

Turning Regioselectivity into Stereoselectivity: Efficient Dual Resolution of P-Stereogenic Phosphine Oxides through Bifurcation of the Reaction Pathway of a Common Intermediate**

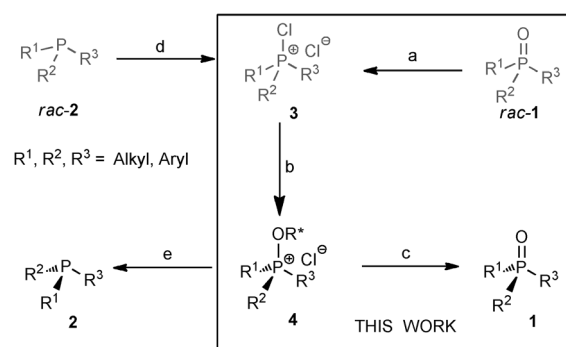
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Abstract: Synthetic routes that provide facile access to either enantiomeric form of a target compound are particularly valuable. The crystallization-free dual resolution of phosphine oxides that gives highly enantioenriched materials (up to 94 % ee) in excellent yields is reported. Both enantiomeric oxides have been prepared from a single intermediate, (*R_P*)-alkoxyphosphonium chloride, which is formed in the course of a selective dynamic kinetic resolution using a single enantiomer of menthol as the chiral auxiliary. The origin of the dual stereoselectivity lies in bifurcation of the reaction pathway of this intermediate, which works as a stereochemical railroad switch. Under controlled conditions, Arbuzov-type collapse of this intermediate proceeds through C–O bond fission with retention of the configuration at the phosphorus center. Conversely, alkaline hydrolysis of the P–O bond leads to the opposite *S_P* enantiomer.

In asymmetric synthesis, an ideal scenario is to generate both enantiomers of the target using only one enantiomer of the chiral agent. In this way, maximum benefit is extracted from the source of chirality, and the decision on the configuration of the product is transferred to the operator.^[1] As asymmetric synthesis has matured, methods for this highly desirable goal have been developed only slowly, but have become an emerging topic in synthetic methodology.^[2]

In organophosphorus chemistry, the need for flexible routes to non-racemic P-stereogenic compounds has been well established,^[3,4] with significant applications in catalytic asymmetric synthesis^[5] and for accessing enantiomerically pure phosphonates and phosphoramidates as nucleotide prodrugs.^[6] Some progress towards dual stereoselection has been achieved and two distinct types of approach towards this ideal scenario for P-stereogenic compounds may be discerned:

- 1) Inversion of the order of attachment of two groups at a phosphorus atom that already bears a chiral auxiliary, for example, ephedrine,^[7] which recently culminated in the development of a very effective route based on 1-phenylethylamine by Han and co-workers.^[8]
- 2) Use of (–)-menthol as an inexpensive template: Introduced by Mislow and co-workers,^[9] it has been used in a number of ways to synthesize both enantiomers of P-stereogenic compounds, commonly by classical diastereomer separation and subsequent separate manipulations of both isomers. Recently, this concept was efficiently applied by Berger and Montchamp.^[10]



Scheme 1. Stereoselective synthesis of P-stereogenic phosphines and phosphine oxides (racemic forms are shown in gray): a) (COCl)₂, CH₂Cl₂, RT; b) (–)-menthol, toluene/CH₂Cl₂, –82 °C; c) Arbuzov-type collapse, 50–60 °C; d) hexachloroacetone or (COCl)₂; e) LiAlH₄.

Our contributions to the synthesis of P-stereogenic compounds (Scheme 1) include an asymmetric three-step one-pot transformation of racemic phosphine oxide *rac*-1 or the parent phosphine *rac*-2 leading to enantioenriched **1** or **2**.^[11] Our current method involves the chlorination of either *rac*-1 or *rac*-2 to form enantiomeric chlorophosphonium salts (CPSs) **3**,^[12] which, according to the present hypothesis, rapidly interconvert and are dynamically resolved in the presence of a chiral auxiliary, such as menthol, to give the diastereomeric alkoxyphosphonium salt (DAPS) **4** (path b).^[13] The final ee of scalemic **1** formed by Arbuzov collapse of **4** (path c) is limited by the diastereomeric purity, *de*, of **4**.^[14] Alternatively, hydride reduction of **4** (path e) leads to enantioenriched **2**.^[13,15]

We have recently been working on the two principal limitations of this approach. First, the desirable stereochemical outcome of at least 90 % ee for the product oxides had not been attained in auxiliary screening.^[11] Second, as the

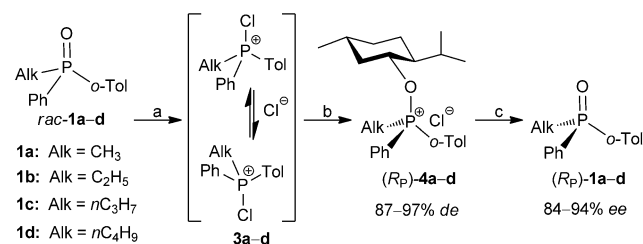
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stereochemical configuration of product **1** is set by the configuration of the chiral auxiliary, preparation of the opposite enantiomer required a change of auxiliary.^[11] Herein, we report two important breakthroughs: the synthesis of enantioenriched **1** with > 90 % *ee* and the preparation of both enantiomers of **1** using the same chiral auxiliary.

We have recently described^[13] an NMR-based method for the determination of the *de* of the crucial DAPS intermediates **4**, and we have now correlated this value with the ultimate *ee* value. Thus, racemic oxides **1a–d** were reacted with oxalyl chloride to give salts **3a–d**, which were then treated with a solution of (–)-menthol at –82 °C (Scheme 2).



Scheme 2. One-pot chiral resolution of phosphine oxides **1**. a) (COCl)₂, CH₂Cl₂, RT; b) (–)-menthol, toluene/CH₂Cl₂, –82 °C; c) Arbuzov-type collapse, 50–60 °C.

After three hours, the reaction mixture was typically allowed to warm up to 0 °C, and a sample of it was used to determine the diastereomeric purity of the resulting DAPS **4** by ³¹P NMR spectroscopy in CDCl₃. The reaction mixture was then heated at 60 °C, and the Arbuzov-type collapse of **4** leading to (R_p)-**1** in quantitative yield was monitored by HPLC analysis on a chiral stationary phase selected results are given in Table 1 (for details, see the Supporting Information). It can be seen that in the absence of any other intervention, there is significant erosion of selectivity during the Arbuzov collapse (Table 1, entries 1, 5, 9, 13). We found that a major factor contributing to this erosion was the acidity of the reaction, as HCl is formed during this process, which may induce racemization of **1**. Indeed, removal of HCl by addition of weak bases or acid-scavenging reagents was found to be very beneficial for the stereochemical outcome, allowing almost complete preservation of the selectivity achieved in the formation of DAPS **4** (Table 1, entries 2–4, 6–8, 15, and 16). A plausible mechanism for the stereochemical erosion involves the equilibrium maintenance of a small concentration of CPS **3**, which then reversibly interacts with scalemic **1** to reduce its *ee* value (for details, see the Supporting Information).

The nature of the solvent also has a significant effect on the erosion of the selectivity. For **4a** (initially 87 % *de*), the loss of stereochemical information was significant in ether and hydrocarbon solvents, but much lower in acetonitrile, CH₂Cl₂, chloroform, and in the more basic dimethyl sulfoxide (DMSO; see the Supporting Information, Table S1).

Having established the set of conditions that enables the preservation of stereochemistry during the collapse of **4**, we are now in a position to comment on the intrinsic selectivity of

Table 1: Thermal collapse of (R_p)-**4a–d** into scalemic (R_p)-**1a–d**.^[a]

Entry	DAPS	Additive ^[b]	<i>de</i> of 4 [%] ^[c]	<i>ee</i> of 1 [%] ^[d]	Preservation of selectivity [%] ^[e]
1	4a	–	87	73	92
2		<i>tert</i> -butanol	87	84	98.5
3		CH(OMe) ₃	87	84.5	98.5
4		pyridine	87	84	98.5
5	4b	–	96	87	95.5
6		<i>tert</i> -butanol	96	92	98
7		CH(OMe) ₃	96	92.5	98
8		pyridine	96	92	98
9	4c	–	95	79	91.5
10		<i>tert</i> -butanol	95	92	98.5
11		CH(OMe) ₃	95	91	98
12		pyridine	95	92	98.5
13	4d	–	97	84	93
14		<i>tert</i> -butanol	97	91	97
15		CH(OMe) ₃	97	93	98
16		pyridine	97	93	98

[a] Mixture of CH₂Cl₂ and toluene (1:3 v/v), 60 °C, 3 h; quantitative conversion into **1** determined by ³¹P NMR spectroscopy. [b] Added before heating: *tert*-butanol or orthoformate (10 % v/v); pyridine (4 % v/v). [c] Determined by ³¹P NMR spectroscopy, error ± 1 %. [d] Determined by HPLC analysis on a chiral stationary phase error ± 0.5 %. [e] 50 (*de* + *ee*) / *de*; see the Supporting Information for details.

the process, namely the *de* value of **4**. The key finding is that the introduction of additional CH₂ fragments in the linear alkyl chain leads to a significant increase in selectivity (Table 1; for the Et, *n*Pr, and *n*Bu derivatives **4b–d**, > 95 % *de*). We have previously shown^[11] that **1a** and other phosphine oxides that containing a P–CH₃ fragment are formed in the R_p form with (–)-menthol as the source of chirality. This was also confirmed for the scalemic oxides (R_p)-**1b–d** (Figure 1), which shows that the introduction of an

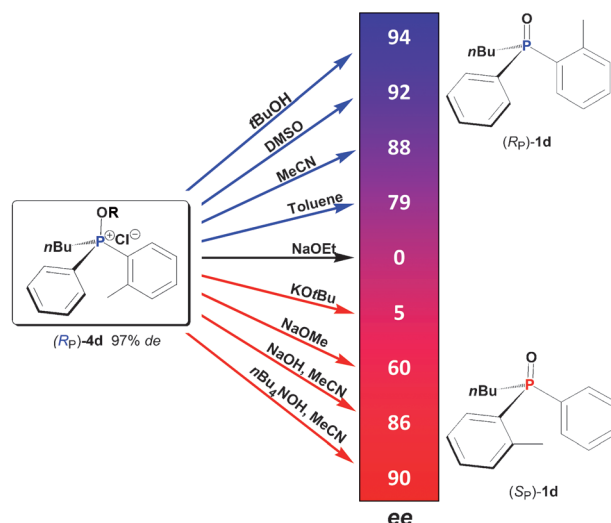
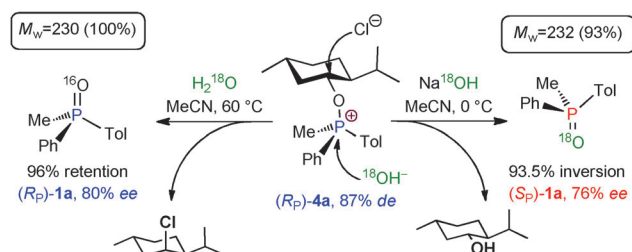


Figure 1. Bifurcation of reactivity: controlled transformation of **4d** into **1d** and stereochemical spectrum showing intermediate and ultimate attained *ee* values. R = (–)-menthyl.

extended *n*-alkyl chain resulted in true amplification of stereoselectivity without a change of its sign, and it is therefore likely that the same selection mechanism is responsible for the stereochemical differentiation.

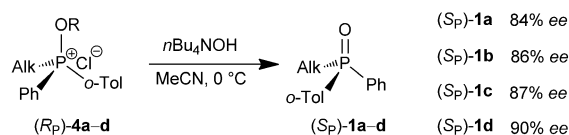
With the R_p selectivity improved, we then focused on the preparation of the opposite S_p enantiomer of **1**. Although this process would normally require (+)-menthol as the chiral auxiliary, one can evoke an alternative reaction pathway that involves a nucleophilic attack on the intermediate **4**,^[10,16] because the hydrolysis of (R_p)-**4** should in principle occur with inversion. On treatment with an excess of aqueous NaOH at 0 °C in acetonitrile for 30 min, salt (R_p)-**4a** (87 % *de*) gave the oxide (S_p)-**1a** (opposite configuration) in 76 % *ee* and 100 % yield, which corresponds to inversion of the configuration at the phosphorus center in 93.5 % of cases during the hydrolysis of (R_p)-**4a**. This experiment was repeated with ^{18}O -labeled reagents; (S_p)-**1a** was furnished with an ^{18}O incorporation of 93 %, whereas thermal collapse of (R_p)-**4a** in the presence of H_2^{18}O in acetonitrile gave only unlabeled (R_p)-**1a** in 80 % *ee*, which is in agreement with the proposed mechanism (Scheme 3).



Scheme 3. Translating regioselectivity into stereoselectivity: Retention of configuration is observed when (R_p)-**4a** collapses through nucleophilic attack of a chloride anion (C–O bond cleavage, going left); however, inversion accompanies alkaline hydrolysis of (R_p)-**4a** leading to (S_p)-**1a** (P–O bond cleavage, going right).

Further improvement of the selectivity could be attained by using aqueous Bu_4NOH in acetonitrile. When these conditions were applied to (R_p)-**4a–d**, scalemic (S_p)-**1a–d** were prepared in 84–90 % *ee* and quantitative yields (Scheme 4). Other nucleophiles, for example, alkali metal alkoxides, yielded **1** with a lower final *ee* value or in the presence of sodium ethoxide even in its racemic form.

As the reactions for the synthesis of enantioenriched phosphine oxides proceed with either retention or inversion, they can be viewed as a “stereochemical spectrum”, which is



Scheme 4. Alkaline hydrolysis of the alkoxyphosphonium salts (R_p)-**4a–d** accompanied by inversion of the configuration at the phosphorus center (initial *de* of **4** given in Table 1, quantitative conversion into **1a–d** determined by ^{31}P NMR spectroscopy). $R = (-)$ -menthyl.

shown in Figure 1 for (R_p)-**4d**. Thus, by carefully adjusting the reaction conditions, a highly *R*- or *S*-selective stereochemical outcome can be achieved with this chiral-resolution method. The process can be conveniently run on a gram scale with high selectivity; for example, the *R* and *S* enantiomers of the oxide **1d** were obtained in 94 and 90 % *ee*, respectively, and the pure oxides **1a–d** can be isolated in 91–96 % yield (for details, see the Supporting Information). Furthermore, the chiral auxiliary (–)-menthol can be recovered after the inversion process.

In conclusion, we have achieved a critical leap in the stereoselectivity of dynamic resolution reactions of tertiary phosphine oxides, owing to three factors. First, an extension of the alkyl chain attached to the phosphorus atom led to significantly increased intrinsic diastereoselectivity. Second, an enantioselectivity of greater than 98 % was attained for the following step by rigorously controlling stereochemical erosion. Finally, the inversion of the stereochemical outcome using the same chiral auxiliary makes this approach very powerful for the practical preparation of various P-stereogenic compounds from the same reaction mixture. We believe that this is the first example in chemistry where dual chiral resolution of a *racemic* substrate (rather than a prochiral entity) was achieved via an intermediate whose bifurcated reactivity leads to the two opposite enantiomers because of two different mechanistic paths.

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