Advanced Synthesis & Catalysis

Accepted Article

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To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201700094

Link to VoR: http://dx.doi.org/10.1002/adsc.201700094

10.1002/adsc.201700094

UPDATE

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Combining Copper-Catalyzed Hydroboration with Palladium-Catalyzed Suzuki Coupling for the One-pot Synthesis of Arylallylamines under Micellar Conditions

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Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201

Abstract. Herein we report the one-pot dual-metal catalytic synthesis of arylallylamines, by combination of a Cu-catalyzed hydroboration with a Pd-catalyzed Suzuki arylation, using a broad range of aryl halides. Importantly, the reaction sequence was entirely performed in water, in the presence of small amounts of SPGS-550M, without the need of solvent switch or addition of organic co-solvents, rendering it operationally simple and environmentally benign. The usefulness of this methodology was highlighted in a short synthesis of the pharmaceutically important compound naftifine.

Keywords: naftifine; tandem reactions; dual-metal catalysis; catalysis in water; one-pot synthesis

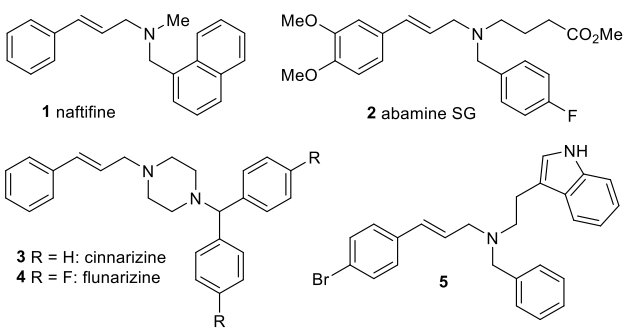


Figure 1. Structures of biologically active arylallylamines.

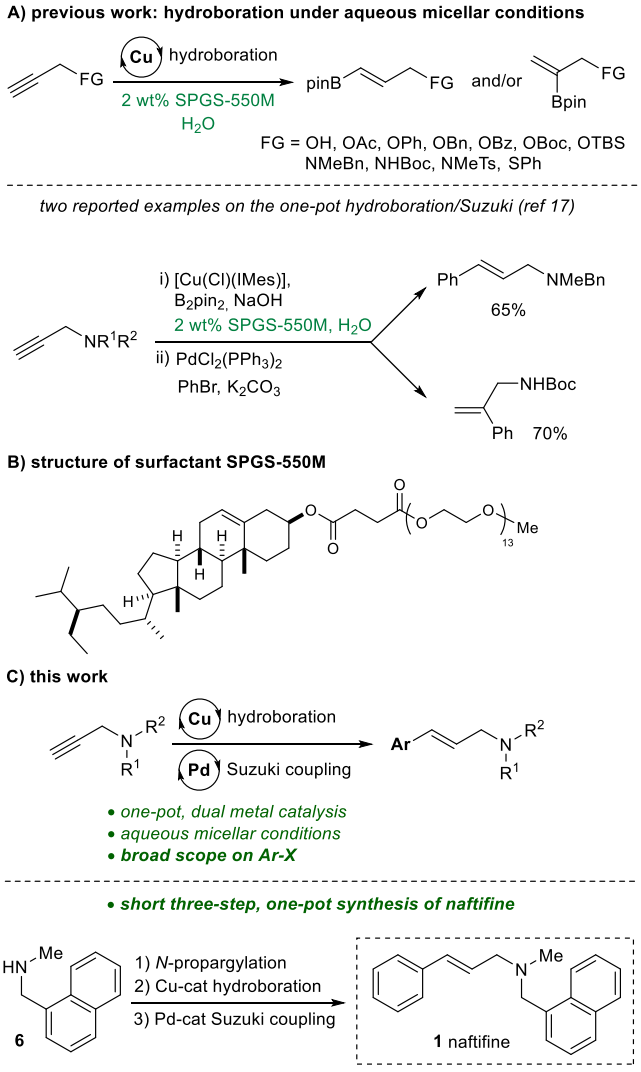
Introduction

The γ-arylallylamine is a structural motif present in a number of biologically relevant molecules that display a broad spectrum of bioactivities (Figure 1). For example, naftifine (**1**) is a commercially available antifungal agent whose mechanism of action involves blocking of sterol biosynthesis by inhibiting the enzyme squalene epoxidase.[1] Moreover, it has been recently discovered that naftifine attenuated the virulence of a variety of clinical *Staphylococcus aureus* isolates, including methicillin-resistant *S. aureus* (MRSA).[2] Additional examples include abamine SG **2**, which is a inhibitor of 9-*cis*-epoxycarotenoid dioxygenase, an enzyme involved in the biosynthesis of abscisic acid,[3] cinnarizine (**3**) and flunarizine (**4**) that are calcium channel blockers and have been prescribed as drugs for the treatment of nausea, migraine, and vascular diseases.[4] Recently, the arylated allylamine **5** was found to be a adenylyl cyclase inhibitor potentially useful for treatment of neuropathic and inflammatory pain.[5]

Arylallylamines have been prepared by different strategies including Petasis reaction using vinylboronic acids,[6] one-pot oxidation of a primary alcohol, followed by reductive amination,[7] Cu-catalyzed hydroamination of allenes,[8] Fe-catalyzed cross-coupling of Grignard reagents with vinyl chlorides,[9] Lewis acid-catalyzed *N*-allylation of electron deficient amides with aldehydes and non-activated alkenes,[10] Pd-catalyzed amination of allylic alcohols in surfactant/water,[11] and Pd-catalyzed arylation of zincated *N*-Boc-allylamines.[12] Another interesting approach to these molecules uses the Pd-catalyzed Heck[13] and Heck-Matsuda arylation of allylamines.[5],[14] Using this method, branched or linear arylated compounds can be obtained, but typically the use of one or even two strongly electron-withdrawing *N*-protecting groups, that attenuate the basicity and coordinating ability of the nitrogen, is necessary for the reaction to occur and to achieve good levels of regioselectivity. Interestingly, the Pd-catalyzed Suzuki, which is a powerful tool for the synthesis of biologically active

and pharmaceutical compounds,[15] has been scarcely used[16] for the synthesis of this class of compounds.

Recently we have reported the regioselective Cu-catalyzed hydroboration of propargyl-functionalized alkynes under aqueous micellar conditions (Scheme 1A).[17],[18] Typically, the reaction was performed using either a NHC-Cu complex as the catalyst to afford the α-arylated product or a $Cu(OAc)_2$/dppe catalytic system to obtain preferentially the β-borylated product. Interestingly, NMeBn-propargylamine and NHBoc-propargylamine resulted in different selectivities using the NHC-Cu catalyst. The potential usefulness of the developed method in two sequential metal-catalyzed reactions was briefly examined, and two examples of an one-pot hydroboration/Suzuki reaction have been reported (Scheme 1A). Key to the success of our protocol was the use of SPGS-550M (Scheme 1B),[19] a surfactant that enabled the desired transformation to occur without using organic solvents despite using water-insoluble reagents.



Scheme 1. A) Previous work from our group. B) Structure of surfactant SPGS-550M. C) This work.

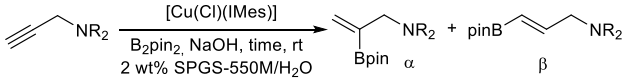
Given the importance of arylated allylamines and encouraged by our successful preliminary results on the combination of the Cu-catalyzed hydroboration of propargylamines with a Pd-catalyzed Suzuki arylation[20],[21] using water as the solvent, we hypothesized that broadening of the scope of the aryl halide used in the Suzuki coupling might result in a general, straightforward and environmentally friendly synthesis of a series of these valuable compounds (Scheme 1C).[22] Herein, we report our results of our study, using a variety of aryl halides as coupling partners. Among the advantages of our protocol are the operationally simplicity of the reaction setup, without the need of inert atmosphere or anhydrous conditions and importantly, the development of a tandem process without isolation of intermediate compounds that obviates even more the use of organic solvents, maximizing the efficiency and minimizing the waste generated. In addition, we have applied our method in a short three-step, one-pot, and environmentally benign synthesis of the pharmaceutically relevant compound naftifine (**1**), starting from commercially available amine **6**.

Results and Discussion

We started our studies investigating the Cu-catalyzed hydroboration of a range of propargylamines (Table 1). We performed the hydroboration under our previously developed conditions,[17] using 5 mol% of [Cu(Cl)(IMes)], 1.1 equiv of B_2pin_2 as the boron source, 5 mol% of NaOH as the base and SPGS-550M/water as the solvent.[23] From our previous work we have already observed that propargylamine and *N*,*N*-dimethyl-propargylamine are not suitable substrates for the hydroboration, since in both cases only small amounts of the borylated product were observed in the crude mixture, probably due to a fast protodeborylation reaction. Moreover, as already observed by Hoveyda, the instability of the product prevented its isolation.[24] Much improved results were found by *N*,*N*-methylbenzyl-propargylamine and gratifyingly the desired product **7** was observed in 71% isolated yield after 2 h, and with an excellent regioselectivity of 95:05 in favor of the β-borylated product (entry 1). The presence of the benzyl group decreases the rate of the protodeborylation reaction. However, performing the reaction in longer times resulted in a decrease in the isolated yield, due to protodeborylation of the product **7** (entry 2). The introduction of a second Bn group at the nitrogen resulted in a slightly better yield but with a decrease in the selectivity (entry 3). A longer linear alkyl chain at the nitrogen is well tolerated and product **9** was obtained as the β-vinylboronate in high selectivity (entry 4). When electron-withdrawing groups were present at the nitrogen, protodeborylation did not occur and an inversion of the regioselectivity was observed in all cases studied (entries 5-11). In most of the examples moderate α-

selectivity was observed and the best result was achieved with *N*-Boc-propargylamine with the product **10** obtained in 85% yield after 20 h and an α:β ratio of 82:18 (entry 6). Since the presence of one Boc group led to the best α-selectivity, a second Boc group was attached (entry 7). Unfortunately, this led to a significant decrease in the selectivity of the reaction.

Table 1. Optimization of the reaction conditions.[a]

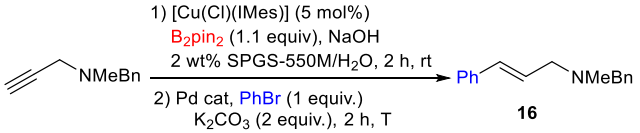


entry	NR_2	time (h)	product, yield(%)	α : β[b]
1[c],[d]	NMeBn	2	**7**, 71	05 : 95
2[c],[d]	NMeBn	20	**7,** 38	05 : 95
3[d]	NBn_2	2	**8**, 78	20 : 80
4[d]	N(*n*Bu)Bn	2	**9**, 60	05 : 95
5[c],[d],[e]	NHBoc	2	**10**, 74	82 : 18
6[c],[d],[e]	NHBoc	20	**10**, 85	82 : 18
7	$NBoc_2$	20	**11**, nd	65 : 35
8[d]	$N(COCF_3)Bn$	20	**12**, 85	80 : 20
9[f]	NHBz	20	**13**, 42	65 : 35
10[f]	NHTs	20	**14**, 60	70 : 30
11[f]	NPhth	20	**15**, 54	65 : 35

[a]Reactions were performed using propargylamine (1.0 equiv), 1.1 equiv of B_2pin_2, 5 mol% NaOH 1 M, 5 mol% of [Cu(Cl)(IMes)] in 0.5 mL of 2 wt% SPGS-550M/H_2O. [b]Determined by ^1H NMR. [c]Previously reported in Ref [17]. [d]Isolated yield. [e]15 mol% NaOH 3 M. [f]NMR yield.

Having identified *N*,*N*-methylbenzyl-propargylamine as the best substrate for the hydroboration reaction, it was used for the sequential hydroboration-Suzuki reaction. Thus, the hydroboration was performed under the optimized conditions and after 2 h, 5 mol% of $PdCl_2(PPh_3)_2$, 2.0 equiv of K_2CO_3 and 1.0 equiv of PhBr were added and the reaction mixture heated at 80ºC for 2 h[17]. Gratifyingly, the desired arylallylamine product **16** was obtained in 65% isolated yield, for the two steps (Table 2, entry 1). Attempts to perform the Suzuki reaction at room temperature resulted in decreased yields, even in longer reactions times (entries 2-3). Reducing the Pd-catalyst loading to 3 mol% resulted in 43% yield (entry 4). In the reaction performed at room temperature for 12 h or using lower amounts of the Pd-catalyst, the desired product **16** is formed alongside significant amounts of the protodeborylation product. These results clearly indicate that when the Suzuki reaction is not efficient enough, the background protodeborylation reaction becomes relevant. When $Pd(PPh_3)_4$ was used, the desired product was obtained in 53% yield (entry 7). Attempts to generate the palladium catalyst from $PdCl_2$ or $Pd(OAc)_2$ and PPh_3 (entries 8-9) led to the formation of the desired product, albeit in lower yields, when compared to $PdCl_2(PPh_3)_2$. Finally, $Pd(OAc)_2$ together the bidentate phosphine dppe, and different palladium catalysts have been tested, and only yields below 20% of the desired product **16** have been obtained (entries 10-13).

Table 2. Optimization of the sequential Hydroboration/Suzuki reaction.

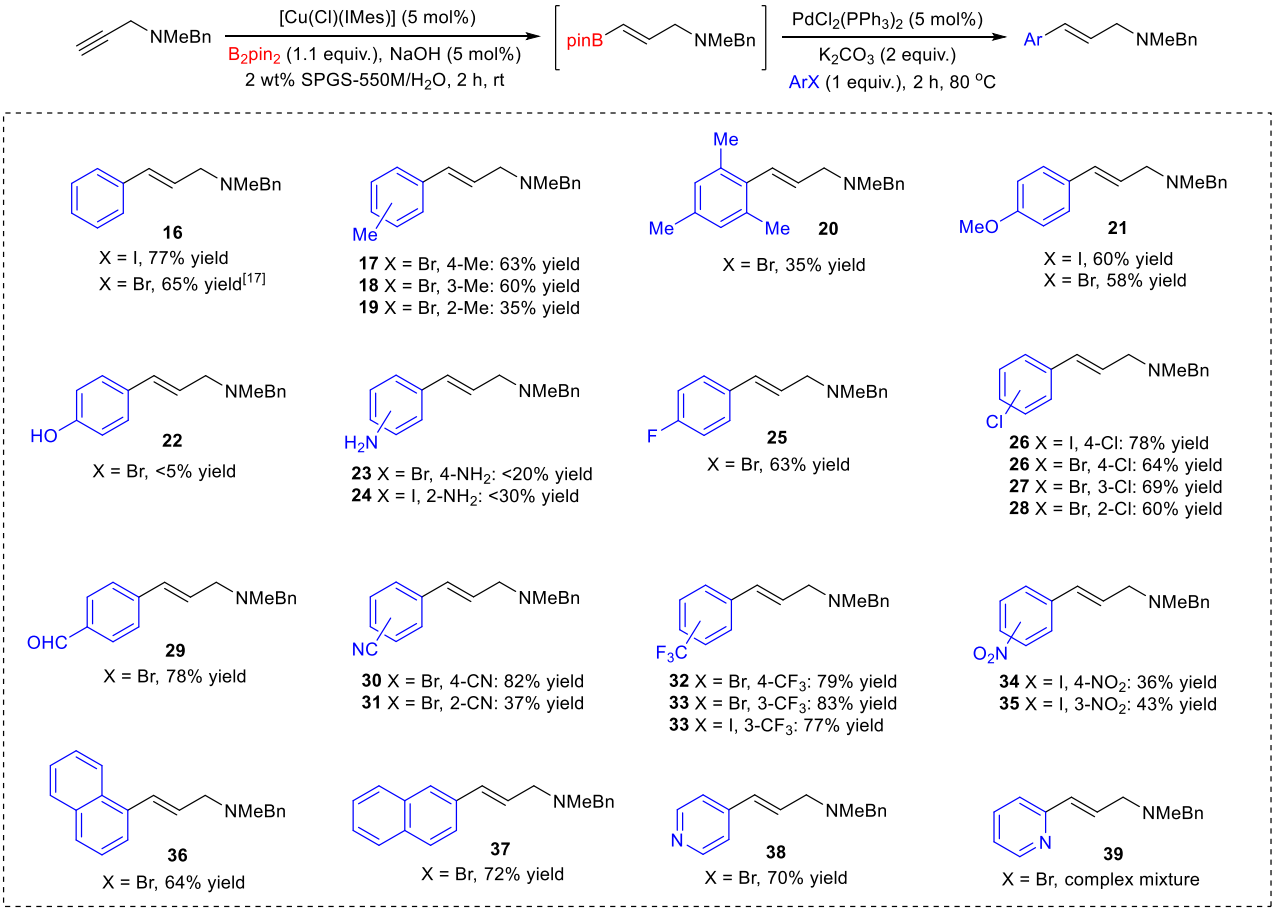


entry	Pd cat (mol%)	T (ºC)	yield (%)[a]
1[b]	$PdCl_2(PPh_3)_2$ (5)	80	65
2	$PdCl_2(PPh_3)_2$ (5)	25	nr
3[c]	$PdCl_2(PPh_3)_2$ (5)	25	<15
4	$PdCl_2(PPh_3)_2$ (3)	80	43
5[d]	$PdCl_2(PPh_3)_2$ (5)	80	49
6[e]	$PdCl_2(PPh_3)_2$ (5)	80	33
7	$Pd(PPh_3)_4$ (5)	80	53
8	$PdCl_2$ (5)/PPh_3 (10)	80	52
9	$Pd(OAc)_2$ (5)/PPh_3 (10)	80	54
10	$Pd(OAc)_2$ (5)/dppe (5)	80	20
11	$PdCl_2(PhCN)_2$ (5)	80	<15
12	Pd_2dba_3 (5)/PPh_3 (10)	80	<15
13	POPd (5)	80	20

[a]Isolated yields. [b]Previously reported in Ref [17]. [c]Reaction perfomed in 12 h. [d]1 equiv of K_2CO_3. [e]2 equiv NaOH instead of K_2CO_3.

With the optimized conditions in hand we examined the scope of the reaction regarding the aryl halide reaction partner (Scheme 2). Replacing the halide from PhBr to PhI resulted in an increase of the yield to 77%. Further studies to expand the scope in respect to aryl halide coupling partner have been carried out. A number of different aryl halides bearing substituents with different steric and electronic effects have been examined as coupling partners in this reaction (Scheme 2).

The weakly electron-donating Me group did not affect the reaction outcome when it was present at *para* and *meta* position of the ArBr. However, when the *ortho* derivative was used a decrease in the yield was observed and product **19** was obtained in 35% yield for the two steps, indicating that steric effects play a role in the reaction. This was further observed when performing the reaction using the more hindered mesitylene derivative as the coupling partner and product **20** was isolated in 35% yield. The stronger electron-donating groups OMe, OH and NH_2 were tested. Good yields were obtained with the 4-OMe group (product **21**, X = I, 60%; X = Br, 58%), while aryl halides bearing 4-OH, 4-NH_2 and 2-NH_2 groups resulted in low yields. The presence of weak electron-withdrawing groups such as F and Cl did not have any significant influence on the Suzuki reaction, regardless of their position in the aromatic ring (compare compounds **26**-**28**).



Scheme 2. Scope of the one-pot dual-metal catalytic synthesis of arylallylamines.

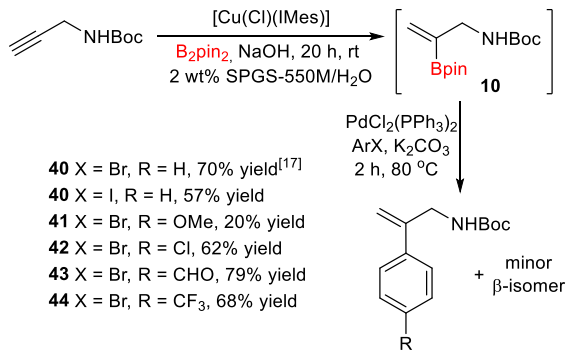
The hydroboration reaction followed by Suzuki coupling in micellar conditions allows for the presence a range of functional groups at the aryl halide such as aldehyde **29**, nitrile **30-31**, trifluoromethyl **32-33**, nitro **34-35**. Notably, the electron-deficient aryl halides resulted in very good yields of the corresponding products **29-33**. In addition, α- and β-naphthyl derivatives have also been efficiently used as coupling partners, delivering the corresponding products **36** and **37** in 64% and 72%, respectively. Finally, when 4-bromopyridine was used as the coupling partner, the corresponding product **38** was obtained in an excellent yield of 70% (two steps). Unfortunately, when 2-bromopyridine was used a complex mixture resulted, and the desired product **39** was not isolated.

Worth to mention is that this dual-metal catalysis was performed entirely in water as the solvent and neither solvent switch nor addition of organic co-solvent was needed to obtain the desired product. This is in contrast with other metal-catalyzed methods for the synthesis of these molecules, in which anhydrous organic solvents are used.[7-10,12-13] Additional advantage of our method relies on the fact that the linear arylated product can be obtained using substrates in which two alkyl groups are attached to the nitrogen atom, therefore minimizing protection/deprotection or non-strategic redox manipulations.

Another interesting observation regarding the overall yield of our one-pot, two-step reaction has been made. When the hydroboration of *N*-MeBn-propargylamine was performed, vinylboronate **7** was isolated in 71%, after purification (Table 1, entry 3). In several cases, however, when the sequential hydroboration-Suzuki protocol was used, higher yields of the final product have been achieved (*e.g.* **29**, 78% yield; **30**, 82% yield, **33**, 83% yield). We attribute this increased yield to some loss of **7** in the purification and also to the fact that in the hydroboration conditions part of the pinacolboronate product might have been hydrolyzed to the vinylboronic acid derivative. Albeit the isolation and purification of this compound is somewhat difficult, presumably being responsible for a decrease in the isolated yield of **7**, it is a competent coupling partner in the Suzuki reaction. Therefore, combining both reactions in a one-pot protocol has another advantage besides its operational simplicity.

In addition, our protocol was also successfully employed using *N*-Boc-propargylamine as the substrate (Scheme 3). In this case, however, the opposite regiochemistry was observed, since the major product in the hydroboration step is the α-vinylboronate **10**. Combining the Cu-catalyzed

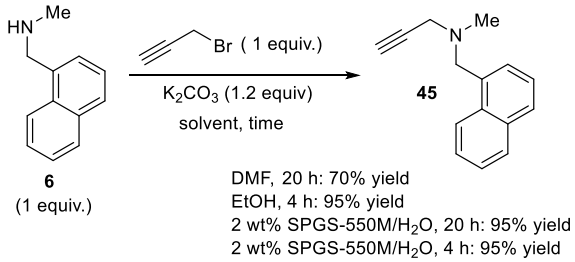
hydroboration with the Suzuki coupling efficiently delivered the desired products **40**-**44** typically in good overall yields, ranging from 57-79% yield. Exception was found for compound **41**, with the electron-rich methoxy group at the aryl halide, with the product being formed in only 20% yield.



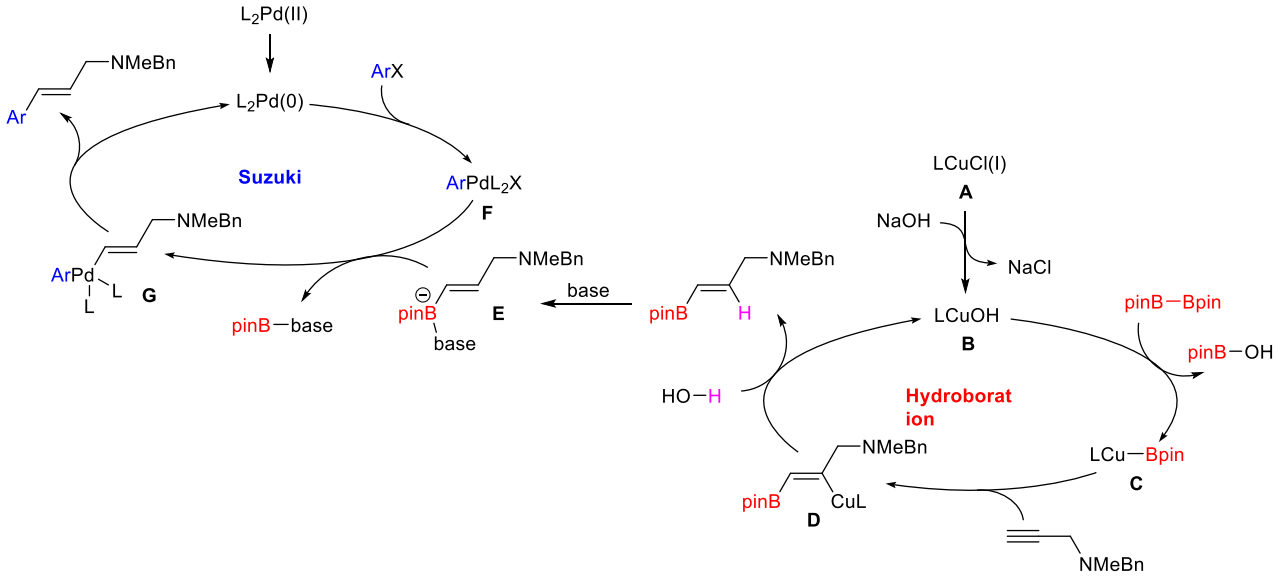
Scheme 3. Scope of the reaction using *N*-Boc propargylamine.

The one-pot synthesis of the arylallylamines starts with the Cu-catalyzed hydroboration of the alkyne (Scheme 4).[25] The proposed catalytic cycle involves the initial formation of a nucleophilic species of boron **C**, generated by the reaction of diboron bispinacolate with copper species **B** (formed *in situ*). Species **C** then reacts with the alkyne *via* a *syn*-borocupration reaction yielding the vinylcopper intermediate **D**. Depending on the nature of the substituents at the amine a difference on the regioselectivity is observed. Finally, protonation of intermediate **D** leads to the formation of the vinylboronate, which enters the second catalytic cycle, after activation by base (**E**). Transmetallation with species **F**, followed by reductive elimination of **G**, delivers the final product and regenerates the active Pd catalyst.

We applied our method in a short synthesis of the potent antifungal agent naftifine (**1**). First, *N*-methyl-α-naphthylamine (**6**) was reacted with propargyl bromide to afford the propargylamine **45** (Scheme 5). Typical conditions employ DMF as the solvent[14] and the product **45** was obtained in 70% yield. Considering that DMF is not a green solvent, we briefly examined whether we could replace it by a more environmentally friendly solvent. When EtOH was used, the desired product was formed in 95% yield, after 4 h. Gratifyingly we found that performing the reaction under micellar conditions, **45** was also obtained in excellent yield. This result opened the possibility of performing the synthesis of naftifine in a single vessel, starting from **6**, involving three different reaction, using water as the solvent.

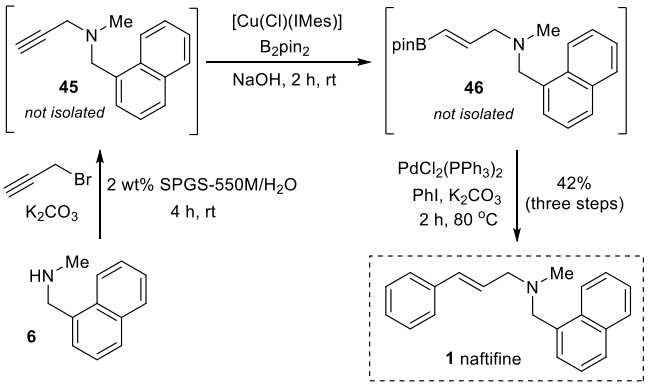


Scheme 5. Optimization of the synthesis of **45**



Scheme 4. Proposed catalytic cycles

Reducing our plan to practice, amine **6** was reacted with propargyl bromide in the presence of K_2CO_3 as base, and using SPGS-550M/water as the solvent (Scheme 6). After 4 h at room temperature, the NHC-Cu(I) catalyst, B_2pin_2 and NaOH were added to the reaction to promote the hydroboration of the propargylamine **45** which was generated in situ. After additional 2 h, the hydroboration was completed and the Pd-catalyst, PhI, and K_2CO_3 have been added to the reaction mixture, without isolation of the vinylboronate intermediate **46**. After further reaction for 2 h at 80 °C, naftifine was isolated in 42% yield (three steps) in a short, efficient and environmentally benign synthesis of this valuable pharmaceutical compound. In order to compare, we have also carried out the synthesis using isolated, pure **45**. In this case, naftifine (**1**) was obtained in 52% yield, after the hydroboration/Suzuki sequence.



Scheme 6. Synthesis of naftifine (**1**)

Conclusions

In summary, we have developed an efficient method for the one-pot dual-metal catalytic synthesis of arylallylamines, through the combination of a Cu-catalyzed hydroboration of a propargylamine followed by a Pd-catalyzed Suzuki arylation. The developed protocol is tolerant to a range of functional groups in the arylation step, including aldehyde, nitrile, nitro, trifluoromethyl, and halide. Importantly, the reaction sequence was entirely performed in water as the solvent, in the presence of small amounts of SPGS-550M surfactant, without the need of solvent switch or addition of organic co-solvents, rendering it operationally simple and environmentally benign. The usefulness of this methodology was highlighted in a straightforward synthesis of the pharmaceutically important compound naftifine.

Experimental Section

Representative Experimental Procedure for the one-pot Hydroboration-Suzuki Coupling. A 5 mL vial equipped with a magnetic stir bar was charged with [Cu(Cl)(IMes)] (5 mol%, 0.025 mmol, 10.1 mg), B_2pin_2 (1.1 equiv., 0.55 mmol, 139.7 mg), propargylamine (1.0 equiv., 0.50 mmol), SPGS-550M (2%, w/w, 0.50 mL) and NaOH 1 $molL^{-1}$ (25 µL). The resulting mixture was vigorously strirred at room temperature for the time indicated. After this period, $[Pd(Cl)_2(PPh_3)_2]$ (5 mol%, 0.025 mmol, 17.5 mg), K_2CO_3 (2.0 equiv., 1.00 mmol, 138.2 mg), and aryl halide (1.0 equiv., 0.50 mmol) were added. The resulting mixture was strirred at 80 °C for 2 h. Then, the reaction was allowed to reach room temperature and anhydrous Na_2SO_4 was added. The solid mixture was washed with ethyl acetate (2 x 1 mL) and the organic layer was transferred to a round-bottomed flask. The solvent was removed under reduced pressure and the crude product was purified by column chromatography using hexane:EtOAc as an eluent to afford the desired product. In a few cases small contamination of the product with pinacol could be removed azeotropically with water on a rotary evaporator.[26]

Acknowledgements

This work was supported by CNPq, CAPES, and INCT-Catálise. We are also grateful to Prof. Luiz C. Dias (IQ-Unicamp) for the gift of chemicals.

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10.1002/adsc.201700094

UPDATE

Combining Copper-Catalyzed Hydroboration with Palladium-Catalyzed Suzuki Coupling for the One-pot Synthesis of Arylallylamines under Micellar Conditions

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