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P-Stereogenic Bicyclo[4.3.1]Phosphite Boranes: Synthesis and Utility of Tunable *P*-Tether Systems for the Desymmetrization of C_2 -Symmetric 1,3-*Anti*-Diols

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Abstract

The development of *P*-stereogenicbicyclo[4.3.1]phosphite borane tether systems for the desymmetrization of C_2 -symmetric dienediols is reported. This report highlights preliminary studies including tether installation and removal, as well as chemoselective functionalization of the exocyclic olefin via diimide reduction or cross metathesis. Most notably, a divergent oxidation strategy allows for the transformation of the bicyclic phosphite borane complexes to the corresponding phosphate or thiophosphate systems, highlighting the electronic attenuation of this *P*-tether system.

Abstract

The development of modifiable methods that allow for the controlled, predictable, and facile functionalization of core structural motifs prevalent in a variety of biologically active natural products stands central to modern day organic synthesis and early stage drug discovery. In particular, strategies that employ tether-mediated processes, which improve substrate selectivity and reactivity through innate intramolecularity, are powerful approaches to generate advanced intermediates from simple and complex chemical fragments.¹ While silicon-based tethers are the most widely used and studied systems,² their phosphorus counterparts have emerged as viable alternatives.³ In particular, we have been interested in

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ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details and spectroscopic data of new compounds (PDF) and X-ray crystallographic files of **4** and **5** (CIF)

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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the development of *P*-stereogenic, bicyclic phosphates as tripodal, temporary tether systems for the synthesis of polyketide natural products (Figure 1).³ Despite the notable features of temporary phosphate-tether methods, current efforts in our group have aimed at exploring alternative tripodal tether systems in order to identify unique reactivity profiles that may be exploited in the synthesis of chemical scaffolds which would be difficult or laborious to access via previously reported methods. To this end, we herein report the development of *P*-stereogenic, bicyclic, P(III)-phosphiteborane systems as electronically tunable, temporary tether strategies for the desymmetrization of 1,3-*anti*-diol-containing dienes.

The synthesis and characterization of caged, cyclic phosphite borane complexes has a rich history, dating back to the seminal work of Heitsch and Verkade in the 1960's (Figure 1).⁴ Though a majority of these complexes are generated via phosphitylation of preformed polyols, several strategies involving the formation of P(III)-phosphorus-borane heterocycles via ring-closing metathesis olefination have been reported.⁵ In 2001, Van Boom and coworkers published the synthesis of mono- and bicyclic phosphinite borane systems using enyne RCM and tandem enyne RCM-olefin RCM, which proceeded in high yield.⁶

Building upon this work and the work of a handful of laboratories involving ring-closing metathesis (RCM) of olefin-containing P(III)-borane complexes,⁵ we first examined the use of phosphite borane triesters for the desymmetrization of 1,3-*anti*-dienediols through a diastereoselective ring-closing metathesis. Enantiomeric dienediols (*R,R*)- and (*S,S*)-**1**⁷ were coupled with commercially available allyl tetraisopropylphosphorodiamidite, in the presence of 1*H*-tetrazole, to provide the intermediate phosphite, which was subsequently protected by the addition of excess BH₃•THF to afford the phosphite-boranetrienes (*R,R*)-**2** and (*S,S*)-**3** in 73% and 72%, respectively (Scheme 1). It should be noted that these trienes were stable for storage under argon atmosphere at lower temperatures (<5 °C) for greater than 1 year; however, extended times for chromatographic separation resulted in partial triene decomposition, even when eluent was doped with triethylamine (5–10%). Thus, purification of crude triene reaction mixture via filter column chromatography (silica, 15% EtOAc in hexanes) is required to separate triene from amine by-product that inhibits the following ring-closing metathesis reaction. RCM of trienes (*S,S*)-**2** and (*R,R*)-**3**, in the presence of Grubbs second-generation catalyst [G-II, (ImesH₂)(PCy₃)(Cl)₂Ru=CHPh],⁸ afforded bicyclo[4.3.1]phosphite boranes (*S_p*,*S,S*)-**4** and (*R_p*,*R,R*)-**5** as off-white solids.

These bicyclic phosphite boranes were stable when stored at low temperature for extended periods of time (>2 years) and were also stable to chromatographic separation without observable decomposition. X-ray crystallographic analysis⁹ of (*R_p*,*R,R*)-**5** and (*S_p*,*S,S*)-**4** showed that each possess concave, caged structures similar to their phosphate counterparts, suggesting that the three-dimensional orientation of these substrates may allow for stereoselective additions to the internal olefin of the bicyclic phosphite borane systems (Scheme 2). In addition to column chromatography, the bicyclic phosphite borane (*S_p*,*S,S*)-**4** was found to be stable to acidic conditions common to a variety of work-up procedures.¹⁰ Reductive tether removal using Red-al provided the corresponding triol **6** in excellent yield, though bicyclic (*S_p*,*S,S*)-**4** was stable to a variety of other reductants/hydride sources (including LiBH₄, NaBH₄, and DIBAL-H). Chemoselective hydrogenation of the exocyclic olefin under diimide reaction conditions¹¹ showed that, much like with the bicyclic

phosphate, selective functionalization of the terminal, exocyclic olefin in the presence of the internal olefin is achievable (**7**).

In addition to chemoselective hydrogenation, the exocyclic olefin of the bicyclic phosphiteborane (in this case, (*R_p*,*R,R*)-**5**) can be further functionalized via a selective cross-metathesis reaction, as shown in Table 1. We hypothesized that the exocyclic olefin of the bicyclic phosphite-borane systems would behave as a Type II/Type III¹² olefin cross-partner in Ru-catalyzed cross metathesis reactions—in a manner similar to the behavior of the corresponding bicyclic phosphate.¹³ Indeed, this hypothesis was consistent with experimental observation, as cross metathesis of **5** was successful with a variety of Type I and Type II olefin cross partners and attempted cross-metathesis with Type III olefin cross partners (acrylonitrile and protected secondary alcohols) were low-yielding and/or unsuccessful. Exposure of **5** to Type I or Type II olefin cross partners, in the presence of catalytic Hoveyda-Grubbs second generation catalyst,¹⁴ provided the corresponding CM products in moderate to excellent yield for the substrates screened. It should be noted that the *cis*-homodimers of Type I olefins allowed for higher conversions and yields than the mono-counterparts (examples **8**, **9**, **10**), and lower yields were often the result of lower conversion, as evident by improved yields based on recovered starting material—which could be re-isolated and re-used in other reactions (examples **9** and **11**).

Finally, in addition to olefin functionalization, we were interested in the controlled transformation of P(III) to P(V) of our bicyclic phosphiteborane systems via deprotection oxidation strategies similar to those reported for other P(III)-borane complexes.¹⁵ In this regard, a divergent oxidation strategy involving deprotection of the bicyclic phosphite borane with DABCO, followed by oxidation with either *tert*-butyl hydrogen peroxide or elemental sulfur (S₈), successfully generated both the bicyclic phosphate (P=O, **14**) and thiophosphate (P=S, **15**) from the phosphiteborane precursor (**4**, Scheme 3). Though predictable, this result was exciting as it implied that the inherent reactivity profiles of both the bicyclic phosphite borane and bicyclic phosphate tether systems could be exploited separately or in tandem in a single synthetic strategy to rapidly build molecular complexity en route to the synthesis of natural products and, thus, increase the synthetic utility of the *P*-tether system overall.

In conclusion, the development of *P*-stereogenic, bicyclic phosphite borane tether systems for the desymmetrization of C₂-symmetric, 1,3-*anti*-diol-containing dienes is reported. These systems are air and acid stable and storable at low temperatures for extended periods (>2 years). These systems can be selectively functionalized—through chemoselective hydrogenation or cross-metathesis of the exocyclic olefin, to provide elaborated structures without disrupting the integrity of the P–B bond. Finally, divergent oxidation strategies to generate the corresponding bicyclic phosphate and thiophosphate from the bicyclic phosphite borane expand the potential utility of this phosphorus tether—as one synthetic strategy could include chemistries unique to both bicyclic phosphite borane and bicyclic phosphate tether systems used separately and in tandem to generate advanced intermediates en route to the total synthesis of natural products. The development of such strategies is currently ongoing in our laboratory and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Bicyclic phosphite boranes, P(III)-mediated ring-closing metathesis, and *P*-tether-mediated desymmetrization of C₂-symmetric dienediols.

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Scheme 3.
Divergent oxidation strategies to bicyclic phosphates and thiophosphates.

Table 1

Chemoselective cross metathesis studies for terminal olefin functionalization.

cross partner	olefin type	product (yield, %)
	1	 8 (87) [dr > 20:1]
	1	 9 (62) [84% BRSM]
	1	 10 (88) [E/Z = 7:1]
	2	 11 (51) [77% BRSM]
	2	 12 (47) [dr > 20:1]
	2	 13 (95) [dr > 20:1]