HHS Public Access

Author manuscript

J Am Chem Soc. Author manuscript; available in PMC 2020 June 19.

Published in final edited form as:

J Am Chem Soc. 2019 April 17; 141(15): 6173–6179. doi:10.1021/jacs.9b02372.

Differential Dihydrofunctionalization of Terminal Alkynes: Synthesis of Benzylic Alkyl Boronates Through Reductive Three-Component Coupling

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Abstract

The differential dihydrofunctionalization of terminal alkynes is accomplished through the reductive three-component coupling of terminal alkynes, aryl halides and pinacolborane. The transformation results in hydrofunctionalization of both π bonds of an alkyne in a single reaction promoted by cooperative action of a copper/palladium catalyst system. The differential dihydrofunctionalization reaction has excellent substrate scope and can be accomplished in the presence of esters, nitriles, alkyl halides, epoxides, acetals, alkenes, aryl halides, and silyl ethers. Mechanistic experiments indicate that the reaction proceeds through copper-catalyzed hydroboration followed by a second hydrocupration. The resulting heterobimetallic complex is the key intermediate that participates in subsequent palladium-catalyzed cross coupling, which furnishes benzylic alkyl boronate products.

Alkynes are extensively used in organic synthesis as readily available and versatile intermediates. They participate in a wide range of transformations, the most common of which are C-H functionalization of terminal alkynes, addition to one of the π bonds, and a double addition to both π bonds. Also known, but significantly less common, are reactions that lead to the differential transformation of the two π bonds. One of the simplest and oldest[1] reactions that mechanistically fits this description is the hydration of alkynes, which involves initial hydration followed by a tautomerization.[2,3] This transformation has been known for a long time, and has inspired development of differential transformations of alkyne π bonds using other hydrofunctionalization reactions. However, these transformations are still rare,[4] and generally rely on intramolecular reactions[5] or reactions of alkynes activated by electron-withdrawing groups.[6]

Our interest in copper-catalyzed hydrofunctionalization reactions[7] led us to explore the application of copper hydride chemistry[8] in differential functionalization of the two alkyne π bonds. Successful applications developed so far have combined copper-catalyzed hydrofunctionalization of one π bond with catalytic reduction of the other (Scheme 1a).[9] In

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Supporting Information.

The Supporting Information is available free of charge on the dure and product characterizatio ACS Publications website.

Experimental procedure and product characterization

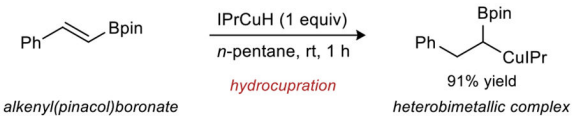
The authors declare no competing financial interest.

2014, Buchwald et al. reported the first example of such a reductive hydrofunctionalization reaction, which combines reduction and hydroamination.[10] More recently, Mankad et al. reported an interesting example of a hydroacylation reaction followed by a reduction.[11]

The methods developed by the Buchwald and Mankad groups demonstrate the utility of copper hydride chemistry in differential transformations of alkyne π bonds. They also suggest a great potential for the development of reactions that would combine copper-catalyzed hydrofunctionalization of one π bond with a different hydrofunctionalization of the other π bond (Scheme 1b). Such reactions would significantly increase the complexity of the products that can be accessed directly from alkynes and would enhance their utility as synthetic intermediates.

In this paper, we describe a method for the differential dihydrofunctionalization of terminal alkynes that formally combines hydroboration with hydroarylation (Scheme 1b). The overall reaction, promoted by synergistic Cu/Pd catalysis, results in reductive coupling of terminal alkynes, aryl bromides, and pinacolborane and the formation of benzylic alkyl boronates.[12]

Inspiration for our approach to differential dihydrofunctionalization came from a report by Sadighi et al. in 2006.[13] The authors describe the hydrocupration of alkenyl Bpin by IPrCuH and formation of a heterobimetallic complex (eq 1).



(1)

While we[7,14] and others[15] have previously established that (NHC)copper hydride complexes are excellent catalysts for hydrofunctionalization of alkynes,[8] this report demonstrated that these same complexes also participate in the selective hydrocupration of functionalized alkenes.[16] Our plan was to combine these two facets of the (NHC)CuH chemistry and develop a differential dihydrofunctionalization of alkynes (Scheme 2).

We reasoned that the heterobimetallic intermediate **IV** could be accessed directly from alkynes through copper-catalyzed hydroboration and the subsequent hydrocupration of the alkenyl boronate ester (**III**). This simple access to the heterobimetallic intermediate provides an opportunity to systematically explore a wide range of differential dihydrofunctionalization reactions of alkynes through further functionalization of this key intermediate. We chose to pursue palladium-catalyzed cross coupling of the heterobimetallic intermediate (**IV**) with aryl bromides (**II**), inspired by known catalytic arylations of related copper(I) alkyl intermediates.[17]

Preliminary investigation of the proposed differential dihydrofunctionalization reaction began with 5-phenyl-1-pentyne (**1**), 4-bromoanisole (**2**) and pinacolborane as coupling partners, with IPrCuO*t*-Bu and a variety of palladium catalysts. Initially, we observed numerous reactions promoted by the Cu/Pd catalyst system. In addition to the desired

product (**3**), products of Miyaura borylation[18] (**4**), hydroboration[15b,19] (**5**), hydroarylation[20] (**6**) and geminal diboration[21] (**7**) of the alkyne were also observed (Scheme 3).

In addition to alkenyl boronate **5**, compounds **6**[22] and **7**[12b] could, in principle, also serve as intermediates in the synthesis of the desired product **3**. However, careful monitoring of the reaction mixture revealed that the formation of either the *E*-styrene (**6**) or alkyl diboronate (**7**) generally corresponded with a decreased yield of the desired product (**3**). On the other hand, any alkenyl boronate (**5**) formed was consumed over the course of the reaction, resulting in the corresponding increase in yield of the desired product. As a result, we focused on identifying reaction conditions that would minimize both hydroarylation and diboration of the terminal alkyne.

Initially, we found that the identity of the palladium catalyst and the alkoxide additive had the greatest effect on the product distribution. Extensive reaction development focused on these two parameters led to an efficient differential dihydrofunctionalization of terminal alkynes shown in Table 1 (entry 1).

During the reaction development, we made several observations summarized in Table 1. Considering that Pd_2dba_3[23] is rarely used in combination with dialkylbiaryl phosphine ligands, we were surprised that it was a significantly better precatalyst than other common palladium sources. For example, $Pd(OAc)_2$ provided the product in only 54% yield at the full conversion (Table 1 entry 2) (see SI for further details). IPrCuO*t*-Bu performed better than IPrCuCl as a catalyst precursor (entry 3). Catalyst loading of both palladium and copper proved crucial. Lower loading of IPrCuO*t*-Bu resulted in decreased yield with full consumption of aryl halide (entry 4). Higher loading of the palladium catalyst increased formation of *E*-styrene (**6**) and lowered product yield (entry 5).

The reaction outcome was also greatly influenced by the choice of phosphine ligand. XPhos[24] provided significantly higher selectivity for the desired product than closely related BrettPhos[25] (entry 6) and other dialkylbiaryl ligands (see SI for details). Bisphosphine ligands like (*R*)-DTBM-SEGPHOS, formed the product of diboration (**7**) almost exclusively (entry 7). The choice of the alkoxide additive also proved important. KO*t*-Bu was superior to both NaO*t*-Bu and LiO*t*-Bu (entry 8 and 9), increasing conversion of alkenyl Bpin (**5**) to product, while suppressing formation of *E*-styrene (**6**).

High yields of the differentially dihydrofunctionalized product were obtained in aromatic hydrocarbon solvents such as toluene and benzene (entries 1 and 10), with lower yields in isooctane (entry 11) and minimal reactivity in ethereal solvents (entries 12 and 13) (see SI for details). Lastly, we observed that the concentration of the reaction mixture had a significant effect on yield. Doubling the concentration of the reaction mixture (entry 14) decreased the yield.[26]

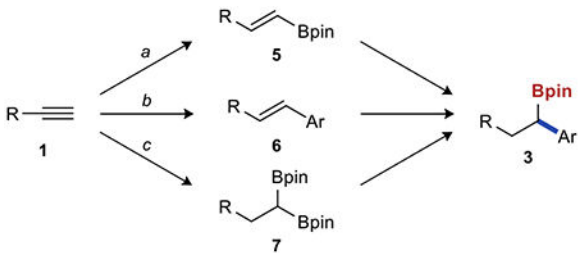
Having established the conditions for the differential dihydrofunctionalization of terminal alkynes (Table 1, entry 1), we explored the scope of the reaction (Table 2). A broad range of aryl bromides serve as coupling partners. Both electron-rich (**3** and **11**) and electron-poor (**8** and **12**) aryl bromides were viable coupling partners. A variety of functional groups were

tolerated, and reaction could be performed in the presence of aryl fluorides (**9**), aryl chlorides (**10**) and acetals (**13** and **24**). Styrenes (**18**) were also compatible with the reaction. Products derived from para (**14**), meta- (**15**) and ortho- (**16**) substituted aryl bromides were isolated in good yields. Notably, a variety of O, N and S containing heterocycles were compatible with this reaction (**19** – **23**).

We also explored the scope of the alkyne coupling partner. Alkynes containing nitriles (**25**), epoxides (**27**), chlorides (**29**), bromides (**30**), acetals (**35**) and esters (**36**) were compatible with the reaction conditions. Protected alcohols (**28, 31** and **32**) and functionalized phenyl ethers (**26**, **40** and **41**) were competent coupling partners in the reaction. Propargylic substitution of the alkyne also provided products in good yields (**32** – **34**). Finally, electron rich (**38**) and electron deficient (**39**) aryl acetylenes can be utilized in this reaction.

We also noted several limitations of the reaction. The reaction is not compatible with aldehydes, ketones, activated alkenes (such as enones), free alcohols, or tertiary alkyl amines. Furthermore, reactions with several aryl chlorides provided no desired products, suggesting that aryl chlorides are not viable substrates. Finally, internal alkynes, including differentially substituted aryl alkyl alkynes provided no desired product in the reaction.

Considering our preliminary observations and the known reactivity of both palladium-catalyzed cross coupling[27] and copper-catalyzed hydrofunctionalization reactions,[8] we envisioned three possible pathways for differential dihydrofunctionalization of terminal alkynes (eq. 2): a) copper-catalyzed hydroboration followed by hydrocupration and electrophilic functionalization, b) hydroarylation followed by hydroboration, or c) diboration to generate the alkyl diboronate, followed by mono-selective cross coupling with the aryl halide. Each pathway proceeds through a unique intermediate: a) alkenyl Bpin (**5**), b) *E*-styrene (**6**) or c) alkyl diboronate (**7**).



(2)

We explored the reactivity of each presumed intermediate under the standard conditions for differential dihydrofunctionalization (Scheme 4). When alkenyl Bpin (**5**) was the substrate, the desired product (**3**) was formed in 43% yield after 6 h (Scheme 4a), whereas neither *E*-styrene (**6**), nor alkyl diboronate (**7**) formed the desired product in appreciable yields even after 24 h (Scheme 4b and c). In both cases, products of other side reactions were observed and/or starting material was recovered. These results strongly suggest that the operative pathway involves hydroboration of the alkyne (eq 2, a).

We also wanted to verify that the heterobimetallic complex (**IV**) could be formed directly from terminal alkynes and is the key catalytic intermediate in the reaction. The stoichiometric reaction between terminal alkyne, IPrCuO*t*-Bu, and HBpin resulted in the formation of hetermobimetallic complex **42**, in excellent yield (Scheme 4d). Additionally, the stoichiometric cross coupling between **42** and aryl bromide (**2**) yielded the desired benzylalkylboronate in 98% yield (Scheme 4e). Altogether, these results support our proposed pathway.

Considering the results of these experiments, we propose the mechanism outlined in Scheme 5. Initial transmetallation between IPrCuO*t*-Bu and HBpin generates IPrCuH, and hydrocupration of the terminal alkyne (**I**) results in alkenyl copper (**VI)**. Additional transmetallation between a second equivalent of HBpin and **VI** delivers alkenyl Bpin (**III)** and regenerates IPrCuH. Reinsertion of **III** into IPrCuH furnishes heterobimetallic complex (**IV)**.

The heterobimetallic complex (**IV**) participates in a standard palladium-catalyzed cross coupling with the aryl bromide to produce the differentially dihydrofunctionalized product **V** and Pd(0). IPrCuO*t*-Bu catalyst is regenerated in the presence of KO*t*-Bu.

In conclusion, we have developed a method for the differential dihydrofunctionalization of alkynes that results in the reductive three-component coupling of terminal alkynes, aryl bromides, and pinacolborane. The benzylic alkyl boronate products are accessed directly from terminal alkynes by accomplishing two different regioselective hydrofunctionalization reactions promoted by a Cu/Pd catalyst system.

The reaction has excellent substrate scope and functional group compatibility, providing the desired products in high yields. The results of mechanistic experiments indicate that the reaction proceeds through copper-catalyzed hydroboration, followed by a second hydrocupration of the alkenyl boronate, and palladium-catalyzed arylation of the resulting heterobimetallic intermediate. The most important finding of our studies is that the heterobimetallic intermediate can be readily accessed directly from the terminal alkyne in the presence of a copper catalyst and HBpin. We believe that the access to this heterobimetallic intermediate provides an exciting opportunity for a systematic development of other differential dihydrofunctionalization reactions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENT

We thank Prof. Forrest Michael for assistance in preparation of this manuscript. We also thank NIH for financial support.

Funding Sources

NIH (1R01GM125791-01A1) is acknowledged.

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(26). Optimal concentration of various componetnts in the reaction mixture was achieved when alkyne concetration was 0.05 M. Further decrease in concentration of reaction components (0.01 M in alkyne) was found to lower the yield of the desired product, with full conversion of starting materials being achieved only after 72 hours.

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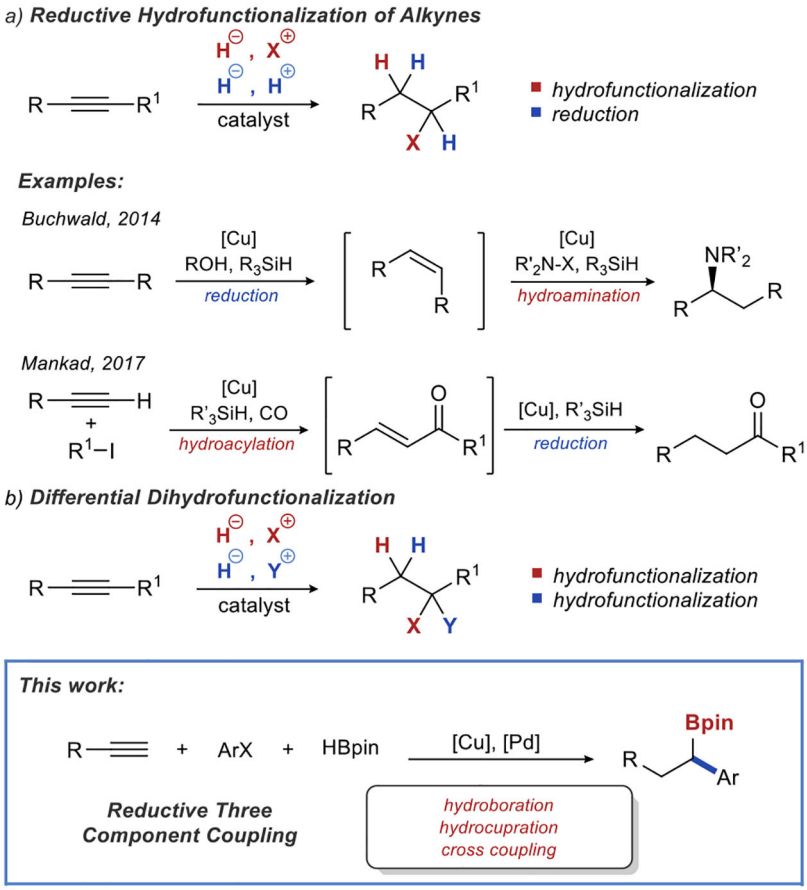
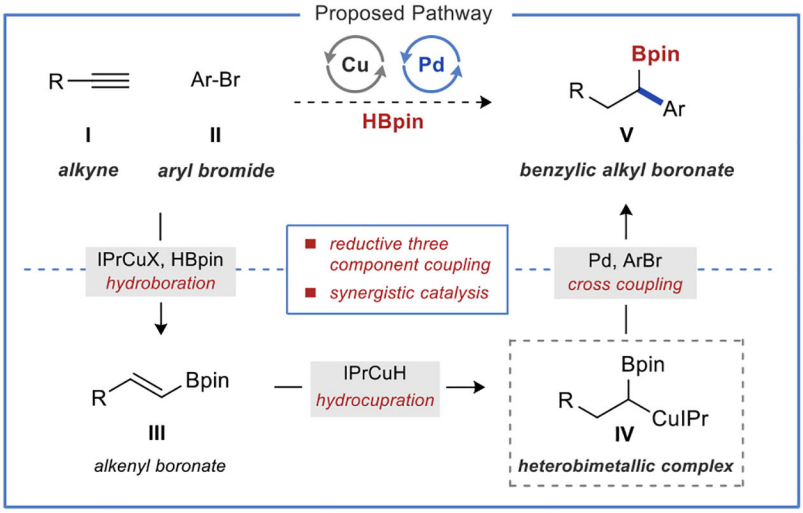
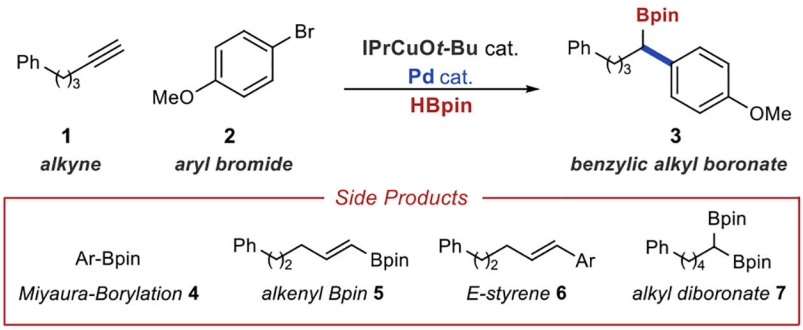


Scheme 1.

Copper Hydride Chemistry in Differential Functionalization of Alkyne π Bonds.

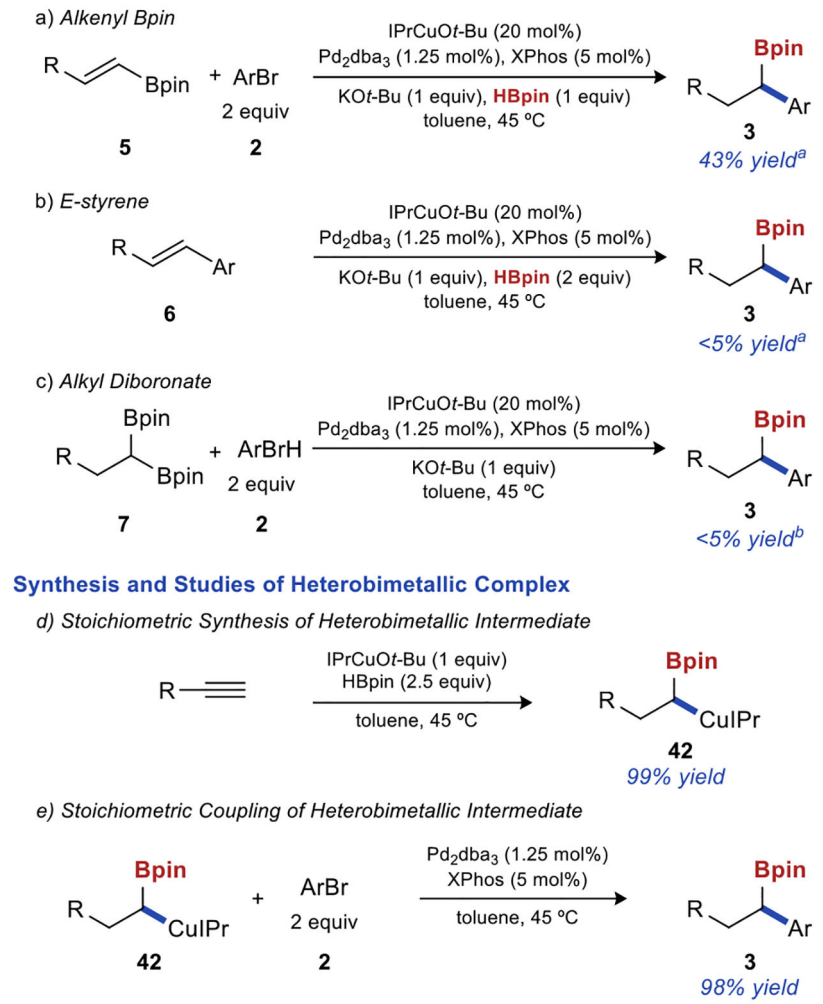


Scheme 2.
Design of Differential Dihydrofunctionalization

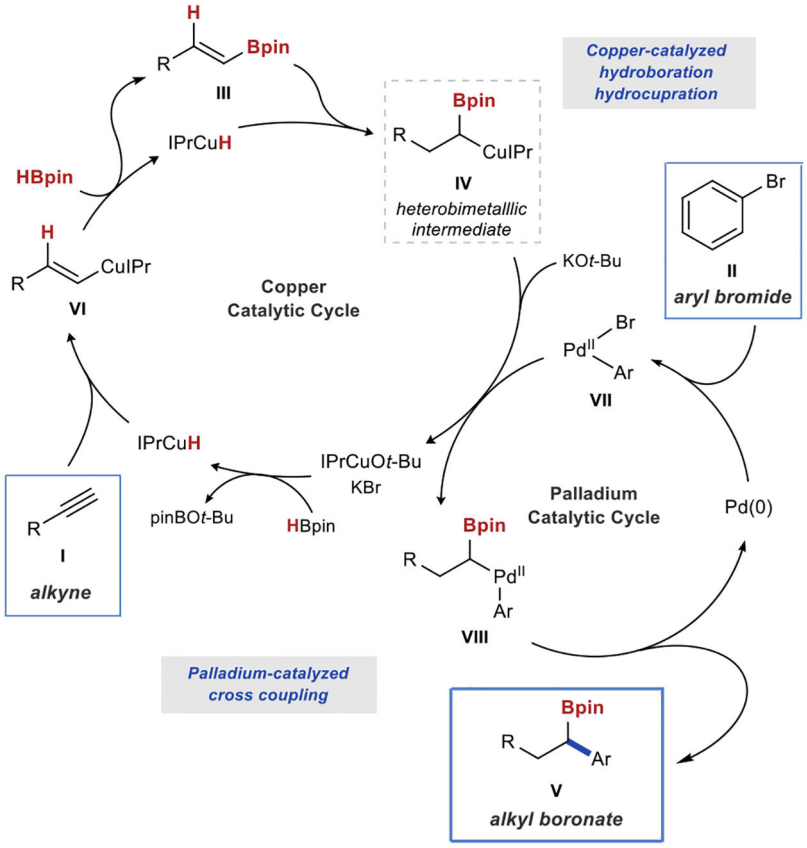


Scheme 3.

Preliminary Investigation of Differential Dihydrofunctionalization



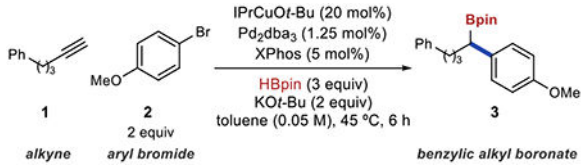
Scheme 4.
Mechanistic Experiments



Scheme 5.
Proposed Catalytic Cycle

Table 1.

Reaction Development



Entry	deviation from above	yield[a]
1	none	86
2	$Pd(OAc)_2$ instead of Pd_2dba_3	54
3	IPrCuCl instead of IPrCuO*t*-Bu	67
4	10 mol% IPrCuO*t*-Bu instead of 20 mol%	31
5	2.5 mol% Pd_2dba_3 instead of 1.25 mol%	59
6	BrettPhos instead of XPhos	20
7	(*R*)-DTBM-SEGPHOS instead of IPr	8
8	NaO*t*-Bu instead of KO*t*-Bu	46
9	LiO*t*-Bu instead of KO*t*-Bu	34
10	benzene instead of toluene	65
11	isooctane instead of toluene	24
12	1,4-dioxane instead of toluene	5
13	THF instead of toluene	0
14	0.1 M instead of 0.05 M[b]	74

[a] A11 reactions performed on 0.05 mmol scale and monitored by GC with 1,3,5-trimethoxybenzene as an internal standard.

[b] Concentration of alkyne in the reaction mixture. EPr 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene, dba = dibenzylideneacetone, pin = pinacolato.

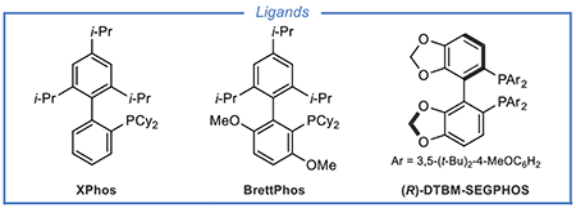
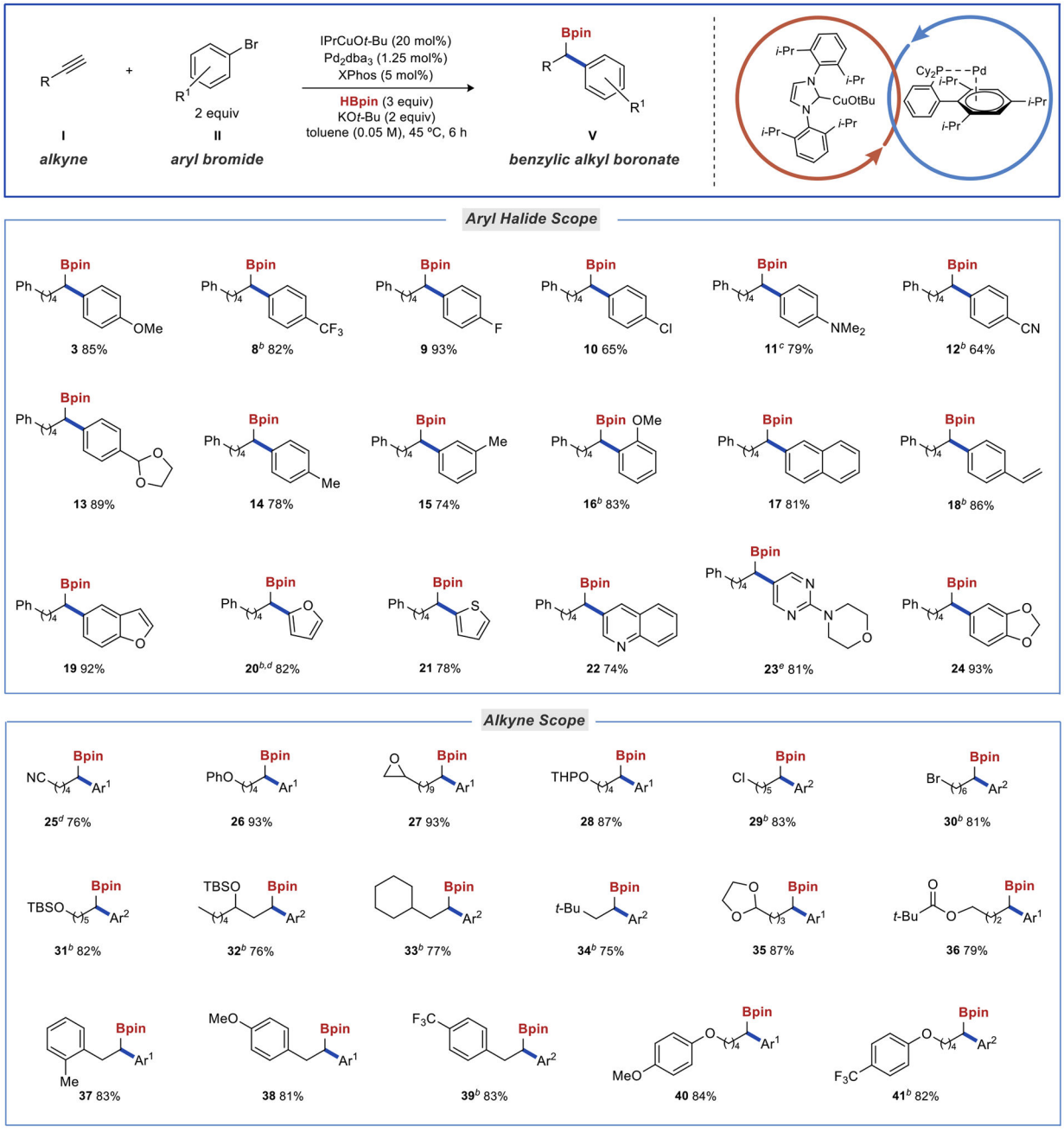


Table 2.

Scope of Differential Dihydrofunctionalization of Alkynes



[a] Reactions run on 0.5 mmol scale.

[b] IPrCuCl instead of IPrCuO*t*-Bu and NaO*t*-Bu instead of KO*t*-Bu.

[c] toluene:isooctane (1:1) used.

[d] GC yield, with 1,3,5-trimethoxybenzene as internal standard.

[e] KOTMS used instead of KO*t*-Bu and toluene:THF (1:1) was used. Ar^1 = 4-OMe(C_6H_4), Ar^2 = 4-CF_3(C_6H_4)