Accepted Manuscript

Inexpensive and rapid hydrogenation catalyst from $CuSO_4/CoCl_2$ — chemoselective reduction of alkenes and alkynes in the presence of benzyl protecting groups

Mario Ficker, Søren Wedel Svenningsen, Thomas Larribeau, Jørn B. Christensen

PII: DOI: Reference:	S0040-4039(18)30196-5 https://doi.org/10.1016/j.tetlet.2018.02.026 TETL 49711
To appear in:	Tetrahedron Letters
Received Date: Revised Date: Accepted Date:	14 December 20176 February 20189 February 2018



Please cite this article as: Ficker, M., Svenningsen, S.W., Larribeau, T., Christensen, J.B., Inexpensive and rapid hydrogenation catalyst from $CuSO_4/CoCl_2$ — chemoselective reduction of alkenes and alkynes in the presence of benzyl protecting groups, *Tetrahedron Letters* (2018), doi: https://doi.org/10.1016/j.tetlet.2018.02.026

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Inexpensive and rapid hydrogenation catalyst from $CuSO_4/CoCl_2$ chemoselective reduction of alkenes and alkynes in the presence of benzyl protecting groups

Mario Ficker,[†] Søren Wedel Svenningsen,[†] Thomas Larribeau, Jørn B. Christensen*

Department of Chemistry, University of Copenhagen, Thorvaldsensvej 40, Frederiksberg, DK-

- 1871 Denmark
- *corresponding author, e-mail: jbc@chem.ku.dk
- ⁺Authors contributed equally

Graphical Abstract:

Alkenes	$R^1_{\gamma} R^2$	CuSO ₄ (3 mol%) / CoCl ₂ (0.3 mol%) NaBH ₄ (2 eq.)	$R^1 \sim R^2$
Alkynes	R' ¹ ————————————————————————————————————	MeOH, 20 min, rt	R'1R'2

- -> Cheap and efficient catalyst prepared in situ
- → Short reaction time
- Easy work-up using extraction
- ➤ Does not cleave benzyl protecting groups

Abstract

The simple reduction of a number of alkenes and alkynes was performed with a typical reaction time of 20 minutes using a copper-cobalt catalytic system. The reduction did not cleave benzyl protecting groups which are usually vulnerable to catalytic hydrogenation reactions. The catalyst can be prepared *in situ* by reduction of the inexpensive precursor salts CuSO₄ and CoCl₂ with NaBH₄. Sodium borohydride was also used as an easily handled hydrogen source for the catalytic reductions. No pressure, heating or inert atmosphere is required and purification/catalyst removal is achieved using extraction procedures, making this approach simple and efficient.

Key words:

Catalytic hydrogenation, alternative hydrogen sources, benzyl protecting group

Introduction

The catalytic reduction of alkenes and alkynes with hydrogen and a transition metal catalyst is a standard reaction in organic synthesis.^{1,2} These reactions typically require expensive metals from groups 8 and 10, with platinum metals representing the most active, and a hydrogen source, such as H₂ gas, hydrazine or formates.³⁻⁷ Specialized glassware and inert atmospheres are typically required, and often these reactions are performed under pressure (H₂) or using highly toxic and environmentally harmful reagents (hydrazine, formates),^{8,9} which are not practical for a non-industrial laboratory use.

Recently, we described the formation and catalytic activity of bimetallic copper-cobalt nanoparticles that were stabilized by encapsulation in a dendrimer.¹⁰ This procedure gave nanoparticles (1-3 nm) capable of reducing alkenes and alkynes with low catalyst loading and short reaction times using NaBH₄ as a solid hydrogen source; however due to cost of the dendrimer this system is expensive, requires a nitrogen atmosphere and is difficult to scale-up. Herein, we describe the development of an inexpensive and simple copper-cobalt catalyst which is prepared *in situ*, and utilises sodium borohydride as a solid and easily manageable hydrogen source. The reaction is fast with an operationally simple extraction work up which could become a viable alternative to Pd/C for standard hydrogenation reactions.

Results and Discussion

A promising bi-metallic nano-catalytic system comprising of a 1:1 mixture of cobalt and copper(Cu₆Co₆@G3-PAMAM-Pyr, 1 nm metal particle size) was previously described.¹⁰ These nanoparticles were highly potent in catalytic reductions with low catalyst loading and linear kinetics. However, the system was difficult to transform into an easy and cheap standard laboratory reaction. In this study we investigated the ability of non-stabilized Cu-Co bimetallic particles to reduce alkenes and alkynes without the need of a dendrimer as support.

Gratifyingly, it was found that a mixture of CuSO₄ and CoCl₂ salts dissolved in methanol formed a metallic catalyst system *in situ* upon the addition of NaBH₄. These bimetallic particles were found to promote the decomposition of NaBH₄ to hydrogen and could be used as a solid hydrogen source. The reduction of 10-undecen-1-ol was used as test substrate. An initial analysis of different ratios between copper and cobalt revealed that the best ratio for catalytic hydrogenation was a catalyst with the original composition of 91% Cu and 9% Co.

As a general experimental procedure, the precursor salts CuSO₄•6H₂O and CoCl₂•5H₂O (10:1) were dissolved in methanol, and the unsaturated starting material added directly to the solution. The reaction was initiated by the addition of NaBH₄ to the solution, which reduced the copper(II) and cobalt(II) salts to the copper-cobalt-boride catalyst as finely dispersed particles, similar to the previously employed dendrimer encapsulated nanoparticles. However, the metal catalyst aggregated to form larger particles during the reaction, due to the lack of a stabilizing polymer. The *in situ* generated catalyst immediately started to decompose the excess NaBH₄ to hydrogen, which was transferred to the double or triple bond of the starting material. Additional portions of NaBH₄ were typically added over 20 minutes, which was sufficient to quantitatively reduce most double and triple bonds. The operationally simple work-up procedure was achieved by extraction with water/CH₂Cl₂, where the catalyst and the boronic acid salts remained in the water phase, while the product was extracted into the organic layer, which was dried over MgSO₄ and evaporated to give isolated yields of typically above 95%.



Scheme 1. Test substrates and products of the catalytic hydrogenation reaction using the copper-cobalt-boride catalyst. Reaction conditions and conversions are listed in Table 1.

Substrate	Catalyst	NaBH ₄	t	t Communication	
		(equiv.)	(min)	conversion	Isolated Yield
1a	1.0 mol% Cu	1.5	10	quant.	01%
	0.1 mol% Co		10		5170
2a	3.0 mol% Cu	2.0	10	quant.	94%
	0.3 mol% Co	2.0	10		
3a	3.0 mol% Cu	2.0	20	quant.	65%
	0.3 mol% Co		20		
4a	3.0 mol% Cu	2.0	20	quant	89%
	0.3 mol% Co		20	quant.	
5a	5.0 mol% Cu	4.0	20	quant	96%
Jd	0.5 mol% Co	4.0	20	quant.	
63	3.0 mol% Cu	2.0	20	quant	95%
0a	0.3 mol% Co	2.0	20	quant.	5570
7a	10 mol% Cu	1.5	10	26% 7b ^c	_e
7 a	1.0 mol% Co		10	56% 7c	
8a	3.0 mol% Cu	2.0	20	quant.	93%
Ja	0.3 mol% Co		20		
9a	5.0 mol% Cu	4.0	20	quant	96%
	0.5 mol% Co		20	ηματιτ.	30%
10a	3.0 mol% Cu	2.0	20	quant	97%
108	0.3 mol% Co		20	quant.	3770
11a	25 mol% Cu	6.0	25	89 ^d	89%
	2.5 mol% Co		25	05	
12a	3.0 mol% Cu	2.0	20	88	66%
	0.3 mol% Co		20		
13a	5.0 mol% Cu	4.0	20	quant 13c	94%
	0.5 mol% Co		20	quant. 130	9476
14a	2.0 mol% Cu	2.0		49% 14c	
	0.2 mol% Co		15	26% 14b	_e
	0.2 110/70 00			25% 14d	
15a	6.0 mol% Cu	4.0	20	35% 15b	e
	0.6 mol% Co		20	36% 15c	
16a	3.0 mol% Cu	2.0	20	64%	93%
	0.3 mol% Co		20	0470	5570

Table 1. Conditions for the catalytic hydrogenation of compounds 1-11a.^a

^{*a*} Reaction performed at ambient temperature and atmosphere. Methanol was used as the standard solvent. Extracted yields and further reaction details can be found in the ESI. ^{*b*} Conversion determined by ¹H-NMR and GC-MS. ^{*c*} 3% of mono reduced compound as the 1,4 addition product. ^{*d*} 2% was doubly reduced and 9% of the starting material remained. ^{*e*} Isolated as a product mixture containing starting material or intermediate products (see ESI for details and composition).

A systematic study of the catalyst potential was performed with the compounds shown in Scheme 1 and reaction conditions presented in Table 1. α , β -Unsaturated esters were readily reduced, leaving the ester group intact. The lowest reaction time and catalyst loading was observed for dimethyl

itaconate 1a (1 mol% Cu, 0.1 mol% Co, 10 min.), where the conjugated double bond is less hindered than in acrylates (2a and 3a), methyl cinnamate (4a) and *cis,cis*-dimethyl muconate (5a). Reduction of a terminal double bond conjugated to an aromatic ring system (styrene 6a) was rapid with low catalyst loading (3mol% Cu and 0.3 mol% Co), while internal double bonds (7a) were harder to reduce (10 mol% Cu and 1 mol% Co), which could also be explained by the trans-trans structure of the compound, which is difficult to reduce *via* the *syn*-addition of hydrogen. In all aromatic compounds the conjugated ring system remained intact during the reaction. Typical ester protection groups such as benzyl ester (2a) and tert-butyl ester (3a) were unaffected by the catalytic system. The stability of the benzyl ester is notable, since this group is usually removed by hydrogenation reactions;¹¹⁻¹³ this could open new pathways for reducing unsaturated carbon systems in the presence of benzyl protecting groups. The chemoselective hydrogenation of olefins is usually achieved by selective poisoning of Pd/C or other expensive rare metal catalysts, which is time consuming due to catalyst preparation and long reaction times of the deactivated catalyst.¹⁴⁻¹⁶ Terminal double bonds not conjugated to another π -system were readily reduced as demonstrated with compounds 8a, 9a and 10a. The acetyl ester in compound 9a and the benzyl ether (10a), a group potentially vulnerable to hydrogenation reactions,^{13,17} remained intact during the reaction. The preference for terminal double bonds was demonstrated with (+)-limonene (11a) where the terminal alkene was selectively hydrogenated, leaving the more hindered double-bond virtually untouched; only 2% of the fully reduced compound was observed by GC-MS. However, the catalyst loading for 11a was almost ten times higher than for the other compounds (25 mol% Cu and 2.5 mol% Co). This suggests that hydrogenation under these conditions is sensitive to the substitution pattern of the double-bond. The internal double bond in β -citronellol (12a) could be almost quantitatively reduced; this could be due to the less sterically hindered nature of the double bond compared to the aliphatic ring system in (+)-limonene where the double bond can hardly be accessed by the catalyst.

Furthermore, alkynes could also be successfully reduced to the alkene and further to the corresponding alkane. The reduction of compounds **13a** was quantitative with a fully saturated product, whereas compound **14a** was chosen for a mechanism study with low catalyst loading (2 mol% Cu and 0.2 mol% Co) and short reaction time (15 min) in order to isolate intermediate products (*vide infra*, Fig. 3).

Amine containing compounds (**15a** and **16a**) showed incomplete reaction (36% **15c**, 64% **16b**) under the applied catalytic conditions. Furthermore, the copper salts from the catalyst seemed to form stable complexes with the amines which interfered with NMR measurements due to the paramagnetic character of Cu(II). Especially, nitrile containing compound **15a** showed, besides the desired reaction product **15c** (36%), mono reduced species **15c** (35%) and starting material **15a**

(16%), and some unidentified products (12%), possibly due to cyclization reactions. Thus, the application of this catalytic system to amine containing compounds may require additional treatment to remove Cu(II), for instance reaction of the Cu(II) with a chelating agent. However, for typical products (e.g. **1-6**, **7-10** and **13**) an operationally simple extraction procedure was sufficient to obtain the desired product without further purification. The catalytic reaction was also demonstrated to be up-scalable, as demonstrated by the 4.7 g reaction scale of θ -citronellol **12a**.





Preliminary studies of the reaction progress indicated that the catalytic system is prone to Ostwaldripening (Fig. 1).¹⁸ Ostwald-ripening is the formation of larger clusters of metal-particles from smaller metal-particles which decreases the available surface area of the catalyst. If the reaction occurs on the surface of the metal this should lower the reaction rate, since the number of available binding sites is lowered. (+)-Limonene (**10a**) was chosen because the reaction rate was sufficiently low to allow several samples to be removed during the reaction. The reaction rate proceeded relatively quickly in the first two minutes, converting 39% of the starting material to compound **10b**. The initial turn over frequency (TOF) for the first 2 minutes was calculated to be 78 h⁻¹. After the first 2 minutes the reaction followed zeroth order kinetics, which is expected for a catalyst with constant surface area. Here, the TOF was calculated to be approximately 8 h⁻¹, a ten-fold decrease in reaction rate. This indicates that the catalyst starts with a large number of available binding sites, which drastically decreases to a constant level within 2 minutes.

The observed difference in reaction times and catalyst loading between isolated- and carbonyl conjugated double bonds was investigated by two mechanistic studies. The carbonyl conjugated

systems can be hydrogenated by at least two possible pathways: (i) *syn* addition of H₂ to the double bond, assisted by the catalyst and (ii) "Michael-type" attack of the hydride to the conjugated double bond followed by proton abstraction from the solvent (Fig. 2). In this experiment the reaction was performed in deuterated methanol under the standard conditions. In the "Michael-type" addition the product would be **4c** with deuterium in the β -position. If the addition is a *syn* type addition of HD, which is produced when NaBH₄ is decomposed by the catalyst in MeOD, the product will be a 1:1 mixture of **4c** and **4d**. Examination of the product ¹H-NMR spectrum would then help to elucidate whether one or both possible pathways are operating by comparing the ¹H-integrals of the α - and β positions. While the "Michael-type" addition would lead to a 2:1 integral ratio between the signals of the α - and β -hydrogens, *syn* addition would lead to a 1:1 integral ratio. The section of the ¹H-NMR spectrum showing the signals from the α,β -region is shown in Figure 2. The integrals displayed a 1.89:1.19 ratio between the α - and β -positions, which does not correlate completely to either pathway. The overserved results indicate that $\frac{3}{4}$ of the product is produced by the "Michael-type" pathway, whereas $\frac{3}{4}$ is produced by the *syn* pathway.



Figure 2. Left: Two possible pathways for the reduction of compound **2a** to **2b**. (a) "Michael-type" addition assisted by the catalyst forming product **2c**. (b) *syn* addition of H-D assisted by the catalyst forming products **2c** and **2d** in a 1:1 mixture. Right: The α , β -region of the product ¹H-NMR spectrum from the reduction performed in MeOD. Integrals are based on the methyl group, set to 3H. Reaction conditions: 6 mol% Cu / 0.6 mol% Co in MeOD (6 mL), NaBH₄ (2 equiv.), 20 min.





Further investigation was performed on diphenyl acetylene. In a study by Magoon and Slaugh, several alkynes were treated with lithium aluminium hydride in THF¹⁹ to afford the *trans*-isomers. The authors explained this outcome by the *anti*-addition of aluminium hydride followed by substitution of the aluminium with hydrogen. Formation of a *cis*-stilbene (**14c**) would suggest a *syn* mechanism, where hydrogen is adsorbed onto the catalyst surface and then transferred to the double-bond. The *trans*-stilbene (**14b**) would be formed if another mechanism was responsible for the observed reduction. As depicted in Figure 3, the reduction proceeds readily to product **14d**; the intermediate stilbene products were quantifiable by NMR and GC-MS. The product ratio between *cis*- and *trans*-stilbene was 3.5:1 was after five minutes reaction time. In this particular case it seems that the reaction proceeds mainly through *syn* addition of H₂. The observed *trans*-stilbene can either be explained by photo isomerization of *cis*-stilbene, to the thermodynamically more stable *trans* isomer during work-up and characterization, or by a second pathway similar to the one proposed by Magoon and Slaugh.¹⁹

Conclusion

In summary, an inexpensive and easily manageable catalyst for the catalytic hydrogenation of alkenes and alkynes was generated *in situ* from the inexpensive starting materials CuSO₄•6H₂O and CoCl₂•5H₂O. The reduction did not cleave hydrogenation sensitive benzyl protecting groups. The reaction can be performed in an open round bottom flask and, thus, does not require specialised

glassware or inert conditions. NaBH₄ is used as solid hydrogen source, which is an advantage compared to H_2 which needs to be handled as a highly flammable gas. The reaction times were fast (typically 20 min.) and a simple extraction procedure could be applied for workup and purification. Including workup and preparation time, the isolated hydrogenated compounds can be obtained within 1 h, which makes this route very useful synthetic procedure in everyday laboratory work.

References

- 1. Blaser HU, Malan C, Pugin B, Spindler F, Steiner H, Studer M, Adv. Synth. Catal. 2003; 345: 103-151.
- 2. Brieger G, Nestrick TJ, Chem. Rev. 1974; 74: 567-580.
- 3. Roessler F, *CHIMIA* 2003; 57: 791-798.
- 4. Hünig S, Müller H, Thier W, Angew. Chem. Int. Ed. 1965; 4: 271-280.
- 5. Furst A, Berlo R C, Hooton S, *Chem. Rev.* 1965; 65: 51-68.
- 6. Johnstone RAW, Wilby AH, Entwistle ID, Chem. Rev. 1985; 85: 129-170.
- 7. Rylander P. N. In *Hydrogenation methods*. Academic Pr: Chambridge, 1990; Vol. 1.
- 8. Witkin LB, Arch. Indust. Health 1956; 13: 34-6.
- 9. Thrasher JD, Kilburn KH, Arch Environ Health 2001; 56: 300-311.
- Ficker M, Petersen JF, Gschneidtner T, Rasmussen AL, Purdy T, Hansen JS, Hansen TH, Husted S, Moth Poulsen K, Olsson E, Christensen JB, *Chem. Commun.* 2015; 51: 9957-9960.
- 11. Felix AM, Heimer EP, Lambros TJ, Tzougraki C, Meienhofer J, J. Org. Chem. 1978; 43: 4194-4196.
- 12. Rao VS, Perlin AS, Carbohydr. Res. 1980; 83: 175-177.
- 13. ElAmin B, Anantharamaiah GM, Royer GP, Means GE, J. Org. Chem. 1979; 44: 3442-3444.
- 14. Sajiki H, Hattori K, Hirota K, J. Org. Chem. 1998; 63: 7990-7992.
- 15. Sajiki H, Hirota K, Tetrahedron 1998; 54: 13981-13996.
- 16. Hattori K, Sajiki H, Hirota K, *Tetrahedron* 2000; 56: 8433-8441.
- 17. Llàcer E, Romea P, Urpí F, Tetrahedron Lett. 2006; 47: 5815-5818.
- 18. Ostwald W. in *Lehrbuch der allgemeinen Chemie*. W. Engelmann: Leipzig, 1886; Vol. 2.
- 19. Magoon E, Slaugh L, *Tetrahedron* 1967; 23: 4509-4515.

Highlights

- Accepter Cheap and efficient catalyst prepared in situ. •