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

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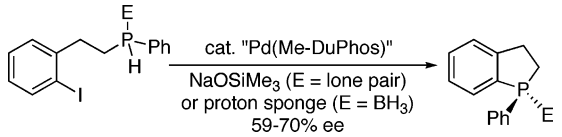
ABSTRACT



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 phosphabicyclooctane (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 intramolecular[8] asymmetric phosphination.[9] Imamoto has prepared related benzophospholanes

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(2) For reviews, see: (a) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029−3070. (b) Clark, T.; Landis, C. *Tetrahedron: Asymmetry* **2004**, *15*, 2123−2137. For some recent examples, see: (c) Dubrovina, N. V.; Jiao, H.; Tararov, V. I.; Spannenberg, A.; Kadyrov, R.; Monsees, A.; Christiansen, A.; Borner, A. *Eur. J. Org. Chem.* **2006**, 3412−3420. (d) Holz, J.; Zayas, O.; Jiao, H.; Baumann, W.; Spannenberg, A.; Monsees, A.; Riermeier, T. H.; Almena, J.; Kadyrov, R.; Borner, A. *Chem.−Eur. J.* **2006**, *12*, 5001−5013. (e) Bilenko, V.; Spannenberg, A.; Baumann, W.; Komarov, I.; Borner, A. *Tetrahedron: Asymmetry* **2006**, *17*, 2082−2087. (f) Berens, U.; Englert, U.; Geyser, S.; Runsink, J.; Salzer, A. *Eur. J. Org. Chem.* **2006**, 2100−2109. (g) Liu, D.; Zhang, X. *Eur. J. Org. Chem.* **2005**, 646−649.
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(8) For related intramolecular cyclizations in Pd-catalyzed amination, see: (a) Wagaw, S.; Rennels, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 8451−8458. (b) Kitagawa, O.; Yoshikawa, M.; Tanabe, H.; Morita, T.; Takahashi, M.; Dobashi, Y.; Taguchi, T. *J. Am. Chem. Soc.* **2006**, *128*, 12923−12931.

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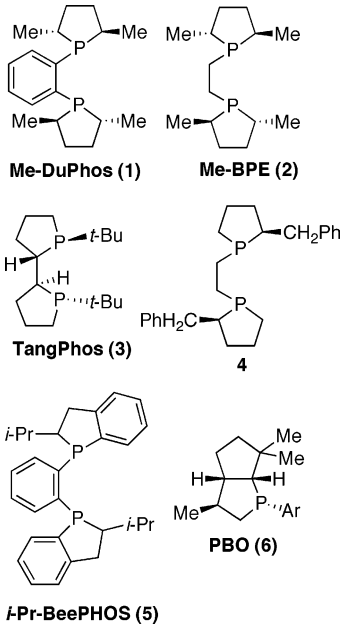
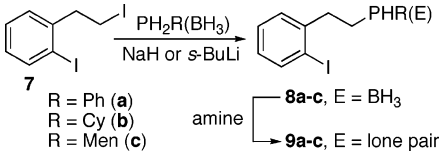


Figure 1. Chiral phospholanes with and without P stereocenters.

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, Et_2NH, or more

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

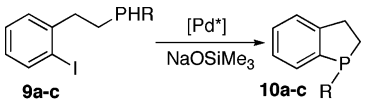


[a] Men = (−)-menthyl.

conveniently piperazinomethyl polystyrene gave the phosphines **9a**−**c**.[12]

As desired, intramolecular cyclization of secondary phosphines **9a**−**c** in the presence of the base $NaOSiMe_3$ 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	(*R*,*R*)-Me-DuPhos	**9a**	3 days	80	59
2	(*R*,*R*)-Me-DuPhos[b]	**9a**	1 day	78	63
3	(*R*,*R*)-Me-DuPhos[c]	**9a·HBF$_4$**	2 days	48	63
4	(*R*,*R*)-*i*-Pr-DuPhos	**9a**	1 day	83	−66[d]
5	(*R*,*R*)-Me-BPE	**9a**	3 days	76	37
6	(*R*,*R*)-Me-BPE[e]	**9a**	1 day	80	40
7	(*S*,*S*)-Me-5-Fc	**9a**	2 days	58	−8[d]
8	(*R*,*S*)-CyPF-*t*-Bu	**9a**	2 days	68	rac[f]
9	(*R*,*S*)-PPF-*t*-Bu	**9a**	5 days	56	rac[f]
10	(*R*,*R*)-Me-DuPhos	**9b**	20 min	86	rac[f]
11	(*S*,*S*)-Et-FerroTANE[g]	**9b**	20 min	95	rac[f]
12	(*S*,*S*)-Me−5-Fc	**9b**	20 min	93	rac[f]
13	(*R*,*R*)-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 $NaOSiMe_3$; 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·HBF$_4$** 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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(10) Imamoto, T.; Yoshizawa, T.; Hirose, K.; Wada, Y.; Masuda, H.; Yamaguchi, K.; Seki, H. *Heteroat. Chem.* **1995**, *6*, 99−104.

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(13) Brunker, T. J.; Blank, N. F.; Moncarz, J. R.; Scriban, C.; Anderson, B. J.; Glueck, D. S.; Zakharov, L. N.; Golen, J. A.; Sommer, R. D.; Incarvito, C. D.; Rheingold, A. L. *Organometallics* **2005**, *24*, 2730−2746.

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(15) Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295−4298.

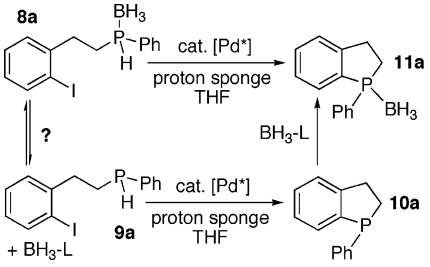
(16) Burk, M. J.; Gross, M. F. *Tetrahedron Lett.* **1994**, *35*, 9363−9366.

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 [Pd*] = Pd(diphos*)(*trans*-stilbene), diphos* = (*R*,*R*)-Me-DuPhos or (*R*,*R*)-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]

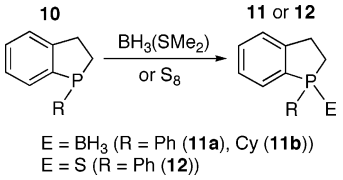
entry	ligand	substrate	time (days)	yield (%)	ee (%)
1	(*R*,*R*)-Me-DuPhos	**8a**	6	60	61
2	(*R*,*R*)-Me-DuPhos[b]	**8a**	5	89	70
3	(*R*,*R*)-Me-DuPhos	**9a**	3	80	59
4	(*R*,*R*)-Me-DuPhos	**9a**	1	78	63
5	(*R*,*R*)-Me-BPE	**8a**	6	63	36
6	(*R*,*R*)-Me-BPE	**9a**	3	76	37
7	(*R*,*R*)-Me-BPE	**9a**	1	80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

[a] Reactions were carried out at room temperature in THF with 5 mol % of the catalyst precursor Pd(diphos*)(*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 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, Pd((*R*,*R*)-Me-DuPhos)-catalyzed cyclization of **8a** was much slower when 1 equiv of $BH_3(SMe_2)$ was added, and *alkyl*phosphine 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 $BH_3(SMe_2)$;[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



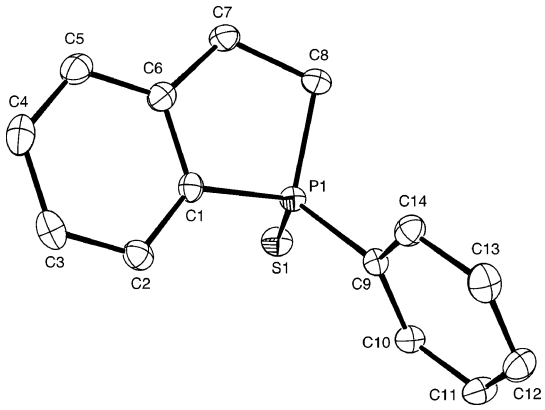


Figure 2. ORTEP diagram of **12**.

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

(17) Blank, N. F.; McBroom, K. C.; Glueck, D. S.; Kassel, W. S.; Rheingold, A. L. *Organometallics* **2006**, *25*, 1742−1748.

(18) Imamoto, T.; Oshiki, T.; Onozawa, T.; Matsuo, M.; Hikosaka, T.; Yanagawa, M. *Heteroat. Chem.* **1992**, *3*, 563−575.

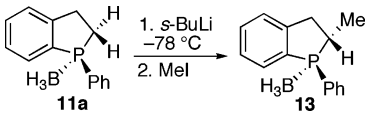
(19) Cyclization of **8a** (3.0 g) with 5 mol % of $Pd(dba)_2$ and $NaOSiMe_3$ in THF gave racemic **11a** in 58% yield; see the Supporting Information for details.

(20) Ohff, M.; Holz, J.; Quirmbach, M.; Borner, A. *Synthesis* **1998**, 1391−1413.

(21) See refs 2a,b and 3. For related examples, see: (a) Ohashi, A.; Imamoto, T. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **2000**, *56*, 723−725. (b) Imamoto, T.; Oohara, N.; Takahashi, H. *Synthesis* **2004**, 1353−1358. (c) Tang, W.; Wang, W.; Zhang, X. *Angew. Chem., Int. Ed.* **2003**, *42*, 943−946. (d) Tang, W.; Wang, W.; Chi, Y.; Zhang, X. *Angew. Chem., Int. Ed.* **2003**, *42*, 3509−3511. (e) Blake, A. J.; Hume, S. C.; Li, W.-S.; Simpkins, N. S. *Tetrahedron* **2002**, *58*, 4589−4602. (f) Kobayashi, S.; Shiraishi, N.; Lam, W. W.-L.; Manabe, K. *Tetrahedron Lett.* **2001**, *42*, 7303−7306.

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 ^{1}H 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-position in **11a** suggest that this chemistry may be useful in the synthesis of phospholanes for applications in asymmetric catalysis.

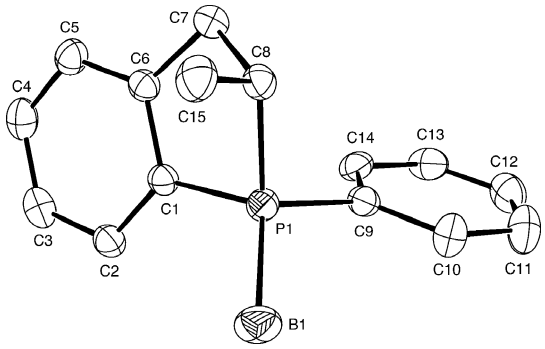


Figure 3. ORTEP diagram of the major diastereomer of **13**.

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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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(22) For a borane-free benzophospholane isomeric to **13** (Me substitution in the benzylic position), see: Egan, W.; Tang, R.; Zon, G.; Mislow, K. *J. Am. Chem. Soc.* **1971**, *93*, 6205−6216.

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