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$AgSbF_6$-Catalyzed *anti*-Markovnikov hydroboration of terminal alkynes†

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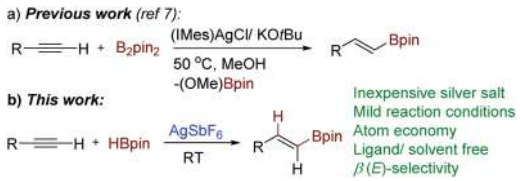
$AgSbF_6$-Catalyzed *anti*-Markovnikov addition of pinacolborane (HBpin) to terminal alkynes to produce the *E*-vinylboronates is reported. This efficient methodology is scalable, compatible with sterically and electronically diverse alkynes, and works at room temperature under solvent-free condition. The utility of this method is demonstrated in the facile synthesis of the clinically important (*E*)-2,4,3′,5′-tetramethoxystilbene.

Selective transformation of alkyne to alkene is an important and challenging reaction in synthetic organic chemistry. Transition metal catalyzed hydroboration of alkynes has become one of the most versatile, selective, and atom-economic reactions in this field[1] as the produced alkenyl organoboron compounds find high synthetic utility in organic, polymer and agro chemistry.[2] However, control over stereo- and regioselectivity of this transformation has remained challenging. Various transition metal catalyzed[3] and more recently transition metal-free hydroboration protocols have been documented.[4] In most of the cases expensive metals with supporting ligands or higher catalyst loadings, bases and/or higher temperature are necessary. Among coinage metals, Cu(I) catalyzed borylation reactions have gained significant momentum in recent years,[5] while the progress of hydroboration reactions catalyzed by Ag(I) is still in its early days.[6] Breakthrough in silver catalyzed alkyne hydroboration process came from Yoshida and co-workers who have described the Ag-NHC (N-heterocyclic carbene) complex catalyzed hydroboration of terminal alkynes using B_2Pin_2 and KO*t*Bu in methanol (Scheme 1a).[7] However, the method has some limitations: requires specially designed ligand, not an atom-economic process (generates a stoichiometric amount of boron-containing by-product), and was demonstrated mostly to the aliphatic terminal alkynes. Therefore, development of atom-economic efficient process which works under mild conditions utilizing readily available simple metal precursor is needed. Herein, we describe the inexpensive $AgSbF_6$-catalyzed solvent and ligand-free regio- and stereoselective hydroboration of terminal alkynes at room temperature (Scheme 1b). The synthetic utility of the method is showcased in various stereoselective C–C and C–X bond formations[8] including the synthesis of a clinically important compound (*E*)-2,4,3′,5′-tetramethoxystilbene.[9b,c]



Scheme 1 Overview of prior Ag(I)-catalyzed hydroboration reaction of alkynes and this work.

Initially, when we performed the hydroboration of phenylacetylene with pinacolborane using $[Ru(p\text{-cymene})Cl_2]_2$, reported to be an efficient alkene hydroboration catalyst,[10a] expected hydroborated product was not observed (Table 1; entry 1). Interestingly, the reaction in presence of $AgSbF_6$ (to *in situ* generate a cationic Ru complex) resulted in exclusive formation of the β-hydroborated product with complete *E*-selectivity in 81% yield (entry 2). Silver salts are reported to be ideal catalysts for various transformations of alkynes due to facile π-coordination with the carbon–carbon triple bond.[6] Hence, we anticipated that the $AgSbF_6$ may also be catalyzing the reaction. To understand this, we performed the reaction using only $AgSbF_6$ and gratifyingly, the hydroborated product was also realized with same selectivity as above in 68% yield (entry 3) which was improved to 92% when catalyst loading was slightly increased to 1 mol% (entry 4). As only $AgSbF_6$ (usually used as additive along with the precious metal catalysts and relatively large loadings are normally necessary when acting as sole catalyst[6a]) performed competently (entries 2–4), we proceeded further with $AgSbF_6$ itself and to the best of our knowledge, a simple silver salt catalyzed hydroboration of alkynes has not been

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† Electronic supplementary information (ESI) available: Experimental details, characterization data, crystallographic details for ***E*-4**, and NMR spectra of the synthesized compounds. CCDC 1863300. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8cc07499b

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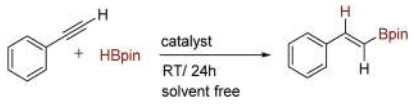
Table 1 Optimization of the hydroboration reaction[a]



Entry	Catalyst	mol%	Yield[b] (%)
1	$[Ru(p\text{-cymene})Cl_2]_2$	0.1	ND[c]
2[d]	$[Ru(p\text{-cymene})Cl_2]_2$	0.1	81
3	$AgSbF_6$	0.4	68
4	**$AgSbF_6$**	**1**	**92**
5	AgOTf	1	74
6	$AgBF_4$	1	68
7	$AgPF_6$	1	76
8[e]	$AgSbF_6$	1	ND[c]

[a] Reaction conditions: phenylacetylene (1 mmol), pinacolborane (1.1 mmol). [b] All are isolated yields and the product configuration is determined by ^{1}H NMR analysis. [c] No borylated product was observed; ND: not detected. [d] 0.4 mol% $AgSbF_6$ was also used. [e] B_2pin_2 instead of HBpin and 0.5 mL toluene were used.

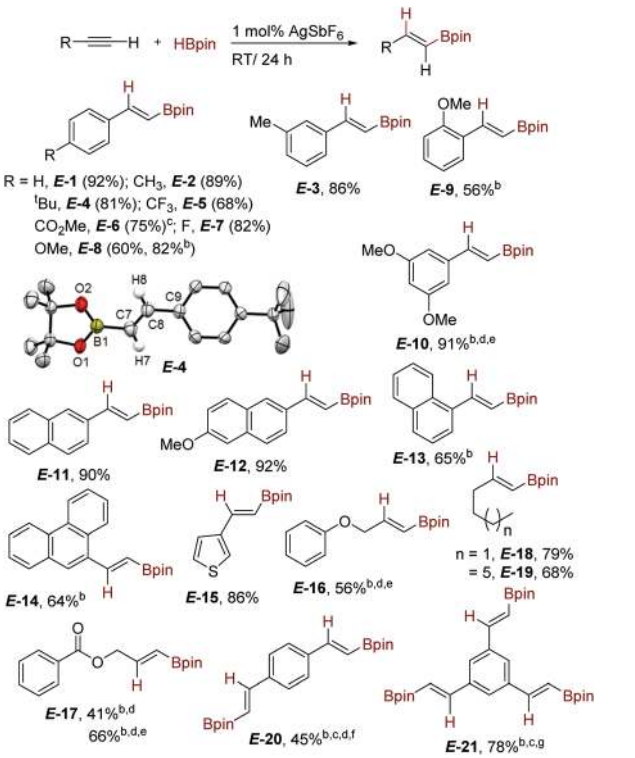
reported so far. Other silver salts were found to be relatively less efficient (entries 5–7).

With these optimized reaction conditions, we focused on the substrate scope of the present catalytic method. We were pleased to find that the hydroboration of electronically and sterically very different terminal alkynes were efficiently attained in regio- and stereoselective manner producing only the β(*E*)-hydroborated product (Table 2). Present hydroboration method offers excellent regioselectivity when compared to that achieved using copper/silver catalysts.[5b,c,7] Phenyl ring bearing electron-donating substituents afforded the product in better yields (***E*-2** to ***E*-4**; 81–89%) as compared to the electron-withdrawing substituents (***E*-5** to ***E*-7**; 68–82%). Thus, most likely the reactive intermediate is stabilized effectively by an electron-donating substituent on the phenyl ring. It is important to note that the ester group is fully preserved during the process (***E*-6**). The presence of methoxy group on the phenyl ring somewhat reduced the activity and therefore, longer reaction time and/or higher catalyst loading are required to attain the products in higher yields (***E*-8** to ***E*-10**). Satisfyingly, 1-ethynyl-3,5-dimethoxy benzene was also found to be hydroborated and the compound ***E*-10**,[9a] precursor for the synthesis of clinically important compounds, was isolated in excellent yield of 91%.

Poly-aromatic compounds 2-ethynylnaphthalene (***E*-11**), 6-methoxy-2-ethynylnaphthalene (***E*-12**), 1-ethynylnaphthalene (***E*-13**) and 9-ethynylphenanthrene (***E*-14**) also yielded the desired compounds in good to excellent yields of 64–92%. Observation of moderate yields for ***E*-13** and ***E*-14** might be reflecting the steric influence of the axial hydrogen. Heteroaromatic alkyne such as 3-ethynyl thiophene (***E*-15**, 86%) also worked well. Electronically different alkynes such as phenylpropargylether (***E*-16**)[11] and propargylbenzoate (***E*-17**) also provided the products in 56% and 66%, respectively although higher catalyst loading and time are necessary.

To our delight, aliphatic alkynes such as 1-hexyne (***E*-18**, 79%) and 1-decyne (***E*-19**, 68%) delivered only the β-hydroborated products in good yields. This demonstrates the potential of the

Table 2 Substrate scope for β(*E*)-selective hydroboration of terminal alkynes[a]

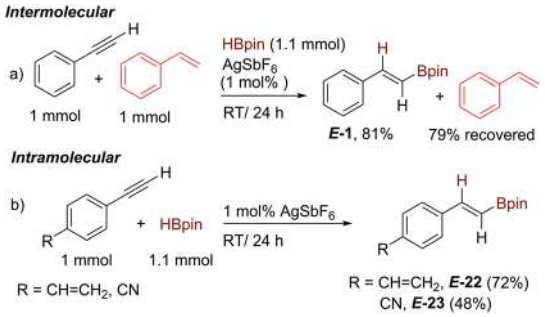


[a] Reaction conditions: alkyne (1 mmol), pinacolborane (1.1 mmol), 1 mol% $AgSbF_6$, 24 h, all are isolated yields. [b] Reactions were performed for 48 h. [c] 0.5 mL toluene was added. [d] 2 mol% $AgSbF_6$ was used. [e] 2 mmol of HBpin was used. [f] 2.2 mmol of HBpin was used. [g] 3 mol% $AgSbF_6$, 3.3 mmol of HBpin were used.

current method as it is regiospecific, atom-economic, and works well under solvent-free mild condition using a ligand-free simple silver salt when compared with the previously reported Pd(II)/Ag(I)-catalyst system.[3c,7]

Stereoselective hydroboration of polyynes is an important process as the corresponding borylated products find versatile synthetic applications in fluorescent dyes and light-emitting copolymers.[12] Satisfyingly, 1,4-diethynylbenzene (***E*-20**, 45%) and 1,3,5-triethynylbenzene (***E*-21**, 78%) also produced the desired products with complete β(*E*)-selectivity. Previously, ***E*-21** was synthesized employing an expensive Rh-phosphine based catalyst system in relatively high catalyst loading along with additive (to achieve exclusive *E*-selectivity).[12]

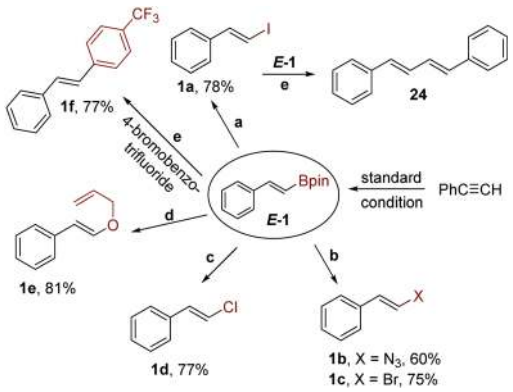
To explore the suitability of this catalytic system in chemoselective hydroboration, 1 : 1 mixture of styrene and phenylacetylene was reacted with pinacolborane and only the hydroboration of phenylacetylene (81% yield) was observed and 79% of the styrene was recovered (Scheme 2a). We further examined substrates installed with both alkyne and alkene/nitrile moiety[10] at the *para*-positions of a phenyl ring in hydroboration. Gratifyingly, present catalyst system showed excellent functional group tolerance for alkene and nitrile and afforded the corresponding alkyne hydroborated products ***E*-22** (72%) and ***E*-23** (48%), respectively without affecting the alkene/nitrile group (Scheme 2b).



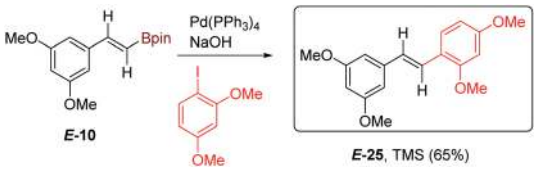
Scheme 2 Chemoselective hydroboration of alkyne (all are isolated yields).

Notably, this catalyst system also works efficiently for large-scale synthesis as demonstrated by gram scale reaction of phenylacetylene (10 mmol) under the optimized conditions producing ***E*-1** in 82% isolated yield.

The usefulness of the produced styrenyl boronates was showcased by the selected stereoselective conversion of ***E*-1** into various other compounds (Scheme 3). Vinyl halides,[8b,i] important coupling partners in various transition-metal-catalyzed syntheses, were obtained in good yields of 75–78% (Scheme 3a–c). Reversal of nucleophilic character of ***E*-1** into electrophilic one *via* derivatization allowed us to couple ***E*-1** and **1a** to perceive the *E*,*E*-diene **24**[13] in 74% yield. Vinyl azide[8d] was prepared *via* Cu-mediated reaction with sodium azide in 60% yield (Scheme 3b). Furthermore, compound **1e**, one of the valuable enol ethers for various organic transformations, was also attained readily in 81% yield (Scheme 3d).[8c] To demonstrate further, a Suzuki–Miyaura cross-coupling reaction between ***E*-1** and 4-bromobenzotrifluoride afforded the corresponding *trans*-stilbene derivative **1f** in 77% yield (Scheme 3e). In addition, syntheses of some other important molecules with $B(OH)_2/BF_3K$ functionalities and phenylacetaldehyde possibly could also be perceived as related reactions are known.[8a,e,h]



Scheme 3 Various stereoselective C–C and C-heteroatom bond formation reactions of compound ***E*-1**. Reaction conditions: for **1a** and **1b** isolated ***E*-1** was used; [a]NaOH (3 M, 1.5 mmol), I_2 (1 mmol), THF, RT, 20 min. [b]NaX (X = N_3, Br; 1.25 mmol), $CuSO_4{\cdot}5H_2O$ (0.5 mmol), MeOH, RT, 4–12 h. [c]$CuCl_2$ (1 mmol), THF/H_2O, 70 °C, 16 h. [d]NEt_3 (2 mmol), allyl alcohol (3 mL), $Cu(OAc)_2$ (1 mmol), RT, 16 h. [e]NaOH (1 mmol), $Pd(PPh_3)_4$ (5 mol%), 1,4-dioxane, 100 °C, 16 h.

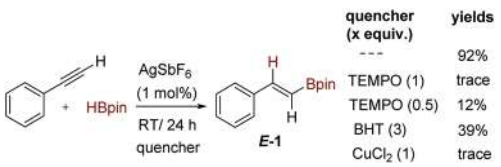


Scheme 4 Synthesis of (*E*)-2,4,3′,5′-tetramethoxystilbene (TMS) utilizing ***E*-10**.

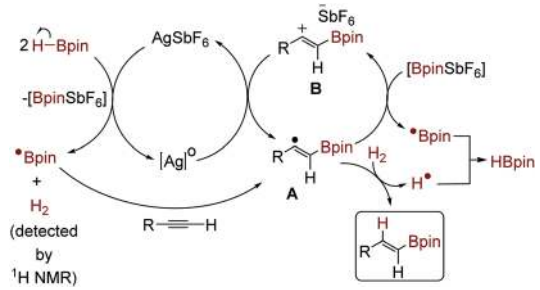
Encouraged by the efficient synthesis of compound **1f**, the synthesis of *trans*-2,4,3′,5′-tetramethoxystilbene (TMS, ***E*-25**) which is a potent and selective human cytochrome P450 1B1 inhibitor[9b] and induces apoptotic cell death in human promyelocytic leukemic HL-60 cells[9c] was also realized *via* coupling of ***E*-10** and 1-iodo-2,4-dimethoxybenzene (Scheme 4).

In order to probe the reaction mechanism various controlled experiments were carried out. Initially, during the addition of pinacolborane to $AgSbF_6$, formation of a black precipitate along with the liberation of gas was observed. The release of H_2 is supported by *in situ* ^{1}H NMR of a reaction between $AgSbF_6$ with HBpin (singlet at 4.52 ppm in toluene-d_8) and the mercury dropping test[14a] suggests the homogeneous nature of the process (89% isolated yield of ***E*-1**). Furthermore, the reaction of 1-deuterio-2-phenylacetylene with pinacolborane gave the *E*-styrenylboronate with deuterium at the β-carbon which indicates that 1,2-hydrogen migration is not involved in the catalytic process.[3b] In addition, the presence of radical scavenger such as TEMPO, BHT, and $CuCl_2$[14b] resulted in either drastically decreased yield of ***E*-1** or the complete inhibition of the reaction (Scheme 5). This indicates that the catalytic cycle is proceeding *via* a radical pathway and inhibition of the reaction in presence of $CuCl_2$ suggests that a single electron transfer (SET) process is involved.[14b]

Based on our experimental findings along with previous literature reports,[15] a plausible reaction mechanism is proposed (Scheme 6). An electron transfer from pinacolborane *via* homolytic cleavage of B–H bond to $AgSbF_6$ possibly reduces Ag(I) to Ag(0) under generation of $[BpinSbF_6]$[16] and a hydrogen radical



Scheme 5 Radical scavenger experiments.



Scheme 6 Proposed mechanism for hydroboration process.

which might react with another molecule of HBpin to form H_2 gas and a Bpin radical.[15b,c] In the next step, Bpin radical may combine with alkyne to produce a α-styrenyl radical (**A**)[15a,17] which then possibly donates an electron to the generated [$BpinSbF_6$] to give the corresponding styrenyl cation **B** and a Bpin radical. Involvement of substituted styrenyl radical and/or cation intermediate in catalytic process have been documented before.[15a,d,e] An electron transfer from the generated silver(0) to **B** would regenerate $AgSbF_6$ and reaction of the produced **A** with dihydrogen would yield the desired hydroborated product *via* elimination of a hydrogen radical which may combine with another molecule of Bpin radical.

In conclusion, we have described a simple silver salt catalyzed efficient solvent free hydroboration of (hetero)aromatic and aliphatic terminal alkynes at room temperature which allows easy access to a diverse synthetically important organoboron compounds exemplified by facile synthesis of the synthon of a clinically important compounds. The present catalytic system provides excellent regio-, stereo- (only β(*E*) isomer formation) and chemoselectivities (conversion of alkyne over alkene and nitrile) and preliminary studies indicate that it follows a radical pathway. Further utilizations of this simple silver salt in other borylation reactions are in progress.

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Conflicts of interest

There are no conflicts to declare.

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