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Enantioselective synthesis of secondary phosphine oxides from (R_P)-(−)-menthyl hydrogenophenylphosphinate

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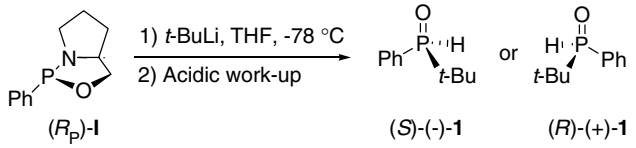
Abstract—Alkyl- and arylphenylphosphine oxides can easily be synthesized with an excellent enantiomeric excess starting from diastereomerically pure (R_P)-(−)-menthylhydrogenophenylphosphinate and organometallic reagents.

Enantiomerically pure secondary phosphine oxides (SPOs) have so far mainly been obtained through chemical resolution[1] or chromatographic separation[2] but rarely by asymmetric synthesis.[3] Such compounds proved to be promising ligands for not only asymmetric catalysis,[2,4] but also precursors of chiral tertiary mono- and diphosphine oxides.[1,5] In a previous Letter,[3a] we described the first synthesis of each enantiomer of *tert*-butylphenylphosphine oxide through an oxazaphospholidine precursor (R_P)-**I** based on (*S*)-prolinol (Scheme 1). However, this method could not be extended to a wide variety of alkyl and aryl substituents on the phosphorus atom. We thus focused on new routes and precursors for efficient and general access to enantiomerically pure SPOs.

The chiral pool is a precious source of asymmetric inductors. In particular, alcohols such as (−)-menthol

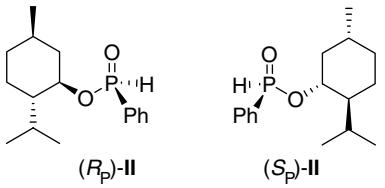


Scheme 1. Asymmetric synthesis of *tert*-butylphenylphosphine oxide **1** from oxazaphospholidine (R_P)-**I**.

can be successfully used for the multigram-scale preparation of diastereomerically pure phosphinates such as **II**, which was successfully crystallized as a single diastereoisomer by Mislow and co-workers (Scheme 2).[6]

Emmick and Letsinger reported that benzylmagnesium chloride reacts cleanly with (−)-menthyl phenylphosphinate **II** to afford unsymmetrical SPO, through substitution of (−)-menthyloxy group. However, the diastereomers of **II** could not be separated to be used in the enantioselective synthesis of a SPO.[7] This method, combined with the straightforward crystallization procedure of diastereomerically pure (R_P)-**II** appeared to be a promising route to enantiomerically pure SPOs that we decided to further explore. In this Letter, we report the first enantioselective synthesis of SPOs using various organometallic reagents for nucleophilic substitution of (−)-menthyloxy group.

We firstly explored the addition of an excess (5 equiv) of *tert*-BuMgCl on (R_P)-**II** at −78 °C (Table 1). Grignard reagent (1 equiv) is required to abstract the proton carried by (R_P)-**II**, generating an intermediate species



Scheme 2. Structure of menthyl hydrogenophenylphosphinate diastereoisomers (R_P)-**II** and (S_P)-**II**.

Keywords: Chiral secondary phosphine oxides; (−)-Menthol; Enantioselective synthesis; Diastereomerically pure phosphinate.
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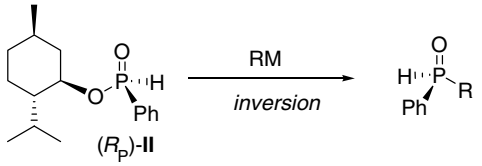
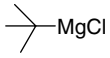
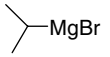
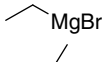
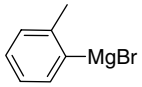
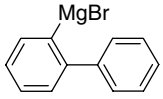
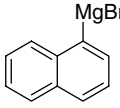
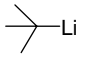
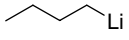
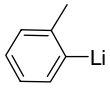
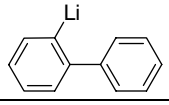
Table 1. Asymmetric synthesis of secondary phosphine oxides from organometallic precursors RM and (R_P)-**II**



Entry	RM	Product	Yield[a] (%)	ee[b] (%)
1		**1**	86	0
2		(−)-**2**	89	56
3		(−)-**3**	60	82
4		(+)-**4**	84	68
5		(−)-**5**	88	2
6		(−)-**6**	91	15
7		(*S*)-(−)-**1**	80	86 (80)[c]
8		(−)-**7**	81	96
9	Me–Li	(−)-**8**	76	97
10		(+)-**4**	74	98
11		(−)-**5**	98	96

[a] Yields after purification.[12]

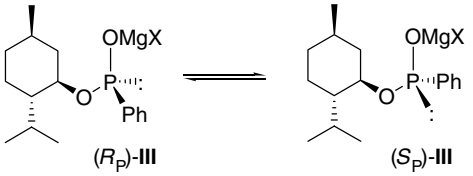
[b] Enantiomeric excesses were determined by HPLC analysis on chiralpak AD-H or chiralcel OD-H column at $\lambda = 254$ nm; flow rate 1 mL/min; eluent: hexane/*i*-PrOH mixtures.

[c] Solution of (R_P)-**II** in dry THF was added dropwise to a stirred and cooled (−78 °C) solution of *tert*-BuLi.

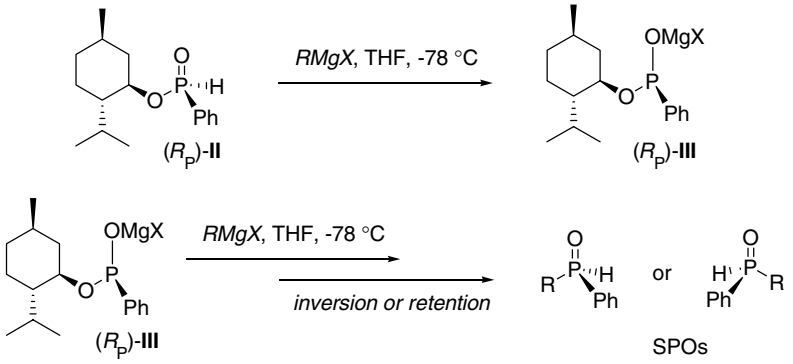
(R_P)-**III** (Scheme 3), which then undergoes nucleophilic substitution with the remaining excess of organometallic species.

The mixture was allowed to slowly come back to room temperature, and the conversion, checked by ^{31}P NMR, appeared to be complete (Table 1, entry 1). However, *tert*-butylphenylphosphine oxide **1** was obtained as a racemic mixture. To evaluate the impact of the alkyl group of the Grignard reagent on the enantioselectivity of the substitution on the phosphorus centre, we conducted the same experiment using *i*PrMgBr as the alkylating agent. The reaction proceeded cleanly and surprisingly the enantiomeric excess measured on *iso*-propylphenylphosphine oxide **2** was 56% (Table 1, entry 2). The best enantiomeric excess (82%) was observed with primary Grignard reagents such as EtMgBr (Table 1, entry 3). In order to further explore the influence of the Grignard reagent on these variations of stereoselectivity, a series of arylmagnesium species were also tested in the same previous conditions. *o*-TolylMgBr, *o*-biphenylMgBr and 1-naphthylMgBr addition on (R_P)-**II**,[8] respectively, yielded the corresponding SPOs **4**–**6** with good to poor ees (Table 1, entries 4–6).

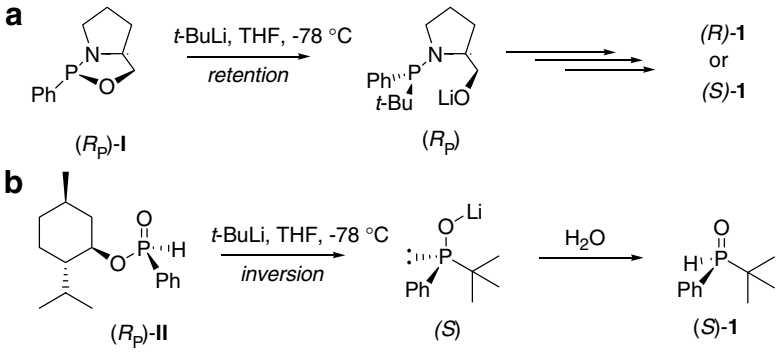
The loss of enantioselectivity was therefore imputed to the excess of Grignard reagent involved in the reaction and most likely to the steric hindrance of the nucleophilic fragment. In order to determine whether the reactant (R_P)-**II** or the SPO product undergoes epimerization on the phosphorus atom, both the compounds were tested individually. As a proof-of-principle, each phosphorus substrate (R_P)-**II** and **4** was treated in the same previous conditions at −78 °C with 1 equiv of *o*-tolylMgBr followed by hydrolysis under acidic conditions. Phosphinate (R_P)-**II** was converted into an equimolar mixture of diastereoisomers (R_P)-**II** and (S_P)-**II**, whereas an enriched mixture of **4** (68% ee) remained unaffected by the confrontation with the Grignard reagent. Thus, using 1 equiv of Grignard reagent results in the epimerization of (R_P)-**II** probably through the formation of intermediate (R_P)-**III** (Scheme 4).



Scheme 4. Epimerization of intermediate species **III**.



Scheme 3. A possible pathway for the enantioselective synthesis of SPOs using Grignard reagents.



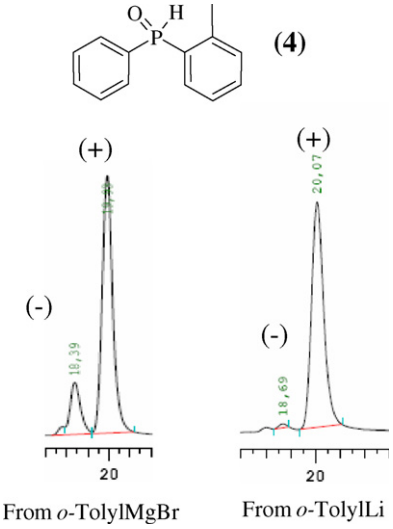
Scheme 5. Compared stereoselectivity for the asymmetric synthesis of (*S*)-**1** as a major product. Nucleophilic attack of *tert*-BuLi proceeds with (a) retention of configuration on oxazaphospholidine (R_P)-**I**, (b) inversion of configuration on phosphinate (R_P)-**II**.

Such an observation is in agreement with previous results indicating that phosphinate species epimerizes in the presence of bases.[6]

These results led us to the conclusion that sterically hindered Grignard reagent used for the substitution reaction of the menthyloxy group on the deprotonated phosphinate **II** proceeds slower than its epimerization. We therefore tested other organometallic species and naturally turned to commercially available or readily accessible organolithium species to generate enantiomerically enriched SPOs. Comparatively to the Grignard analogue, *tert*-butyllithium (2 equiv) in THF at −78 °C reacted as cleanly but yielded the corresponding SPO (*S*)-(−) **1**[9] with a significant increase in enantiomeric excess (86%) (Table 1, entry 7). Interestingly, whereas the nucleophilic attack on oxazaphospholidine precursor (R_P)-**I** proceeds with retention of configuration at the phosphorus centre,[3a] in the case of phosphinate species derived from menthol (R_P)-**II** the substitution of the menthyloxy fragment occurs with inversion of configuration (Scheme 5).

Similarly, *n*-BuLi and MeLi reacted stereoselectively on (R_P)-**II** yielding *n*-butylphenylphosphine oxide **7** and methylphenylphosphine oxide **8** with 96% and 97% ee, respectively (Table 1, entries 8 and 9). This method was extended to aromatic nucleophiles using the corresponding lithiated species. *o*-Tolyl- and 2-biphenyl- were prepared by the treatment of the corresponding bromide precursors at −30 °C in THF with 2 equiv of *tert*-butyllithium.[10] This general procedure afforded the desired SPOs **4** and **5** with excellent enantiomeric excess (Table 1, entries 10 and 11). HPLC chromatograms reported in Scheme 6 illustrate the contrasted enantioselectivities depending on the nature of the metal on the tolyl derivative **4**, which could be obtained from *o*-TolylLi almost as a single enantiomer without recrystallization.[11] In addition this procedure allows recovery of the (−)-menthol chiral auxiliary without any loss of optical activity.

In conclusion, we have explored the influence of the metal and of the alkyl fragment of various organometallic species on the obtention of chiral SPOs from a readily accessible diastereomerically pure phosphinate precursor. The use of an organolithium reagent offers a straightforward access to phosphorus species with excellent optical purities. Interestingly, whereas oxazaphospholidines react with the retention of configuration with organolithium species, the phosphinate precursors afford the same products with inversion of configuration. Organolithium reagents of various natures, combined with diastereomerically pure phosphinates, should therefore prove to be a valuable method providing an easy entry to chiral SPOs and subsequent related ligands such as tertiary mono- and diphosphine oxides. Further investigations of these optically active SPOs ligands in enantioselective catalytic carbon–carbon bond forming reactions will be reported in due course.



Scheme 6. HPLC chromatograms of SPO mixtures **4** obtained from *o*-TolylMgBr (left) and *o*-TolylLi (right).

Acknowledgements

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8. *General procedure:* To a suspension of Mg (6 mmol, $m = 146$ mg) activated by 1% of 1,2-dibromoethane in dry THF (1 mL) was added dropwise a solution of the halogenoalkane (5 mmol, c 1.25 M) at room temperature followed by heating up at reflux for 15 min. The former solution is then added at once at −78 °C to a solution of phosphinate (R_P)-**II** ($n = 1$ mmol, 280 mg, c 1 M in THF). After stirring at room temperature, the reaction mixture is then diluted with Et_2O (5 mL) and the organic phase is washed with a solution of H_2SO_4 (0.02 M, 4 mL). After separation, the aqueous phase is re-extracted twice with AcOEt (2 × 5 mL). The combined organic phases are dried over $MgSO_4$, concentrated under vacuum and a large part of the (−)-menthol was removed by means of bulb to bulb distillation (60 °C, 10^{-1} mm Hg). The crude material obtained is then purified by chromatography on a short plug of deactivated silica gel (10% H_20) using Et_2O/light petroleum/MeOH mixtures to afford compounds **1**–**6**.
9. Retention times on identical conditions were related to absolute configuration. See Ref. 5c.
10. When *n*-BuLi was used to generate aryllithium, (−)-menthyl *n*-butylphenylphosphinate was obtained as a major product. Such species is likely to be generated by the attack of **II**, after deprotonation, on 1-bromobutane. In comparison, *tert*-BuLi produces *tert*-butylbromide as a side product which undergoes elimination upon reaction the excess of *tert*-BuLi, being hence converted to isobutene which is cleanly expelled from the reaction mixture. If the reaction is conducted above −30 °C, the alkyllithium reagents react slowly with THF.
11. *Typical procedure for the preparation of (+)-phenyl-o-tolylphosphine oxide* (+)-**4**: *tert*-BuLi (2.6 mL of 1.7 M solution in pentane, 4.4 mmol) was added slowly to a stirred and cooled (−30 °C) solution of 2-bromotoluene (377 mg, 2.2 mmol) in dry THF (2 mL) and stirring was continued for 1 h. The former solution is then added at once at −78 °C to a solution of phosphinate (R_P)-**II** ($n = 1$ mmol, 280 mg, c 0.5 M in THF) and the solution was allowed to come back to room temperature. The reaction mixture is then diluted with Et_2O (5 mL) and NH_4Cl saturated aqueous solution (5 mL). The organic phase was separated off, and the aqueous phase was extracted with AcOEt (2 × 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated under vacuum and 118 mg of (−)-menthol was removed by means of bulb to bulb distillation (60 °C, 10^{-1} mm Hg). Purification of the crude by chromatography on a short plug of deactivated silica gel (10% H_2O) using Et_2O/light petroleum/MeOH 4/1/0.05 as eluent, afforded 74% of (+)-**4** (98% ee) as a white solid. Enantiomeric excess was determined by HPLC analysis on a Chiralpak AD-H column at $\lambda = 254$ nm; flow rate 1 mL/min; eluent: hexane/*i*-PrOH 90/10, R_t: (−) = 18.7 min, (+) = 20.1 min $[\alpha]_D^{20}$ ($CHCl_3$, c 1.6) = +2.0. Mp 157–158 °C. R_f (Et_2O) 0.14; IR (KBr) ν 3352, 3059, 2954, 2922, 2869, 1708, 1594, 1454, 1439, 1178 cm^{-1}; ^{31}P {^1H} NMR (81 MHz, $CDCl_3$): δ 22.84 (s). ^1H NMR ($CDCl_3$, 200 MHz): δ 2.33 (s, 3H), 8.07 (d, $^1J_{P\text{-}H} = 480.2$ Hz, 1H), 7.15–7.36 (m, 2H), 7.38–7.75 (m, 4H), 7.77–7.85 (m, 3H). ^{13}C {^1H} NMR ($CDCl_3$, 50 MHz): δ 20.2 (d, $^3J_{P\text{-}C} = 6.7$ Hz), 126.0 (d, $J_{P\text{-}C} = 13.5$ Hz), 128.7 (d, $^1J_{P\text{-}C} = 26.0$ Hz), 128.9 (d, $J_{P\text{-}C} = 12.7$ Hz, 2C), 130.5 (d, $^2J_{P\text{-}C} = 4.7$ Hz), 130.8 (d, $J_{P\text{-}C} = 11.4$ Hz, 2C), 131.4 (d, $J_{P\text{-}C} = 10.3$ Hz), 132.2 (d, $J_{P\text{-}C} = 11.1$ Hz), 132.4 (s, 2C), 132.8 (d, $J_{P\text{-}C} = 2.5$ Hz), 141.4 (d, $^1J_{P\text{-}C} = 9.0$ Hz).
12. (a) For the synthesis of unsymmetrical SPOs involving displacement of alkoxide by a Grignard reagent see: Ref. 7; (b) Busacca, C. A.; Lorenz, J. C.; Grinberg, N.; Haddad, N.; Hrapchak, M.; Latli, B.; Lee, H.; Sabila, P.; Saha, A.; Sarvestani, M.; Shen, S.; Varsolona, R.; Wei, X.; Senanayake, C. H. *Org. Lett.* **2005**, *7*, 4277–4280; (c) Olszewski, T. K.; Boduszek, B.; Sobek, S.; Kozlowski, H. *Tetrahedron* **2006**, *62*, 2183–2189.