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Copper-Catalyzed Hydroboration of Propargyl-Functionalized Alkynes in Water

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The Cu-catalyzed hydroboration of alkynes in operationally simple and environmentally friendly conditions is reported. The reactions are performed in water, at room temperature, under micellar catalysis. Conditions to form the α or β borylated products selectively have been found and as an application a protocol for the tandem hydroboration/Suzuki coupling in water was developed.

Introduction of a boron moiety into organic molecules constitutes a central research interest in organic synthesis due to the stability of organoboron compounds under atmospheric conditions, low toxicity and high reactivity under specific conditions, such as in the Suzuki coupling reaction.[1] Therefore, the presence of C-B bonds in organic frameworks offers many interesting possibilities for the subsequent functional group transformations and application in the synthesis of complex molecules.[2] In this context, vinylboronates are an important class of organoboron compounds. These compounds can be accessed by either conventional[3] or metal-catalyzed hydroboration of alkynes.[4-6] Although these methods are efficient for the synthesis of a number of different vinylboronates, the experimental conditions for these reactions are typically performed under strictly anhydrous conditions, using dry organic solvents and frequently require the use of glovebox for the manipulation of reagents and/or catalysts. Recently, hydroboration of alkynes in aqueous media has emerged as an interesting alternative,[7] however the reported methods have limited scope, even though high regioselectivity has been reported mainly using ynones as the substrates.[8]

Therefore the development of methodologies for the synthesis of these valuable compounds in greener conditions is desired. Herein we report the systematic study of the copper-catalyzed hydroboration of propargyl-functionalized alkynes in operationally simple and environmentally friendly conditions, without using organic solvents. The Cu-catalyzed hydroboration is performed in water, at room temperature, enabled by the presence of SPGS-550M, a designer surfactant, introduced by Lipshutz.[9] The use of a small amount of a surfactant in water leads to the spontaneous formation of micellar agregates that might behave as a nanoreactor, which is the actual reaction vessel.[10] This technology allows a desired transformation, using water-insoluble reagents, to occur without using organic solvents. Several types of reactions have been studied using nanomicelles in water:[11] Heck, Sonogashira, Stille, Negishi and Suzuki couplings, alkene metathesis,[9-12] SNAr,[13] silylcupration of alkynes,[14] and hydrophosphination.[15]

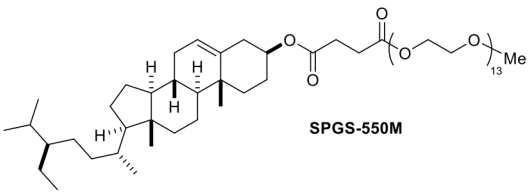

Figure 1. Structure of surfactant SPGS-550M

We started our investigation using propargyl acetate as the starting alkyne. The hydroboration of this substrate was investigated by screening the copper source and ligand, in the presence of B_2pin_2 (1.1 equiv) and NaOH (5 mol%), at room temperature, using a 2% aqueous solution of SPGS-550M as the reaction solvent. The data are summarized in Table 1.

First, $Cu(OAc)_2.H_2O$ (5 mol%) was used as the catalyst and PPh_3 (5 mol%) as ligand, and the product **1** was obtained in moderate yield, in an unselective reaction (entry 1). In the absence of the ligand, no reaction was observed (entry 2). Performing the reaction in pure water, in the absence of the surfactant, resulted in a sharp decrease in the product yield (entry 3). We next evaluated the influence of the ligand on the reaction outcome. In addition to PPh_3, another monophosphine, $P(p\text{-}CF_3C_6H_4)_3$, was tested and the product **1** was obtained in essentially the same yield, but with improved

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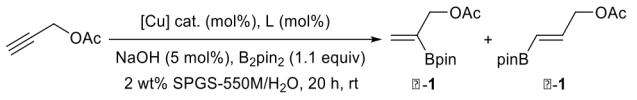
α:β selectivity (entry 4). Several bis-phosphines with different bite angles, including DPEphos, BINAP, dppf, dppm, dppe, dppp, and dppb, were also tested (entries 5-13). The best results were achieved when 5 mol% of dppe was employed as the ligand and the borylated product **1** was obtained in 71% yield in high regioselectivity in favor of β-vinyl boronate (ratio α:β=17:83, entry 10). Increasing the amount of $Cu(OAc)_2.H_2O$ to 8 mol% and of dppe from 5 mol% to 10 mol% resulted in further increase in both yield and selectivity of the hydroboration reaction in favor of the β-vinyl boronate (78% yield, α:β=09:91, entry 11). Attempts to use phenanthroline as ligand for copper, resulted in no reaction (entry 14). On the other hand, when a N-heterocyclic carbene (NHC)-copper(I) complex was used as the catalyst for the reaction, a reversal in the regioselectivity of the hydroboration was observed and the α-vinyl boronate was isolated as the main product (entries 15-18). Using 5 mol% of [Cu(Cl)(IMes)] resulted in 75% yield and a α:β selectivity of 84:16 (entry 15). Attempts to improve this results by increasing the catalyst loading to 10 mol% (entry 16) did not lead to any further improvement on yield or selectivity. Again, conducting the reaction in pure water, in the absence of the surfactant, resulted in an erosion of the yield and regioselectivity (entry 17), confirming that the presence of small amounts of SPGS-550M has a beneficial effect on the reaction outcome. Finally, changing the NHC structure to [Cu(Cl)(IPr)], resulted in an improvement of the α:β ratio, however, with significantly lower yield (21% yield, α:β=91:09, entry 18).

Table 1. Screening of the Cu-catalyzed hydroboration of propargyl acetate



entry	[Cu] cat. (mol %)	ligand (mol%)	yield (%)[a]	α:β[b]
1	$Cu(OAc)_2.H_2O$ (5)	PPh_3 (5)	62	50:50
2	$Cu(OAc)_2.H_2O$ (5)	-	0	-
3[c]	$Cu(OAc)_2.H_2O$ (5)	PPh_3 (5)	23	50:50
4	$Cu(OAc)_2.H_2O$ (5)	P(*p*-$CF_3C_6H_4$)$_3$ (5)	60	16:84
5	$Cu(OAc)_2.H_2O$ (5)	DPEphos (5)	18	05:95
6	$Cu(OAc)_2.H_2O$ (5)	*rac*-BINAP (5)	54	06:94
7[d]	$Cu(OAc)_2.H_2O$ (5)	*rac*-BINAP (5)	0	-
8	$Cu(OAc)_2.H_2O$ (5)	dppf (5)	48	06:94
9	$Cu(OAc)_2.H_2O$ (5)	dppm (5)	68	28:72
10	$Cu(OAc)_2.H_2O$ (5)	dppe (5)	71	17:83
11	**$Cu(OAc)_2.H_2O$ (8)**	**dppe (10)**	**78**	**09:91**
12	$Cu(OAc)_2.H_2O$ (5)	dppp (5)	64	37:63
13	$Cu(OAc)_2.H_2O$ (5)	dppb (5)	32	50:50
14	$Cu(OAc)_2.H_2O$ (5)	phen (5)	0	-
15	**[Cu(Cl)(IMes)] (5)**	**-**	**75**	**84:16**
16	[Cu(Cl)(IMes)] (10)	-	75	84:16
17[c]	[Cu(Cl)(IMes)] (5)	-	40	68:32
18	[Cu(Cl)(IPr)] (5)	-	21	91:09

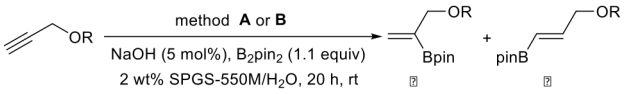
[a]Isolated yields. [b]Determined by ^{1}H-NMR of the crude product. [c]Reaction performed in pure water, without SPGS-550M. [d]Using NaCl 3M.

Having identified two different catalytic systems in which the α and β products can be produced selectively, we next examined both the hydroboration of a broader range of propargyl-functionalized alkynes, in water, at room temperature, using 2% of SPGS-550M. The results are presented in Tables 2 and 3.

We first focused our efforts to evaluate the efficiency of the reaction using substrates bearing oxygen-based functional groups (Table 2). In all reactions, the regioselectivity followed the trend observed with propargyl acetate with the β-vinyl boronate formed as the major product with method **A** [8 mol% $Cu(OAc)_2$, 10 mol% dppe] whereas the α-vinyl boronate was the preferred product using method **B** [5 mol% Cu(Cl)(IMes)].

The reaction with propargyl alcohol led to the borylated product **2** in low yield (entries 1-2). When propargyl ethers were evaluated, the corresponding products **3** and **4** were isolated in very good yields and selectivity (entries 3-6). Particularly interesting is the result observed using benzyl propargyl ether as the substrate, using method **A**, since the product **4** was isolated in 88% yield and a α:β ratio of 14:86 (entry 5). Ester (Bz) and carbamate (Boc) groups were also well tolerated under the reaction conditions (entries 7-10). Borylated product **6** was formed in excellent yield using method **B** and only moderate yield with method **A**, while product **5** was formed in very good yields using both methods. Notably, very good results have been achieved for these substrates, in terms of regioselectivity, using method **B**, delivering the α-**5** and α-**6** products in 86:14 and 94:06 ratio, respectively (entries 8 and 10). The hydroboration of TBS-protected propargyl alcohol led to product **7** in good yield, however with only moderate selectivity (entries 11 and 12). Finally, no reaction was observed when propargyl tosylate was used as substrate, and only a complex mixture of decomposition products was achieved (entry 13).

Table 2. Scope of hydroboration of *O*-functionalized propargyl alkynes



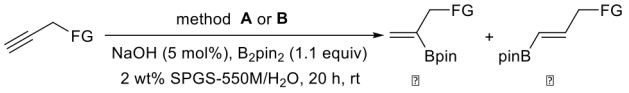
method **A**: $Cu(OAc)_2.H_2O$ (8 mol%), dppe (10 mol%)
method **B**: [Cu(Cl)(IMes)] (5 mol%)

entry	R	method	product, yield (%)[a]	α:β[b]
1	H	**A**	**2**, 20	40:60
2	H	**B**	**2**, 46	75:25
3	Ph	**A**	**3**, 78	22:78
4	Ph	**B**	**3**, 85	78:22
5	Bn	**A**	**4**, 88	14:86
6	Bn	**B**	**4**, 90	72:28
7	Bz	**A**	**5**, 80	33:67
8	Bz	**B**	**5**, 87	86:14
9	Boc	**A**	**6**, 51	25:75
10	Boc	**B**	**6**, 95	94:06
11	TBS	**A**	**7**, 78	25:75
12	TBS	**B**	**7**, 90	67:33
13	Ts	**A** or **B**	**8**, 0	-

[a]Isolated yields. [b]Determined by ^{1}H-NMR of the crude product.

We next focused on the examination of different alkyne functionalities and the results are depicted in Table 3. Performing the hydroboration of homopropargyl alcohol led to excellent selectivity but unfortunately the product **9** was isolated in low yield using either method **A** or **B** (entries 1-2). Moderate yield and selectivity have also been achieved using the homopropargyl-Boc derivative (entries 3-4). Propargyl amine-derivatives have also been examined (entries 5-12). Albeit free NH_2 or NMe_2 groups are not tolerated under the reaction conditions, we gratifyingly observed that excellent results were obtained using a sterically more demanding NMeBn group and borylated product **13** was isolated in 58% yield using method **A** and 71% yield using method **B**. Using this substrate, the hydroboration was performed in 2 h, since in longer reaction times protodeborilation of the product **13** was observed. Interestingly, in both cases the β-**13** product was formed in nearly perfect regioselectivity (entries 7 and 8). It is worth to point out that this result is complementary to what was observed by Hoveyda *et. al.* who obtained preferentially the α-product in the hydroboration of propargyl amines using NHC-Cu(I) catalysts.[6b] The presence of electron-withdrawing groups at the nitrogen such as Boc and Ts groups was also possible (entries 9-12), however some erosion on the α:β ratio was observed for **14** and **15**, particularly when using the $Cu(OAc)_2$/dppe catalytic system (entries 9 and 11). Finally, thioether-substituted alkyne showed itself as a good substrate for the hydroboration, delivering the corresponding product **16** in good yields and moderate to good selectivity (entries 13 and 14).

Table 3. Scope of hydroboration of different functionalized alkynes

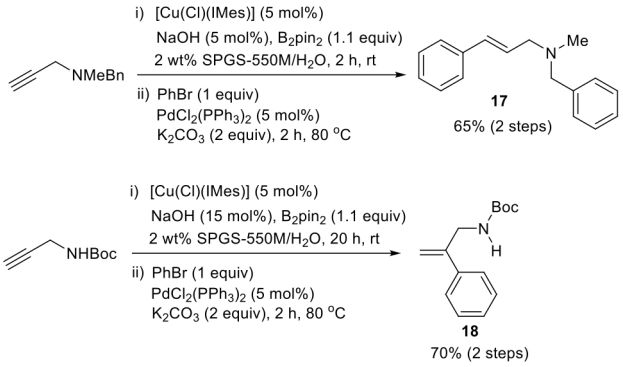


method **A**: $Cu(OAc)_2.H_2O$ (8 mol%), dppe (10 mol%)
method **B**: [Cu(Cl)(IMes)] (5 mol%)

entry	FG	method	product, yield (%)[a]	α:β[b]
1	CH_2OH	**A**	**9**, <20	04:96
2	CH_2OH	**B**	**9**, <20	08:92
3	CH_2OBoc	**A**	**10**, 34	28:72
4	CH_2OBoc	**B**	**10**, 50	32:68
5	NH_2	**A or B**	**11**, 0	-
6	NMe_2	**A or B**	**12**, 0	-
7[c]	NMeBn	**A**	**13**, 58	05:95
8[c]	NMeBn	**B**	**13**, 71	05:95
9[d]	NHBoc	**A**	**14**, 43	50:50
10[d]	NHBoc	**B**	**14**, 85	82:18
11	NMeTs	**A**	**15**, 68	50:50
12	NMeTs	**B**	**15**, 60	65:35
13	SPh	**A**	**16**, 78	15:85
14[d]	SPh	**B**	**16**, 87	67:33

[a]Isolated yields. [b]Determined by ^{1}H-NMR of the crude product. [c]Reaction performed in 2 h. [d]15 mol% of NaOH was used.

Finally, in order to demonstrate the usefulness of our methodology, we designed a tandem hydroboration/Suzuki coupling that would be entirely performed in aqueous micellar media (Scheme 1). Given the importance of arylated allylamines,[16] which is a structural motif present in a number of drugs and biologically active natural products (*e.g.* naftifine,[17] flunarizine,[18] and abamines[19]), we have selected amino alkynes as reaction partners and [Cu(Cl)(IMes)] as the hydroboration catalyst. After consumption of NMeBn-substituted alkyne in the hydroboration reaction, bromobenzene (1 equiv), 5 mol% of $PdCl_2(PPh_3)_2$ and potassium carbonate have been added to the reaction mixture which was then heated at 80 °C for 2 h, to deliver the pure (*E*)-**17** product in 65% isolated yield, after two steps. Similarly, when NHBoc-propargyl amine was subjected to the same conditions, the product **18** was obtained in 70% overall yield. Notably, there is no need for the isolation of vinylboronate intermediates and the entire process was performed in water, thus minimizing the use of organic solvents.



Scheme 1. Tandem hydroboration/Suzuki reaction in water, using SPGS-550M

In summary, we have developed an environmentally friendly and operationally simple copper-catalyzed hydroboration of propargyl-functionalized alkynes, in water, that was enabled by the use of small amounts of SPGS-550M, as surfactant, which in water forms nanomicelles. The reaction worked for a range of propargyl-functionalized alkynes and we have found conditions that can be used to selectively form the α or β borylated products. As an application we have also developed a protocol for the tandem hydroboration/Suzuki coupling in water, to afford arylated allylamines in good overall yields. We believe that the present protocol should find its way in the toolbox of synthetic chemists as a greener and operationally simpler alternative for the synthesis of vinylboronates.

Acknowledgments

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GRAPHICAL ABSTRACT