

Ligand-Free (*Z*)-Selective Transfer Semihydrogenation of Alkynes Catalyzed by *in situ* Generated Oxidizable Copper Nanoparticles

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ABSTRACT: Herein, we present (*Z*)-selective transfer semihydrogenation of alkynes based on *in situ* generated Cu NPs in the presence of hydrogen donors, such as ammonia-borane and a protic solvent. This environmentally-friendly method is characterized by operational simplicity combined with high stereo- and chemoselectivity and functional group compatibility. Auto-oxidation of Cu NPs after the semihydrogenation reaction is completed results in the formation of water-soluble ammonia complex, so that the catalyst may be reused several times by simple phase-separation with no need of any special regeneration process. Formed $\text{NH}_4\text{B(OR)}_4$ can be easily transformed back to ammonia-borane or to boric acid. In addition, one-pot tandem sequence involving Suzuki reaction followed by semihydrogenation was presented.

Among the various methods of stereocontrolled olefin synthesis, semihydrogenation of a triple C–C bond seems to be one of the most efficient and straightforward approaches. The very first catalytic system capable of (*Z*)-selective partial hydrogenation of alkynes was developed by Herbert Lindlar in 1952. The Lindlar catalyst is composed of a poisoned Pd/CaCO₃.¹ Complementary, the best known coursebook method for (*E*)-selective reduction is Birch-reaction involving alkali metal in liquid ammonia.^{2–3} Due to known limitations of these well-established methods, new efficient solutions for stereoselective semihydrogenation are sought. In terms of hydrogen source, both direct⁴ or transfer semihydrogenation have been tested. The former is waste-free in contrast to the latter, however, demanding gaseous hydrogen use, often under high pressure and thus might be inconvenient to an experimenter. Hitherto, several hydrogen sources were utilized in alkynes semihydrogenation, namely, water⁵, formic acid⁶, alcohols⁷, silanes⁸ or ammonia-borane⁹. Especially, interest in the last one is observed, due to its high hydrogen capacity, non-toxicity and easy applicability.^{10, –12} Semireduction may involve homogeneous or heterogeneous catalytic process. Superiority of the latter is the easier separation of the catalyst from the reaction mixture so that it may be recycled. There are several papers concerning the heterogeneous transfer semihydrogenation of triple C–C bond. One of them was published in 2010, by Liu et al. Authors applied Hantzsch ester in the presence of Pd/C to obtain alkenes in moderate to good yields.¹³ In 2014, Lipshutz described a catalytic system based on Pd nanoparticles (NPs) formed from Pd(OAc)₂ using sodium borohydride, water and a surfactant. The system is capable of (*Z*)-selective olefin production in high yields.¹⁴ Asao group utilized unsupported nanoporous gold as a catalyst of alkynes (*Z*)-semihydrogenation in the presence of formic acid (2014). The methodology was successfully applied towards substrates bearing various functional groups.¹⁵ In 2015, Stratakis et al. reported on (*Z*)-selective catalytic system involving supported AuNPs. Authors proved that ammonia-borane and EtOH are hydrogen donors in this transformation.¹⁶ Similar catalyst was applied

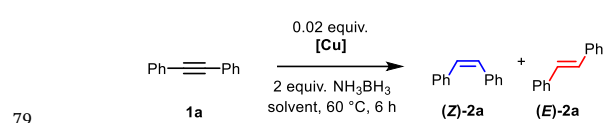
by Cao in 2016, to carry out (*Z*)-semihydrogenation of alkynes using formic acid.¹⁷ Analogous approach may be found in Xu et al.'s paper (2016), with the difference that formic acid was replaced with ammonium formate.¹⁸ In 2017, Bai et al. presented catalytic (*Z*)-selective system based on generated *in situ* NiNPs from NiCl₂ using sodium borohydride and MeOH. The simplicity of this method is remarkable, however over-reduction process seems to be strictly dependent on catalyst loading and reaction time.¹⁹ In 2018, two groups used PdNPs in alkynes (*Z*)-selective semireduction. Yang et al. carried out this transformation in a presence of silane and water mixture²⁰ while Endo et al. developed system using PdCl₂, base and formic acid.²¹ In the same year, synthesized polyhedral copper(I) oxide was used by Huang et al. to achieve transfer (*Z*)-semihydrogenation of two alkynes in a presence of ammonia-borane and EtOH. In contrast to previous papers, the authors proved that alcohol is not a hydrogen donor.²² Recent example of (*Z*)-selective system was proposed by Balaraman et al. in 2020. *N*-graphitic modified CoNPs were capable of alkynes semireduction using ammonia-borane and MeOH.²³ It is worth pointing out that the presented above methods are not free of limitations (concerning e.g. stereoselectivity, over-reduction, functional group tolerance or applicability) and despite such a great progress in the field of alkyne semihydrogenation better solutions are yet to be discovered.

Results

Optimization of the reaction conditions. Our quest for new, simple but efficient and highly stereoselective methods of triple C–C bond reduction stem from our previous studies concerning ruthenium complexes.²⁴ During the present research, we found that copper(II) chloride in a presence of ammonia-borane and methanol is capable of highly (*Z*)-selective semihydrogenation of diphenylacetylene (Table 1, entry 1). This observation encouraged us to test different commercially available copper complexes, which led to similar results of the model reaction (Table 1, entries 2–6). In contrast, the use of CuI afforded low conversion (Table 1, entry 7). This may be caused

by an inert character of this complex in comparison to other Cu(I) halides.²⁵ Due to easy applicability, CuCl₂·2H₂O was chosen for further studies.

THF, other copper complexes were tested and gave similar results to the reactions with MeOH (Table 1, entries 21-24).



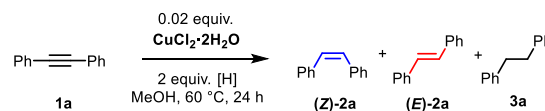
Entry	Catalyst	Solvent	Conversion [%] ^f	Z:E ^f
1	CuCl ₂	MeOH	99	98:2
2	CuCl ₂ ·2H ₂ O	MeOH	100	98:2
3	Cu(NO ₃) ₂ ·2H ₂ O	MeOH	100	98:2
4	Cu(OTf) ₂	MeOH	93	98:2
5	Cu(acac) ₂	MeOH	100	97:3
6	CuCl	MeOH	100	98:2
7 ^b	CuI	MeOH	12	90:10
8 ^b	CuCl ₂ ·2H ₂ O	MeOH	100	98:2
9 ^c	CuCl ₂ ·2H ₂ O	MeOH	100	98:2
10 ^d	CuCl ₂ ·2H ₂ O	MeOH	76	98:2
11	CuCl ₂ ·2H ₂ O	EtOH	74	97:3
12	CuCl ₂ ·2H ₂ O	<i>i</i> PrOH	64	97:3
13 ^e	CuCl ₂ ·2H ₂ O	THF	51	—
14 ^e	CuCl ₂ ·2H ₂ O	DMF	19	—
15	CuCl ₂ ·2H ₂ O	MeCN	18	—
16	CuCl ₂ ·2H ₂ O	H ₂ O + MeCN	61	98:2
17	CuCl ₂ ·2H ₂ O	H ₂ O + DMF	93	98:2
18	CuCl ₂ ·2H ₂ O	H ₂ O + AcOEt	100	98:2
19	CuCl ₂ ·2H ₂ O	H ₂ O + <i>n</i> -hexane	5	—
20	CuCl ₂ ·2H ₂ O	H ₂ O + THF	100	98:2
21	CuCl	H ₂ O + THF	100	98:2
22	CuI	H ₂ O + THF	39	98:2
23	Cu(NO ₃) ₂ ·2H ₂ O	H ₂ O + THF	100	98:2
24	Cu(acac) ₂	H ₂ O + THF	98	98:2

80 **Table 1 | Screening of Copper Catalysts and Solvents.** ^aConditions: 0.02 equiv. [Cu], 2 equiv. NH₃BH₃, 60 °C 6 h, ^b0.01 equiv. [Cu], ^c0.005 equiv. [Cu], ^d0.0025 equiv. [Cu], ^eNo semihydrogenation products, ^fConversion and products distribution were determined by GC analysis

84 Catalyst loading as low as 0.5 mol% was found to be successful (Table 1, entries 8-9) while the amount of 0.25 mol% did not provide full conversion (Table 1, entry 10). Changing methanol for its homologues led to lower conversions. Obtained results indicate that the reaction rate decreases with the longer carbon chain of alcohol which affects its acidity (Table 1, entries 11-12). In the case of aprotic solvents, like THF, DMF, or MeCN, no semihydrogenation products were found in the reaction mixtures (Table 1, entries 13-15). Finally, the model reaction was carried out in mixtures of water and organic solvent to allow an equal distribution of the lipophilic substrate in the reaction mixture. H₂O + AcOEt and H₂O + THF turned out to be the most efficient (Table 1, entries 18, 20). The former allows semihydrogenation in a biphasic system, while the latter enables the reaction in emulsion. In mixtures of water with DMF or MeCN, the reduction is slower (Table 1, entries 16-17). In the case of H₂O + *n*-hexane, no products of semihydrogenation were detected (Table 1, entry 19). For the system H₂O +

104 In the next step of optimization of the model reaction conditions, we attempted to search for the most convenient and effective hydrogen source. The results indicated that ammonia-borane used in >1 equiv. is the most effective. In this case, the amount of the over-reduction product was negligible (Table 2, entries 1-3), while the use of dimethylamine-borane and *tert*-butylamine-borane led to higher amounts of the corresponding alkane (Table 2, entries 4-5). It should be noted that the semihydrogenation process is possible only when at least one hydrogen atom is attached to both the nitrogen and boron atoms of ammonia-borane derivative R₃N-BR₃. Accordingly, the application of trimethylamine-borane or ammonia-triphenylborane failed to provide products of triple C–C bond reduction (Table 2, entries 6-7). In the case of sodium borohydride used as a hydrogen source, no semihydrogenation was observed.

Substrates scope. Having the optimized conditions in hand, the scope of different alkynes was tested (Fig. 1). In general, the semihydrogenation reaction was carried out using CuCl₂·2H₂O (0.02 equiv.), ammonia-borane (2 equiv.) in a mixture of water and THF at 60 °C. Functional group tolerance was tested with tolans bearing different substituents. The results showed that the studied catalytic system may be successfully applied to substrates with both electron-donating and electron-withdrawing groups. (*Z*)-Stilbene and its derivatives with alkyl or alkoxy groups ((*Z*)-2a-e) were obtained in very good yield and selectivity. In the case of halogenated substrates, THF was replaced with AcOEt, to enable more effective semihydrogenation to corresponding olefins. Importantly, no products of protodehalogenation were detected (*Z*)-2f-h). Moreover, the catalytic system is compatible with alkynes bearing groups prone to reduction, such as ester, amide or nitrile ((*Z*)-2i-k). The presented method can be also successfully applied towards sulfur-containing compounds, such as sulfone or even rather labile sulfonate group bearing alkynes ((*Z*)-2l-m).

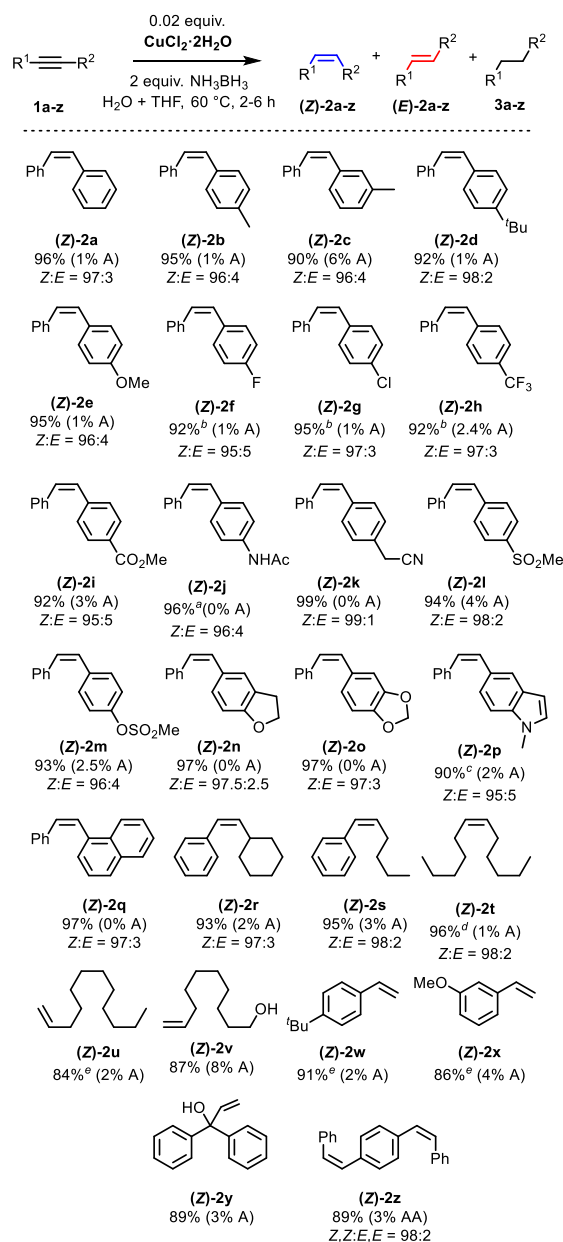


Entry	Hydrogen source	Conversion [%] ^e	Z:E:A ^e
1	NH ₃ BH ₃	100	97:2:1
2 ^b	NH ₃ BH ₃	100	97:2:1
3 ^c	NH ₃ BH ₃	81	76:2:1
4	Me ₂ NHBH ₃	100	96:2:2
5	<i>t</i> BuNH ₂ BH ₃	100	90:2:8
6 ^d	NMe ₃ BH ₃	26	—
7 ^d	NH ₃ BPh ₃	0	—
8 ^d	NaBH ₄	5	—

Table 2 | Screening of Hydrogen Sources. ^aConditions: 0.02 equiv. CuCl₂·2H₂O, 2 equiv. [H], 60 °C 24 h. ^b1.5 equiv. NH₃BH₃. ^c1 equiv. NH₃BH₃. ^dNo semihydrogenation products. ^eConversion and products distribution were determined by GC analysis. A – over-reduction product.

Semihydrogenation of heterocyclic or bicyclic substrates afforded the corresponding stilbenes in also high yields and selectivities ((*Z*)-2n-q). Reaction with indole derivative (1p)

required higher loading of the catalyst and ammonia-borane and higher temperature, but proceeded in a satisfactory manner, too. Broader applicability of the described method was proved by the reduction of both aryl-alkyl and alkyl-alkyl alkynes which were smoothly transformed into the corresponding alkenes ((*Z*)-**2r-t**).

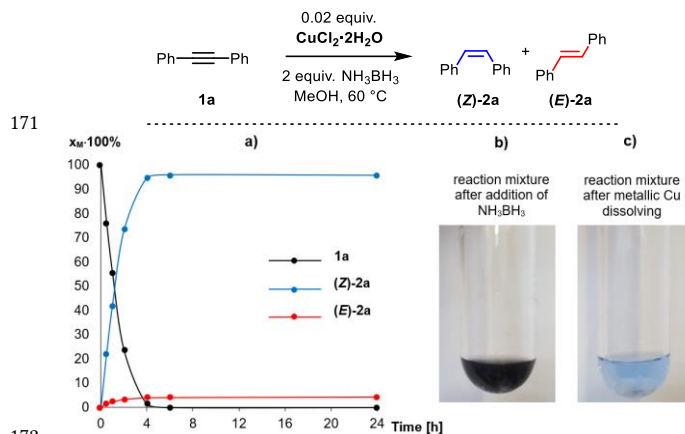


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Fig. 1 | Substrate Scope and Functional Groups Tolerance of The Title Reaction. ^aGeneral Conditions: 0.02 equiv. $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$, 2 equiv. NH_3BH_3 , $\text{H}_2\text{O} + \text{THF}$, 60 °C. Isolated yields. Products distribution was determined by GC analysis. ^bA – over-reduction product. ^cSolvent: $\text{H}_2\text{O} + \text{AcOEt}$. ^dSolvent: $\text{H}_2\text{O} + 1,4$ -dioxane, 90 °C. ^eSolvent: MeOH. ^f0.04 equiv. $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$, 3 equiv. NH_3BH_3 80 °C.

In the case of dodec-6-yne (**1t**), MeOH was used as a solvent. Furthermore, the reactions with terminal alkynes under the defined conditions provided olefins in good yields ((*Z*)-**2u-y**). Of note, some substrates demanded higher amounts of a catalyst and ammonia-borane complex at higher temperature to be effectively reduced (**1u**, **1w-x**). In some cases, side products of

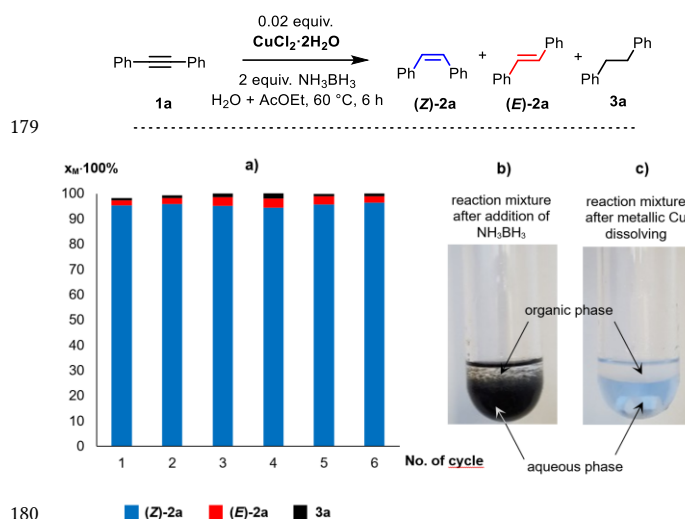
presumably Glaser-Hay coupling and the further reduction were noticed. Nevertheless, in the highly reducing environment the semihydrogenation process was overwhelmingly favorable. Finally, the catalytic system may be applied in the efficient synthesis of dienes ((*Z*)-**2z**).



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Fig. 2 | Reaction Profile for 1a Semihydrogenation. ^aConditions: 0.02 equiv. $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$, 2 equiv. NH_3BH_3 , MeOH, 60 °C. Conversion and products distribution were determined by GC analysis.

It is noteworthy that in the vast majority of the tested alkynes over-reduction of triple C–C bond was negligible, and all products were isolated in pure form by a simple biphasic extraction.



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Fig. 3 | Recyclability Test. ^aConditions: 0.02 equiv. $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$, 2 equiv. NH_3BH_3 , $\text{H}_2\text{O} + \text{AcOEt}$, 60 °C. Products distribution was determined by GC analysis.

Mechanistic studies. To understand nature of the title semihydrogenation process, the reaction of diphenylacetylene (**1a**) reduction was analyzed in time using GC technique (Fig. 2a). The resulted time-conversion profile indicates that substrate **1a** is consumed within 6 h to produce (*Z*)-stilbene ((*Z*)-**2a**). Very small amount of initially produced (*E*)-stilbene ((*E*)-**2a**) is not altered even if the reaction is prolonged (for comparison see Ru-based system previously studied by us²⁴).

The pivotal point in our studies was the observation of the reaction mixture which turns black after the addition of ammonia-borane (Fig. 2b) to change its color again to light-blue

in time (Fig. 2c). The former is connected with copper nanoparticles production, while the latter is presumably caused by spontaneous oxidation of copper(0) in air²⁶ and the formation of a water-soluble blue-colored complex with ammonia. This intriguing phenomenon might be useful in terms of indication of the reaction completion and the catalyst recycling. The same portion of catalyst may in theory be used to carry out a number of subsequent semihydrogenation reactions. To reduce such possibility to reality we attempted to run the semihydrogenation of **1a** for multiple times with one portion of the catalyst using a biphasic system composed of water and an organic solvent (AcOEt) (Fig. 3a). After each reaction cycle, when the initial black color of the mixture (Fig. 3b) turns to light-blue (Fig. 3c) the water phase containing the blue Cu(II)-ammonia complex was separated and reused. After removal of organic phase, and washing the aqueous one (which contains water-soluble copper complex) with AcOEt, semihydrogenation of another portion of substrate is made in the same vessel. No deterioration of catalytic activity was noticed over six runs under such conditions (Fig. 3a). In contrast to previously reported nanoparticles-based catalytic systems, the generated *in situ* catalyst does not require any prior regeneration process (centrifugation, filtration, washing, drying, etc.) before being recycled.

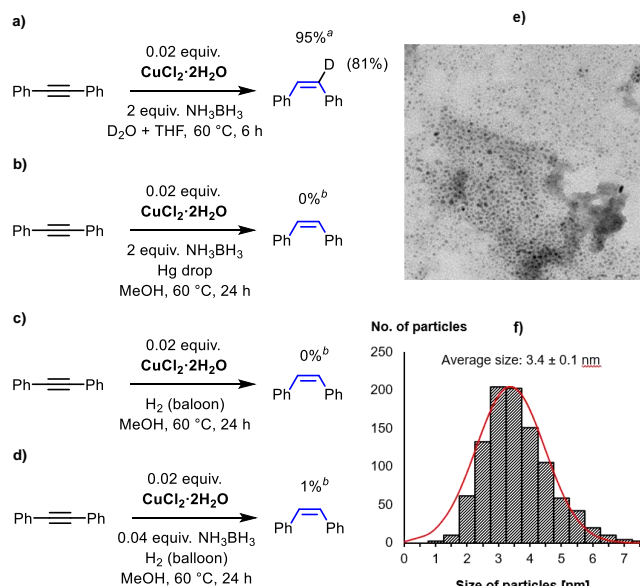


Fig. 4 | Mechanistic Experiments. ^aIsolated yield. ^bGC yield.

Some mechanistic studies were conducted to propose a plausible explanation of the studied semihydrogenation process. Firstly, deuterium labeling experiment with D₂O brought mono-deuterated (*Z*)-stilbene (Fig. 4a). This outcome is consistent with previous observations (Table 1) indicating that the protic solvent acts as a donor of the hydrogen atom. To confirm that copper nanoparticles are produced during the semihydrogenation reaction, mercury-drop test was carried out. As we found, mercury effectively scavenged CuNPs to form amalgam and thus prevented semihydrogenation to proceed (Fig. 4b). Presence of Cu-NPs was also proved by means of transition electron microscopy (TEM) (Fig. 4e). An analysis of TEM images revealed that the average particle size was 3.4 ± 0.1 nm (Fig. 4f). Next, we studied the possibility that *in situ* formed gaseous hydrogen is the actual hydrogenation agent (it was observed that metal-NPs in a presence of a protic solvent can decompose ammonia-borane with the evolution of hydrogen

occurs¹⁰). To exclude the participation of gaseous hydrogen in the semihydrogenation process, two model reactions with gaseous H₂ were conducted. Both of these experiments did not yield the expected product, even in the case where a catalytic amount of ammonia-borane led to the formation of copper nanoparticles (Fig. 4c-d). Although Fedorov et al. proved that CuNPs are capable of direct hydrogenation of alkynes to alkanes, they used a supported catalyst on silica and higher pressure of gaseous hydrogen.^{4h}

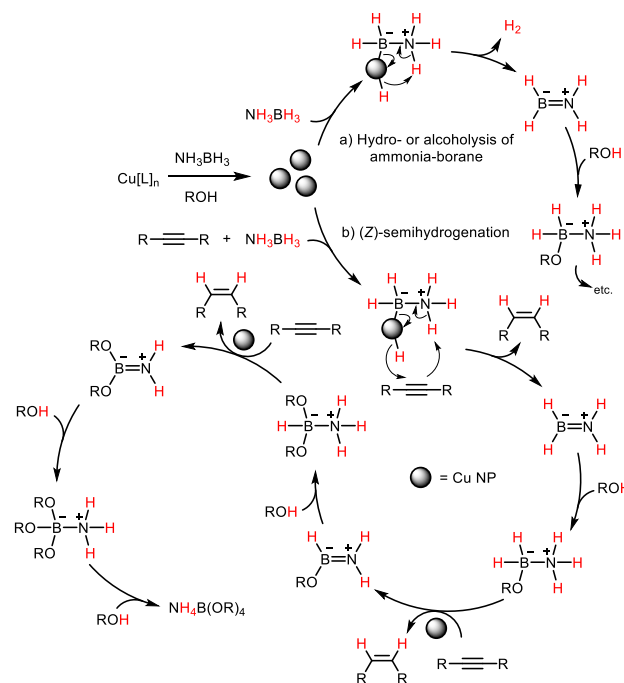


Fig. 5 | Proposed Mechanism.

Taking into account all results of the carried out experiments, a plausible mechanism might be proposed (Fig. 5). This proposition is in part inspired by Stratakis paper.¹⁶ The first step is the reduction of copper complex to CuNPs which participate later in two reactions. The first one is hydro- or alcoholysis of ammonia-borane, depending on the solvent used. This is backed by the noticeable gas evolution during the reaction and explains why an excess of ammonia-borane is necessary. The second cycle involves semihydrogenation of an alkyne. First, incorporation of two hydrogen atoms into a triple C-C bond results in the production of alkene and a NH₂BH₂ moiety. Addition of a protic solvent to a double B-N bond leads to the formation of an ammonia-borane derivative and the whole process repeats until there are no hydrogen atoms attached to a boron atom. Such produced NH₃B(OR)₃ may undergo further transformations to other boron species and can be easily transformed back to ammonia-borane or to boric acid.¹⁰ Different reactivities of alcohols in semihydrogenation suggest that O-H bond cleavage occurs (Table 1, entries 11-12). During the process, some amount of ammonia is produced, of which an odor is perceptible.¹⁰ The anticipated mechanism explicates necessity of protic solvent use as well as an ammonia-borane derivative containing at least one hydrogen atom attached to both nitrogen and boron atoms. Hydrolysis of ammonia-borane might be perceived as a concerted process of dissociation of B-N bond and release of hydrogen through hydrolysis of BH₃.²⁷ However, this path should be excluded because in this case, use of NMe₃BH₃ should lead to the reduction

of alkyne while no hydrogenation products were detected whatsoever (Table 2, entry 6).

Copper is widely used in many C–C coupling reactions as an alternative to the expensive palladium catalysts.²⁸ This inspired us to check out the possibility of a tandem sequence which includes copper-catalyzed C–C coupling and a subsequent copper-catalyzed semihydrogenation under one-pot conditions (Fig. 6). In order to try this, a slightly modified Wang’s protocol of Suzuki reaction was used.²⁹ In a presence of CuI (0.1 equiv.) and 8-hydroxyquinoline (0.2 equiv.) phenyl boronic acid and 2-bromo-1-phenylacetylene were transformed into diphenylacetylene **1a**. Once this reaction was complete, ammonia-borane was added to the reaction mixture to yield (*Z*)-stilbene in an overall yield of 74%. After ammonia-borane addition, the mixture turned black, which indicates the reduction of Cu species to metallic copper. Satisfactorily, the semihydrogenation proceeded well despite the use of a less active copper precursor (CuI, see Table 1, entry 7). This tandem sequence, yielding (*Z*)-alkenes might be seen as a complementary method to the well-known Heck reaction which brings (*E*)-olefins and is the subject of our current studies.

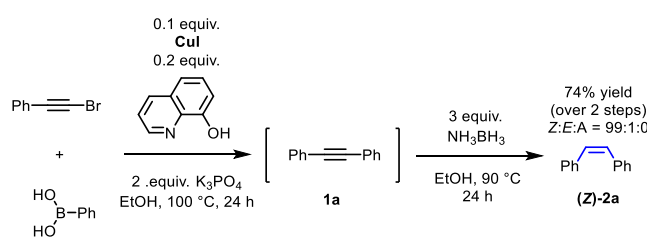


Fig. 6 | One-pot Tandem Sequence: Suzuki Coupling Followed by Semihydrogenation of Triple C–C Bond. ^aYield and products distribution was determined by GC analysis. A – over-reduction product.

Conclusions

In summary, a heterogenic, ligand-free Cu-based catalytic system for (*Z*)-selective semihydrogenation of triple C–C bonds was developed. This catalyst consists of copper nanoparticles generated *in situ* from simple copper salts (e.g. CuCl₂) while ammonia-borane/a protic solvent acts as a hydrogen donor. The described system is characterized by high stereo- and chemoselectivity and may find application in the semihydrogenation of different types of alkynes (aryl-aryl, aryl-alkyl, alkyl-alkyl, terminal or diynes) substituted with a number of “problematic” functionalities such as halogen atoms, nitro, cyano or sulfur groups. Over-reduction of a triple C–C bond is negligible even if the reaction is prolonged. The purification process involves extraction only, so this reaction is operationally simple and user-friendly. Most notably, the formation of CuNPs is followed by their oxidation to form blue-colored water-soluble Cu(II)-ammonia complex which also indicates reaction completion. This phenomenon was utilized by us for catalyst recycling, which was achieved by simple separating and reusing the copper containing aqueous phase (importantly, *no additional treatment nor regeneration of the catalyst was needed before reuse*). One portion of the catalyst was thus sufficient to carry out the semihydrogenation reaction in the biphasic system at least six times without deterioration of its activity (*in fact a fresh portion of CuNPs is formed de novo in every recycle step*). Based on the results of carried out model experiments and the literature precedence, a plausible mechanism was proposed. Catalytic activity of copper in C–C coupling reactions was utilized also to conduct a one-pot tandem sequence involving Suzuki reaction followed by

semihydrogenation of the produced alkyne. The developed semihydrogenation protocol based on oxidizable nanoparticles is environmentally friendly and follows green chemistry rules. If needed, also NH₄B(OR)₄ can be easily transformed back to ammonia-borane or to boric acid.¹⁰ We believe that this methodology would constitute an interesting alternative to already published methods.

Methods

General procedure for alkynes semihydrogenation: A vial was charged with alkyne (1 equiv.), solvent and CuCl₂·2H₂O (0.02 equiv.). Subsequently, ammonia-borane (2 equiv.), solvent and water (in the case of reaction carried out in water) were added to the solution. The mixture was stirred at 60 °C for 2–24 h. After completion of the reaction, which was indicated by GC or TLC, the mixture was quenched with water and the aqueous phase was extracted with DCM. The combined extracts were dried over Na₂SO₄ and the solvents were evaporated under reduced pressure to obtain the pure product.

Data availability

The findings of this study are available within the paper and its Supplementary Information.

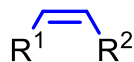
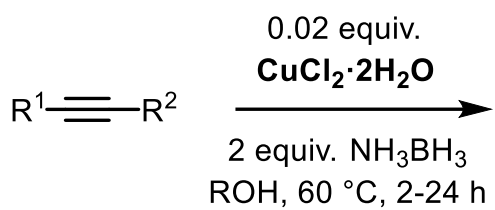
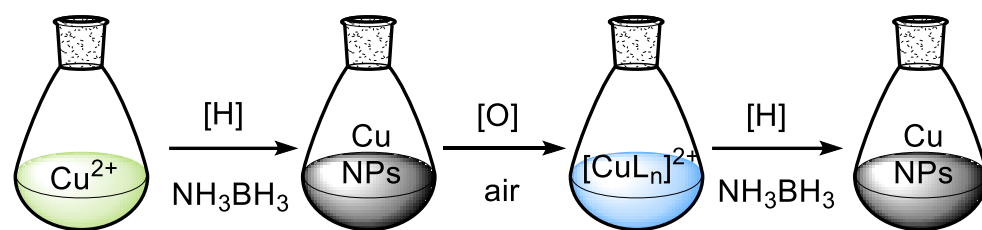
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- very good selectivity
- yields up to 99%
- no over-reduction
- easy purification
- catalyst generated *in situ*
- reusable catalyst
- color indication of reaction end
- tandem process possible