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Phosphine-Catalyzed Regio- and Stereo-selective Hydroboration of Ynamides to (*Z*)-*β*-borylenamides†

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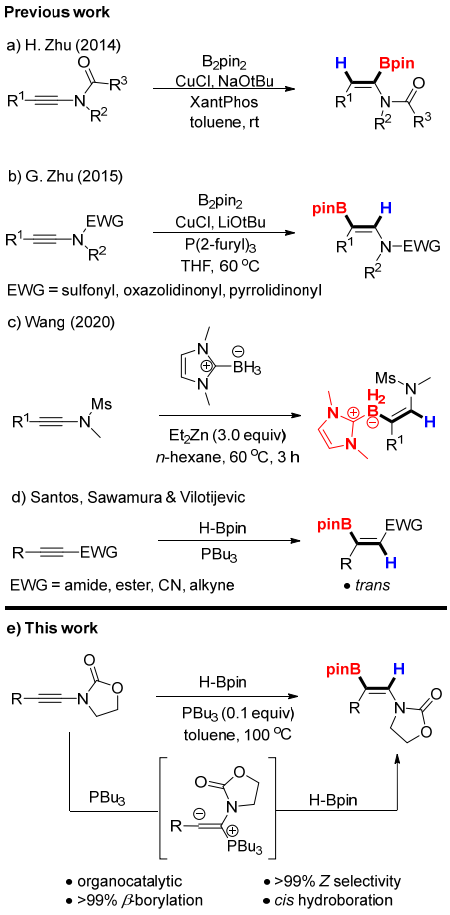
We report a tri-*n*-butyl phosphine catalyzed regio- and stereo-selective hydroboration of ynamides to yield (*Z*)-β-borylenamides in good yields. Surprisingly, a formal *cis* addition to the triple bond was observed as confirmed by NMR and X-ray crystallography. ^{31}P NMR studies suggest that a zwitterionic vinylphosphonium intermediate is key in the mechanism. The resulting products were further transformed to β-CF_3 enamides *via* stereoretentive trifluoromethylation.

Ynamides are versatile modern-day building blocks in organic synthesis with potential applications in the construction of complex molecules.[1] The strongly polarized triple bond fosters reactivity that proceeds with chemo-, regio- and stereo-selectivity.[2] They are notably versatile starting materials for enamides, which are essential intermediates for the synthesis of heterocycles and bioactive molecules such as salicylihalamides,[3] lobatamides,[4] and oximidines.[1c, 5] In particular, the transformation of ynamides to vinylboronic acid derivatives bearing a nitrogen atom offers unique atom connectivity and an opportunity for further elaboration using Suzuki-Miyaura[6] or Chan-Lam-Evans[7] coupling reactions. In contrast to borylations of alkynes,[8] methods for the borylation of ynamides are scarce. In 2000, Witulski and co-workers reported the first hydroboration of ynamides by reacting catecholborane with β-*E*-N-sulfonyl ynamides.[9] Similar to the zirconocene-catalyzed hydroboration by Hoffmann,[10] the substrate scope was limited to terminal ynamides however. More recently, complementary borylation methods were reported using *bis*(pinacolato)diboron, *tert*-butoxide and CuCl (Scheme 1a-b). Interestingly, a regiodivergent installation of Bpin on the alpha[11] or beta[12] carbon was controlled by the phosphine ligand used. In both cases, hydroboration occurred in a *cis* fashion. In contrast, diethylzinc-mediated



Scheme 1. Borylation of ynamides and electron deficient alkynes.

hydroboration using *N*-heterocyclic carbene ligated borane resulted in a *trans* selective, β borylation (Scheme 1c).[13] While attractive, some of these methods are limited by the substrate scope as well as the use of transition metal catalysts. Over the past decades, organocatalysis has emerged as alternative to transition metal-based catalysis due to the cost-effectiveness, lower toxicity (*i.e.*, no metal contamination), ready availability

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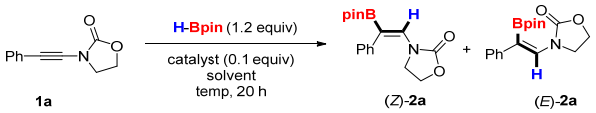
Table 1. Optimization of reaction conditions. [a]



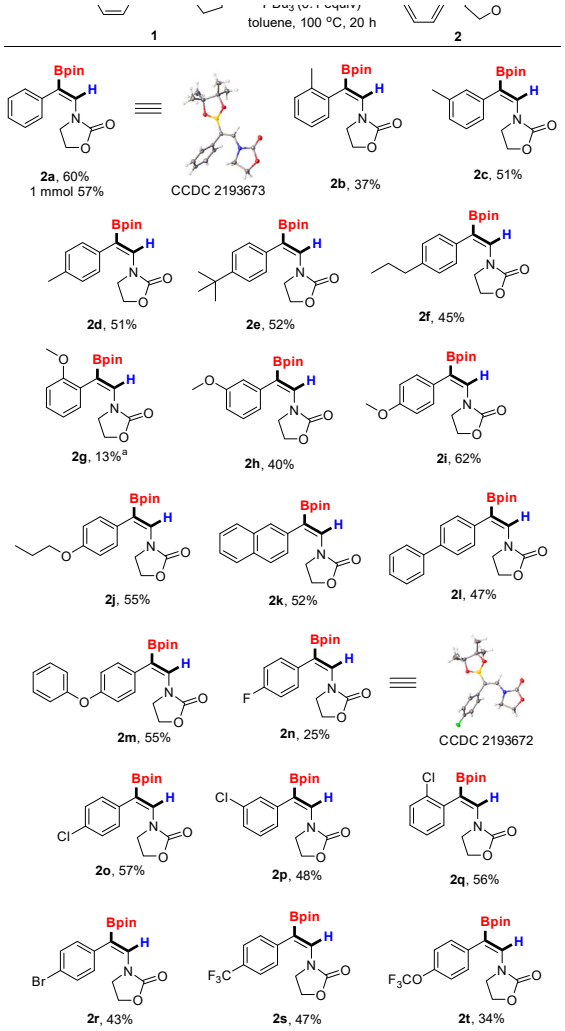
entry	catalyst	solvent	temp	% convn[b]	*Z*/*E*[b]
1	PBu_3	toluene	rt	3	>99:1
2	PBu_3	toluene	70	90	>99:1
3	PBu_3	THF	70	31	>99:1
4	PBu_3	MeCN	70	5	>99:1
5	PBu_3	toluene	100	100 (60)	>99:1
6	PPh_3	toluene	70	26	36:64
7	PCy_3	toluene	100	10	8:92
8	PMe_3	toluene	100	28	24:76
9	none	toluene	100	0	N/A
10[c]	PBu_3	toluene	100	100	>99:1
11[d]	PBu_3	toluene	100	100	>99:1
12[e]	PBu_3	toluene	100	100	>99:1
13[e]	none	toluene	100	12	85:15

[a]0.1 mmol of **1a**, 0.01 mmol of catalyst, 0.12 mmol of pinacol borane in solvent for 20 h. [b]Based on GC-MS of crude reaction mixture. Parenthesis indicates isolated yield. [c]1.0 equiv of PBu_3. [d]0.5 equiv of PBu_3. [e]with 0.1 mmol BH_3.

of reagents, and 'environmental friendliness'.[14] Among many, organophosphorus catalysts have gained much attention,[15] and our as well as Sawamura's and Vilotijevic's laboratories have previously reported organophosphorus catalyzed *trans* hydroboration of electron deficient alkynoates[16] and propiolonitriles (Scheme 1d).[17] In the current work, we investigated the potential hydroboration of oppositely polarized ynamides (Scheme 1e). We hypothesized that the high energy ynamide can be activated by the addition of a phosphine catalyst on the α- carbon thereby rending the β-carbon nucleophilic towards pinacolborane. Herein, we report the hydroboration of ynamides in a regio- and stereo-selective fashion. Notably, the boron pinacol ester was installed on the β-carbon forming (*Z*)-*β*-borylenamides through a formal *cis* hydroboration pathway. To our knowledge, this is the first method for the transition metal-free hydroboration of substituted ynamides. Surprisingly, in sharp contrast to previously reported phosphine catalyzed *trans* addition of HBpin to alkynes, the current reaction occurs in a formal *cis* fashion.

Our investigation commenced by reacting 3-(phenylethynyl) oxazolidin-2-one (**1a**) with HBpin and tri-*n*-butyl phosphine in toluene at room temperature (Table 1, entry 1). While conversion to the hydroborated product was low, heating the reaction to 70 °C resulted in the formation of **2a** with 90% conversion. GC/MS analysis of the crude reaction mixture revealed the preference for *Z*-**2a** in >99% (entry 2). Screening of aprotic polar solvents such as THF and MeCN drastically decreased conversion to product (entries 3-4). When the temperature was further increased to 100 °C using PBu_3, a complete conversion (60% isolated yield) of **1a** was observed with excellent *Z* selectivity (entry 5). To identify the optimal phosphine catalyst, triphenylphosphine, tricyclohexylphosphine, and trimethylphosphine were explored (entries 6-8). Unfortunately, these phosphine catalysts not only decreased conversion but also deteriorated *Z*:*E* ratios. As expected, the omission of PBu_3 resulted in no reaction suggesting the key role of the phosphine as catalyst (entry 9). Increasing the equivalency of PBu_3 to 0.5 and 1 equiv was equally effective (entries 10-11). To determine the possibility of 'hidden borane catalysis',[18] we performed the reaction in the presence of BH_3▪THF with (entry 12) and without the phosphine catalyst (entry 13). The results suggest that hydroboration with BH_3 is occurring with concomitant Bpin exchange. However, BH_3 addition proceeds at a much slower rate and stereoselectivity than phosphine catalysis.

With the optimal set of conditions in hand (1.2 equiv HBpin, 0.1 equiv PBu_3 in toluene at 100 °C), we investigated the scope and limitations of the reaction (Scheme 1). The reaction of **1a** afforded (*Z*)-β-borylenamide **2a** in 60% isolated yield. The structure of **2a** was unambiguously assigned from a single crystal X-ray structure indicating the addition of the Bpin moiety on the β position in a *cis* fashion with hydrogen generating **2a** with a Z configuration (CCDC 2193673).[19] At the 1 mmol scale, (*Z*)-β-borylenamide **2a** was isolated in a similar yield of 57% indicating the scalability of the reaction. We then tested *ortho*, *meta*, and *para* substitution patterns on the aryl ring with a methyl group and found that the reaction was sensitive to sterics as *ortho* substituted **2b** was afforded in 37% yield whereas the other borylated enamides **2c** and **2d** were isolated in 51% yield. Bulkier *tert*-butyl (**2e**) and *n*-propyl (**2f**) groups on the 4-position of the phenyl ring gave moderate yields. Electron donating groups such as methoxy (**1g**-**1i**) and propoxy (**1j**) substituents were readily tolerated, affording the corresponding (*Z*)-β-borylenamide products **2g**-**2j** in moderate yields. The low yield of **2g** corroborates the steric influence on the *ortho* position. We next investigated other aryl systems such as naphthalene (**2k**), biphenyl (**2l**), and diphenyl ether **2m**. These compounds were obtained in 47-55% yields. Finally, we studied the effects of electron-withdrawing substituents on the aryl ring. Halogens such as fluorine, chlorine, and bromine were tolerated and compounds **2n**-**2r** were obtained in moderate yields. Interestingly, the fluorine substituted **2n** was isolated in



Scheme 1. Substrate scope. Reaction conditions: 0.25 mmol of **1**, 0.025 mmol of PBu_3, 0.30 mmol of HBpin in toluene at 100 °C for 20 h. [a]GC yield.

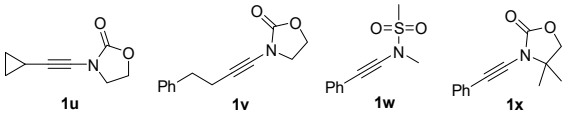
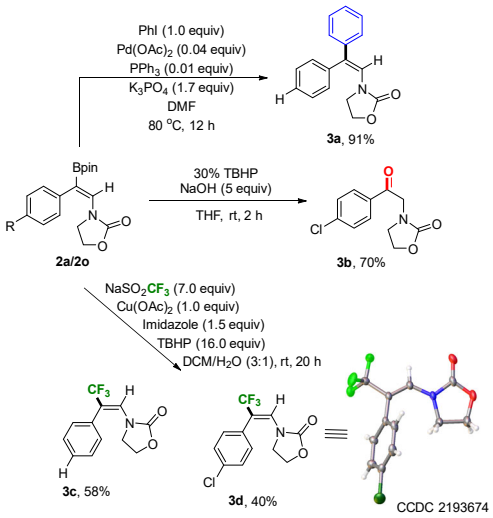
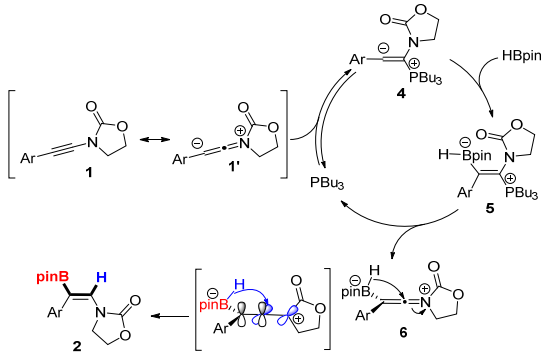


Figure 1. Substrate limitations

slightly lower yield, but *ortho*-chloro substituted **1q** served as a good substrate. Fortunately, (*Z*)-β-borylenamide **2p** afforded crystals suitable for single crystal X-ray structure elucidation, which confirmed the regio- and stereo-selectivity of the reaction (CCDC 2193672).[19] We also probed substrates bearing trifluoromethyl (**1s**) and trifluoromethoxy (**1t**) groups that are important in the pharmaceutical industry. These stronger



Scheme 2. Transformations of (*Z*)-β-borylenamide products.



Scheme 3. Proposed mechanism.

electron withdrawing groups gave the corresponding products in 47% and 34%, respectively. Unfortunately, when we used alkyl instead of aryl substitutions on the starting ynamides (**1u-v**), only trace amounts of products were observed (Fig. 1). In addition, methylsulfonamide **1w** or 4,4-dimethyloxazolidinone **1x** were inefficient substrates likely due to electronic and steric effects, respectively.

With the scope and limitation of the reaction at hand, we explored the potential applications of (*Z*)-β-borylenamide products. As shown in Scheme 2, Suzuki-Miyaura cross coupling of **2a** with phenyl iodide in the presence of $Pd(OAc)_2$, K_3PO_4, and PPh_3 in DMF at 80 °C afforded diphenylvinyloxazolidinone **3a** in 91% yield. Oxidation of **2o** with 30% *tert*-butylhydroperoxide (TBHP) produced 3-phenacyl-2-oxazolidinone **3b** in 70% yield. In addition, we utilized a trifluoromethylation protocol previously published by our group that converts trifluoborate salts into trifluoromethyl groups using $NaSO_2CF_3$, TBHP, and $Cu(OAc)_2$.[20] In contrast to our previous studies and to our surprise, direct transformation of (*Z*)-β-borylenamide pinacolate **2a**/**2o** proceeded efficiently to generate **3c** and **3d** in 58% and 40%

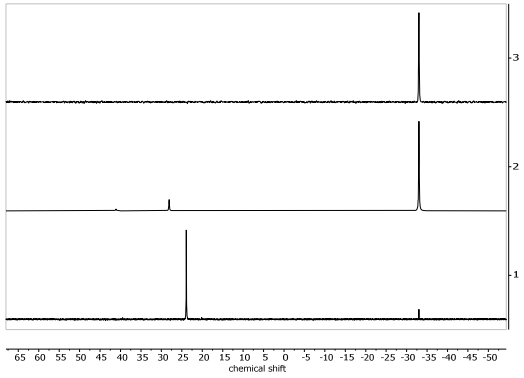


Figure 2. ^{31}P NMR studies. Top: PBu_3 only (rt). Middle: stoichiometric PBu_3 and **1n** (rt). Bottom: **1n** (1 equiv), HBpin (1.2 equiv), and PBu_3 (0.1 equiv) at 70°C.

yields, respectively. The stereoretentive nature of the trifluoromethylation was unambiguously confirmed using single crystal X-ray diffraction (CCDC 2193674).[19] The strategic installation of a CF_3 group changes pharmacokinetic properties (metabolic stability and lipophilicity) improving the drug-like properties of lead compounds;[21] thus, these transformations overall demonstrate the utility of (*Z*)-β-borylenamide products.

A proposed mechanism is shown in Scheme 3. Considering the ynamide triple bond has resonance with **1'**, **1** is susceptible to nucleophilic attack by a Lewis base such as PBu_3 to generate a vinylphosphonium intermediate **4**.[22] To provide support for the reaction mechanism, we performed ^{31}P NMR studies using stoichiometric amounts of **1n** and PBu_3. As shown in Fig. 2, a new signal at 29 ppm appeared along with the signal for PBu_3 at -30 ppm (middle). We suspect that the new peak is consistent with **4**[23] that is in equilibrium with **1**. As we have previously shown that premixing PBu_3 and HBpin at -40 °C does not produce a Lewis acid-base adduct (at least on the NMR time scale),[24] it is unlikely that this adduct participates in the catalysis. Thus, in the presence of HBpin, a zwitterionic vinylphosphonium intermediate **4** forms a new B-C bond on the β carbon to produce **5**, which can eliminate PBu_3 to afford keteniminium **6**. ^{31}P NMR of the reaction mixture under standard conditions showed the disappearance of PBu_3 within 30 min[25] with a concomitant appearance of a new peak at (25.1 ppm)[26] that can be attributed to **5** or **6** (bottom), which can undergo 1,3-hydride shift to produce the desired product **2**. Hydride transfer occurs on the orbital of the sp hybridized central carbon of **6** that is on the same side of Bpin to exclusively afford *cis* products (Scheme 3).

In conclusion, we developed a transition metal-free hydroboration of substituted ynamides to afford (*Z*)-β-borylenamides in a regio- and stereoselective fashion. The proposed mechanism is suggested to occur through a zwitterionic vinylphosphonium intermediate. To the best of our knowledge, this is the first example of a phosphine-catalyzed *cis* hydroboration of alkynes. We acknowledge financial support by the National Science Foundation (CHE-1414458), VT Chemistry Department, and ULB.

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