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Synthesis of *P*-Stereogenic Phospholene Boranes via Asymmetric Deprotonation and Ring-Closing Metathesis

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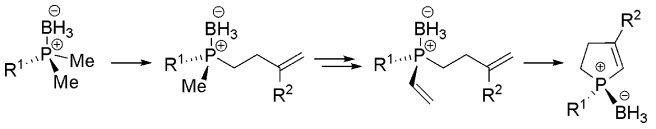
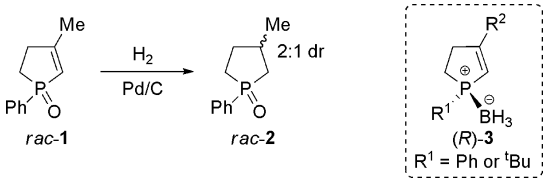
ABSTRACT



The first examples of the asymmetric synthesis of *P*-stereogenic vinylic phospholene boranes are described. The synthetic approach is concise and flexible. The route involves (i) asymmetric deprotonation–allylation of a dimethyl phosphine borane; (ii) telescoped regioselective deprotonation, paraformaldehyde trapping, and hydroxyl group elimination to give a diene; and (iii) ring-closing metathesis.

3-Methyl-1-phenyl-2-phospholene-1-oxide *rac*-**1** (Scheme 1) is a commercially available phosphine oxide that has been exploited in two rather different catalytic processes. For example, Marsden et al. reported the use of *rac*-**1** in the catalytic synthesis of phenanthridines and benzoxazoles.[1] This process involves a catalytic aza-Wittig reaction and is related to the same group's work on a chiral phosphine-mediated aza-Wittig reaction.[2] In addition, O'Brien and co-workers described the use of phospholane oxide *rac*-**2** (2:1 mixture of diastereomers, obtained from *rac*-**1** by hydrogenation, Scheme 1) as a precatalyst in a catalytic Wittig process.[3] Although both applications of phospholene oxide *rac*-**1** were used to prepare achiral products, we reasoned that enantiopure (*R*)- or (*S*)-**1** could be a versatile catalyst for future developments of catalytic asymmetric aza-Wittig, (*E*)- and/or (*Z*)-selective Wittig, and other chiral phosphine-mediated reactions. Herein, we report the asymmetric synthesis of *P*-stereogenic phospholene boranes (*R*)-**3** (R^1 = Ph or *t*-Bu) via a concise and synthetically flexible route.

Scheme 1. Useful Phospholene and Phospholane Oxides



There are no previous reports on the asymmetric synthesis of *P*-stereogenic phospholenes such as **1**, **2**, or **3**.[4] Indeed, to the best of our knowledge, there are only two examples of the preparation of enantioenriched cyclic vinyl phosphines similar to **1**, both of which were reported by Pietrusiewicz and co-workers: a bicyclic phospholene oxide (98% ee) was prepared via a resolution route,[5] and a hydroxy phospholene borane (55% ee) was prepared by

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[§] Celtic Catalysts.

(1) Marsden, S. P.; McGonagle, A. E.; McKeever-Abbas, B. *Org. Lett*. **2008**, *10*, 2589.
(2) (a) Headley, C. E.; Marsden, S. P *J. Org. Chem*. **2007**, *72*, 7185. (b) Lertpibulpanya, D.; Marsden, S. P.; Rodriguez-Garcia, I.; Kilner, C. A. *Angew. Chem., Int. Ed*. **2006**, *45*, 5000.
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(5) Pakulski, Z.; Demchuk, O. M.; Frelek, J.; Luboradzki, R.; Pietrusiewicz, K. M. *Eur. J. Org. Chem*. **2004**, 3913.
(6) Pakulski, Z.; Koprowski, M.; Pietrusiewicz, K. M. *Tetrahedron* **2003**, *59*, 8219.

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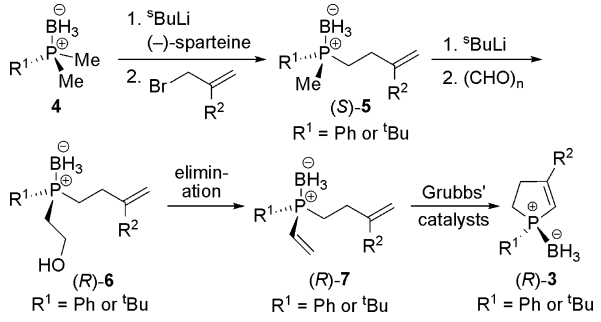
s-BuLi/(−)-sparteine-mediated deprotonation−elimination of an epoxy phospholane borane.[6] Thus, we recognized the need to develop a simple and general approach for the asymmetric synthesis of phospholene boranes (*R*)-**3**. Our strategy is presented in Scheme 2.

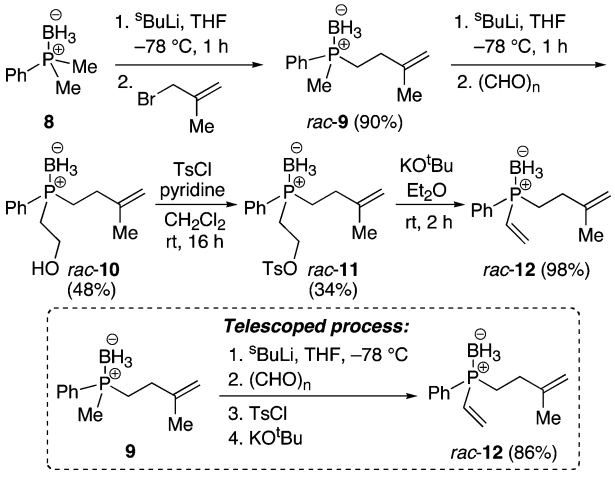
Scheme 2. Strategy for the Synthesis of Phospholene Boranes



The asymmetry in the synthesis of phospholene boranes (*R*)-**3** would be introduced in the first step by chiral base-mediated deprotonation of phosphine boranes **4** using *s*-BuLi and (−)-sparteine (via the Evans protocol[7]);[8] subsequent allylation would then afford allylated phosphine boranes (*S*)-**5**. Next, regioselective lithiation[9] of the less sterically hindered methyl group followed by trapping with paraformaldehyde should generate hydroxy phosphine boranes (*R*)-**6**. Then, elimination of the hydroxy group (via the tosylate) would give dienes (*R*)-**7**. Finally, ring-closing metathesis should deliver the desired phospholene boranes (*R*)-**3**. This route is flexible to allow different R^1 and R^2 substituents to be incorporated, and the enantiomeric products (*S*)-**3** could be accessed using our group's (+)-sparteine surrogate[10] in place of (−)-sparteine in the first step.[11]

To start with, the proposed route was validated and optimized with the preparation of racemic phospholene oxide *rac*-**13** (Scheme 3 and Table 1). Thus, phosphine borane **8** was lithiated using *s*-BuLi in THF at −78 °C for 1 h and then reacted with methallyl bromide. This gave *rac*-**9** in 90% yield (Scheme 3). Next, regioselective lithiation of *rac*-**9** was achieved using *s*-BuLi in THF (−78 °C, 1 h); subsequent trapping with a solution of solid paraformaldehyde in THF gave hydroxy phosphine borane *rac*-**10** in 48% yield. There was no evidence of the other regioisomeric trapped product from this reaction. Tosylation of *rac*-**10** (TsCl, pyridine, CH_2Cl_2) gave tosylate *rac*-**11** in only 34% yield, but elimination to give diene *rac*-**12** proceeded efficiently (98% yield) using potassium *tert*-butoxide in Et_2O at rt. The low yields in the preparation of hydroxy phosphine borane *rac*-**10** and tosylate *rac*-**11** were due to problems during chromatography: for *rac*-**10**, polarity was the issue, whereas, for *rac*-**11**, degradation to unknown byproducts occurred. Since the ^{1}H NMR spectra of the crude products *rac*-**10** and *rac*-**11** obtained after workup indicated they were cleanly formed, we explored a telescoped process for the conversion of *rac*-**9** into *rac*-**12** where the crude product from each step was taken forward into the next step. In this way, diene *rac*-**12** was generated in 86% yield from *rac*-**9** over three steps, with only chromatographic purification in the last step (Scheme 3).

Scheme 3. Synthesis of Diene Phosphine Borane *rac*-**12**



Next, the ring-closing metathesis step was investigated. This approach to cyclic phosphine boranes/oxides and phosphonates is well-known,[12] including a few examples of 5- and 6-ring vinyl phospholenes.[13] However, there are

(7) Muci, A. R.; Campos, K. R.; Evans, D. A. *J. Am. Chem. Soc.* **1995**, *117*, 9075.

(8) For our previous work on Evans-style asymmetric synthesis of phosphine boranes and sulfides, including catalytic asymmetric deprotonation, see: (a) McGrath, M. J.; O'Brien, P. *J. Am. Chem. Soc.* **2005**, *127*, 16378. (b) Genet, C.; Canipa, S. J.; O'Brien, P.; Taylor, S. *J. Am. Chem. Soc.* **2006**, *128*, 9336. (c) Gammon, J. J.; Canipa, S. J.; O'Brien, P.; Kelly, B.; Taylor, S. *Chem. Commun.* **2008**, 3750. (d) Canipa, S. J.; O'Brien, P.; Taylor, S. *Tetrahedron: Asymmetry* **2009**, *20*, 2407. (e) Granander, J.; Secci, F.; O'Brien, P.; Kelly, B. *Tetrahedron: Asymmetry* **2009**, *20*, 2432. (f) Gammon, J. J.; Gessner, V. H.; Barker, G. R.; Granander, J.; Whitwood, A. C.; Strohmann, C.; O'Brien, P.; Kelly, B. *J. Am. Chem. Soc.* **2010**, *132*, 13992. (g) Carbone, G.; O'Brien, P.; Hilmersson, G. *J. Am. Chem. Soc.* **2010**, *132*, 15445. (h) Granander, J.; Secci, F.; Canipa, S. J.; O'Brien, P.; Kelly, B. *J. Org. Chem.* **2011**, *76*, 4794.

(9) For the regioselective lithiation trapping of a phosphine sulfide, see: Gammon, J. J.; O'Brien, P.; Kelly, B. *Org. Lett.* **2009**, *11*, 5022.

(10) (a) Dearden, M. J.; Firkin, C. R.; Hermet, J.-P. R.; O'Brien, P. *J. Am. Chem. Soc.* **2002**, *124*, 11870. (b) O'Brien, P. *Chem. Commun.* **2008**, 655.

(11) Kann was the first to report the use of the (+)-sparteine surrogate in the asymmetric deprotonation of phosphine boranes: (a) Johansson, M. J.; Schwartz, L. O.; Amedjkouh, M.; Kann, N. C. *Eur. J. Org. Chem.* **2004**, 1894. (b) Johansson, M. J.; Schwartz, L. O.; Amedjkouh, M.; Kann, N. *Tetrahedron: Asymmetry* **2004**, *15*, 3531.

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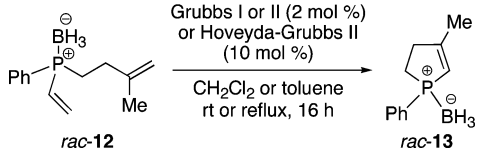
(13) (a) Hanson, P. R.; Stoianova, D. S. *Tetrahedron Lett.* **1999**, *40*, 3297. (b) Timmer, M. S. M.; Ovaa, H.; Filippov, D. V.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **2001**, *42*, 8231. (c) Dunne, K. S.; Bisaro, F.; Odell, B.; Paris, J.-M.; Gouverneur, V. *J. Org. Chem.* **2005**, *70*, 10803. (d) Harvey, J. S.; Malcolmson, S. J.; Dunne, K. S.; Mek, S. J.; Thompson, A. L.; Schrock, R. R.; Hoveyda, A. H.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2009**, *48*, 762. (e) Fourgeaud, P.; Midrier, C.; Vors, J.-P.; Volle, J.-N.; Pirat, J.-L.; Virieux, D. *Tetrahedron Lett.* **2010**, *66*, 758. (f) Harvey, J. S.; Giuffredi, G. T.; Gouverneur, V. *Org. Lett.* **2010**, *12*, 1236.

no reported examples of the preparation of carbocyclic vinyl phospholenes such as *rac*-**13**. Initial attempts using 2 mol % of Grubbs' first and second generation catalysts[14] at rt were disappointing (Table 1, entries 1−3). Use of Grubbs' second generation catalyst in CH_2Cl_2 at rt led to formation of the phospholene borane *rac*-**13** in ~20% conversion (entry 2) which was not improved upon heating at reflux for 16 h in a subsequent experiment (entry 3).

Table 1. Investigation of the Ring-Closing Metathesis of Diene *rac*-**12** To Give Phospholene Borane *rac*-**13**



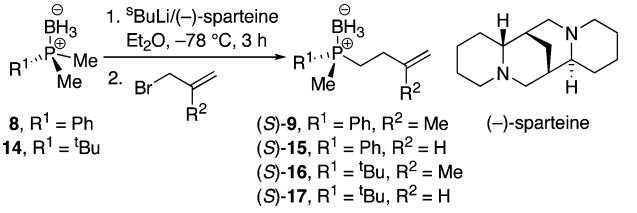
entry	catalyst[a]	solvent	temp	**12**:**13**[b]
1	Grubbs I	CH_2Cl_2	rt	100:0
2	Grubbs II	CH_2Cl_2	rt	77:23
3	Grubbs II	CH_2Cl_2	reflux	83:17[c]
4	Hoveyda-Grubbs II	CH_2Cl_2	rt	87:13[d]
5	Hoveyda-Grubbs II	CH_2Cl_2	rt	50:50
6	Hoveyda-Grubbs II	CH_2Cl_2	rt	40:60[e]
7	Hoveyda-Grubbs II	CH_2Cl_2	reflux	40:60[f,g,h]

[a] 2 mol % of Grubbs I or Grubbs II catalyst and 10 mol % of Hoveyda-Grubbs II catalyst were used. [b] Ratio of *rac*-**12**/*rac*-**13** determined from the ^{1}H NMR spectrum of the crude product. [c] Crude product from entry 2 was used as starting material. [d] 2 mol % of Hoveyda-Grubbs II catalyst was used. [e] Crude product from entry 5 was used as starting material. [f] Crude product from entry 6 was used as starting material. [g] 16 h at rt then 16 h at reflux. [h] After purification by chromatography, 36% of *rac*-**13** and 40% of recovered *rac*-**12** were obtained.

Better results were obtained with the Hoveyda-Grubbs second generation catalyst[15] (entries 4−6) in CH_2Cl_2 at rt provided a higher catalyst loading of 10 mol % was used. For example, reaction for 48 h at rt and then 16 h at reflux gave *rac*-**13** in 36% yield, together with 40% of recovered *rac*-**12** (entry 7). It was also shown that the heating at reflux did not change the ratio of *rac*-**12** and *rac*-**13** (entries 6−7). Based on the results from other examples reported later (vide infra), we conclude that steric hindrance around the disubstituted alkene leads to inefficient ring-closing metathesis of *rac*-**12**.

Although the final ring-closing metathesis step was low yielding, we did establish a viable synthetic approach to phospholene boranes such as *rac*-**13**. Our attention thus switched to investigating additional examples and to carrying out the asymmetric synthesis of phospholene boranes. Thus, using the Evans protocol, phosphine boranes **8** and **14** were lithiated using *s*-BuLi and (−)-sparteine in Et_2O at −78 °C for 3 h. Trapping with methallyl or allyl bromide was then carried out to give allylated phosphine boranes (*S*)-**9** and (*S*)-**15**-**17** in 57−73% yield (Table 2). The configuration of the products was assigned as (*S*) based on the established sense of induction using *s*-BuLi/(−)-sparteine with phosphine boranes **8**[7] and **14**.[16] In line with literature precedent,[7,16] the enantioselectivity was slightly lower with phenyl-substituted **8** (88:12−89:11 er, entries 1 and 2) than with *tert*-butyl-substituted **14** (93:7−96:4 er, entries 3 and 4).

Table 2. Asymmetric Lithiation−Allylation of Phosphine Boranes



entry	R^1	R^2	product	yield (%)[a]	er
1	Ph	Me	(*S*)-**9**	73	89:11[b]
2	Ph	H	(*S*)-**15**	57	88:12[b]
3	*t*-Bu	Me	(*S*)-**16**	57	96:4[c]
4	*t*-Bu	H	(*S*)-**17**	58	93:7[c]

[a] Yield after purification by chromatography. [b] Enantiomer ratio (er) determined by CSP-HPLC (see Supporting Information). [c] Enantiomer ratio (er) determined by CSP-HPLC of the corresponding phosphine sulfides (see Supporting Information).

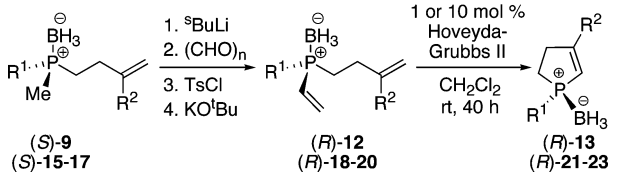
With enantioenriched allylated phosphine boranes (*S*)-**9** and (*S*)-**15**−**17** in hand, their conversion into cyclic phospholene boranes (*R*)-**13** and (*R*)-**21**−**23** was carried out (Table 3). In each case, the telescoped regioselective lithiation, paraformaldehyde trapping, tosylation, and elimination process worked well to give dienes (*R*)-**12** and (*R*)-**18**−**20** in 56−71% yields. Finally, ring-closing metathesis was accomplished using the Hoveyda-Grubbs second generation catalyst in CH_2Cl_2 at rt for 40 h. When R^2 = H, 1 mol % of catalyst worked well, but for the more sterically hindered alkenes with R^2 = Me, 10 mol % catalyst loading was required for satisfactory conversions. Of note, good yields of (*R*)-**21** (71%) (entry 2) and (*R*)-**23** (85%) (entry 4) were obtained indicating that ring-closing metathesis is efficient when R^2 = H (even with 1 mol % catalyst). Thus, steric hindrance in the 1,1-disubstituted alkene (when R^2 = Me) explains the lower yields of (*R*)-**13** and (*R*)-**22** (entries 1 and 3). We have confirmed in two cases that the diene preparation and ring-closing metathesis steps proceed (as expected) without loss of enantiomer ratio. Thus, CSP-HPLC of (*R*)-**21** showed it to be 87:13 er, having been prepared from allylated phosphine borane (*S*)-**15** of 88:12 er (Table 2, entry 2). In addition, (*R*)-**23** (prepared from allylated phosphine borane (*S*)-**17** of 93:7 er) was

(14) (a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039. (b) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

(15) Garber, S. B.; Kinsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168.

(16) Imamoto, T.; Watanabe, J.; Wada, Y.; Masuda, H.; Yamada, H.; Tsuruta, H.; Matsukawa, S.; Yamaguchi, K. *J. Am. Chem. Soc.* **1998**, *120*, 1635.

Table 3. Synthesis of Enantioenriched Phospholene Boranes



entry	R^1	R^2	product	yield (%)[a]	product	yield (%)[a]
1	Ph	Me	(*R*)-**12**	58	(*R*)-**13**	46[b]
2	Ph	H	(*R*)-**18**	71	(*R*)-**21**	71[c]
3	*t*-Bu	Me	(*R*)-**19**	56	(*R*)-**22**	41[b]
4	*t*-Bu	H	(*R*)-**20**	60	(*R*)-**23**	85[c]

[a] Yield after purification by chromatography. [b] 10 mol % of Hoveyda-Grubbs II catalyst. [c] 1 mol % of Hoveyda-Grubbs II catalyst.

converted, via reaction with DABCO in the presence of sulfur, into the corresponding phosphine sulfide which was shown to be 95:5 er (by CSP-HPLC). The borane deprotection−phosphine sulfide formation thus proceeds with configurational integrity of the intermediate phosphine.

In summary, the first examples of the asymmetric synthesis of vinyl phospholene boranes (*R*)-**3** are reported. Crucially, we have established a convenient three-step asymmetric synthesis that delivers enantioenriched (*R*)-**13** and (*R*)-**21**−**23**. The route is flexible to allow the easy variation of substituents. Since phosphine boranes can be easily converted into the free phosphines or phosphine oxides, our work will enable future investigations into stereoselective aspects of catalytic aza-Wittig/Wittig reactions[1−3] and related processes.

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Supporting Information Available. Full experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.