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A facile and practical preparation of *P*-chiral phosphine oxides†

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A practical and cost-effective synthetic method of *P*-chiral diarylalkyl, aryldialkyl, and triaryl phosphine oxides by using readily available chiral diphenyl-2-pyrrolidinemethanol as the auxiliary is developed. The long-standing racemization issue during solvolysis has been addressed and well controlled by employing a suitable solvent, a low reaction temperature, and an appropriate reaction time.

The preparation of *P*-chiral phosphorus compounds has received significant attention, not only because of the increasing applications of *P*-chiral phosphorus ligands for asymmetric catalytic reactions,[1,2] but also due to the ever-growing number of *P*-chiral oligonucleotide drugs in the pharmaceutical industry.[3] Over the last several decades, a series of efficient synthetic methods of *P*-chiral phosphorus compounds have been developed, by employing a number of chiral auxiliaries (Fig. 1). Among them, Jugé's ephedrine,[4] Corey's camphor,[5] Buono's menthol,[6] Jones' oxazolidinone,[7] Baran's limonene-based thiol,[8] Han's 2-(1-aminoethyl)-4-chlorophenol,[9] Verdaguer's amino indanol,[10] Andrioletti's 2-amino-cyclohexanol,[11] and Framery's glucosamine[12] are most well-known, however, they are not without issues. For example, some chiral auxiliaries such as ephedrine were controlled substances, not amenable for scale-up activities; some were relatively expensive, requiring a multi-step synthetic sequence from readily available starting material. More importantly, some phosphine oxides prepared with reported methods were not highly optically pure, indicating a severe racemization during preparation. Thus, a practical, economically viable, and racemization-free preparation of *P*-chiral phosphine oxides remains highly desirable. Herein we report a facile and practical preparation of *P*-chiral phosphine oxides using readily available chiral diphenyl-2-pyrrolidinemethanol as the auxiliary.[13] The method features good scalability, excellent stereochemical control, broad substrate scope, and minimal enantiomeric loss.

We reasoned that an auxiliary from a chiral α-amino acid would be among the most ideal in terms of both ready availability and cost effectiveness. In addition, excellent stereocontrol was reported in the reaction between arylphosphoryl dichloride and chiral diphenyl-2-pyrrolidinemethanol, which was readily available as a proline derivative.[13b,c] Thus, the main issue was the stereospecificity of the three consecutive displacements with Grignard reagents or solvent (Scheme 1), which was not solved completely from the literature reports.[4,8] Herein we detailed our studies on the stereocontrol during the consecutive displacements, leading to a practical synthetic method for a variety of diarylalkyl, aryldialkyl, and triaryl phosphine oxides.

We commenced our synthesis with the reaction between (*S*)-diphenyl-2-pyrrolidinemethanol (**1**) and $PhP(O)Cl_2$ to form

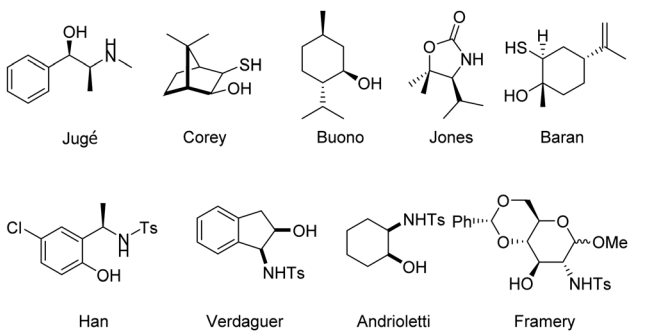

Fig. 1 Reported chiral auxiliaries applied to the synthesis of *P*-chiral phosphorus compounds.

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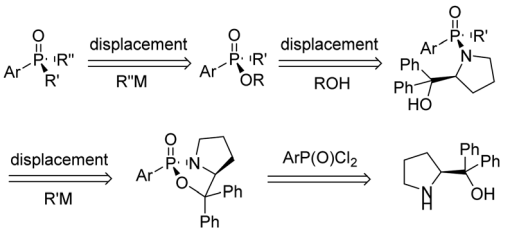
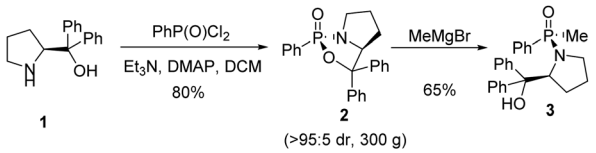


Scheme 1 Synthetic design of *P*-chiral phosphine oxides with diphenyl-2-pyrrolidinemethanol as a chiral auxiliary.

1,3,2-oxazaphospholidine-2-oxide **3** (Scheme 2). By employing a reported procedure[13c] with trimethylamine and DMAP as the bases, the desired product **2** was obtained in 80% yield with >95 : 5 diastereomeric ratio at a 300 g scale. The excellent diastereomeric control and suitability for scale-up activity set the foundation for studying the stereospecific displacements in the next three steps. Pleasingly, treatment of **2** with methyl Grignard reagent formed **3** in 65% yield as a single diastereomeric isomer. Since the direct S_N2 replacement of (*S*)-diphenyl-2-pyrrolidinemethanol under basic conditions was not possible, the stage was set to remove the chiral auxiliary stereospecifically by solvolysis in alcohol (Table 1).

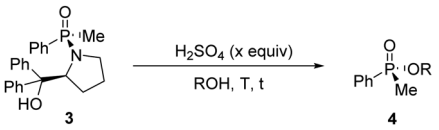
It was reported that alcoholic solvolysis could smoothly remove the diphenyl-2-pyrrolidinemethanol component,[13a] however, often resulting in diminished enantioselectivities. We reasoned that the enantiomeric loss could be largely due to a second solvolysis of the resulting product **4** (Scheme 3), which could be well controllable after optimization of the reaction conditions (Table 2).

Thus, the alcoholysis conditions were studied in order to find a best yield and ee. Screening of the solvent from methanol, to ethanol, to isopropanol under conditions of 1 equiv. H_2SO_4 at −78 °C for 2 h showed that both methanol and ethanol provided excellent ees as well as yields, while a low conversion was obtained with isopropanol as the solvent (entries 1–3). Further studies after a number of experiments showed that more reliable yields and ees were obtained in ethanol, which was chosen as the solvent for further studies. The amount of H_2SO_4 appeared to play a significant role in both the yields and enantioselectivities. While employment of 0.5 equiv. H_2SO_4 proved to be less reactive (entry 4), more H_2SO_4 turned out to be detrimental to both the yields and enantioselectivities (entries 4–8). The reaction temperature was highly important to inhibit the second ethanolysis and prevent racemization. A low reaction temperature (<70 °C) was the key to keep the high enantioselectivity, which was not mentioned or controllable with Jugé's protocol and others. Indeed, a significant loss of ee (30%) was observed when ethanolysis was conducted at r.t. and only 10% ee was observed from the reaction



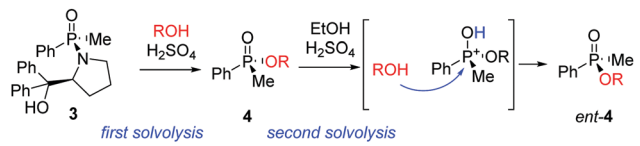
Scheme 2 Synthesis of **3**.

Table 1 Alcoholysis of **3**



Entry	R	*x*	*T* (°C)	*t* (h)	Yield (%)	ee
1	Me	1	−78	2	90	98
2	iPr	1	−78	2	40	96
3	Et	1	−78	2	90	98
4	Et	0.5	−78	2	20	98
5	Et	2	−78	2	80	94
6	Et	3	−78	2	80	94
7	Et	5	−78	2	75	90
8	Et	10	−78	2	60	87
9	Et	1	−70	2	90	98
10	Et	1	−50	2	60	80
11	Et	1	−30	2	65	75
12	Et	1	−10	2	50	51
13	Et	1	0	2	45	45
14	Et	1	r.t.	2	45	30
15	Et	1	80	2	50	10
16	Et	1	−78	1	55	98
17	Et	1	−78	2	90	98
18	Et	1	−78	3	80	87
19	Et	1	−78	6	74	63
20	Et	1	−78	12	60	37

Conditions: the reactions were conducted in alcohol in the presence of *x* equiv. H_2SO_4 at the specified reaction temperature *T* for *t* h. Isolated yields. The enantioselectivities were determined by chiral HPLC.

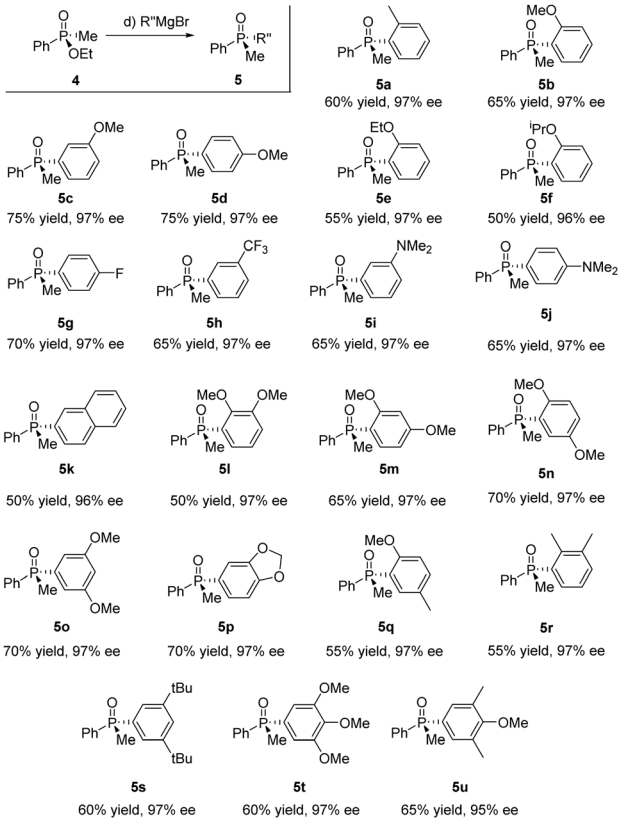


Scheme 3 Rationale of racemization.

carried out at 80 °C. The reaction time was also crucial to the enantioselectivity. While the methanolysis was not complete in 1 h (entry 16), a longer reaction time (>3 h, entries 18–20) gave low ees. The results were consistent with the mechanism proposed in Scheme 3, which provided an excellent yield and ee under the optimized conditions (2 equiv. H_2SO_4, −78 °C, 2 h) and significant ee loss was observed with a prolonged reaction time or a higher reaction temperature. Thus, compound **4** was prepared at 98% ee in 90% yield under the optimized conditions at a decagram scale.

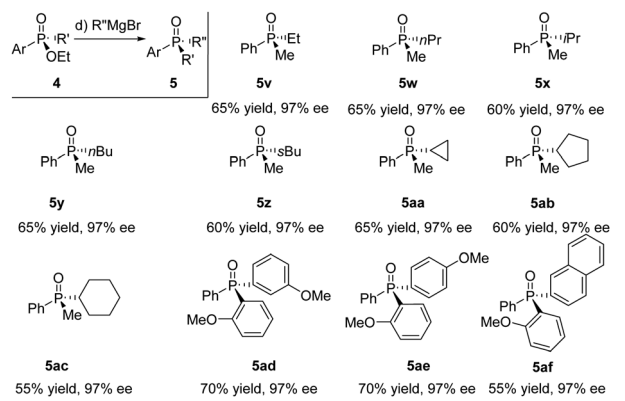
With ample **4** in hand, our next task was to develop a stereospecific displacement of **4** with a Grignard reagent. Gratifying, the reaction of **4** with a number of aryl Grignard reagents with different steric and electronic properties proceeded smoothly at r.t. with THF as the solvent system (Table 3). Thus, a series of chiral diarylalkyl phosphine oxides were formed in good yields and excellent enantioselectivities. Either electron-donating or -withdrawing substituents at *ortho*, *meta*, or *para* positions were all compatible. Functionalities such as methoxy, dimethylamino, acetal, and trifluoromethyl were all compatible. It should be noted that most *P*-chiral phosphine oxides were obtained in >= 95% ee with minimum

Table 2 Scope of *P*-chiral diarylalkyl phosphine oxides[a]



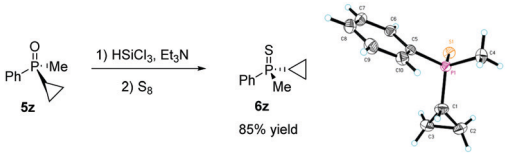
[a] Conditions: the reactions were conducted in THF at r.t. in the presence of **4** (1 mmol) with R″MgBr (5 equiv.) overnight (12 h). Isolated yields. The enantioselectivities were determined by chiral HPLC.

Table 3 Scope of *P*-chiral diarylalkyl and triaryl phosphine oxides[a]

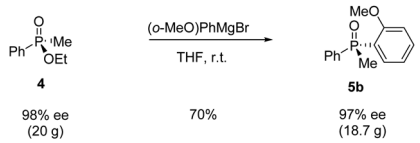


[a] Conditions: the reactions were conducted in THF at r.t. in the presence of **4** (1 mmol) with R″MgBr (5 equiv.) overnight (12 h). Isolated yields. The enantioselectivities were determined by chiral HPLC.

enantiomeric loss. We also looked into the reaction of **4** with alkyl Grignard reagents (Table 3). Under similar reaction conditions, primary alkyl, secondary alkyl, and cyclic alkyl Grignard reagents were all suitable, providing the corresponding aryldialkyl phosphine oxides **5v–5ac** in moderate to good yields and excellent enantioselectivities without loss of optical purity. Under similar reaction conditions, triaryl phosphine oxides **5ad–af** were also prepared successfully in excellent ee's and satisfactory yields.



Scheme 4 Synthesis of phosphine sulfide **6z**.



Scheme 5 Gram-scale synthesis of phosphine oxide **5b**.

In order to rationalize the stereochemical transformation of the sequence, the absolute stereochemistry of **5z** was studied by reduction with $HSiCl_3/Et_3N$ and further treatment with S_8 to form phosphine sulfide **6z**, whose absolute configuration was determined by X-ray crystallography[14] (Scheme 4). The inversed stereochemical process of the reduction of phosphine oxide under conditions $HSiCl_3/Et_3N$ determined the *S*-configuration of **5z**. On the basis of the absolute configuration of **2**, **3**, **4**, and **5**, we concluded that the three consecutive displacements from **2** to **5** are all inversed processes.

To demonstrate the practicality of this method with (*S*)-diphenyl-2-pyrrolidinemethanol as the auxiliary, the final displacement of **4** with (*o*-MeO)PhMgBr was conducted at 20 gram scale, and the resulting product **5b** was obtained in 70% yield and 97% ee (18.7 g) (Scheme 5).

In conclusion, we have developed a practical and cost-effective synthetic method of *P*-chiral diarylalkyl, aryldialkyl, and triaryl phosphine oxides by using readily available chiral diphenyl-2-pyrrolidinemethanol as the auxiliary. The long-standing racemization issue during solvolysis was addressed and solved by employing a suitable solvent, a low reaction temperature and a suitable reaction time. The high enantioselectivities (>= 95% ee) and scalability of this method should facilitate the study of various *P*-chiral ligands[15] in asymmetric catalysis and research on *P*-chiral oligonucleotide drugs in the pharmaceutical industry.

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Conflicts of interest

There are no conflicts to declare.

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