Organosuperbase Catalyzed 1,1-Diboration of Alkynes

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Abstract: 1,1-diboryl alkenes are versatile building blocks in organic synthesis and medicinal chemistry. There have been only a small number of established methods to prepare this class of compounds and most of them used transition metal catalysts, which are undesirable in the preparation of bioactive compounds. Herein, we report an unprecedented application of P$_1$-tBu as an organocatalyst to promote 1,1-diboration reactions of unactivated aromatic as well as electron-deficient terminal alkynes. The strong basicity of this phosphazene enables the activation of reaction substrates while its steric bulk allows for high regio- and stereo-selectivity to be obtained. A combination of experimental and computational studies suggests interesting mechanistic insights for these phosphazene-catalyzed diboration reaction, which are also discussed in detail.
Introduction

Organoboron compounds are unarguably one of the most valuable families of synthetic building blocks in organic chemistry. Multiboronate precursors have recently attracted immense attention from synthetic chemists due to their versatile and tunable reactivity, especially in the cross-coupling chemistry that leads to a plethora of organic structures, bioactive compounds and advanced functional materials. Diborylalkenes are probably the most utilized synthetic precursors in this sub-class, as they offer distinctive pathways to the construction of multi-substituted alkenes in regio- or stereo-selective manner. Diborylalkenes in turn are typically produced by diboration of alkynes via addition reactions. However, the nature of these addition reactions often leads to 1,2-diborylalkenes being formed as the products.

Methods to synthesize the 1,1-diborylalkene counterparts have only been reported more frequently in the recent years. Most of them involved transition metals catalysts such as [Co], [Zn], [Cu], [Pd] or [Ir] to facilitate diboration of non-activated terminal alkynes (Scheme 1, top). The diboration of activated terminal alkynes bearing electron-withdrawing substituents is relatively easier and can be promoted with alkali-metal bases as catalysts. These methods, despite being elegant and valuable, were either developed for specific types of alkyne substrates or associated with undesirable issues like traces of transition metal impurities in the final products.

The aforementioned transition metal catalyzed diboration reactions of terminal alkynes typically proceed via a dehydrogenative monoboration at the C(sp)-H moiety, followed by a direct or formal hydroborative addition reaction to the C-C triple bond to give 1,1-diborylalkenes. In the pursuit of an organocatalytic system that is capable of promoting the diboration reaction of terminal alkynes in a similar fashion, we envision that this new catalyst should have strong Brønsted basicity to break the weakly acidic C(sp)-H bond. It should also possess either strong p-Lewis acidity to activate the C-C triple bond or s-Lewis basicity to activate the boron reagent. The former feature is incompatible with the desired Brønsted basicity, so it has to be the latter. Being informed by our earlier boration work and chemistry with N-heterocyclic carbenes and olefins, which are very strong Brønsted bases and or s-Lewis donors themselves but unsuitable for this type of chemical transformation, we focus our initial effort on the investigation of 1,1-diboration reaction of terminal alkynes using phosphazene superbase P₁⁻Bu-tris(tetramethylene), denoted in this work as P₁⁻Bu, as reaction promoter (Scheme 1, bottom).
Phosphazenes are a family of non-ionic organic superbases that have been known to promote a wide variety of chemical transformation.\textsuperscript{34-41} \(\text{P}_1\text{-}t\text{Bu}\) is not the strongest base in this family but it was chosen as the catalyst of choice for this study due to its simple structure, relatively low costs and good tolerance to air and moisture.\textsuperscript{34,36,39} Bulkier phosphazenes were considered unsuitable for this initial study, as the steric bulks of their structures render the imino nitrogen centres very poor s-Lewis donors,\textsuperscript{41} but we will not rule them out of future investigations. Using \(\text{P}_1\text{-}t\text{Bu}\) as the catalyst instead of alkali-metal bases is also advantageous for reaction mechanistic insights,\textsuperscript{34,39} as the reaction mixture is typically homogenous and free of transition metal traces, an issue often led to confusion on the source of catalytic activity.\textsuperscript{42} In this work, we report the first organocatalytic method for the synthesis of 1,1-diboryl alkenes from both non-activated and activated terminal alkynes, using \(\text{P}_1\text{-}t\text{Bu}\) as catalyst under practical conditions.

**Results and Discussion**

Our proposed reaction concept was met with instant success as a test reaction between two equivalents of HBpin and 4-trifluoromethylphenylacetylene 1a as model substrates in the presence of catalytic amount of \(\text{P}_1\text{-}t\text{Bu}\) led to the formation of 1,1-diboryl product 3a in moderate yield.\textsuperscript{43} An optimization study of reaction medium, catalyst loading, reaction temperature and time as well as reagent stoichiometry led to the best reaction efficiency using 15 mol\% of \(\text{P}_1\text{-}t\text{Bu}\) catalyst in neat conditions.
conditions at 90 °C with 36 hours reaction time (Scheme 3a, also see pages S5-S6 in the experimental SI for further details).\textsuperscript{43}

**Scheme 2.** P\textsubscript{1}-catalyzed 1,1-diboration of terminal alkynes: Substrate scope and experimental mechanistic studies.

Using the optimal conditions developed, we were able to convert a range of terminal aromatic alkynes into their corresponding 1,1-diborylalkene derivatives with moderate to excellent efficiencies.
Substrates with electron-withdrawing groups on the aromatic rings generally worked better than the ones with electron-donating groups (3a-g in comparison to 3h-l, Scheme 2a). This difference in reactivity can be attributed to the acidity of the C(sp)-H moiety, which is the determining factor for the reaction initiation (see mechanistic discussion associated with Figure 2, *vide infra*). The reaction worked well for bis(alkynyl) substrates, giving valuable tetraboryl products (3m and 3n) in good yields. Heterocyclic alkyne tolerated the reaction conditions (3o). Non-terminal alkynes were used, the standard reaction setup led to the formation of hydroboration product (3p and 3q) whilst reactions with an higher excess of HBpin resulted in gem-diboryl alkanes (3p' and 3q') in good to high yields. The reaction did not work with aliphatic terminal alkynes, presumably due to lower reactivity of these compounds.

As discussed in the introduction, all previously reported methods used transition-metal catalysts to enable 1,1-diboration of the terminal alkynes of this type. This is, to the best of our knowledge, the first example of such reaction promoted by an organic superbase, so it is curious to us how this P$_{1-t}$Bu works to catalyze the reaction. Thus, we carried out some experimental mechanistic studies with model substrate 1a. Firstly, when only one equivalent of HBpin was used and the reaction mixture was analyzed within the first one hour under optimal conditions (Scheme 2b), we found clear evidence of the exclusive formation of monoboryl alkyne INT3a by $^1$H and $^{19}$F NMR spectroscopy (see pages S9-S10 in the experimental SI). This monoboryl alkyne can also be isolated from the reaction mixture. This clearly indicates that the first step of the reaction was a dehydrogenative boration process, which was further supported by the detection of H$_2$ gas in the reaction by $^1$H NMR (see page S8 in the experimental SI). The time-dependent reaction profile as monitored by $^1$H NMR with mesitylene as internal standard (Scheme 2c, see pages S11-S13 in the experimental SI for details) shows the total conversion of substrate 1a to the monoboryl alkyne intermediate INT3a within the first four hours, which then slowly converted to the 3a. This reaction profile suggests that the second step was a hydroboration reaction of INT3a to form the 1,1-diborylalkene product, which gratifyingly match our initially proposed reaction design.

Having this experimental knowledge in hand, we subsequently carried out density functional theory (DFT) calculations to elucidate the reaction mechanism for this P$_{1-t}$Bu organic superbase-catalyzed diboration of alkynes with HBpin, using the structurally simpler 1h as a representative case. The computed free energy profile is shown in Figure 1a. The first step of this reaction is calculated to be the concerted deprotonation/nucleophilic addition process via TS-1, in which 1h is deprotonated by P$_{1-t}$Bu superbase followed by a nucleophilic addition to Hbpin, giving contact ion pair INT1. Because
of the weak acidity of 1h, this step takes place in a concerted manner rather than a stepwise one.\textsuperscript{22}

From \textbf{INT1}, a heterolytic recombination of the H$^{\delta+}$ and H$^{\delta-}$ containing species via \textbf{TS-2} can then occur to generate monoboryl species \textbf{INT2}, which also regenerates the P$_1$-tBu superbase, and expels hydrogen (which was detectable from the reaction mixture with 1h by $^1$H NMR spectroscopy, similar to with 1a in Scheme 2b). The activation barriers of \textbf{TS-1} and \textbf{TS-2} are calculated to be 24.5 and 21.5 kcal/mol relative to 1h, respectively. The formation of monoboryl species \textbf{INT2} was also confirmed experimentally by $^1$H NMR spectroscopy of the crude reaction mixture, similar to with \textbf{INT3a} in Scheme 2b.

\textbf{Figure 1.} Computed free energy profile (kcal/mol) and optimized structures of transition states for the organic superbase-catalyzed diboration of terminal alkyne using HBpin. Bond distances are in Å. The CH–π distance is calculated from the H atom to the ring plane. Non-pertinent hydrogen atoms are omitted for clarity.

From monoboryl species \textbf{INT2}, our calculations suggest that a hydride transfer from HBpin to the C2 atom of \textbf{INT2} via \textbf{TS-3} giving contact ion pair \textbf{INT3}, which is the combination of a P$_1$ $^6\pi$–N(tBu)–Bpin cation and a vinylideneborate species (see Figure CS4 – page S166 in the computational SI for molecule orbitals of the vinylideneborate). The hydride transfer is enabled by the P$_1$-tBu catalyst, where it acts...
as a Lewis base stabilizing the partial positive charge on the boron atom of Bpin moiety. Upon the formation of ion pair \textbf{INT3}, a boryl transfer can then take place via transition state \textbf{TS-4} giving 1,1-diboryl species \textbf{3h}. The activation barrier of \textbf{TS-3} and \textbf{TS-4} are calculated to be 25.4 and 19.1 kcal/mol relative to \textbf{2}, respectively.

It should be pointed out that the hydride can also transfer from HBpin to the C1 atom of \textbf{2} via \textbf{TS-3'} (highlighted in red in Figure 1a). By scrutinizing the optimized structures of hydride transfers, we find that \textbf{TS-3} is stabilized by a stronger CH-π interaction than that in \textbf{TS-3'}. Therefore, \textbf{TS-3'} is calculated to be 6.2 kcal/mol higher in energy than \textbf{TS-3} and CH-π interaction is likely the origin of regioselectivity of the second step of this diboration reaction. Our calculations show that the superbase-catalyzed diboration is exergonic by 34.6 kcal/mol and the rate-determining step is the hydride transfer via \textbf{TS-3} with an overall activation barrier of 25.4 kcal/mol. This result is consistent with the fact that monoboryl alkyne intermediate can be generated more rapidly than diborylalkene product (Scheme 2c, \textit{vide supra}).

It is interesting that the \textit{P$_1$-tBu} catalyst might have played two different roles in this 1,1-diboration reaction of alkynes, based on our proposed mechanism. For the first boration, it clearly acts as a Brønsted base to deprotonate the alkyne for the nucleophilic addition to HBpin. For the second boration step, it acts as a Lewis base that stabilizes positive charge on Bpin group, enabling the hydride transfer from HBpin to monoboryl species \textbf{INT2} (see Figure CS3 – page S166 in the computational SI for molecular electrostatic potential of \textit{P$_1$-tBu}, which indicates its potential role as Lewis base). We carried out some experimental studies that validated these potential roles of \textit{P$_1$-tBu} and our proposed mechanism. First, in the presence of 15 mol\% \textit{P$_1$-tBu}, phenylacetylene \textbf{1h} did proton/deuterium exchange with CDCl$_3$ to \textbf{1h-D}, as indicated by NMR studies in this solvent (Figure 1b, also see page S14 in the experimental SI for NMR spectra). When the 1,1-diboration reaction was carried out on \textbf{1h-D}, the final product turned out to be the non-deuterated \textbf{3h} (Figure 1b), which agrees well with our proposal of the dehydrogenative monoboration, as the acetylenic D/H is eliminated in this step. In a non-protic solvent such as C$_6$D$_6$, we observed evidence for weak coordination or partial deprotonation of \textbf{1h} by \textit{P$_1$-tBu} \textit{a}, (\textit{pre-}TS-\textit{1}, Figure 1c, also see pages S15-S16 in the experimental SI for NMR spectra), which is consistent with our computational proposal for \textbf{TS-1}. When \textit{P$_1$-tBu} was replaced with \textit{P$_4$-tBu} (see Scheme 3b), a stronger Bronsted base but weaker Lewis base due to its steric bulk, the reaction stalled at \textbf{INT2} and failed to produce \textbf{3h}, supporting our proposal that Lewis coordinations of the base to Bpin moiety in \textbf{TS-3} and \textbf{INT3} are crucial for the second step of this reaction.
To further explore the catalytic activity of $P_{1-}tBu$ and to expand the scope of this reaction, we subsequently carried out some screening reactions. First, the replacement of superstoichiometric HBpin with diboration reagent such as $B_2pin_2$ (5a) did not lead to any product formation (Scheme 3a), confirming that the deprotonation/nucleophilic addition via $TS-1$ followed by the dehydrogenation reaction via $TS-2$ is crucial for this type of reaction. On the other hand, application of our optimal conditions from Scheme 2 to propiolate ester such as 4a, another common class of alkyne substrates, did not lead to any conversion to the expected 1,1-diboryl product (Scheme 3a). Interestingly, when HBpin was replaced with $B_2pin_2$, the diboration reaction then occurred on this propiolate ester to give product 6a with promising outcomes.

Scheme 2. a) Expanding the reaction scope to propiolate ester. (b) Catalytic activities of common Brønsted bases. Reactions were carried out under optimal conditions (see pages S7 and S34 in the experimental SI). Yield determined by $^1H$ NMR integration with mesitylene as internal standard. (c) Reactions with substituted propiolate esters.

After an extensive optimization study, we found that 5 mol% of $P_{1-}tBu$ can readily promote 1,1-diboration of methyl propiolate (4a) with just one equivalent of $B_2pin_2$ under solvent-free conditions at ambient temperature with excellent efficiency (see pages S30-S34 in the experimental SI, and also Scheme 4, vide infra). $P_{1-}tBu$ proved to be a superior catalyst for this reaction (reaction #2, Scheme 3b), as indicated by a comparison of its catalytic activity with other commonly used organic and inorganic bases. These included alkali-metal salts such as KO'Bu and $K_2CO_3$, which were known to promote this reaction at elevated temperatures. We repeated reactions with these inorganic bases several times with chemicals obtained from different suppliers but could not reproduce any efficiency close to the outcomes reported in literature. Nevertheless, the superiority of this $P_{1-}tBu$ catalyst is even
more apparent for the 1,1-diboration of aromatic alkynes with HBpin from Scheme 2, which none of the other catalysts tested gave any favorable outcomes (reaction #1, Scheme 3b). While P$_2$-Bu was ineffective for reaction #1, it worked comparably well to P$_1$-Bu for reaction #2, however was not the catalyst of choice due to its higher cost and moisture sensitivity. It should also be noted here that substituted propiolate esters such as 8 or dimethyl acetylenedicarboxylate 10 did not lead to any diboryl products when subjected to the P$_1$-Bu catalyzed reaction with B$_2$pin$_2$ (Scheme 3c).

Scheme 4. P$_1$-catalyzed 1,1-diboration of electron-deficient alkynes with B$_2$pin$_2$ and Bpin-Bdan.

The optimal reaction conditions with substrate 4a were amenable to a range of other propiolate esters and propiolamides to convert them to the corresponding 1,1-diboryl acrylate products in good to excellent yields (6a-n, Scheme 4a). By imposing different stoichiometry for B$_2$pin$_2$, we could also precisely control how many Bpin groups can be installed on *bis* (propiolate) substrate (6h and 6i, Scheme 4a). P$_1$-Bu catalyst was also capable of promoting 1,1-diboration with Bpin-Bdan, giving mixed boryl products in similar efficiencies, as shown by the substrate scope 7a-o in Scheme 4b. This reaction required higher catalyst loading and temperature, as well as a solvent to enable consistent mixing (see page S35 in the experimental SI for optimization studies), but produced a diverse family of highly valuable mixed 1,1-diboryl alkene products in highly stereoselective manner. Notably, a *tris* (propiolate) substrate led to a product with three Bpin and three Bdan group (7l) with a very good overall efficiency. The reaction also worked well with a sulfone substrate to give product 7m in high yield.
We subsequently carried out DFT calculations to elucidate the reaction mechanism for the organic superbase-catalyzed diboration of electron-deficient alkynes with $\text{B}_2\text{pin}_2$, using methyl propiolate 4a as the model substrate. The computed free energy profile is shown in Figure 2. The reaction starts with the deprotonation of 4a by $\text{P}_1$-$\text{tBu}$ via TS-5, giving a contact ion pair species INT5 between acetylide anion and protonated phosphazene. Because of the strong basicity of $\text{P}_1$-$\text{tBu}$, the activation barrier of this step is calculated to be as low as 13.6 kcal/mol relative to 4a. Our experimental $^1\text{H}$ and $^{13}\text{C}$ NMR complexation studies revealed evidence for the formation of this species (see pages S36-S37 in the experimental SI).

To proceed, the nucleophilic addition of acetylide anion to $\text{B}_2\text{pin}_2$ is found to occur via TS-6, which is followed by a concerted 1,2-migration of Bpin moiety and proton transfer from the protonated phosphazene to methoxycarbonyl group of the substrate via TS-7, giving allenol species INT7. The activation barriers of TS-6 and TS-7 are calculated to be 15.2 and 14.2 kcal/mol relative to 4a, respectively. Upon the formation of allenol intermediate INT7, its tautomerization via TS-8 can occur to form diboration product 6a. Our calculations suggest that this reaction is exergonic by 51.5 kcal/mol.

**Figure 2.** Computed free energy profile (kcal/mol) and optimized transition states for the organic superbase-catalyzed diboration of alkynes with $\text{B}_2\text{pin}_2$. Distances are in Å. Non-pertinent hydrogen atoms are omitted for clarity.
via TS-7' (see Figure CS5 – page S167 in the computational SI) can occur giving diboration product 6a. However, TS-7' is calculated to be 2.4 kcal/mol higher in energy than TS-7. Therefore, this pathway (highlighted in red in Figure 2) is unlikely to occur. Similar DFT calculations were carried out to rationalize the stereoselectivity for the superbase-catalyzed diboration of alkynes with BpinBdan 5b, which can be seen in pages S164-S165 of the computational SI.43

Conclusion

We have developed a completely metal-free method to promote 1,1-diboration reactions of unactivated aromatic as well as electron-deficient terminal alkynes, using P1-tBu as catalyst. A combination of experimental and computational studies suggests interesting mechanistic insights for these phosphazene-catalyzed diboration reactions, in which the Brønsted and Lewis basicity of this phosphazene enables the activation of reaction substrates while its steric bulk allows for high regio- and stereo-selectivity to be obtained.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge: Experimental details and spectroscopic data for all products, full Gaussian reference, Cartesian coordinates, electronic and free energies.

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Author Contributions

‡SHD and NNHT contributed equally to this work. The manuscript was written through contributions of all authors. SHD and NNHT carried out all experimental work; TVN conceived the ideas and designed the project. BKM carried out all computational studies. All authors have given approval to the final version of the manuscript.

CONFLICTS OF INTEREST

There is no conflicts of interest to declare.
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REFERENCES


See the Supporting Information for further details.

DFT calculations were carried out at the MN15/6-311+G(2d,2p)/CPCM(solvent)//M06-2X/6-31G(d,p) level of theory. See the computational Supporting Information for details.
