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Cobalt-Catalyzed Markovnikov-Type Selective Hydroboration of Terminal Alkynes

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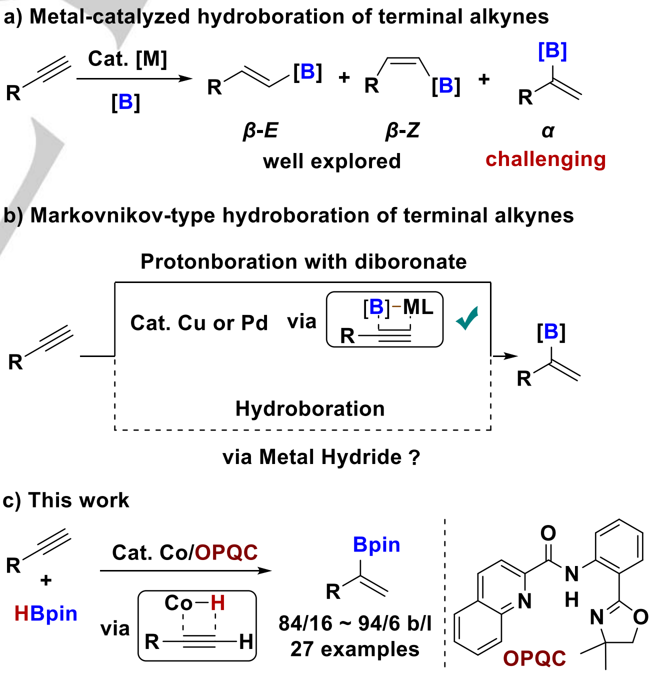
Dedicated to the 70th anniversary of Shanghai Institute of Organic Chemistry

Abstract: Here, we reported a cobalt-catalyzed Markovnikov-type hydroboration of terminal alkynes with HBpin to access *α*-alkenyl boronates with good regioselectivity and atom economy. A new ligand has been developed for cobalt hydride catalyst which has been used for a unique Markovnikov selective insertion of terminal alkynes into metal hydride bond. This operationally simple protocol exhibits excellent functional group tolerance to deliver valuable alkene derivatives.

Alkenyl boronates are widely used as important synthons, for instance, in Suzuki–Miyaura coupling, Petasis reaction, conjugative addition, and so on.[1] Traditionally, the borylation of alkenyl metallic reagents has been widely used for the selective preparation of these useful compounds.[2] Avoiding the use of the stoichiometric amount of alkenyl metallic reagents, hydroboration of alkynes has been regarded as a step-economic and atom-economic synthetic pathway to access alkenyl boronates from readily available starting materials.[3] Commonly, the *anti*-Markovnikov products with *β*(*E*)-selectivity are usually obtained in noncatalytic hydroboration of terminal alkynes.[4] Various metal catalysts have been discovered for selective hydroboration of terminal alkynes to efficiently produce *β*(*E*)- and *β*(*Z*)-alkenyl boronates, respectively.[5,6] However, hydroboration of terminal alkynes to access *α*-alkenyl boronates is still challenging and less explored. In 2011, Hoveyda and coworkers reported a catalytic strategy for *α*-selective protonboration of terminal alkynes with B_2pin_2 by using a NHC-Cu catalyst with moderate to excellent regioselectivity.[7] Subsequently, Yoshida and coworkers used 1,8-diaminonaphthalene (dan) as a protecting group for boron to achieve the same transformation with a better regioselectivity.[8] Later, the palladium catalyst has been found by Prabhu and co-workers to promote protonboration of terminal alkynes with a moderate to excellent Markovnikov-type regioselectivity.[9] Although these reactions involving boryl-metal intermediates could deliver *α*-alkenyl boronates via copper- or palladium-catalyzed protonboration pathways, the use of diboron reagents would cause the stoichiometric extra amount of undesired byproduct, reducing the atomic economy of the reaction.[10]

Compared to the protonboration, metal-catalyzed selective hydroboration of alkynes using hydroboranes offers an atom-economic way to access *α*-alkenyl boronates. Nevertheless, Markovnikov-type selective hydroboration of terminal alkynes with HBpin via a metal hydride strategy has not been explored due to several challenges in this system: (1) The insertion of terminal alkyne into metal hydride species usually delivers the intermediate bearing the metal at terminal carbon due to the steric and electronic effect;[11] (2) The intrinsic background reactions affording *anti*-Markovnikov selective hydroboration products may lower the regioselectivity;[4] (3) In the presence of metal hydride species, the side-reactions including alkyne hydrogenation, double hydroboration, and isomerization may become dominant.[12]



Scheme 1. Metal-Catalyzed Selective Hydroboration of Terminal Alkynes

In recent years, cobalt-hydride catalysis, which emerged as an economical and ecologically tool for sustainable synthesis, has shown its unique reactivity and selectivity on various organic transformations.[11d] Our group reported a sequential hydroboration/hydrogenation of internal alkynes in 2017.[13]

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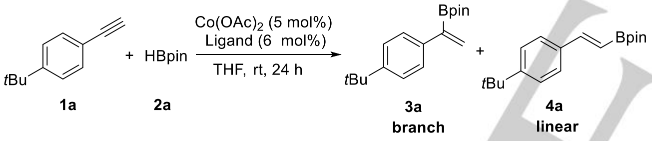
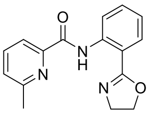
However, only linear product was observed when phenylacetylene was used as a starting material. With our continuous interests on cobalt-catalyzed hydrofunctionalization of alkynes,[14] here we report a mechanistically distinctive cobalt-catalyzed α-selective hydroboration of terminal alkynes with HBpin to access branched alkenyl boronates with good regioselectivity and excellent functional group tolerance.

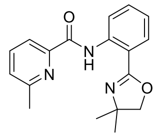
We performed the study to use 1-(*tert*-butyl)-4-ethynylbenzene **1a** as a model substrate and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (HBpin) **2a** as a boryl source (Table 1). The reaction was carried out in the presence of 5 mol% of $Co(OAc)_2$ and 6 mol% of **L1** in a solution of tetrahydrofuran (THF) at room temperature to afford a mixture of alkenyl boronates products in 84% yield with a ratio of 70/30 **b**/**l** selectivity (entry 1). Introducing a *gem*-methyl group onto the oxazoline ring (**L2**) resulted in 78% yield with 91/9 **b**/**l** selectivity. Removing the methyl group on the pyridine moiety (**L3**) led to 89% yield with 85/15 **b**/**l** selectivity (entry 3). When we changed the group on the pyridine moiety, the regioselectivity of the product changes (entries 4 and 5). When *N*-(oxazolinylphenyl)quinoline-2-carboxamide (**L6**, **OPQC**) was used, the regioselectivity was improved to 93/7 **b**/**l** selectivity. Unsymmetrical ligand **L7** (entry 7) or symmetrical ligand **L8** (entry 8) showed poor regioselectivities for this transformation. The time course shown that the model reaction could completed in 3 h (See supporting information). In order to make all the reactions with full conversion, the reaction time is still extended to 24 h. The standard conditions are identified as 0.6 mmol of alkyne, 0.72 mmol of HBpin, 5 mol% of $Co(OAc)_2$, and 6 mol% of **L6** in 2.4 mL of THF for 24 h.

Table 1. Ligand Optimization [a]

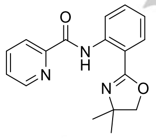




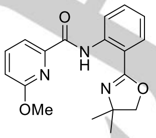
L1



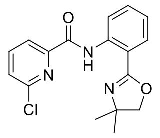
L2



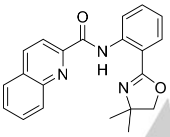
L3



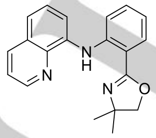
L4



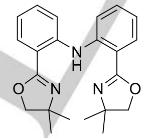
L5



L6



L7



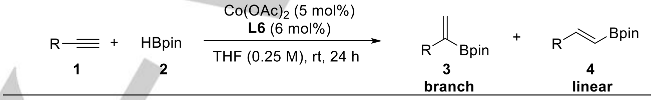
L8

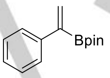
Entry	Ligand	Yield (%)[b]	b/l[b]
1	**L1**	84	70:30
2	**L2**	78	91:9
3	**L3**	89	85:15
4	**L4**	64	72:28
5	**L5**	81	88:12
6	**L6**	84	93:7
7	**L7**	63	71:29
8	**L8**	95	80:20

[a] The reaction was conducted using **1a** (0.6 mmol), **2a** (0.72 mmol), $Co(OAc)_2$ (5 mol %), and ligand (6 mol %) in a solution of THF (2.4 mL) at room temperature for 24 h in glovebox. [b] Determined by ^1H NMR using TMSPh as an internal standard.

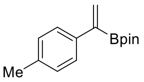
With the optimized conditions in hand, the substrate scope was explored and shown in Table 2. A variety of alkynes could undergo this reaction smoothly to afford various branched alkenyl boronates in 47-85% yields. Phenyl acetylene with *para*-, *meta*-, or *ortho*-methyl substituent (**1c**, **1j**, **1p)** could undergo this reaction to deliver branched products with good regioselectivity. Among which, the yield decreased slightly when the more steric hindered substrate (**1p**) was employed, but a slightly higher regioselectivity (**b**/**l** = 93/7) was observed. Both electron-enriched and electron-deficient substrates could undergo this transformation smoothly. For broader synthetic interests, various functional groups were investigated. Protected alcohol, ether, sulfide, halide, nitrile, and ester could be well tolerated. Notably, 1-ethynyl-4-vinylbenzene (**1g**) and 1-(4-ethynylphenyl)ethan-1-one (**1h**), which could easily undergo reduction of alkene or ketone in the presence of HBpin, were transformed into the corresponding branched alkenyl boronates (**3g**, **3h**) successfully. It turned out that the reactions possess good functional group tolerance. Terminal alkynes with multi-substitution on phenyl rings (**3s**-**3u**) could deliver products

Table 2. Reaction Scope[a]

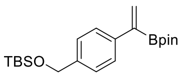




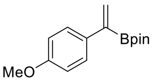
3b, 98% (88%)
b/**l** = 92/8



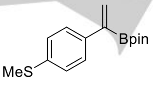
3c, 75% (70%)
b/**l** = 90/10



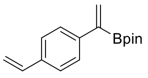
3d, 75% (60%)
b/**l** = 90/10



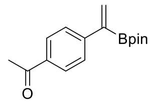
3e, 84% (74%)
b/**l** = 90/10



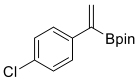
3f, 95% (73%)
b/**l** = 89/11



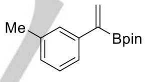
3g, 71% (67%)
b/**l** = 91/9



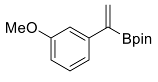
3h, 54% (47%)
b/**l** = 93/7



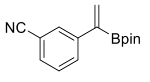
3i, 77% (75%)
b/**l** = 93/7



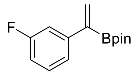
3j, 81% (66%)
b/**l** = 92/8



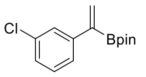
3k, 79% (74%)
b/**l** = 90/10



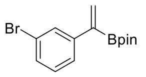
3l, 70% (60%)
b/**l** = 90/10



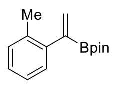
3m, 68% (64%)
b/**l** = 89/11



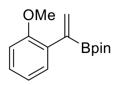
3n, 71% (61%)
b/**l** = 90/10



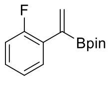
3o, 74% (69%)
b/**l** = 91/9



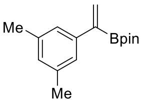
3p, 55% (43%)
b/**l** = 93/7



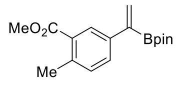
3q, 70% (62%)
b/**l** = 94/6



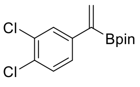
3r, 68% (62%)
b/**l** = 91/9



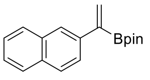
3s, 97% (74%)
b/**l** = 94/6



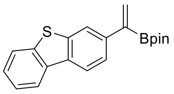
3t, 63% (55%)
b/**l** = 90/10



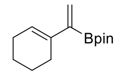
3u, 82% (70%)
b/**l** = 92/8



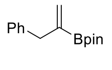
3v, 86% (60%)
b/**l** = 89/11



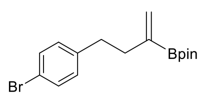
3w, 85% (83%)
b/**l** = 94/6



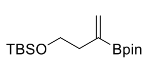
3x, 64% (51%)
b/**l** = 88/12



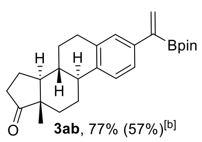
3y, 72% (49%)
b/**l** = 86/14



3z, 85% (69%)
b/**l** = 84/16



3aa, 83% (60%)
b/**l** = 84/16



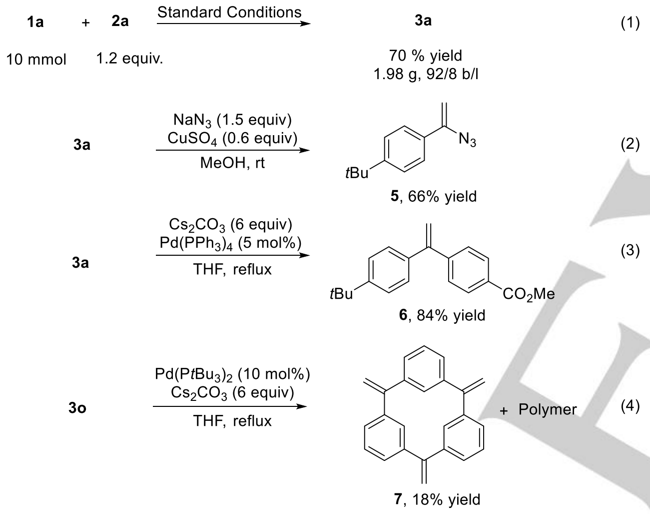
3ab, 77% (57%)[b]
b/**l** = 92/8

[a] **1** (0.6 mmol), **2** (0.72 mmol), $Co(OAc)_2$ (5 mol%), and **L6** (6 mol%) in THF (2.4 mL) under N_2 at rt for 24 h, NMR yield using TMSPh as an internal standard (isolated yield was in the parentheses). [b] 0.2 mmol scale.

in moderate to good yields. Fused ring (**1v**) and heterocyclic ring (**1w**), were converted to branched alkenyl boronates in 60%-83% yields with good regioselectivities.

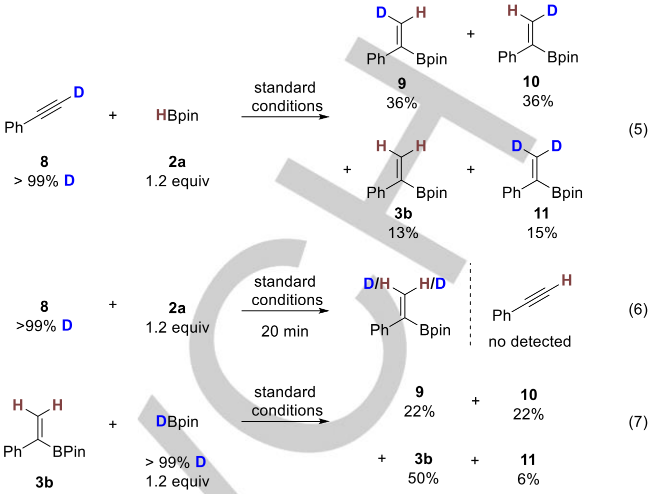
Alkenyl substituted terminal alkyne (**1x**) could also undergo this transformation to afford branched alkenyl boronate as major product although with a slightly lower regioselectivity (**b**/**l** = 88/12). Furthermore, aliphatic terminal alkynes (**1y**, **1z**, and **1aa**) could deliver branched product as major products. Terminal alkyne contained in bioactive moiety(**1ab**) could also be converted into corresponding α-alkenyl boronates, which demonstrated that this transformation would be suitable for late-stage functionalization of complicated molecules.

The reaction could be carried out on gram scale at room temperature to afford 1.98 g of **3a** with 92/8 **b**/**l** selectivity (70% yield) (eq 1). To showcase the utility of α-alkenyl boronates, **3a** could be converted into alkenyl azide[15] (eq 2) or 1,1-diaryl olefins[1] (eq 3), respectively. Additionally, alkenyl boronate with a bromo substituent at *meta*-position (**3o**) could undergo Suzuki-Miyaura coupling reaction to construct cyclic trimer compound (eq 4), which could be potentially applied in materials science.[16]



Scheme 2. Gram-Scale Reaction and Synthetic Applications

To elucidate the possible reaction pathway, several control experiments were conducted. The alkyne hydroboration could proceed smoothly in the presence of radical scavengers, such as BHT or 1,1-diphenylethylene, which suggest this transformation did not undergo radical process (See supporting information). The deuterium experiment of deuterated alkyne **8** with HBpin was conducted under standard condition to give four alkenyl boronates (eq 5). No phenylacetylene was observed, even when shortening the reaction time to 20 min, which ruled out the possible H-D exchange between alkyne and HBpin reported by literatures[17] (eq 6). The alkenyl boronates (**3b**) with DBpin was conducted to give deuterated alkenyl boronates, indicating that the product might undergo insertion into Co-H, then β-H elimination to give deuterated alkenyl boronates (eq 7). Although the single crystal of **L6**·Co(OAc)$_2$ was failed to obtain, we got the X-ray diffraction of **L6**·CoBr, which indicated the formation of an unsymmetrical *NNN* tridendate cobalt complex.[18] The reaction of **1b** with HBpin using **L6**·CoBr did not occur. However, the reaction using cobalt complex **L6**·CoBr and NaOAc as an additive could give **3b** in 76% NMR yield with 92/8 **b**/**l** (eq 8).



Scheme 3. Deuterium Labelling

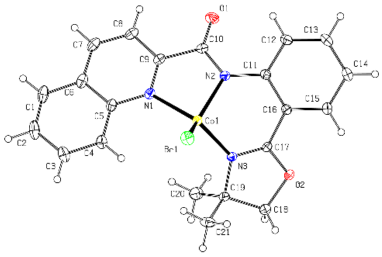
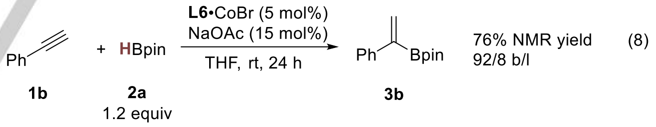
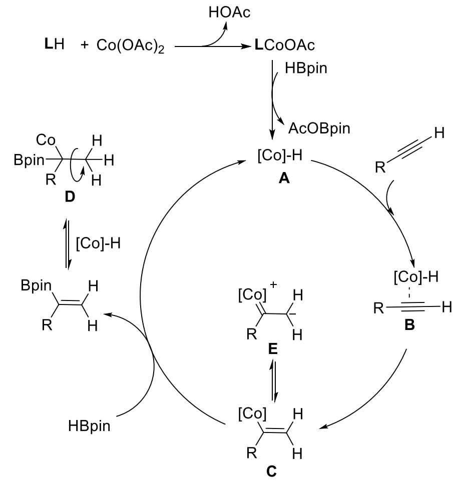


Figure 1. X-ray diffraction of **L6**·CoBr



Scheme 4. Reaction Conducted Using Complex **L6**·CoBr

On the basis of the experimental studies and previously reported literatures,[11d,13,14g] a possible mechanism is shown in Scheme 5. The cobalt hydride species **A** is obtained from the reaction of Co(OAc)$_2$ with **L6** and HBpin. The alkyne coordination with species **A** followed by the insertion of terminal alkyne into the cobalt hydride bond delivers majorly α-selective cobalt alkenyl species **C**. The following σ-bond metathesis of **C** with HBpin regenerates species **A** and delivers the corresponding alkenyl boronate. The cobalt-hydride species will insert into the alkenyl boronate, then β-H elimination to give product. However, the Crabtree-Ojima-type[19] isomerization between **C** and **E** could not be ruled out.



Scheme 5. Proposed Mechanism

In summary, we reported a mechanistically distinctive cobalt-catalyzed Markovnikov-type hydroboration of terminal alkynes with HBpin to access branched alkenyl boronates with good atom economy and functional group tolerance. The unsymmetrical *NNN*-tridentate ligand OPQC was found to efficiently promote a unique Markovnikov-type terminal alkynes insertion via metal hydride intermediate. The reaction could be carried out on a gram scale, and *α*-alkenyl boronates could easily be transferred to potentially useful alkene derivatives. The development of various metal-catalyzed regioselective hydrofunctionalization of alkynes via metal hydride species is currently ongoing in our laboratory.

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Keywords: cobalt catalysis • hydroboration • terminal alkyne • metal hydride species • branched alkenyl boronates

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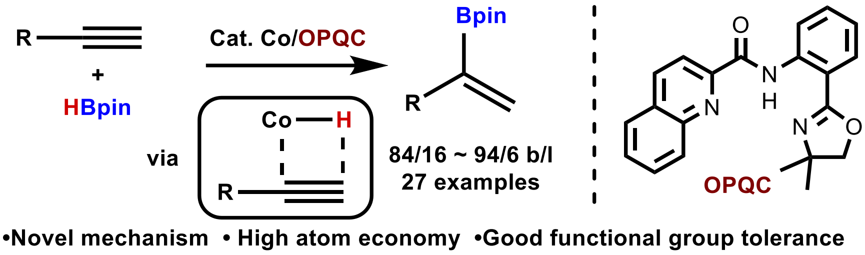

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Cobalt-Catalyzed Markovnikov-type Selective Hydroboration of Terminal Alkynes

A cobalt-hydride catalyst has been developed to promote Markovnikov-type selective insertion of the terminal alkyne to access branched alkenyl boronates. This method exhibits high atom economy and broad substrate scope with excellent functional group tolerance.