

Bulky, Optically Active P-Stereogenic Phosphine–Boranes from Pure H-Menthylphosphinates

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Supporting Information

ABSTRACT: The transformation of readily available pure-H-menthylphosphinates into chiral phosphinous acid-boranes permits the elaboration of bulky P-stereogenic secondary phosphine-boranes. Taking advantage of the synthetic potential of these compounds, a broad range of hindered P-chiral tertiary phosphine-boranes has been prepared with excellent enantiomeric excesses. The utility of bulky o-tolylphosphines was illustrated by the synthesis of a rare enantiopure phosphapalladacycle (S_{P}, S_{P}) -12.

The development of new metal-catalyzed pathways calls for L the design of new phosphine ligands with emphasis on the electronic and steric parameters.¹ For instance, electron-rich and hindered-tertiary phosphines are of paramount importance in C-C bond-forming reactions.² Although various methods to prepare these ligands are available, very little attention has been paid to enantiomerically pure counterparts useful in asymmetric catalysis.³ Processes leading to enantiomerically pure phosphorus compounds for asymmetric catalysis still remain a challenging topic.⁴ In this context, during the past decade, the synthesis of P-stereogenic phosphines has been an intensive field of research.⁵ P-stereogenic phosphines are very attractive since the element of chirality is brought closer to the metal center in organometallics or metal complexes.⁶ To date, the method of Jugé and co-workers for the preparation of optically active tertiary phosphine-boranes is the most convenient in terms of versatility and stereoselectivity.⁷ However, the introduction of bulky groups by this methodology remains difficult to achieve.⁸ Dynamic resolution/alkylation of lithiated tert-butylarylphosphine-boranes with (-)-sparteine is useful procedure to alleviate these difficulties.⁹ Recently, Pietrusiewicz and Stankevic have also shown that the resolution of tert-butylphenylphosphinous acid-borane offers an entry for the preparation of P-stereogenic compounds containing a *tert*-butyl substituent.¹⁰ Our interest in enantioselective catalysis¹¹ has prompted us to develop the synthesis of chiral secondary phosphine oxides (SPOs) as chiral preligands.¹² Recently, we disclosed a straightforward route to optically active phosphinous acid-boranes from SPOs.¹³ In continuation of these studies, we decided to examine the possibility to convert SPOs to optically active hindered phosphine-boranes. Hopefully this approach would preclude the P=O bond reduction which is difficult to achieve when stereochemical control is required.¹⁴ Herein, we report a convenient procedure for the synthesis of optically active hindered tertiary phosphine-boranes and their utility for the enantioselective synthesis of chiral phosphapalladacycle.

Scheme 1. Synthesis of Diastereomerically Pure H-Menthylphosphinates 1^a



^a Reagents and conditions: a) NaH, rt, THF; b) PCl₃, -50 °C, THF; c) ArMgCl, -50 °C, THF; d) two recrystallizations from hexane at -20 °C for 48 h. Tol = *o*-tolyl; Naph = 1-naphthyl.

Scheme 2. Preparation of Optically Pure Phosphinous Acid–Boranes 4^a



^a Reagents and conditions: a) *t*-BuLi (2.2 equiv), -78 °C, THF; b) H₂O, H⁺; c) recrystallization from hexane/Et₂O; d) *n*-BuLi, -78 °C, THF; e) TMSCl, $-78 \,^{\circ}\text{C} \rightarrow \text{rt}$, THF; f) BH₃·SMe₂, THF; g) TBAF, THF.

First, we prepared various H-menthylphosphinates 1a-c from inexpensive PCl_3 and (-)-menthol through addition of arylmagnesium bromides to dichloro-((-)-menthyloxy)phosphine 2. Diastereomerically pure 1a-c were obtained after two recrystallizations on the multigram scale (up to 50 g).¹⁵ The absolute configuration at the phosphorus atom was determined by X-ray structural analysis for 1c and assigned by deduction for **1b** (Scheme 1).

New enantiopure SPOs 3a-c were prepared and converted to chiral phosphinous acid-boranes 4a-c according to our procedures (Scheme 2).¹³

Second, we examined the reactivity of various chiral phosphinous acid-boranes 4 in stereoselective transformations. The development of this method would be a straightforward entry to optically pure hindered tertiary phosphine-boranes. Starting from 3b, we first focused on the formation of

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Scheme 3. Conversion of Optically Pure (S_P) -4b into Secondary Phosphine–Borane $(S_{\rm P})$ -8b^a



^a Reagents and conditions: a) MeSO₂Cl, Et₃N, 0 °C, CH₂Cl₂; b) (MeSO₂)₂O, Et₃N, -15 °C, CH₂Cl₂; c) NaBH₄, 0 °C \rightarrow rt, EtOH.

Scheme 4. Preparation of Enantiopure Bulky Secondary Phosphine-Boranes 8



sulfonyloxyphosphine-boranes 5 as key precursor of sec-phosphine-boranes 8. Attempts to apply the Pietrusiewicz and Stankevic procedure using 4b instead 4a proved to be unsuccessful. Indeed, when enantiopure 4b was treated with mesyl chloride in the presence of triethylamine in dichloromethane to form mixed anhydride 5b, a complex mixture was obtained in which the desired product was contaminated by products 6 and 7 (Scheme 3a).¹⁶

The formation of these could be explained by the presence of chloride ions in the medium. A competitive nucleophilic substitution takes place to form chlorophosphine-borane 6, which then reacts with deprotonated 4b to give phosphinous acid anhydride bis-borane 7. Noteworthy in this case is that the reaction carried out with mesyl anhydride instead of mesyl chloride resulted in the total suppression of byproducts. The resulting mixed anhydride (S_P) -**5b** was then reduced by sodium borohydride in ethanol to afford cleanly (Sp)-8b in 90% yield after purification.¹⁷ The whole transformation can be achieved in two successive steps with excellent yields (Scheme 3b).¹⁸

These promising results prompted us to test other chiral phosphinous acid-boranes 4 using the optimized conditions (See experimental section in SI). We were pleased to observe that this one-pot procedure afforded the desired bulky P-stereogenic sec-phosphine-boranes 8 in satisfactory yields (Scheme 4). This new procedure for the preparation of this class of compounds is complementary to the related approaches.¹⁹ As such, taking advantage of the reactivity of the P-H bond, the synthetic potential of these compounds opens new ways to a wide range of chiral P-stereogenic phosphines.

Having in hand the sec-phosphine-boranes 8, the synthesis of optically pure tertiary hindered phosphine-boranes 9 was investigated. Alkylation of sec-phosphine-boranes was performed with various halide compounds to extend its applicability (Table1).

By using this procedure, the syntheses were achieved with high levels of enantioselectivity. Absolute configuration of 9a, 9b, 9h,

1	(<i>S</i> _P)-8a	Mel	(<i>R</i> _P)-9a	85	99
2	(<i>S</i> _P)-8a	PhCH ₂ Br	(<i>R</i> _P)-9b	91	98
3	(<i>S</i> _P)-8a	<i>▶ B</i> r	(<i>R</i> _P)-9c	83	89
4	(<i>S</i> _P)-8a	Br	(<i>R</i> _P)-9d	65	89
5	(<i>S</i> _P)-8a	Me_3SiCH_2I	(<i>R</i> _P)-9e	93 (87) ^c	86 (92)
6	(<i>S</i> _P)-8a	CI	(<i>R</i> _P)-9f	68	99
7	(<i>S</i> _P)-8a	CI CI	(<i>R</i> _P)-9g	60	86
8	(<i>S</i> _P)-8b	Mel	(<i>R</i> _P)-9h	77	98
9	(<i>S</i> _P)-8b	PhCH ₂ Br	(<i>R</i> _P)-9i	90	99
10	(<i>S</i> _P)-8b	<i>▶ B</i> r	(<i>R</i> _P)-9j	90 (82) ^c	78 (85)
11	(<i>S</i> _P)-8b	Br	(<i>R</i> _P)-9k	68 (61) ^c	77 (94
12	(S _P)-8c	Mel	(<i>R</i> _P)-91	89	91

^a Yield after purification. ^b Enantiomeric excess was determined by HPLC analysis (see Supporting Information). ^cYield after recrystallization. ^d Enantiomeric excess after recrystallization.

91 was established by comparison with known compounds,^{9c} and absolute configuration of 9i was established by X-ray structural analysis.²⁰ In accordance with Pietrusiewicz and Stankevic results, transformation of 4 into 9, resulted in inversion of configuration at phosphorus atom with excellent stereoselectivity.²¹ The highest enantioselectivities (>98 ee) were observed for compounds 9a, 9b, 9f, 9h and 9i (entries 1, 2, 6, 8, 9). P-stereogenic,N-bidentate ligand 9f seems to be promising for the design of new metal complexes and asymmetric catalysis.²² When allyl or propargyl bromide, (iodomethyl)trimethylsilane and furfuryl chloride were used as alkylating agents, tertiary phosphine-boranes 9c, 9d, 9e, 9g, 9j, 9k were obtained with fairly to good yields and satisfactory enantioselectivities (Entries 3, 4, 5, 7, 10, 11), which can be improve by a single crystallization when crystals are obtained. The loss of enantioselectivity could be imputed to the slow reaction at -78 °C. Thus, these results suggest that, on warming up the reaction media, the conjugated base of sec-phosphine-boranes 8 racemize slowly.²³

Ligand 9i containing o-tolyl substituent appears to be a good candidate for the preparation of optically pure metallacyle.²⁴ As a proof of principle, phosphapalladacycle (\pm) -11 was conveniently formed from the racemic free tertiary phosphine 10 and $Pd(OAc)_2$. The structure was in full agreement with the NMR data (Scheme 5a) and secured by a single-crystal X-ray analysis. Unfortunately, when the phosphapalladacyle formation was performed with chiral $(R_{\rm P})$ -9i, no suitable crystals of $(S_{\rm P}, S_{\rm P})$ -11 were obtained for X-ray spectroscopy. Attempted recrystallization of $(S_{P_1}S_{P_2})$ -11 resulted in partial degradation (black palladium deposit). Acetato to chloro ligand exchange for the phosphapalladacycle (\pm)-11 (LiCl, acetone, rt)²⁵ provided the

ee

 BH_3

9

Yielda

r-Bu

Table 1. Preparation of Optically Active Hindered Tertiary Phosphine-Boranes 9

1) n-BuLi, -78 °C

Product

2) RX

RX

 BH_3

8a Ar = Ph 8b Ar = o-Tol 8c Ar = Naph

Substrate

Entry

t-Bu

Scheme 5. Preparation of Optically Active Phosphapalladacycles $(S_{P_1}S_P)$ -11 and $(S_{P_2}S_P)$ -12^{*a*}



^{*a*} Reagents and conditions: a) DABCO, 50 °C, toluene; b) $Pd(OAc)_2$ (0.8 equiv); c) LiCl, rt, acetone/methanol; 3/1. DABCO = 1,4diazabicyclo[2.2.2]octane.



Figure 1. Crystal structure of complex *trans*- (S_{P},S_{P}) -**12** (ORTEP drawing showing thermal ellipsoids at 40% probability). Hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles (deg): C(1)-Pd(1) 2.039(5); Cl(1)-Pd(1) 2.460(1); Cl(2)-Pd(1) 2.416(1); P(1)-Pd(1) 2.203(1); C(1)-Pd(1)-Cl(2) 91.9(2); C(1)-Pd(1)-P(1) 83.8(2); Cl(1)-Pd(1)-Cl(2) 85.89(4); Cl(1)-Pd(1)-P(1)-P(1) 98.39(4).

chloropalladacycle (\pm)-12 which exhibits complex NMR spectrum. In contrast, with chiral ligand ($R_{\rm P}$)-9i, NMR spectrum of the phosphapalladacycle ($S_{\rm P}$, $S_{\rm P}$)-12 were dramatically simplified compared to (\pm)-12. Two diastereomeric complexes were observed in 2:1 molar ratio and mass spectroscopy data are in agreement with a dimeric structure, which suggested retention of configuration at phosphorus atom (Scheme 5b).^{26,27}

Ninety-five percent enantiomeric excess was determined by ³¹P NMR spectroscopy using known methods based on the formation of two monomeric diastereomers with (*S*)- α -methylbenzylamine²⁸ (see SI).

Finally, the optically pure *trans*-chloropalladacycle (S_P,S_P) -**12** was slowly crystallized in EtOH, and suitable crystals for X-ray analysis were isolated. The structure of (S_P,S_P) -**12** was unambiguously assigned and showed a square-planar geometry and retention of configuration at the phosphorus atom (Figure 1). To the best of our knowledge, structurally characterized enantiopure P-stereogenic phosphapalladacycles are scarce, and only one example of a chiral Pd(II) phosphapalladacycle has been reported so far.²⁹

To test the activity of (S_{P},S_{P}) -11, we briefly examined the asymmetric version of addition reaction of alkynes 14 to norbornadiene 13. Indeed, the Hermann–Beller phosphapallada-cycle was known as the key catalyst for this interesting transformation.³⁰ Our results are listed in Table 2.

We found that palladacycle (S_{P},S_{P}) -11 was a highly active catalyst for this addition reaction. Using mild conditions, all

Table 2. Asymmetric Addition of Alkynes 14 to 13



^{*a*} Yield after purification. ^{*b*} Enantiomeric excess was determined by HPLC analysis (see Supporting Information).

products were obtained in excellent yields (Table 2, entries 1-3). These preliminary results are promising since an enantiomeric excess of 36% was observed without optimization of the design of palladacycle (Table 2, entry 4).

In conclusion, a route to optically active electron-rich bulky P-stereogenic secondary and tertiary phosphine—boranes has been developed from (–)-menthol as convenient and friendly chiral auxiliary to prevent the utilization of (–)-ephedrine and (–)-sparteine. To make the most of the borane-free tolylphosphine **10** a rare enantiopure palladacycle ($S_{\rm P}$, $S_{\rm P}$)-**12** was prepared with retention of configuration at the phosphorus atom. Asymmetric addition reactions of alkynes to alkenes³¹ with this conformationally restricted chiral palladacycle as catalyst are in progress in our laboratories.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, compound characterization data, and spectra for all new compounds; CIF files for compounds **1c**, **11**, **9i**, and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) On the basis of the result wherein the other absolute configurations of compounds 9 were assigned by deduction. The X-ray structure of (R_p) -9i confirms our hypothesis for absolute configuration at the phosphorus atom of 1b.

(21) Reduction step occurs with total inversion of configuration, whereas the mesylation and alkylation steps proceed with full retention of configurations.

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(26) Comparison of the enantiomeric excesses of **9h** before and after the DABCO deprotection—reprotection sequence confirmed P-stereochemical integrity.

BH3	DABCO	- R'Me	1.2 BH3*SMe2	BH3
o-Tol VMe	50 °C, toluene, 1h	o-Tol [®] t-Bu	2h, rt	o-Tol VMe
(R_P)-9h 98.5 % ee				(R_P)-9h 97.8 % ee

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