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Synthesis, Reactivity, and Resolution of a C_2–Symmetric, P–Stereogenic Benzodiphosphetane, a Building Block for Chiral Bis(phosphines)

Samantha C. Reynolds,[†] Russell P. Hughes,[†] David S. Glueck,*[,†] and Arnold L. Rheingold[‡]

6128 Burke Laboratory, Department of Chemistry, Dartmouth College, Hanover, New Hampshire 03755, United States, and Department of Chemistry, University of California, San Diego, 9500 Gilman Drive, La Jolla, California, 92093

Glueck@dartmouth.edu

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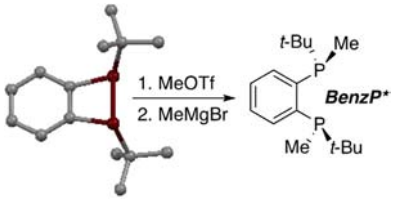
ABSTRACT



Although the pyramidal inversion barriers in diphosphines ($R_2P–PR_2$) are similar to those in phosphines (PR_3), P-stereogenic chiral diphosphines have rarely been exploited as building blocks in asymmetric synthesis. The synthesis, reactivity, and resolution of the benzodiphosphetane *trans*-1,2-(P(*t*-Bu))$_2C_6H_4$ are reported. Alkylation with MeOTf followed by addition of a nucleophile gave the useful C_2-symmetric P-stereogenic ligand BenzP* and novel analogues.

P-Stereogenic phosphines such as DiPAMP[1] are valuable ligands in asymmetric catalysis.[2] The barrier to pyramidal inversion in the diphosphines $R_2P–PR_2$ (22–26 kcal/mol)[3] is similar to that in phosphines PR_3 (29–36 kcal/mol),[4] but *chiral* diphosphines have received little attention in asymmetric synthesis. The reactive P–P bond makes these compounds potentially useful building blocks in the synthesis of chiral phosphines.[5] For example, enantiomerically pure diphosphine **1** was recently used to prepare P-stereogenic Josiphos ligands.[6] However, isolating C_2-symmetric menthyl-substituted diphosphine **2** required separation of a 1:3 mixture of C_2- and *meso*-**2**, and C_2-**2** rapidly epimerized in solution below room temperature (Figure 1).[7]

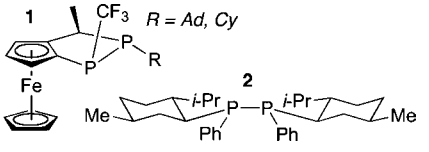


Figure 1. P-Stereogenic chiral diphosphines.

[†] Dartmouth College.
[‡] University of California.

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These examples suggest that chiral diphosphines such as **2** might be useful synthons if the C_2-symmetric isomer could be prepared selectively and if the P-inversion barrier was high enough to enable routine manipulations. Therefore, we investigated a rare class of heterocycles, the benzodiphosphetanes, in which steric effects make the *meso*-isomer less stable than the C_2 one and should also increase the P-inversion barrier (Figure 2).

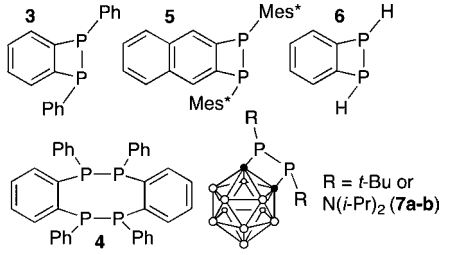


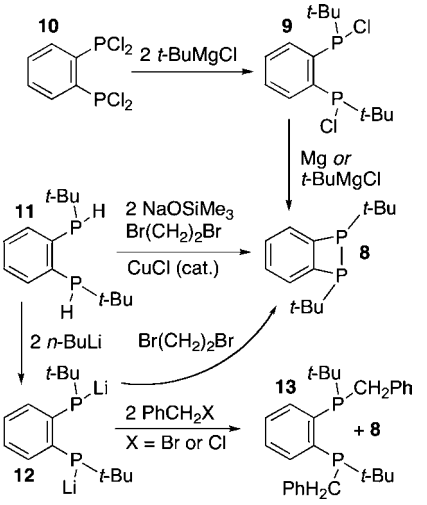
Figure 2. Benzodiphosphetanes and analogous dicarbaborane derivatives.

Although the all-carbon analogues (cyclobutarenes)[8] have been intensively studied, and silicon[9] and sulfur derivatives are known,[10] very few benzodiphosphetanes have been prepared. After unsuccessful attempts to make **3**, which gave its dimer **4** in $<1\%$ yield,[11] the sterically protected **5** (Mes* = 2,4,6-(t-Bu)$_3$C$_6$H$_2$) was reported,[12] and the parent compound **6** was observed as a reaction intermediate (Figure 2).[13] More recently, the synthesis and structures of analogous carbaborane derivatives **7a**−**b** were reported,[14] but little is known about the reactivity and possible applications of the P−P bond in these compounds.

Here we report a simple synthesis of *trans*-1,2-(P(t-Bu))$_2$C$_6$H$_4$ (**8**), studies of its reactivity, its resolution using a Pd complex, and its use as a building block for synthesis of P-stereogenic bis(phosphines) of known and potential utility in asymmetric catalysis.

Benzodiphosphetane **8** was prepared in 78% yield by reduction of the known chlorophosphine **9** with Mg;[14,15] this reaction may be carried out in one pot without isolation of **9** after its generation from commercially available **10** with t-BuMgCl (Scheme 1).[16] Treatment of **9** with excess t-BuMgCl also generated **8**. This reaction had been reported in 1986 by Kyba and co-workers, who observed benzodiphosphetane **8** by ^{31}P NMR spectroscopy but were not able to identify or isolate it.[16]

Scheme 1. Synthesis of Benzodiphosphetane **8**



Alternatively, a copper-catalyzed reaction of bis(secondary phosphine)[16] **11** with 2 equiv of NaOSiMe$_3$ and dibromoethane gave **8**.[17] Similarly, treatment of **11** with 2 equiv of n-BuLi gave dianion **12**; quenching with dibromoethane gave **8** as the major product. More surprisingly, treatment of **12** with benzyl bromide or chloride gave **8** in a mixture with the expected product, bis(tertiary benzylphosphine) **13**. The **8**/**13** product ratios (5:1 for Br, 1.2:1 for Cl) were consistent with formation of **8** via attack of the phosphido nucleophile at a halide instead of carbon, or an electron transfer process (Scheme 1).[18]

Despite the strained ring system, **8** distilled without decomposition under vacuum at 110 °C. It was air-stable for several days, even in solution. The volatility of **8** was consistent with its formulation as a monomer, not a dimer such as **4**, as were ^{1}H NMR DOSY studies, using **11** as an internal standard.[19] DFT calculations on **8** predicted a P−P bond length (2.292 Å) in the normal range[20] and the expected acute CPC angle (75.9°, Figure 3). C_2-Symmetric **8**, the only isomer observed, was calculated to be 12 kcal/mol more stable than its *meso* isomer. The computed barrier to pyramidal inversion in **8** (35 kcal/mol) was, as

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(20) Average P-P distance in diphosphines = 2.221 ± 0.11 Å (Forster, D.; Nieger, M.; Gudat, D. *Organometallics* **2011**, *30*, 2628–2631).

expected, higher than usual for diphosphines and similar to values calculated for carbaborane **7a**.[14]

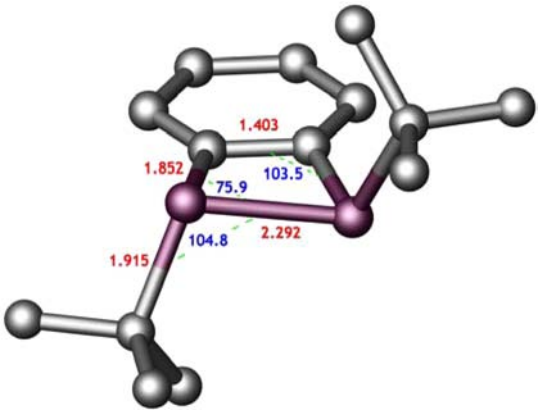
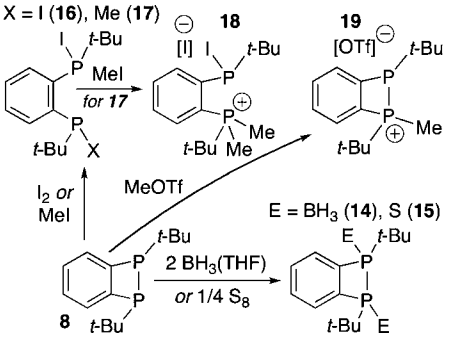


Figure 3. Computed structure (B3LYP/LACV3P**++) of benzodiphosphetane **8** with selected bond lengths (Å, red) and angles (deg, blue).

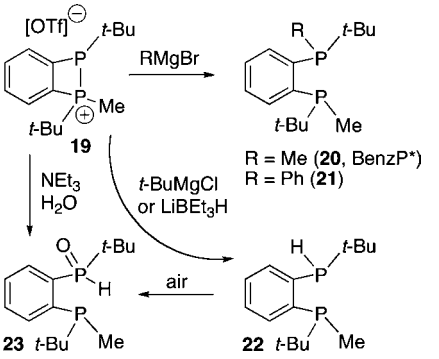
Diphosphetane **8** formed BH_3 adduct **14**, which readily lost borane on attempted chromatography or aqueous workup; bis(phosphine sulfide) **15** also could not be obtained in pure form (Scheme 2). Addition of I_2 across the P−P bond gave the diiodophosphine **16**, which was also formed from diiodoethane.[5,14] Reaction of 1 equiv of MeI with **8** yielded cation **18** and unreacted **8**; methylation of the (unobserved) presumed initial product **17** was apparently faster than its formation. Excess MeI gave full conversion to **18**.[5] In contrast, **8** reacted with methyl triflate to form phosphonium salt **19** (J_{PP} = 175 Hz), which retained the P−P bond.[6a,21]

Reaction of **19** with nucleophiles resulted in P−P cleavage to form bis(phosphines) with high diastereoselectivity (Scheme 3).[6a,21] Thus, MeMgBr gave C_2-symmetric BenzP* (**20**),[22] while PhMgBr yielded **21**. However, *t*-BuMgCl transferred a hydride instead of a *t*-Bu group to yield, as the major product, the mixed tertiary/secondary phosphine **22** (2:1 dr), which could also be formed using borohydrides such as $LiEt_3BH$.[23] Reaction of **19** with NEt_3/H_2O gave the analogous secondary phosphine oxide (SPO) **23** as a single isomer, presumably via tautomerization of the P−OH intermediate.[24] The structure of secondary phosphine **22** was confirmed by its oxidation to SPO **23**.

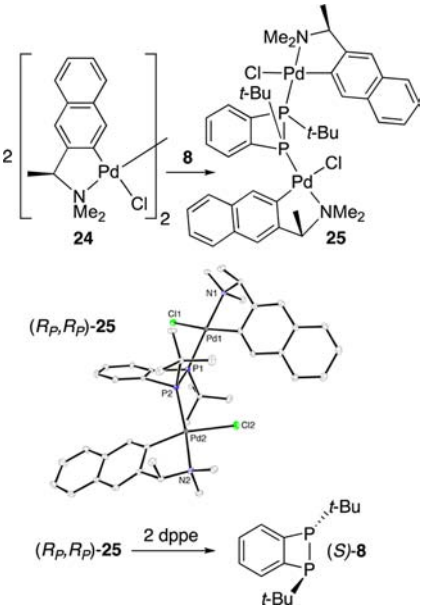
Scheme 2. Reactions of **8**



Scheme 3. Reaction of Cation **19** with Nucleophiles



Scheme 4. Resolution of **8**



Treatment of **8** with 2 equiv of chiral Pd complex **24** gave dinuclear **25** (Scheme 4).[25] Recrystallization from

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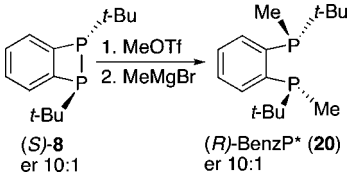
Scheme 5. Synthesis of Nonracemic BenzP* from Enriched **8**



CH_2Cl_2/pentane effected separation of diastereomers **25**, giving the less soluble (R_P,R_P) isomer in >100:1 dr, and (S_P,S_P)-**25** in 14:1 dr. In the crystal structure of (R_P,R_P)-**25**, the cyclometalated Pd-naphthyl moieties occupied inequivalent positions (Scheme 4). This structure was maintained in solution for both diastereomers (AB ^{31}P NMR spectra), as confirmed for (R_P,R_P)-**25** by NOESY studies.

Separate treatment of enriched samples of diastereomers **25** with the bidentate bis(phosphine) dppe ($Ph_2PCH_2CH_2PPh_2$) liberated enantiomerically enriched **8**,[26] which did not epimerize on heating to 105 °C in toluene for 18 h, consistent with the high computed barrier to inversion. Repeating the chemistry of Scheme 3 with nonracemic **8** gave enantiomerically enriched BenzP* with efficient chirality transfer (Scheme 5), with similar results for the synthesis of SPO **23**.

In conclusion, we report the synthesis and resolution of a chiral benzodiphosphetane, whose structure was designed to avoid formation of the unwanted *meso* diastereomer and to increase the pyramidal inversion barrier at phosphorus. Sequential electrophilic and nucleophilic alkylation gave Imamoto's valuable C_2-symmetric P-stereogenic bis(phosphine) BenzP* (**20**) and novel analogues **21**–**22**. These results establish chiral benzodiphosphetanes, and, more generally, diphosphines, as potentially useful building blocks in the synthesis of chiral phosphines. Such processes would be more practical if they used cheaper resolving agents or exploited (catalytic) asymmetric synthesis;[27] we are now investigating these possibilities.[28]

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

The authors declare no competing financial interest.

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(28) Although deprotonation of **11** with *n*-BuLi/(−)-sparteine gave predominantly one bis(phosphido) dianion, whose simple ^{31}P and ^{7}Li NMR spectra were consistent with C_2 symmetry (Hitchcock, P. B.; Lappert, M. F.; Leung, W.-P.; Yin, P. *J. Chem. Soc., Dalton Trans.* **1995**, 3925–3932), P−P bond formation occurred without any enantioenrichment.