Cl	107.9	109.5
C_2-P-Cl	108.0	106.3
C_2-P-C_3	116.1	110.1
C_1-P-C_3	116.2	112.7
Cl-P-C_3	109.8	106.3
C_1-P-C_2	98.1	111.6

The geometry analysis of the cations was followed by investigating the kinetics of the spontaneous racemization of cyclic and acyclic chlorophosphonium salts (**2a** and **5**). According to the literature, the proposed and computed reaction was the attack of the chloride anion on the corresponding chiral cation, in order to form the other enantiomer of the given chlorophosphonium salt (**2a** and **5**).[37,38] In both cases, the reference point was the anions and cations separated, therefore energetic data for **2a** and **5** represents the formation energy of the ion pairs (Scheme 6).



Scheme 6. Computational study on the spontaneous racemization of the cyclic and acyclic chlorophosphonium salts (**2a** and **5**).

The kinetic profile of the racemization was mapped in our computations by scanning the chloride anion to the phosphorus atom of the (*S*) enantiomer [(S_P)-**2a** or (S_P)-**5**] leading to the leave of the opposite Cl resulting in the formation of the (*R*) stereoisomer [(R_P)-**2a** or (R_P)-**5**]. It can be concluded that the formation of the reaction complex ion pair is energetically more favorable in case of the model acyclic chlorophosphonium salt (**5**), leading to the assumption that this acyclic salt (**5**) is more stable than the corresponding cyclic derivative (**2a**). Moreover, the transition state enthalpy and *Gibbs* free energy were much larger for the acyclic model compound (**5**), ΔH = 22.5 kJ mol^{-1}, ΔG = 34.9 kJ mol^{-1}) than for that of **2a** (ΔH = 5.4 kJ mol^{-1}, ΔG = 13.2 kJ mol^{-1}), which allows us to conclude that the racemization of cyclic derivatives (**2**) is much faster than that of the corresponding acyclic species (**5**). As it was expected, the calculated energies for the formation of the other antipode of the chlorophosphonium salts (**2a** or **5**) were the same (See Supporting information). It is noteworthy, that the calculated *Gibbs* free energy for the racemization of the acyclic chlorophosphonium salt (**5**) showed good agreement with the experimental value.[38]



Scheme 7. Computed reaction mechanism for the formation of cyclic and acyclic alkoxyphosphonium diastereomers (**4aA** and **6**).

As the last part of the computations, the reaction of (−)-menthol (**3A**) with 1-chloro-3-methyl-1-phenyl-3-phospholenium chloride (**2a**), or with the chloro-methyl-(2-methylphenyl)-phenyl-phosphonium chloride (**5**) was studied, as it is the crucial diastereoselective step of the dynamic resolution procedure. These computations let us investigate the energetic difference between the reaction of the cyclic or acyclic derivatives (**2a** or **5**). Scheme 7 shows the computed mechanism, with the transition state Free *Gibbs* energies. According to the calculated mechanism, the reaction starts with the nucleophilic attack of the oxygen atom of the (−)-menthol (**3A**) from the most open side of the phosphonium cation (**2a** or **5**), which was the opposite side of the chloride atom. This step is followed by the leave of a chloride anion resulting in the formation of the corresponding diastereomers (**4aA** or **6**). In all cases, the chloride counter anion served as the base for taking the proton of OH group of the (−)-menthol (**3A**) (Scheme 7).

Our computations showed that the formation of the cyclic alkoxyphosphonium salt diastereomers [(S_P)- and (R_P)-**4aA**] goes through an identically low transition state around 40 kJ mol^{-1} with a slight difference (2.8 kJ mol^{-1} in terms of ΔG). On the contrary, in the case of the acyclic derivative [(S_P)- and (R_P)-**6**], the transition state is higher, and the difference between the two is 24.9 kJ mol^{-1}. These data also support the observed trend that the diastereoselectivity is lower for the cyclic alkoxyphosphonium species (**4**) (*de*: 21%) than for the corresponding acyclic derivatives (**6**) (*de*: 87%).

3. Conclusion

In summary, a dynamic resolution method was elaborated for 1-substituted-3-methyl-3-phospholene oxides (**1**). One of the key steps of this process was the conversion of the 3-phospholene oxides (**1**) to chlorophospholenium salts (**2**) which enantiomers interconvert into each other in solution. The cyclic chlorophosphonium salts (**2**) were reacted with a given chiral auxiliary (**3**) bearing an OH-group to form diastereomerically enriched alkoxyphosphonium species (**4**). These covalent diastereomers (**4**) can be converted to enantiomerically enriched 3-phospholene oxides [(S_P)- or (R_P)-**1**] upon heating. In this study, the reaction conditions were optimized, and several chiral auxiliaries (**3**) were tested, among which the (–)-menthol (**3A**) or (+)-1-phenylethanol (**3F**) were the best ones. Applying the optimal reaction conditions, the aryl- and alkyl-3-methyl-3-phospholene oxides (**1**) could be prepared with an ee up to 35% in good or excellent yields. The theoretical background of the lack of high diastereoselectivity was investigated by quantum chemical calculations. The experimental observations could be explained on the basis of the geometries of the molecules and reaction energetics.

4. Experimental section

4.1. General (instruments)

The ^{31}P, ^{13}C, ^{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. All moisture-sensitive NMR samples were prepared under nitrogen with dry $CDCl_3$ purchased from Merck.

ESI-MS mass measurements were performed using an Agilent 1100 and Agilent 6130 LCMS system in positive electrospray mode.

All reactions were carried out using dry reagents and solvents,[39] under N_2 atmosphere in dry glassware using Schlenk-techniques.

Flash column chromatography was performed using a CombiFlash® (Teledyne ISCO).

The enantiomer excess values of 1-substituted-3-methyl-3-phospholene 1-oxides (**1**) were determined by chiral HPLC or GC (See Supporting Information for details).

The optical rotation was measured by Perkin Elmer 241 Polarimeter.

*4.2. Racemization of 1-chloro-3-methyl-1-phenyl-3-phospholenium chloride (**2a**)*

To the solution of 0.025 g (0.13 mmol) of the (*S*)-1-phenyl-3-methyl-3-phospholene 1-oxide [(S_P)-**1a**] [$[\alpha]_D^{25}$ = −37.0 (c=1; $CHCl_3$), *ee* = 99 %] in 0.5 mL dichloromethane, 0.012 mL (0.14 mmol) oxalyl chloride was added dropwise at 0 °C. The reaction mixture was stirred for 15 min, then the volatiles were removed at 0 °C to furnish the 1-chloro-3-methyl-1-phenyl-3-phospholenium chloride (**2a**) in a quantitative yield. The chloro-3-phospholenium salt (**2a**) was dissolved in 2 mL of dry chloroform, and the optical rotation was measured immediately. α_D^{25} = 0.0 (c=1.6; $CHCl_3$). ^{31}P NMR ($CDCl_3$) δ 92.7 (δ_{lit} 92.5).[34]

*4.3. General procedure for the optimization of dynamic kinetic resolution of 1-substituted-3-methyl-3-phospholene 1-oxides (**1**)*

The 1-chloro-3-methyl-1-phenyl-3-phospholenium chloride (**2a**) was freshly prepared in the reaction of 0.19 g (1.0 mmol) of 1-phenyl-3-methyl-3-phospholene oxide (**1a**) and 0.086 mL

(1.1 mmol) of oxalyl chloride at 0 °C according to the method described by us.[34] The chlorophospholenium salt **2a** was dissolved in 2.0 mL of dichloromethane, and the solution was cooled to -78°C followed by the addition of 0.23 g (1.5 mmol) of (–)-menthol (**3A**) in 2.0 mL of dichloromethane over the period of 10 min. The reaction mixture was stirred for 2 h at -78 °C, and it was allowed to warm to 0°C. A small sample was taken from the reaction mixture, the solvent was removed at 0°C. The residue was dissolved in dry $CDCl_3$ to determine diastereomeric excess by ^{31}P NMR. 2.0 mL of Toluene and 0.16 mL (2.0 mmol) of pyridine were added to the reaction mixture. The flask was placed into an oil bath, and the reaction mixture was heated for 2 h at 60 °C. The volatiles were evaporated, the residue was dissolved in 2.0 mL of dichloromethane. The solution was extracted with 1.0 mL of water, the organic phase was dried (Na_2SO_4), and the solvent was removed in vacuo. The crude product was purified by column chromatography (silica gel, 3% methanol in dichloromethane) to give 0.17 g (91%) of (S_P)-1-phenyl-3-methyl-3-phospholene 1-oxide [(S_P)-**1a**] in an ee of 21%. (Table 1, Entry 11).

In the optimization study, the amount of (–)-menthol (**3A**), the addition time, the reaction time and the temperature of each reaction steps were changed. All reactions were accomplished according to the general procedure described above by setting the parameters as detailed in Table 1. The screening of the chiral auxiliaries (**3**) was accomplished according to the general procedure by using 1.15 equivalent of the auxiliary. The best results are summarized in Table 2 (See Supporting Information for the complete list of chiral auxiliaries, as well as for the results).

*4.4. General procedure for the dynamic kinetic resolution of 1-substituted-3-methyl-3-phospholene oxides (**1**)*

The 1-chloro-3-methyl-3-phospholenium chloride derivatives (**2**) were freshly prepared in the reaction of 1.0 mmol of 3-phospholene oxide (**1**) (**1a**: 0.19 g, **1b**: 0.21 g, **1c**: 0.21 g, **1d**: 0.24 g, **1e**: 0.14 g, **1f**: 0.16 g, **1g**: 0.17 g, **1h**: 0.17 g, **1i**: 0.19 g) and 0.086 mL (1.1 mmol) of oxalyl chloride at 0 °C according to our method.[34] The chlorophospholenium salt **2** was dissolved in 2.0 mL of dichloromethane, and the solution was cooled to -78°C followed by the addition of 0.18 g (1.15 eq.) of (–)-menthol (**3A**) or 0.13 g (1.15 eq.) of (+)-1-phenylethanol (**3F**) in 2.0 mL of dichloromethane over the period of 10 min. The reaction mixture was stirred for 2 h at -78 °C, and it was allowed to warm up to 0°C. 2.0 mL of Toluene and 0.16 mL (2.0 mmol) of pyridine were added to the reaction mixture. The flask was placed into an oil bath, and the reaction mixture was heated for 2 h at 60 °C. The volatiles were evaporated, the residue was dissolved in 2.0 mL of dichloromethane. The solution was extracted with 1.0 mL of water, the organic phase was dried (Na_2SO_4), and the solvent was removed in vacuo. The crude product was purified by column chromatography (silica gel, 3% methanol in dichloromethane) to give the corresponding enantiomerically enriched 1-substituted-3-methyl-3-phospholene oxides (**1**). The results are summarized in Table 3.

4.5. Computational methods

In all quantum chemical calculations, the B3LYP/6-31+g(d,p) method and basis set was used under the Gaussian09 program package.[40–42] The calculations were performed at 298 K and 1 bar. Dichloromethane was considered as the implicit solvent applying the IEFPCM method.[43–45] The H, G and S values obtained are given at standard conditions. The reaction pathways and energetics were calculated by scanning and the calculated TS indeed connected the two corresponding minima. The transition states were optimized with the QST3 method. Transition states were identified by having one imaginary frequency in the Hessian matrix. All the geometries and transition states were optimized and frequency calculations were made to assure that the structures are in a local minimum. The reported ΔH, ΔG, ΔS values are the differences of the calculated sum of electronic and thermal enthalpy, *Gibbs* free energy and total entropy, respectively, between the corresponding structures.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data related to this article can be found at

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