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Efficient Asymmetric Syntheses of 1-Phenyl-phosphindane, Derivatives, and 2- or 3-Oxa Analogues: Mission Accomplished

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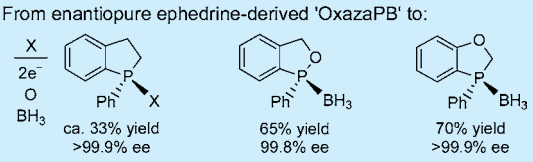
Supporting Information

ABSTRACT: A highly enantioselective synthesis of unsubstituted 1-phenyl-phosphindane and its *P*-borane and *P*-oxide derivatives was effectively established via a new fluoride-triggered desilylative carbocyclization strategy. Preparation of the "oxygen atom-doped" 1-phenyl-3-oxa-1-phosphindane-*P*-borane analogue was otherwise achieved via a tandem *P*-α-iodination−intra-*O*-alkylation.



A high level of development both academically and industrially has been attained especially in asymmetric hydrogenation of olefins catalyzed by transition-metal complexes of enantiopure phosphorus-based ligands.[1] P-Stereogenic ligands backed by well-adapted processes for their preparation have greatly impacted these advances.[2] A multitude of chiral ligand designs were proven to be quite efficient in catalysis, among which phosphacyclic motif-incorporated ones displayed notable performance. The 4−7-membered phosphacyclic ligands are the most encountered in the literature of this last category with phospholanes occupying center stage.[2,3] Various mono- and diphosphine designs have been invented wherein the core skeleton is optionally decorated with arenes, heteroatoms, and/or neighboring bulky groups (Figure 1). The diverse plethora of chiral P-compounds excludes devising one general access route to them all, but a best-route-per-design approach is the most adequate.

Clearly, synthetic hurdles still remain for some of the basic sought-after structures preventing their application in full-power catalysis. For instance, the chiral 1-aryl-phosphindane framework (Figure 1) proved to be notoriously difficult to access. Prepared for the first time in 2007 in 70% ee by the Glueck group via Pd(Me-DuPHOS)(*E*-stilbene)-catalyzed intramolecular asymmetric iodoarene phosphination,[4a] the preparation of the *P*-oxide in 82% ee under asymmetric oxidative Appel conditions was recently published by the Gilheany group.[4b] In the same period, we have reported the formation of its 3-spiro derivatives 5TwistP·BH_3 in >99.9% ee (20% yield) via a radical intramolecular benzannulation following the Jugé−Stephan asymmetric route to phosphines.[4c] Also, the closely related 1-*o*-anisyl-phosphindane-*P*-borane has been obtained by Imamoto et al. in 65% ee relying on an *l*-menthyl phosphinite-*P*-borane reduction/Pd(PPh_3)$_4$ cross-coupling sequence.[4d] Nevertheless, providing a convenient general solution for this long-standing challenge appeared to be relevant to our ongoing asymmetric catalysis-related P-research.[5]

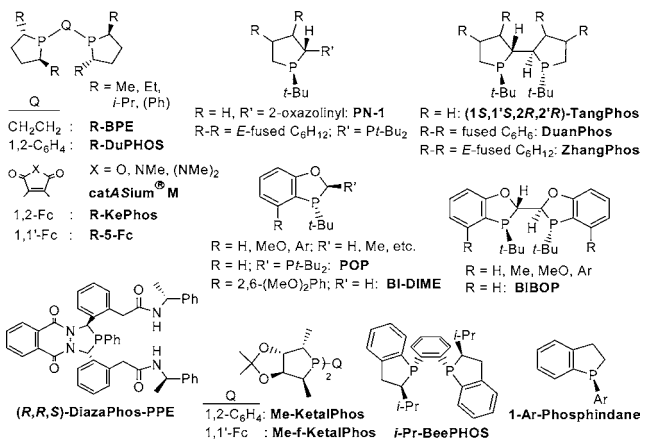


Figure 1. Selection of chiral (hetero)phospholanes.

We referred again to the particularly well-suited Jugé−Stephan asymmetric route which generally enables access to a broad spectrum of P-stereogenic compounds.[5d,6] Its prime advantage is the chemospecific and highly stereoselective stepwise displacement of the (+)- or (−)-ephedrine auxiliary from an enantiopure 1,3,2-oxazaphospholidine-2-borane complex (oxazaPB) toward either P-compound enantiomer.[7] Aiming at the stepwise construction of the 1-phosphindane cyclic core, we have contemplated a novel key ring-closure step between a suitably α-functionalized *o*-tolyl group and a functionalized methyl group following their successive introduction onto the P-atom.

Thus, applying an adapted Jugé−Stephan approach to the target molecule,[8] (2*R*,4*S*,5*R*)-oxazaPB (derived from (−)-ephedrine) ring opening with lithium *o*-lithio-benzyloxide led to (*o*-hydroxymethyl-phenyl)aminophosphine-*P*-borane **1** (86% yield) as a single diastereomer after recrystallization of the crude (Scheme 1).[9] Noteworthy, diethyl ether as the solvent was crucial for the reaction success instead of the recommended THF in the standard route conditions. The

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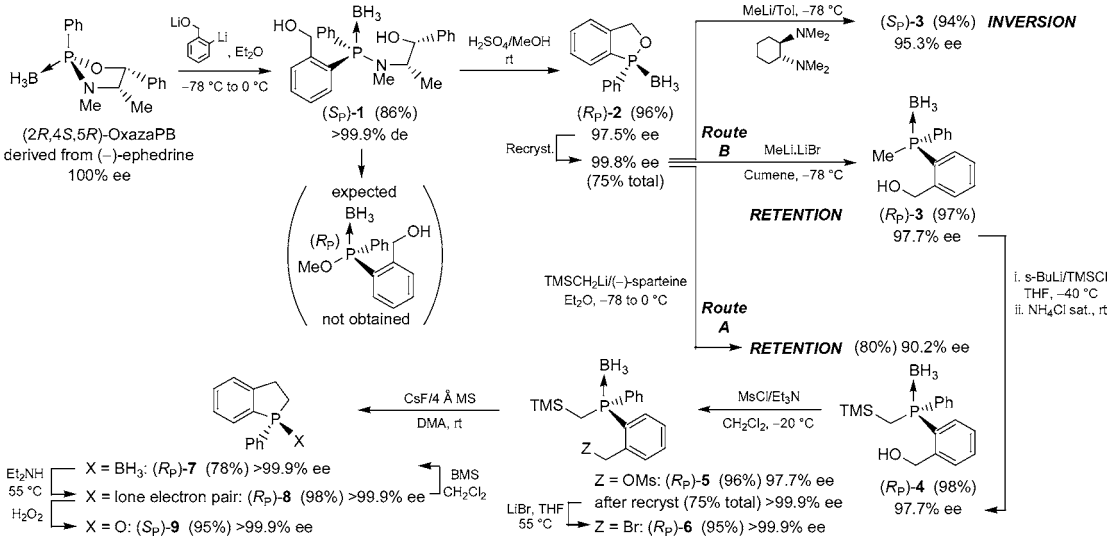
Scheme 1. Enantioselective Synthesis of 1-Phenyl-phosphindane (8) and Derivatives



subsequent H_2SO_4-mediated "methanolysis step" also according to the general route furnished the unexpected 1-phenyl-2-oxa-1-phosphindane-*P*-borane (**2**, 96% yield) instead of the methyl phosphinite-*P*-borane.[10] Interestingly, this crystalline cyclic phosphinite-*P*-borane was formed in 97.5% ee, and further ee upgrading to 99.8% was achieved by single recrystallization from MeOH (75% total yield) (Figure 2).[11,12] This phosphinite-*P*-borane is a valuable synthon for

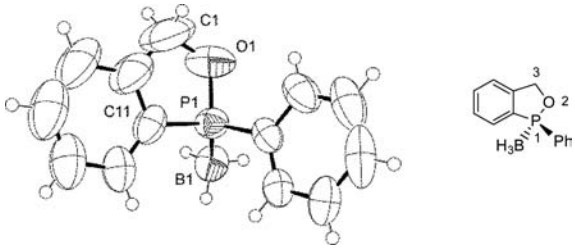


Figure 2. ORTEP drawing of *ent*-**2** (S_P) derived from (+)-ephedrine at the 50% probability level (one of the two molecules of the unit cell is shown). Selected bond lengths (Å) and angles (deg): P1−B1 1.880(4), P1−O1 1.599(2), O1−C1 1.492(7), B1−P1−O1 115.3(2), B1−P1−C11 114.9(2).

the preparation of a variety of P-chiral compounds due to its minimal sterics, high reactivity of the cycle, and the possibility to manipulate subsequently the benzylic position.

Conversion of the hydroxyl group of *P*-(*o*-hydroxymethylphenyl) into a leaving group which would be intramolecularly displaced by a generated *P*-α-anion was the contemplated key ring-formation step. In general, α-deprotonation of (alkyl)-phosphine-*P*-boranes is readily achieved with organolithiums, but a compatible approach was required in this particular case for the subsequent intramolecular cyclization onto the *P*-(α-activated *o*-tolyl) group present in the same molecule. A *P*-CH_2TMS group as a masked *P*-α-anion appeared to be appropriate allowing a F^--induced desilylative carbocyclization.[13] Thus, a direct introduction of the *P*-CH_2TMS group (*Route A*) or a *P*-Me group followed by its silylation (*Route B*) was pursued.

The ring opening of the cyclic phosphinite-*P*-borane **2** with the organolithiums proceeded well regioselectively with exclusive attack on the P-atom even at very low temperatures.[14] However, the enantioselectivity was dependent on the reaction conditions, affording lower ee's than usually obtained with methyl phosphinite-*P*-boranes.[5,6,15] Initial results in THF were <40% ee. Hence, an optimization study was conducted with this very reactive yet easily handled intermediate **2**, varying temperature, solvent, and the organolithium additive (see the Supporting Information, Table S1).[16] Of the conditions examined following *Route A*, a maximum of 90.2% ee (R_P) was attained for **4** (80% yield) in the presence of (−)-sparteine (1.1 equiv) in Et_2O at −78 °C. Fortunately, the two-step *Route B* via **3** was more selective leading to (R_P)-**3** (97% yield) in up to 97.7% ee in cumene at −78 °C employing MeLi·LiBr. Curiously, with MeLi in the presence of (*R*,*R*)- or (*S*,*S*)-*trans*-*N*,*N*,*N*′,*N*′-tetramethyl-1,2-cyclohexanediamine (TMCDA, 2.2 equiv) in toluene at −78 °C, the *ent*-**3** was obtained in 95.3% ee (S_P).[17] Thus, the additive chirality does not seem to influence the P-attack sense. However, the switch in the major attack sense observed with MeLi vs $TMSCH_2Li$ must stem from their relative steric bulk which influences the reagent aggregation[18] in the different media and the approach to **2** (Figure 3). Subsequently, *P*-α-silylation of (R_P)-**3** led to (R_P)-**4** in high yield (98%).[19]

Further on, the hydroxyl group of (R_P)-**4** was mesylated[21] into (R_P)-**5**, but this unfortunately failed to react under the desilylative conditions en route to cyclization.[22] However, this

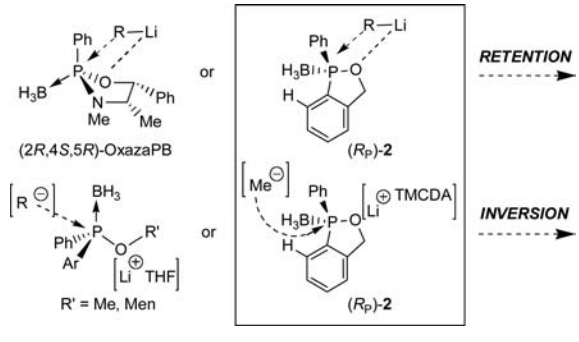


Figure 3. Organolithiums attack sense on oxazaPB,[5,6,20a] and cyclic (**2**) or acyclic (methyl[5,6] or *l*-menthyl[20c]) phosphinite-*P*-boranes.

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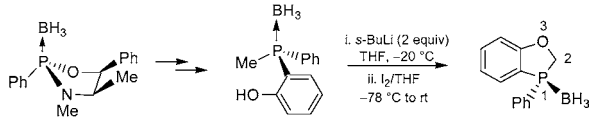
product allowed advantageously ee upgrading to >99.9% by recrystallization from MeOH at −15 °C.[15] Substitution of the MsO group with a Br ((*R*P)-**6**, 95%) overcame the reactivity issue, and the targeted transformation to (*R*P)-**7** proceeded smoothly in 78% yield using CsF/4 Å molecular sieves in DMA.[23] Conversion under nonracemizing mild conditions of (*R*P)-**7** into its BH_3-free phosphine (*R*P)-**8** (98%) and the corresponding *P*-oxide (*S*P)-**9** (95%) was high-yielding with full preservation of the enantiomeric integrity.[4a,15,24]

Finally, additional interest arose to prepare the yet unknown 3-oxa analogue **11** (Scheme 2). The BH_3-free *P*-Ph-substituted

Scheme 2. Enantioselective Synthesis of Unsubstituted 1-Phenyl-3-oxa-1-phosphindane-*P*-borane ((*R*P)-11) from an SMS-Phos Precursor



cycle is the aromatic counterpart of the resolved *P*-*t*Bu-substituted component unit of BIBOP.[3j,k] Starting from our previously described enantiopure (*o*-hydroxyphenyl)(methyl)(phenyl)phosphine-*P*-borane ((*R*P)-**10**, 85% overall yield from oxazaPB),[5d] a tandem iodination−intra-*O*-alkylation of its *P*-*α*-anion resulted in the cyclized product (*R*P)-**11** in 82% yield.[15]

In conclusion, although we had the Jugé−Stephan route as a template for our enantioselective synthesis of 1-phenylphosphindane (**8**), the surmounted challenges encountered along the proceeding steps reassert the difficulty entailed in the preparation of such a structure and bear testimony to the versatility of the followed route. The basic cyclic structure **8** and its *P*-BH_3 **7** and *P*-oxide **9** derivatives were prepared in >99.9% ee and 32−34% overall yields via a new facile F^--triggered desilylative carbocyclization strategy. Moreover, the highly enantiodivergent ring opening of the cyclic precursor **2** offers a stereocomplementary advantage to the opposite enantiomer access by switching the ephedrine chirality. Finally, 1-phenyl-3-oxa-1-phosphindane-*P*-borane (**11**) an analogue of **7**·BH_3, was also efficiently prepared (>99.9% ee, 70% overall yield). Application of these compounds and the developed key steps are manifold.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(7) This is contrary to the reproach for this route as presented in: Han, Z. S.; Goyal, N.; Herbage, M. A.; Sieber, J. D.; Qu, B.; Xu, Y.; Li, Z.; Reeves, J. T.; Desrosiers, J.-N.; Ma, S.; Grinberg, N.; Lee, H.; Mangunuru, H. P. R.; Zhang, Y.; Krishnamurthy, D.; Lu, B. Z.; Song, J.; Wang, G.; Senanayake, C. H. *J. Am. Chem. Soc.* **2013**, *135*, 2474−2477.

(8) For the preparation of the lower homologue intermediates towards SMS-Phos ligands' precursor, see ref 5d.

(9) X-ray crystal structure analysis of *ent*-**1** prepared from (2*S*,4*R*,5*S*)-oxazaPB (derived from (+)-ephedrine) confirmed the retention of the P-configuration. For this, see the Supporting Information.
(10) (a) Conversion of (S_P)-**1** in ∼96% was reached within 1.5 h compared to the usual 12−15 h for other (*o*-substituted aryl)(*N*-ephedrino)(phenyl)phosphine-*P*-boranes.[5,6] (b) Exploration of this step using BF_3·Et_2O (1 equiv) Lewis acid[5d] at rt in Et_2O, toluene, or THF led to (R_P)-**2** in 95%, 95%, and 92% ee, respectively.
(11) The ee of enriched **2** collected from the recrystallization filtrate was determined by HPLC on a Daicel Chiralcel OD column (25 cm) conjugated with a Daicel Chiralcel OD-H column (15 cm), referenced with *ent*-**2** prepared from (2*S*,4*R*,5*S*)-oxazaPB (derived from (+)-ephedrine). For details, see the Supporting Information.
(12) Full X-ray crystal structure analysis of *ent*-**2** prepared from (2*S*,4*R*,5*S*)-oxazaPB (derived from (+)-ephedrine) is contained in the Supporting Information.
(13) To the best of our knowledge, the closest work in the literature is Ph_2PCH_2TMS addition to carbonyls promoted by CsF (10 mol %) in DMF at 50 °C. For this, see: Kawashima, T.; Mitsuda, N.; Inamoto, N. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 708−710. Therein, use of 4 Å molecular sieves as a drying agent caused a decrease in yields.
(14) No RLi attack at the benzylic position was observed.
(15) (a) Ee was determined by HPLC analysis on chiral columns. For details, see the Supporting Information. (b) The P-configurations of compounds **3**−**9** were attributed based on the chiral HPLC order of elution of the *P*-oxide **9** and comparison with the literature;[4b] therein, the X-ray structure of (R_P)-**9** was also reported. (c) Phosphine-*P*-boranes decomplexation in Et_2NH and phosphines P-oxidation with H_2O_2 occur usually with retention of the P-configuration;[20c] however, the absolute P-configuration can change according to the stereochemistry CIP priority rules.
(16) Commercial $TMSCH_2Li$ (1 M in pentane), MeLi (1.6 M in Et_2O), or MeLi·LiBr (1.5 M in Et_2O) were used in the study.
(17) A reverse P-attack sense was also noted in THF or using TMEDA or (−)-sparteine with MeLi but not in the $TMSCH_2Li$ case.
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(19) NH_4Cl aq. treatment hydrolyzed the *O*-TMS-protected product into **4**.
(20) (a) Rippert, A. J.; Linden, A.; Hansen, H.-J. *Helv. Chim. Acta* **2000**, *83*, 311−321. Therein, a retention of the P-configuration was also observed with the (*S*,*S*,*S*)-oxazaPB derived from (1*S*,2*S*)-(+)-pseudoephedrine. (b) León, T.; Riera, A.; Verdaguer, X. *J. Am. Chem. Soc.* **2011**, *133*, 5740−5743. Therein, an inversion of the P-configuration was observed for the ring opening of (2*R*,4*S*,5*R*)-2-*t*-*Bu*-(1,3,2)-oxazaphospholidine-*P*-borane derived from (1*S*,2*R*)-1-amino-2-indanol. (c) Imamoto, T.; Oshiki, T.; Onozawa, T.; Kusumoto, T.; Sato, K. *J. Am. Chem. Soc.* **1990**, *112*, 5244−5252.
(21) Mesylation of (2-hydroxymethyl-phenyl)(methyl)(phenyl)phosphine-*P*-oxide using MsCl/Et_3N led to the *P*-(2-chloromethyl-phenyl) derivative. For this, see: Kaczmarczyk, S.; Madalińska, L.; Kiełbasiński, P. *Phosphorus, Sulfur Silicon* **2013**, *188*, 249−253.
(22) According to ^1H NMR a straight desilylation of **5** ensued without cyclization.
(23) Under the adopted unoptimized reaction conditions, ∼3 equiv of CsF were used, and addition of 4 Å molecular sieves proved to be beneficial (on the contrary for the transformation in ref 13). Also, byproducts were formed for the reaction in DMF.
(24) Decomplexation of **7** was carried out at rt in order to avoid partial racemization of **8**, as heating at 50 °C for 2 h resulted in a 2% ee loss. This was confirmed by P-recomplexation of **8** with BH_3 using BMS and chiral HPLC analysis.