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

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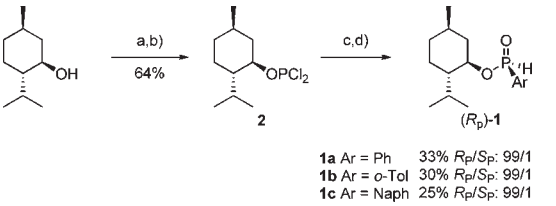
Supporting Information

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**.

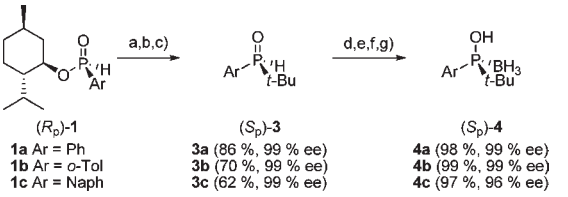
The development of new metal-catalyzed pathways calls for the design of new phosphine ligands with emphasis on the electronic and steric parameters.[1] For instance, electron-rich and hindered-tertiary phosphines are of paramount importance in C−C bond-forming reactions.[2] Although various methods to 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 catalysis[11] 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) PCl_3, −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) H_2O, H^+; c) recrystallization from hexane/Et_2O; d) *n*-BuLi, −78 °C, THF; e) TMSCl, −78 °C→rt, THF; f) $BH_3 \cdot SMe_2$, 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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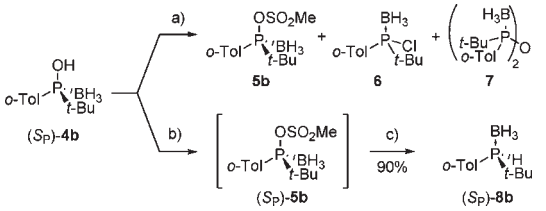
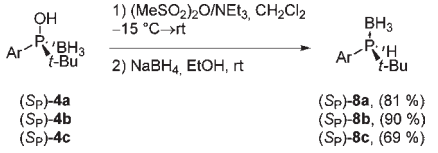
Scheme 3. Conversion of Optically Pure (S_P)-4b into Secondary Phosphine−Borane (S_P)-8b[a]



[a] Reagents and conditions: a) $MeSO_2Cl$, Et_3N, 0 °C, CH_2Cl_2; b) $(MeSO_2)_2O$, Et_3N, −15 °C, CH_2Cl_2; c) $NaBH_4$, 0 °C→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]

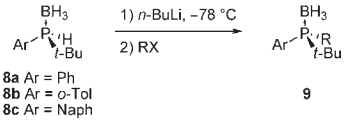
The formation of these could be explained by the presence of chloride ions in the medium. A competitive nucleophilic substitution takes place to form chlorophosphine−borane **6**, which then reacts with deprotonated **4b** to give phosphinous acid anhydride bis-borane **7**. Noteworthy in this case is 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 (S_P)-**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**,

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



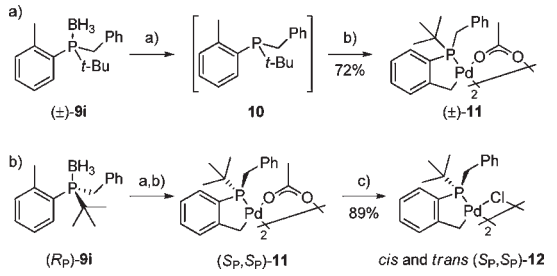
Entry	Substrate	RX	Product	Yield[a]	ee[b]
1	(S_P)-**8a**	MeI	(R_P)-**9a**	85	99
2	(S_P)-**8a**	$PhCH_2Br$	(R_P)-**9b**	91	98
3	(S_P)-**8a**		(R_P)-**9c**	83	89
4	(S_P)-**8a**		(R_P)-**9d**	65	89
5	(S_P)-**8a**	Me_3SiCH_2I	(R_P)-**9e**	93 (87)[c]	86 (92)[d]
6	(S_P)-**8a**		(R_P)-**9f**	68	99
7	(S_P)-**8a**		(R_P)-**9g**	60	86
8	(S_P)-**8b**	MeI	(R_P)-**9h**	77	98
9	(S_P)-**8b**	$PhCH_2Br$	(R_P)-**9i**	90	99
10	(S_P)-**8b**		(R_P)-**9j**	90 (82)[c]	78 (85)[d]
11	(S_P)-**8b**		(R_P)-**9k**	68 (61)[c]	77 (94)[d]
12	(S_P)-**8c**	MeI	(R_P)-**9l**	89	91

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

9l 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 (±)-**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_P)-**9i**, no suitable crystals of (S_P,S_P)-**11** were obtained for X-ray spectroscopy. Attempted recrystallization of (S_P,S_P)-**11** resulted in partial degradation (black palladium deposit). Acetato to chloro ligand exchange for the phosphapalladacycle (±)-**11** (LiCl, acetone, rt)[25] provided the

Scheme 5. Preparation of Optically Active Phosphapalladacycles (S_P,S_P)-11 and (S_P,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 = 1,4-diazabicyclo[2.2.2]octane.

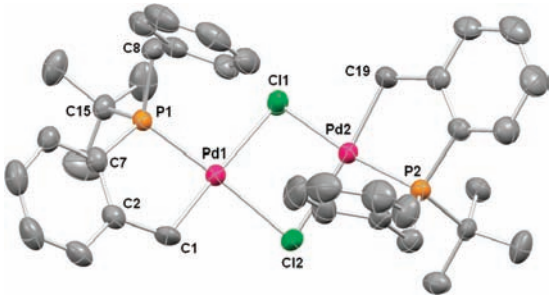


Figure 1. Crystal structure of complex *trans*-(S_P,S_P)-**12** (ORTEP drawing showing thermal ellipsoids at 40% probability). Hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles (deg): C(1)−Pd(1) 2.039(5); Cl(1)−Pd(1) 2.460(1); Cl(2)−Pd(1) 2.416(1); P(1)−Pd(1) 2.203(1); C(1)−Pd(1)−Cl(2)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

chloropalladacycle (±)-**12** which exhibits complex NMR spectrum. In contrast, with chiral ligand (R_P)-**9i**, NMR spectrum of the phosphapalladacycle (S_P,S_P)-**12** were dramatically simplified compared to (±)-**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]

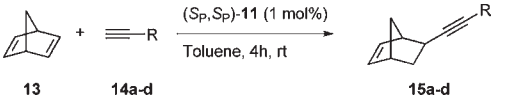
Ninety-five percent enantiomeric excess was determined by ^{31}P NMR spectroscopy using known methods based on the formation of two monomeric diastereomers with (*S*)-α-methylbenzylamine[28] (see SI).

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 phosphapalladacycle 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



entry	alkyne	product	yield[a]	ee[b]
1	**14a** R = phenyl	(−)-**15a**	98	27
2	**14b** R = *p*-MeOPh	(−)-**15b**	90	29
3	**14c** R = 1-cyclohexen-1-yl	(−)-**15c**	91	24
4	**14d** R = CH_2OAc	(−)-**15d**	82	36

[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_P,S_P)-**12** was prepared with retention of configuration at the phosphorus atom. Asymmetric addition reactions of alkynes to alkenes[31] with this conformationaly 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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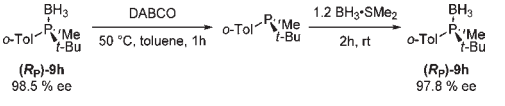

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