

Enantioselective Synthesis of P-Stereogenic Benzophospholanes via Palladium-Catalyzed Intramolecular Cyclization

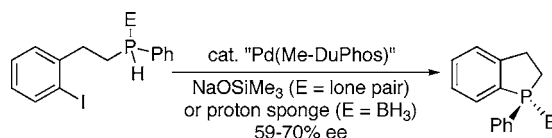
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ABSTRACT



Enantioselective or diastereoselective intramolecular cyclization of functionalized secondary phosphines or their borane adducts catalyzed by chiral Pd(diphosphine) complexes gave P-stereogenic benzophospholanes in up to 70% ee. These results provide a new method for the synthesis of chiral phospholanes, which are valuable ligands in asymmetric catalysis.

Chiral phospholanes such as Me-DuPhos (**1**) and Me-BPE (**2**) are outstanding ligands for catalytic asymmetric hydrogenation.¹ The success of these phosphines has encouraged the synthesis and application of a wide variety of analogues with chiral carbon centers on the phospholane rings.² More recently, related useful P-stereogenic phospholanes such as TangPhos (**3**),³ ligand **4**,⁴ *i*-Pr-BeePhos (**5**),⁵ and phosphabi-

cyclooctane (PBO) acylation catalyst **6**⁶ have been prepared in industrial and academic labs (Figure 1).

Because of the lack of general synthetic routes to P-stereogenic phosphines,⁷ such ligands remain relatively uninvestigated. For this reason, “not only are P-chirogenic 1,2-bisphospholanes interesting from a practical standpoint (i.e., their use in catalysis), but they also represent a worthy synthetic challenge”.⁴ Here, we report a new method for enantioselective synthesis of P-stereogenic benzophospholanes via Pd-catalyzed intramolecular⁸ asymmetric phosphination.⁹ Imamoto has prepared related benzophospholanes

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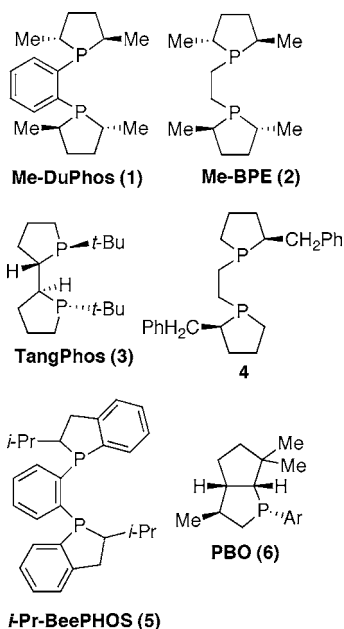
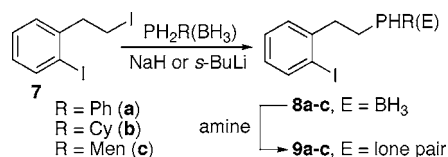


Figure 1. Chiral phospholanes with and without P stereocenters.

in high ee using menthol as a chiral auxiliary, but this method required fractional crystallization of diastereomers, for which overall yields were not reported.¹⁰

Treatment of the known diiodide **7**¹¹ with a primary phosphine-borane in the presence of base (NaH or *sec*-BuLi) gave the functionalized secondary phosphine-boranes **8a–c** (Scheme 1). Deprotection with DABCO, Et₂NH, or more

Scheme 1. Synthesis of Substrates for Pd-Catalyzed Intramolecular Phosphination^a



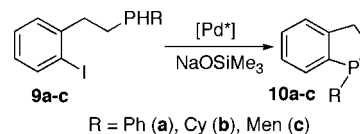
^a Men = (–)-menthyl.

conveniently piperazinomethyl polystyrene gave the phosphines **9a–c**.¹²

As desired, intramolecular cyclization of secondary phosphines **9a–c** in the presence of the base NaOSiMe₃ and a

chiral catalyst precursor Pd(diphos*)(*trans*-stilbene) gave benzophospholanes **10a–c** (Scheme 2, Table 1).¹³

Scheme 2. Pd-Catalyzed Intramolecular Phosphination^a



^a The catalyst precursor ([Pd*]) was Pd(diphos*)(*trans*-stilbene). See Table 1 for diphos* ligands, whose structures are included in the Supporting Information (SI).

Table 1. Asymmetric Synthesis of Benzophospholanes via Pd-Catalyzed Intramolecular Phosphination^a

entry	ligand	substrate	time	yield (%)	ee (%)
1	(<i>R,R</i>)-Me-DuPhos	9a	3 days	80	59
2	(<i>R,R</i>)-Me-DuPhos ^b	9a	1 day	78	63
3	(<i>R,R</i>)-Me-DuPhos ^c	9a·HBF₄	2 days	48	63
4	(<i>R,R</i>)- <i>i</i> -Pr-DuPhos	9a	1 day	83	–66 ^d
5	(<i>R,R</i>)-Me-BPE	9a	3 days	76	37
6	(<i>R,R</i>)-Me-BPE ^e	9a	1 day	80	40
7	(<i>S,S</i>)-Me-5-Fc	9a	2 days	58	–8 ^d
8	(<i>R,S</i>)-CyPF- <i>t</i> -Bu	9a	2 days	68	rac ^f
9	(<i>R,S</i>)-PPF- <i>t</i> -Bu	9a	5 days	56	rac ^f
10	(<i>R,R</i>)-Me-DuPhos	9b	20 min	86	rac ^f
11	(<i>S,S</i>)-Et-FerroTANE ^g	9b	20 min	95	rac ^f
12	(<i>S,S</i>)-Me-5-Fc	9b	20 min	93	rac ^f
13	(<i>R,R</i>)-Me-DuPhos	9c	1 h	48	1:1 dr ^h
14	none ⁱ	9c	20 h	49	1.2:1 dr ^h

^a Reactions were carried out at room temperature in toluene with 5 mol % of the catalyst precursor Pd(diphos*)(*trans*-stilbene) and 0.12 mmol of substrate (40 mg of **9a**). Isolated yields, after column chromatography, are reported. Reactions have not been optimized. ^b 300 mg of **9a**. ^c With 2 equiv of NaOSiMe₃; reaction slowed after 40% conversion but went to completion when another equiv of base was added. ^d The preferred enantiomer of **10a** differed for (*R,R*)-Me-DuPhos/(*R,R*)-Me-BPE vs (*R,R*)-*i*-Pr-DuPhos/(*S,S*)-Me-5-Fc. ^e In THF. ^f The product was racemic. ^g Catalyst precursor = Pd(*S,S*)-Et-FerroTANE(Ph)(I).¹³ Ca. 5% of the expected byproduct, presumably containing a P–Ph group, was observed. ^h dr = diastereomeric ratio. ⁱ Catalyst precursor = Pd(OAc)₂ (9 mol %); 0.32 mmol of **9c**.

Phenylphosphine **9a** slowly gave benzophospholane **10a** in good yields and moderate ee.¹⁴ Replacing air-sensitive **9a** with air-stable salt **9a·HBF₄** gave comparable ee's (entries 1 and 3).¹⁵ DuPhos-ligated catalysts (entries 1–4) gave higher ee's than those with the ethane-bridged BPE (entries 5 and 6), whereas use of the 1,1'-ferrocene-bridged bis(phospholane) Me-5-Fc (entry 7) resulted in very low ee.¹⁶ Josiphos-ligated catalysts (entries 8 and 9) gave racemic

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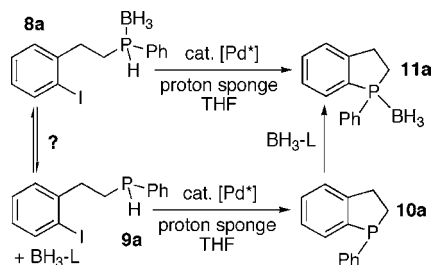
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product, and several byproducts were formed when the bis-(phosphetane) (*S,S*)-Et-FerroTANE was used.

In contrast, reaction of cyclohexylphosphine **9b** was complete in minutes to give racemic cyclic phosphine **10b** in high yields (entries 10–12). This reaction was accompanied by displacement of the chiral diphosphine from Pd. Similarly, little diastereoselectivity was observed for the intramolecular coupling of **9c** (entries 13 and 14).¹⁷

The displacement of the chiral ligand observed in cyclization of alkylphosphine **9b** is a common problem in metal-catalyzed asymmetric P–C bond formation. It can sometimes be avoided by using phosphine-boranes instead of phosphines as substrates.^{9b,d} The alkylphosphine-boranes **8b** and **8c** did not undergo Pd-catalyzed cyclization at room temperature, and byproducts were formed from **8b** at 50 °C. However, the phenylphosphine-borane substrate **8a** reacted smoothly to yield benzophospholane-borane **11a** in moderate ee; the preferred enantiomer was the same as that formed in cyclization of phosphine **9a** (Scheme 3, Table 2).

Scheme 3. Pd-Catalyzed Enantioselective Cyclization of Phosphine-borane **8a** and Its Possible Relationship to Cyclization of Phosphine **9a**^a



^a Catalyst precursor $[\text{Pd}^*] = \text{Pd}(\text{diphos}^*)(\text{trans-stilbene})$, $\text{diphos}^* = (R,R)\text{-Me-DuPhos}$ or $(R,R)\text{-Me-BPE}$. L is a Lewis base, such as the solvent THF.

Table 2. Pd-Catalyzed Enantioselective Cyclization of Phosphine-borane **8a** and the Analogous Phosphine **9a**^a

entry	ligand	substrate	time (days)	yield (%)	ee (%)
1	(<i>R,R</i>)-Me-DuPhos	8a	6	60	61
2	(<i>R,R</i>)-Me-DuPhos ^b	8a	5	89	70
3	(<i>R,R</i>)-Me-DuPhos	9a	3	80	59
4	(<i>R,R</i>)-Me-DuPhos	9a	1	78	63
5	(<i>R,R</i>)-Me-BPE	8a	6	63	36
6	(<i>R,R</i>)-Me-BPE	9a	3	76	37
7	(<i>R,R</i>)-Me-BPE	9a	1	80	40

^a Reactions were carried out at room temperature in THF with 5 mol % of the catalyst precursor $\text{Pd}(\text{diphos}^*)(\text{trans-stilbene})$ and 0.14 mmol of substrate (50 mg of **8a**). Isolated yields, after column chromatography, are reported. Entries 3 and 4 and 6 and 7 are reproduced from Table 1 (entries 1 and 2 and 5 and 6) for comparison. ^b 500 mg of **8a**.

Because the ee in the cyclization of **8a** and its phosphine analogue **9a** was similar with two different catalysts, the true

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active species in catalysis with **8a** might be **9a**, formed in an unfavorable equilibrium by reversible dissociation of borane from **8a** (Scheme 3).¹⁸ Consistent with this hypothesis, $\text{Pd}((R,R)\text{-Me-DuPhos})$ -catalyzed cyclization of **8a** was much slower when 1 equiv of $\text{BH}_3(\text{SMe}_2)$ was added, and alkylphosphine boranes **8b,c**, in which the borane is expected to be less labile, did not undergo cyclization.^{19,20}

Benzophospholane-boranes **11a** and **11b** could also be prepared from **10** and $\text{BH}_3(\text{SMe}_2)$;²⁰ similarly, treatment of **10a** with sulfur gave **12** (Scheme 4; the crystal structure in Figure 2 confirmed the presence of the benzophospholane ring system).

Scheme 4. Protection of Benzophospholanes

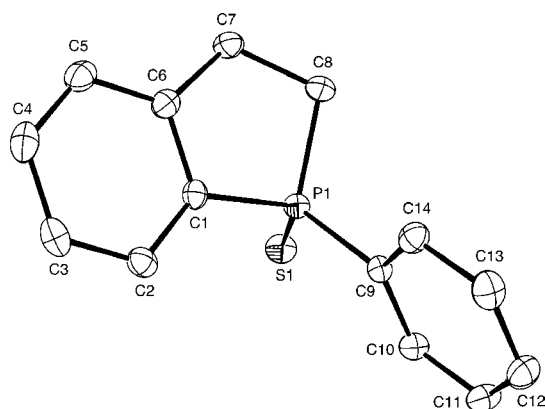
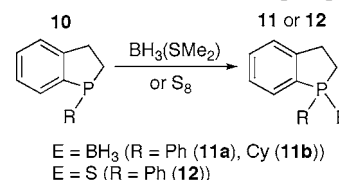


Figure 2. ORTEP diagram of **12**.

Both P and C stereochemistries have been controlled by chiral base-mediated α -deprotonation of the phospholane ring.²¹ Instead, stereocontrol of α -alkylation in enantioenriched benzophospholanes might occur by a relay from the P stereocenter. Indeed, α -methylation of **11a** gave a 7:1

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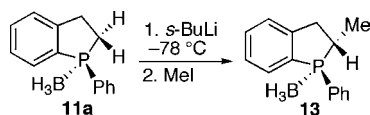
(19) Cyclization of **8a** (3.0 g) with 5 mol % of $\text{Pd}(\text{dba})_2$ and NaOSiMe_3 in THF gave racemic **11a** in 58% yield; see the Supporting Information for details.

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mixture of diastereomers of **13**; the major diastereomer was isolated in 64% yield (Scheme 5). As expected from steric

Scheme 5. Diastereoselective Methylation of Benzophospholane **11a**^a



^a Absolute configuration of these compounds has not been established. The stereochemistry has been drawn arbitrarily to emphasize the *trans* relationship of the Me and P–Ph groups in the major diastereomer of **13**.

considerations,²¹ it contained *trans*-Ph and -Me groups, according to X-ray crystallography (Figure 3) and a ¹H NMR NOE study.²²

In summary, we have investigated Pd-catalyzed asymmetric phosphination as a novel approach to the valuable phospholane ring structure.²³ Promising enantioselectivity in the cyclization of phenylphosphine substrates **8a** and **9a** along with the diastereoselective methylation of the α-posi-

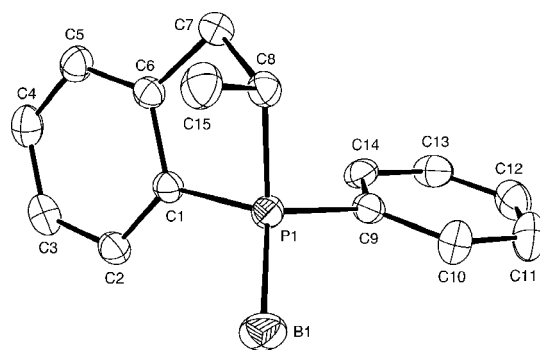


Figure 3. ORTEP diagram of the major diastereomer of **13**.

tion in **11a** suggest that this chemistry may be useful in the synthesis of phospholanes for applications in asymmetric catalysis.

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

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