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A *P*-Tether-Mediated, Iterative S_N2' -Cuprate Alkylation Strategy to Skipped Polyol Stereotetrads: Utility of an Oxidative “Function Switch” with Phosphite-Borane Tethers

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Abstract

The development of a *P*-tether-mediated, iterative S_N2' -cuprate alkylation protocol for the formation of 1,3-skipped polyol stereotetrads is reported. This two-directional synthetic strategy builds molecular complexity from simple, readily prepared C_2 -symmetric dienediols and unites the chemistry of both temporary phosphite-borane tethers and temporary phosphate tethers—through an oxidative “function switch” of the *P*-tether itself—to generate intermediates that were previously inaccessible via either method alone.

Abstract

ability to mediate multiple transformations in one-pot sequential processes—in the two-directional synthesis of complex polyols.³ Much like the synthetic community at large, we seek intriguing targets containing interesting chemical fragments to help catalyze method development and expansion. One such family of targets, the ulapualide polyketide natural products (Figure 1),⁴ was found to contain a 1,3-skipped polyol stereotetrad comprised of a 1,3-*anti*-diol flanked by methyl-branched alkyl chains.

We proposed that fragments of this type could be synthesized utilizing a *P*-tether-mediated iterative alkylation strategy, similar to that outlined in Figure 2, where a regio- and diastereoselective S_N2'-cuprate displacement of an exocyclic leaving group, followed by a second regio- and diastereoselective S_N2'-cuprate displacement of the tether itself, would allow for the formation of functionalized versions of the desired intermediate. However, while the behavior of bicyclic phosphate tethers in the presence of *in situ*-generated, dialkyl cuprate has been established,^{5,1a} the ready leaving group ability of phosphates—combined with its ability to activate multiple carbinol centers for nucleophilic attack—significantly complicates the development of a competitive alkylation strategy mediated by a phosphate tether.⁶ Thus, we envisioned that the development of an alternative tether with “tunable” electronic character would allow for the successful competitive S_N2'-cuprate displacement of an external leaving group, followed by subsequent modification of tether electronics and a second selective cuprate displacement of the tether itself to form the desired stereotetrad.

In the preceding report, we introduced the use of *P*-stereogenic, bicyclic P(III)-phosphite borane complexes as new tripodal, temporary tether systems for the desymmetrization of 1,3-*anti*-diol-containing dienes,⁷ and we highlighted the ability of this new *P*-tether system to facilitate chemoselective cross-metathesis reactions with Type I and Type II olefins⁸ and undergo divergent oxidation protocols that transform the P–B bond to P=O or P=S bonds. We proposed that this oxidative “function switch” of the *P*-tether expands its utility, as a single synthetic strategy could employ the unique chemistries of both phosphite-borane and phosphate tethers to access fragments en route to the total synthesis of natural products. In line with this proposal, we herein report one such strategy that employs bicyclic P(III)-phosphite borane tethers and phosphate tethers for the desymmetrization of *C*₂-symmetric, 1,3-*anti*-diols to provide 1,3-skipped polyol stereotetrads that were previously inaccessible via phosphate tether strategies alone (Figure 1). In addition to providing unique *P*-containing scaffolds with interesting potential as biological probes, this method may serve as a useful alternative to aldol-like coupling strategies⁹ or other asymmetric crotylation¹⁰ protocols to provide functionalized 1,3-skipped polyol intermediates for the synthesis of complex natural products.

To probe the viability of a phosphite-borane tether-mediated competitive S_N2'-cuprate allylation, we first aimed to generate a model substrate by installing an allylic, exocyclic leaving group to simple bicyclic phosphite-borane **1** (Scheme 1). As previously described,⁷ *C*₂-symmetric, 1,3-*anti*-diol **2**¹¹ is coupled to commercially available allyl tetraisopropylphosphorodiamidite, in the presence of 1*H*-tetrazole, to form the intermediate phosphite, which is complexed with BH₃ to generate pseudo-*C*₂-symmetric phosphite-borane triene **3** (Scheme 1). Diastereoselective ring-closing metathesis (RCM) of triene **3** with Grubbs second generation catalyst [G-II, (ImesH₂)(PCy₃)(Cl)₂Ru=CHPh]¹² smoothly

provides bicyclo[4.3.1]phosphite borane **1** in excellent yield. Chemoselective cross metathesis of **1** with diallyl phosphate **4**, in the presence of Hoveyda-Grubbs second-generation catalyst,¹³ generates functionalized bicyclic phosphite borane **5**, with the appropriate exocyclic, allylic leaving group for competitive S_N2' -cuprate allylation studies. In this regard, cross-metathesis product **5** was treated with *in-situ*-generated dimethyl- and diethyl-cyanocuprates (1.5 equivalents and 3 equivalents, respectively)¹⁴ to generate bicyclic phosphite borane-containing alkylation products **6** and **7** in moderate yields (50% and 54%, respectively) and diastereomeric ratios of ~2:1 [major to minor] (Scheme 4). These results indicated that the bicyclic phosphite borane had only minor control over the stereoselectivity of the cuprate addition to the exocyclic olefin, and as such, implied that secondary substrate control via the stereospecific S_N2' -cuprate displacement of an exocyclic leaving group on a stereogenic carbon would allow for the generation of either the *syn*- or *anti*-alkylated products. Thus, attention was turned to the generation of such alkylation precursors.

To represent all diastereomers that can be formed through this strategy, we synthesized two bicyclic phosphite borane substrates bearing exocyclic allylic phosphates on stereogenic, secondary carbons as cuprate-addition precursors (Scheme 2). Direct metathesis with the pre-formed allylic phosphates was challenging—as the reaction was slow and low-yielding; however, sequential cross metathesis of either (*R*_p,*R*,*R*)-**3** or (*S*_p,*S*,*S*)-**8** with chiral, non-racemic allylic alcohol *R*-**9**,¹⁵ followed by phosphorylation or phosphitylation-oxidation, provided the desired precursors (**10** and **11**) in excellent yields over two steps. In particular, the phosphitylation-oxidation protocol highlights the stability of the phosphite-borane complex with respect to external oxidants (without prior BH₃-decomplexation). While this strategy was sufficient as a proof of concept, a second generation synthesis of these precursors using an RCM-CM-phosphorylation strategy would allow for the facile formation of diastereomeric **10** and **11** in two pots from simple dienediol precursors (4 total pots, overall) to streamline syntheses of these intermediates en route to the total synthesis of natural products. In line with recent, related work involving phosphate tether systems, current efforts to explore one pot sequential processes mediated by a phosphite-borane tether system are ongoing in our laboratory and will be reported in due course.

Phosphite-borane phosphates **10** and **11** were next subjected to dimethylcuprate conditions, and each generated the desired *anti*- or *syn*-alkylated bicyclic phosphite boranes **12** and **13** in moderate to excellent yields and excellent diastereoselectivities (dr > 20:1, Scheme 3). It should be noted that the alkylation of substrate **10** to provide *syn*-**12** was significantly slower than the corresponding *anti*-substituted transformation, and as a result, it required additional warming (to 0 °C). However, if the reaction was quenched at lower temperature (-10 °C), the corresponding product could be isolated in 45% yield, along with unreacted starting material (84% yield of *syn*-**12** based upon recovered starting material). Though an iterative cuprate strategy resulting in the formation of 1,3-skipped polyol stereotetrads was the goal of this study, these mono-alkylated products are also useful intermediates in their own right, in particular **13** contains a large portion of the backbone of franklinolide A, a family of cytotoxic phosphodiester isolated and characterized from an Australian marine sponge sample by the Capon group in 2010 (highlighted in Scheme 6).¹⁶

Finally, to complete the iterative alkylation cycle, we performed an oxidative “function switch” of the phosphorus tether via a decomplexation-oxidation of diastereomeric phosphite-boranes **12** and **13** to provide the corresponding bicyclic phosphates (only **14** shown below, Scheme 4) in nearly quantitative yield. A second stereospecific S_N2' -cuprate displacement of the bicyclic phosphate,⁵ methylation of the resultant phosphoric acid (only **15** shown below), and subsequent reductive tether removal, afforded the desired 1,3-skipped polyol stereotetrads **16** and **17** in 8 pots from simple dienediol precursors.

In conclusion, a *P*-tether-mediated, iterative S_N2' -cuprate alkylation strategy to provide 1,3-skipped polyol stereotetrads from simple 1,3-*anti*-dioldienes is reported. This multifunctional, tripodal *P*-tether facilitates multiple transformations, including: (i) the initial desymmetrization of the 1,3-*anti*-dienediol, (ii) the regioselectivity of the S_N2' -displacement of an exocyclic leaving group, and (iii) the regio- and diastereoselectivity of a second cuprate displacement of an intermediate bicyclic phosphate tether—resulting from an oxidative “function switch” of the phosphite borane tether—to generate stereotetrads that were previously inaccessible via other traditional phosphate tether strategies alone. Efforts toward the generation of more complex bicyclic phosphite borane tether systems, as well as the development of phosphite borane tether-mediated, one-pot sequential processes that will further streamline the facile formation of intermediates en route to the total synthesis of natural products are in progress and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Ulupualide family of marine natural products.

Figure 2.

Iterative alkylation strategy to provide diastereomeric ulapualide-like polyol stereotetrads.

Scheme 1.

P-Tether-mediated, competitive S_N2'-cuprate alkylation of model substrate 5.

Scheme 2.
Synthesis of diastereomeric alkylation precursors.

Scheme 3.
Competitive $\text{S}_{\text{N}}2'$ -cuprate alkylation of 10 and 11.

Synthesis of 1,3-skipped polyol stereotetrads from alkylated intermediates 12 and 13.