RESEARCH ARTICLE

Organocatalytic *trans* Phosphinoboration of Internal Alkynes

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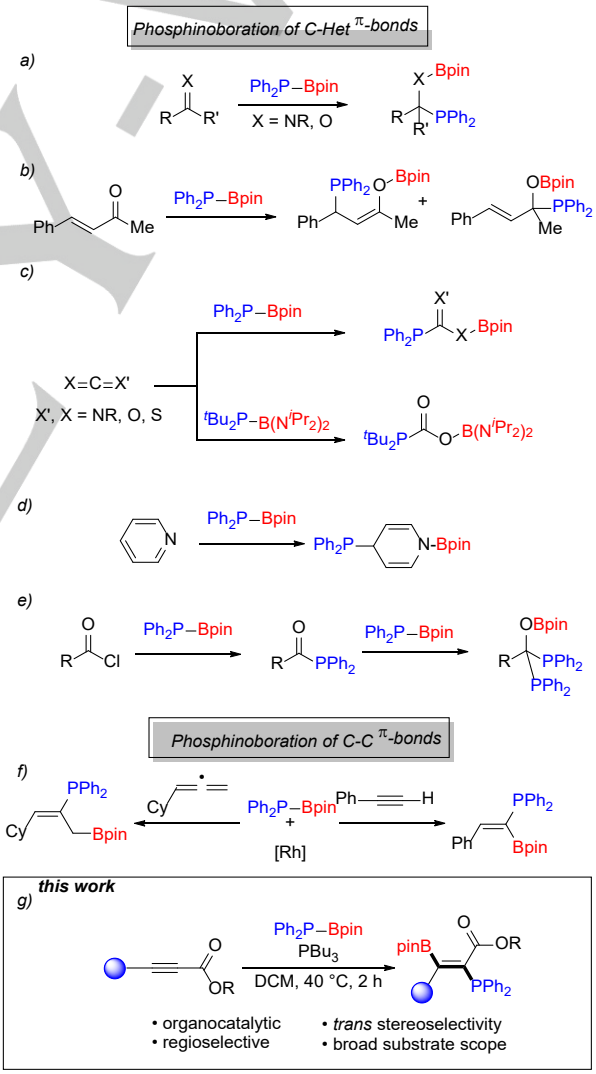
Abstract: We report the first *trans* phosphinoboration of internal alkynes. Employing an organophosphine catalyst, alkynoate esters and the phosphinoboronate Ph_2P–Bpin are efficiently converted to the corresponding *trans* α-phosphino-β-boryl acrylate products in moderate to good yield with high regio- and *Z*-selectivity. This reaction operates under mild conditions and demonstrates good atom economy, requiring only a modest excess of the phosphinoboronate. X-ray crystallography experiments allowed structural assignment of the unprecedented and densely functionalized (*Z*)-α-phosphino-β-boryl acrylate products.

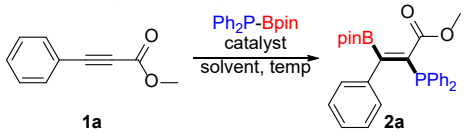
Organoboron compounds are distinguished for their versatility in organic synthesis and unique physical properties.[1] Notably, organoboron species serve as substrates for the Nobel prize winning Suzuki-Miyaura cross-coupling reaction.[2] Beyond synthetic utility, the presence of boron in end products such as FDA approved drugs[3] and BODIPY-derived fluorescent materials[4] has garnered significant attention. The increasingly diverse applications of boron in organic chemistry warrant the continued development of efficient synthetic strategies. Classically, organoboron species are prepared through a hydroboration reaction with C-C or C-heteroatom π-bonds. However, a recent focus has been on the development of difunctionalization reactions in which the addition of B-X reagents (X = B,[5] N,[6] O,[7] Si,[8] Se[9] or R[6d, 10]) affords access to substrates with two functional groups suitable for subsequent transformations. One example that has only recently received limited attention is the phosphinoboration reaction.

In this case, a phosphinoboronate (PB) bearing a P-B bond reacts with a π-bond to simultaneously incorporate boron and phosphorous functionalities in a single synthetic step. Excitingly, this strategy has potential to supply products with applications in ligand development for transition metal chemistry,[11] frustrated Lewis pair (FLP) chemistry,[12] and tools for biological studies[13]; however, examples of phosphinoborations are scarce. This is likely due to the relatively obscure and ligand dependent nature of the P-B bond in PB species. Previous X-ray crystallography studies in the 1980s indicated that the P-B bond in Ph_2P–$BMes_2$ has high double bond character as indicated by the bond angles and the 1.859 Å P–B distance.[14] More recently, Lerner *et al.*



Scheme 1. Phosphinoboration reactions.

Table 1. Solvent and catalyst screening of the phosphinoboration of alkynoates.



1a 2a

Entry	Solvent	P–B (equiv)	Temp (°C)	Catalyst[a]	*Z*:*E*[b]	Yield (%)[c]
1	THF	1.1	rt	PBu_3	>99:1	32
2	THF	1.1	40	PBu_3	98:2	46
3	THF	1.3	60	PBu_3	97:3	45
4	DCM	1.3	40	PBu_3	96:4	63
5	MeCN	1.3	40	PBu_3	96:4	56
6	Toluene	1.3	40	PBu_3	98:2	48
7	EtOAc	1.3	40	PBu_3	99:1	43
8	CPME	1.3	40	PBu_3	98:2	22
9	DCM	1.1	40	PBu_3	96:4	52
10	DCM	1.2	40	PBu_3	96:4	56
11	DCM	2.0	40	PBu_3	96:4	52
12	DCM	1.3	40	PBu_3[d]	96:4	64
13	DCM	1.3	40	PEt_3	96:4	53
14	DCM	1.3	40	PCy_3	>99:1	14
15	DCM	1.3	40	PPh_3	-	0
16	DCM	1.3	40	$P(OEt)_3$	-	0
17	DCM	1.3	40	DBU	-	0
18	Toluene	1.1	40	-	-	0

[a] 0.1 equiv used. [b] Determined by GCMS. [c] Isolated yield. [d] 0.3 equiv used.

summarized the physical properties of PB species and the authors highlighted the ambiphilic and the strong π-bond character of phosphaboradibenzofulvene which can undergo Diels-Alder reactions.[15] However, this contrasts with the PB Ph_2P–Bpin characterized by Westcott and co-workers. In the case of Ph_2P–Bpin, the authors concluded that the 1.927 Å length of the P–B bond suggests single bond character and minimal contribution of the phosphorus lone pair to boron's vacant p-orbital. Consequently, coordination with a Lewis base would activate the P-B bond and generate a highly nucleophilic phosphorous species.[16] In contrast to other B-X additions that often require catalysts or harsh conditions, this innate reactivity of the P-B species has been demonstrated to afford addition products under considerably milder conditions.

Recent developments in phosphinoborations have focused on addition of PB species across C-heteroatom[11, 16-17] and N-N[12c, d] π-bonds. In pioneering studies by Westcott and co-workers, it was revealed that PBs Ph_2P–Bpin and Ph_2P–Bcat readily reacted with various aldehydes, ketones, and aldimines without any additives at room temperature to afford the corresponding 1,2-addition products (Scheme 1a).[11, 16] In the case of an α,β-unsaturated ketone, the authors noted that PBs react in either 1,2- or 1,4-additions depending on temperature and solvent choice (Scheme 1b). Use of halogenated solvents at room temperature favored 1,4-addition, while non-halogen solvents or colder temperatures selected for 1,2-addition products.[16] Work by Westcott, Stephan, and co-workers demonstrated that Ph_2P–Bpin readily adds in a 1,2-fashion to carbon dioxide, carbodiimides, cyanates and isothiocyanates.[17a] More recently, Grubba *et al.* reported the synthesis of diaminophosphinoboranes and their reaction with carbon dioxide (Scheme 1c).[18] However, while these additions occurred at room temperature with no additives, significantly longer reaction times were necessary, and the products were obtained in only moderate yield. In addition to C-heteroatom π-bonds, Stephan and co-workers reported the phosphinoboration of diazomethane derivatives. Surprisingly, the PBs added in a 1,1-fashion in the absence of any additives.[12c] In the case of diazobenzene derivatives, the phosphinoboration occurs in a 1,2-fashion to afford products with reactivity as FLPs.[12d] Additional examples of a conjugate addition reaction with PBs have been disclosed, demonstrating the reduction of N-heterocycles with PB species (Scheme 1d).[16, 17b] More recently, the phosphinoboration of acyl chlorides was disclosed.[19] Under these conditions, acyl phosphines can be generated at room temperature or be transformed to a diphosphine analog upon further reaction with Ph_2P–Bpin without the need for a catalyst precursor or additional base to activate the P–B bond (Scheme 1e).

Despite these recent advances, examples of phosphinoborations of C-C π-bonds are even more limited. In the initial report by Westcott and co-workers, the authors noted that uncatalyzed addition of the PB species did not occur in the case of C-C π-bonds, such as in the cases of terminal allenes and alkynes. However, utilizing a Rh catalyst afforded 1,2- or 1,1-phosphinoboration products in good yield, respectively (Scheme 1f). In an effort to expand utility of phosphinoborane reagents and access novel products containing both boron and phosphine moieties, we sought to develop a phosphinoboration reaction of internal alkynes. Previous work by our group and others demonstrated that trialkylphosphines facilitate the *trans* addition of boron reagents across alkyne bearing derivatives.[9c, 20] Inspired by this work and others, we hypothesized that the required transition metal catalysis to activate the P-B bond to add across C-C triple bonds can be overcome by trialkylphosphine catalysts. Herein, we disclose an unprecedented *trans* phosphinoboration reaction that adds the borylpinacolyl group on the β carbon and phosphinyl moiety on the α carbon of propiolate esters in a regio- and *trans* selective manner (Scheme 1g).

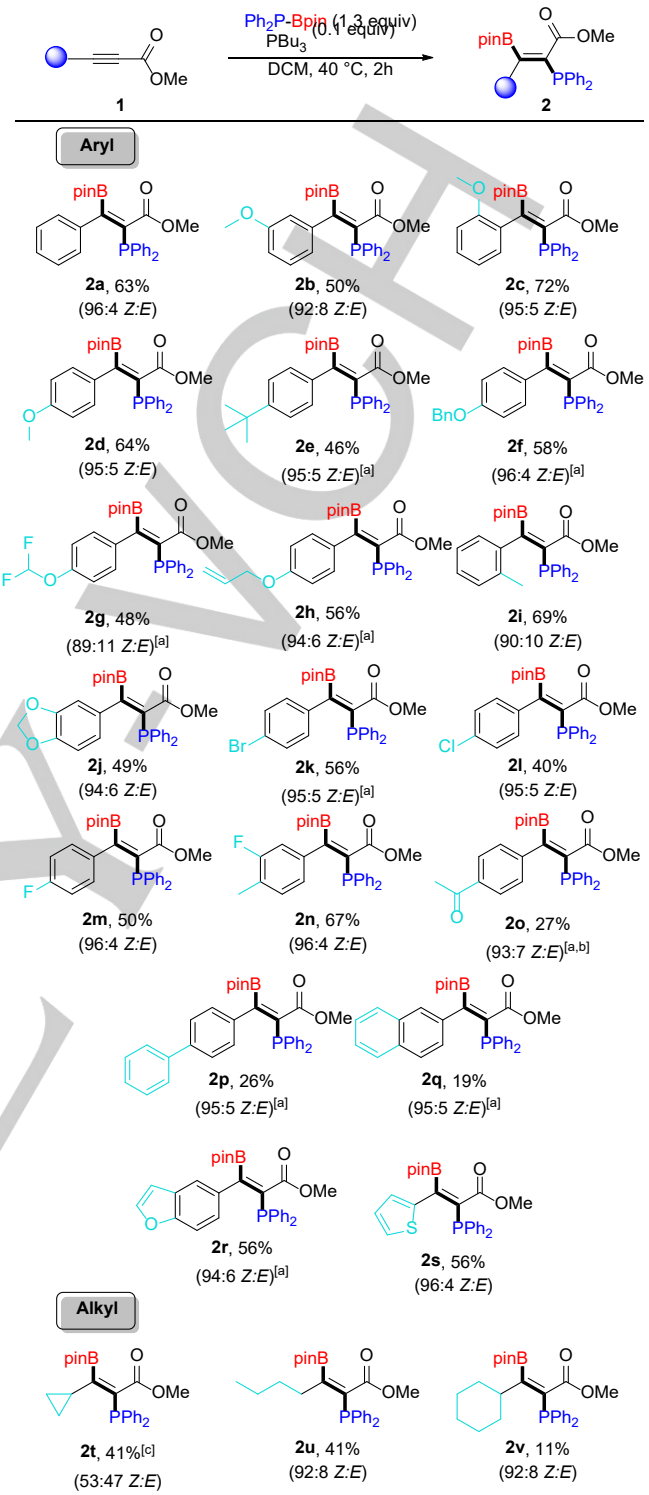
We initiated our studies by employing the tributylphosphine catalysis conditions previously developed by our group for the corresponding hydroboration.[20e] To our delight, simply switching the boron reagent to Ph_2P–Bpin afforded the desired *trans* phosphinoboration product **2a**, albeit only in poor yield (entry 1). Raising the reaction temperature resulted in only a modest increase in yield (entry 2). Attempts to improve yield by increasing temperature and excess Ph_2P–Bpin reagent were unsuccessful (entry 3). Considering solvent choice significantly influenced similar phosphine catalyzed reactions,[20c, f] we screened additional polar aprotic solvents (entries 4-8). Excitingly, employing dichloromethane as the solvent afforded **2a** in good yield (entry 4). Similarly, acetonitrile afforded the desired product in reasonable yield (entry 5). Toluene and ethyl acetate were suitable solvents (entries 6 & 7), albeit not as effective as dichloromethane. In the case of cyclopentyl methyl ether (CPME), the product **2a** was only obtained in poor yield (entry 8). We also

sought to determine optimal stoichiometry of the P-B reagent (entries 4, 9-11). We concluded that 1.3 equiv of Ph_2P–Bpin afforded optimal conversion and yield of **2a** (entry 4). Interestingly, two-fold excess of Ph_2P–Bpin led to a slight decrease in yield (entry 11). To further improve the yield, we attempted to increase catalyst loading of tributylphosphine; however, this had minimal effect on yield of **2a** (entry 12). Next, we sought to determine the optimal catalyst for this transformation (entries 13-17). Excitingly, triethylphosphine could also serve as an effective catalyst with only a minimal reduction in yield of **2a** (entry 13). However, use of a catalyst with bulkier substituents, such as tricyclohexylphosphine, was detrimental to product yield (entry 14). Unfortunately, triphenylphosphine and triethylphosphite were not efficient catalysts for this transformation (entries 15 & 16). Furthermore, use of the amine DBU was also ineffective (entry 17). In the absence of catalyst, no conversion of starting material was observed (entry 18). In all cases, the desired product was obtained regio- and diastereoselectively with ≥96:4 preference for the (*Z*) isomer (**2a**). Compound isolation was performed using silica gel column chromatography.

With the optimal conditions in hand (Table 1, entry 4), we turned our attention to the substrate scope and limitations for this method (Scheme 2). We started by investigating the effects of various substitutions on the aromatic ring. To our delight, substrates bearing electron-donating groups (**1b-j**) were well tolerated. Surprisingly, sterically hindered *ortho*-substituted methoxy ether (**2c**) was isolated in higher yield than *meta*- and even *para*-substituted ones. For these substrates, the yields ranged from 46 to 72% with the exclusive formation of the *trans* products. In the presence of a competing alkene in allylether **2h**, the phosphinoborane reagent chemoselectively reacted on the alkynyl portion. For aryl groups bearing halogen substituents (**2k-n**), the desired products were achieved in good yields (up to 67% and excellent diastereoselectivity). A substrate with electron withdrawing acetyl group (**2o**) was transformed but with decreased yield and slight reduction in selectivity. We suspect that a competing 1,2-addition with the ketone in **2o** is occurring as further optimization of reaction conditions (60 °C, MeCN) were required for conversion. Likewise, biphenyl (**2p**) and naphthyl (**2q**) were afforded in modest yield but excellent selectivity. Next, we investigated various substrates with heteroaromatic moiety. Fortunately, benzoxazole (**1r**) and thiophene (**1s**) afforded the desired products (**2r-2s**) in moderate yields (56%) with excellent *Z* selectivity.

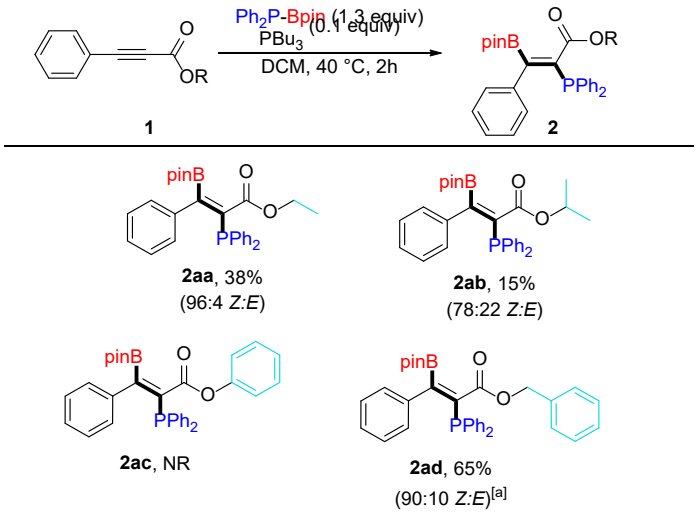
We next investigated non-aromatic substituents on the propiolate esters. While cyclopropyl containing substrate **2t** resulted in moderate yield and low *Z*:*E* selectivity, linear alkane such as **2u** and cyclohexyl **2v** were obtained in 92:8 *Z*:*E* selectivity. Lastly, we determined the effect of substituents on the ester group and found that the reaction is sensitive to steric effects (Scheme 3). While methyl 3-phenylpropiolate **2a** was obtained in 63% yield (Scheme 2), the yield with the ethyl counterpart (**2aa**) was lower and exacerbated in isopropyl ester **2ab** with the products obtained at 38% and 15%, respectively. Indeed, this trend continued with phenyl ester (**2ac**) where no reaction was observed, but the corresponding benzyl analog (**2ad**) was isolated in good yield (65%) and diastereoselectivity (90%).

A proposed catalytic cycle is shown in Scheme 4. Based on previous work with phosphine-based catalysis,[20b, e, 21] tributylphosphine undergoes a Michael addition with alkynoate



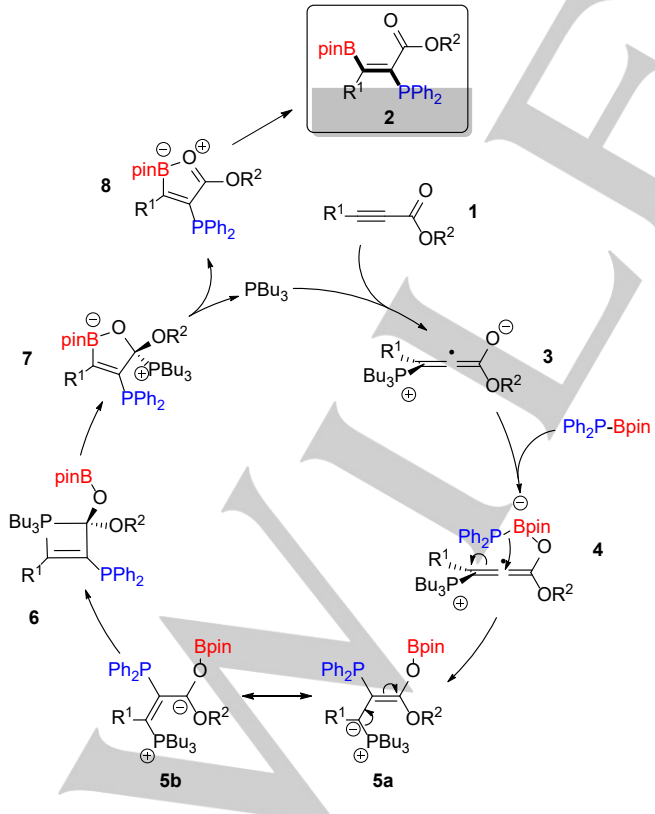
Scheme 2. Substrate scope with various alkyl, aryl and heteroaryl groups under standard conditions mentioned in Table 1, entry 4. Isolated yields for the *Z* isomer reported. *Z*:*E* ratio determined by GCMS (unless otherwise stated). [a] Determined by quantitative ^{31}P NMR. [b] 60°C, MeCN. [c] Yield is a combined mixture of isomers.

ester **1** to form allenolate **3**, which bears a Lewis basic oxygen moiety. Complexation with Ph_2P–Bpin activates the P-B bond for diphenylphosphino transfer to the central sp hybridized carbon



Scheme 3. Substrate scope of various ester groups under standard conditions mentioned in Table 1, entry 4. Isolated yields for the *Z* isomer reported. *Z*:*E* ratio determined by GCMS (unless otherwise stated). [a] Determined by quantitative ^{31}P NMR. NR = no reaction.

via **4** to generate ylide **5a**. Previous theoretical calculations from our group suggests that resonance form **5b** is energetically more favorable to facilitate the formation of the key phosphinocyclobutane **6**,[20e] which is prone for a ring expansion to the five membered ring **7** because of the energetically constrained cyclobutene ring and Lewis acidic boron. Expulsion of tributylphosphine yields the desired *trans* phosphinoborated product **2**.



Scheme 4. Proposed catalytic cycle.

The *trans* selectivity of the reaction was confirmed by the X-ray structure of **2f** where the orientation of phosphorus (P1) and boron (B1) is clearly in the *Z* configuration (Figure 1).[22] In contrast with amide counterparts,[20e, 23] internal coordination between boron and carbonyl oxygen is negligible (2.397Å).

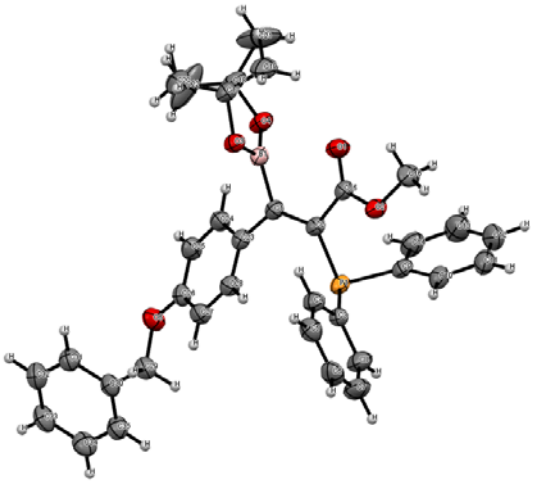


Figure 1. The molecular structure of **2f** (CCDC 1998870) drawn at the 50% probability level.

In conclusion, we have developed a novel organocatalytic reaction that regioselectively installs the phosphorus and boron atoms on the alpha and beta carbons of unsymmetrical alkynoic esters, respectively, and afford *trans* alkenes with excellent selectivity. Phosphinoboronates can be utilized in Suzuki-Miyaura couplings, as valuable synthetic precursors, as ligands, and in the study of frustrated Lewis pairs.

Acknowledgements

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Keywords: phosphinoboration • alkynes • phosphorus • boron • organocatalysis

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[22] CCDC 1998870 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.)

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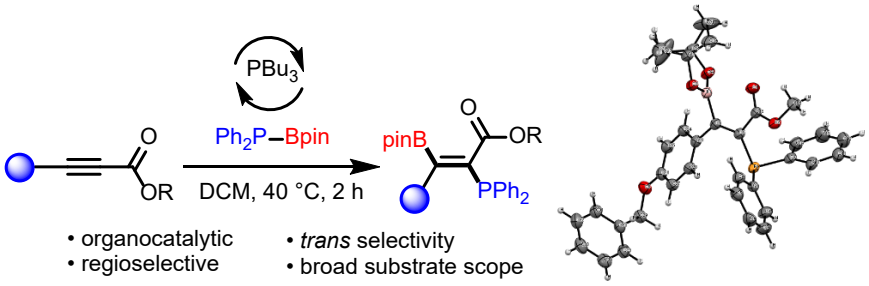

PB&J? No, it's phosphinoboration across a triple bond catalyzed by tributyl phosphine. α-Phosphino-β-boryl acrylate products are generated with excellent *Z* selectivity.

Institute and/or researcher Twitter usernames: @SantosLabVT