

Using alcohols as simple H₂-equivalents for copper-catalysed transfer hydrogenations

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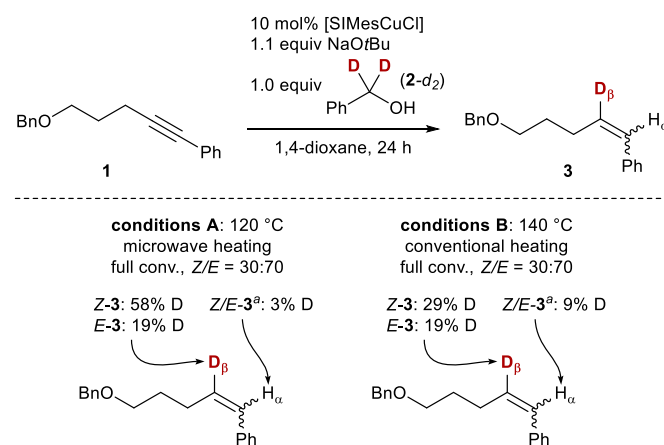
Catalytic transfer hydrogenations are among the most practical synthetic methods for the selective reduction of functional groups. Cheap and readily available dihydrogen (H₂) equivalents are highly desirable for catalytic transfer hydrogenations, as inevitably, waste is generated by the formal H₂ source. Copper hydride catalysis generally relies on stoichiometric use of waste-generating hydrosilanes. Here, we demonstrate that simple alcohols can be employed as H₂ equivalents in stereoselective alkyne semihydrogenations, prototypical copper hydride-catalysed transformations.

Catalytic transfer hydrogenations (TH) are attractive for the reduction of a variety of functional groups, as they offer practical protocols circumventing the need for high pressure equipment.¹ In general, for catalytic TH there is a need for easy-to-use and safe dihydrogen (H₂) sources, as these reactants are associated with the generation of one molecule of waste per turnover. Alcohols, such as the commonly employed isopropanol, fulfil the abovementioned criteria.¹

Copper-catalysed reductive transformations (so-called copper hydride catalysis)² pose formidable challenges with regard to transfer hydrogenations: On the one hand, copper hydride catalysis almost exclusively relies on hydrosilanes as reducing agents,² bringing forward a problem of atom economy due to silicon-based waste generated. On the other hand, copper(I)-catalysed homogeneous hydrogenations (based on the atom economic H₂) as investigated by us and others^{3–5} generally require elevated H₂ pressure, hampering their overall practicability. Finally, copper is a readily available metal, which renders it highly attractive for catalytic (transfer) hydrogenations.⁶ It comes to a surprise that for homogeneous copper hydride catalysis, transfer hydrogenations using alcohols as H₂ equivalents have not been reported so far, as this would manifest an atom economic and practical access to copper hydride chemistry.^{7–9} Herein, we show that simple alcohols (such as isopropanol) can be employed as H₂ equivalents for a prototypical copper hydride-based catalytic transformation, namely the semireduction of internal alkynes to alkenes.^{10–12}

The alkyne semihydrogenation poses challenges in stereoselectivity (*E* vs. *Z*) and chemoselectivity (overreduction of the formed alkene to the corresponding alkane, Scheme 1),¹⁰ and thus serves as an ideal model reaction for catalyst development. To probe a possible transfer of a hydrogen atom from the α -position of an alcohol by means of a copper(I) catalyst, we investigated the transfer semihydrogenation of internal alkyne **1**, using α,α -dideuterated benzyl alcohol (**2-d₂**, Scheme 1). Employing readily available [SiMesCuCl]¹³ in

catalytic amounts (10 mol%) and NaOtBu as base, full conversion either with microwave or conventional heating to the corresponding alkene **3** was found. Furthermore, significant ²H-incorporation (19–58%) in the β -position of the styrene moiety of **3** was observed, which suggested the envisaged presence of a copper(I) hydride/deuteride intermediate.^{14–16}



Scheme 1. β -Hydride elimination from alcohols as key step in a copper-catalysed transfer hydrogenation; deuterium labelling. Reaction was carried out on a 0.2 mmol scale. Conversion monitored by GC analysis. Deuterium incorporation determined by ¹H/²H NMR spectroscopy. ^a The H $_{\alpha}$ resonances could not be resolved by ²H NMR spectroscopy.

No formation of the overreduced alkane was observed in this initial experiment, which encouraged us to further develop the copper-catalysed transfer semihydrogenation of alkynes. Therefore, the viability of alcohols as H₂ sources for copper hydride catalysis in a transfer hydrogenation setting was established.

To optimise the conditions of the catalytic protocol (Table 1), we opted for toluene (**4**) as model substrate. We first demonstrated that 10 mol% of well-defined copper(I) complexes of standard N-heterocyclic carbene (NHC) ligands¹⁷ (SiMes, IMes, SIPr and IPr, respectively)¹⁸ sufficed to achieve high or full conversion in the catalytic transfer semihydrogenation of **4** employing readily available isopropanol as H₂ equivalent (Table 1, entries 1–5). Along these lines, SiMesCuCl as catalyst delivered the highest conversion and stereoselectivity to give stilbene **5** (100%, *Z/E* = 92:8, Table 1, entry 2). Notably, none of the NHC/copper(I) complexes investigated gave any overreduction to 1,2-diphenylethane (**6**). Other primary and/or secondary alcohols such as benzyl alcohol (**2**), glycerol or ethanol also gave detectable conversion, however, these H₂ equivalents could not compete with isopropanol in terms of either conversion or *Z/E* selectivity (Table 1, entries 6–8). The change in stereoselectivity

is an indication that the alcohol employed alters the structure and/or reactivity of the active catalyst. The omission of NHC ligands led to diminished or complete loss of chemoselectivity, as with CuCl itself either 6% (with NaOtBu as base) or complete conversion to undesired alkane **6** (using LiOtBu) was detected (Table 1, entries 9 and 10). Finally, we established that under optimised conditions, the reaction could also be carried out with microwave heating to deliver the same results as conventional heating (Table 1, entry 11).

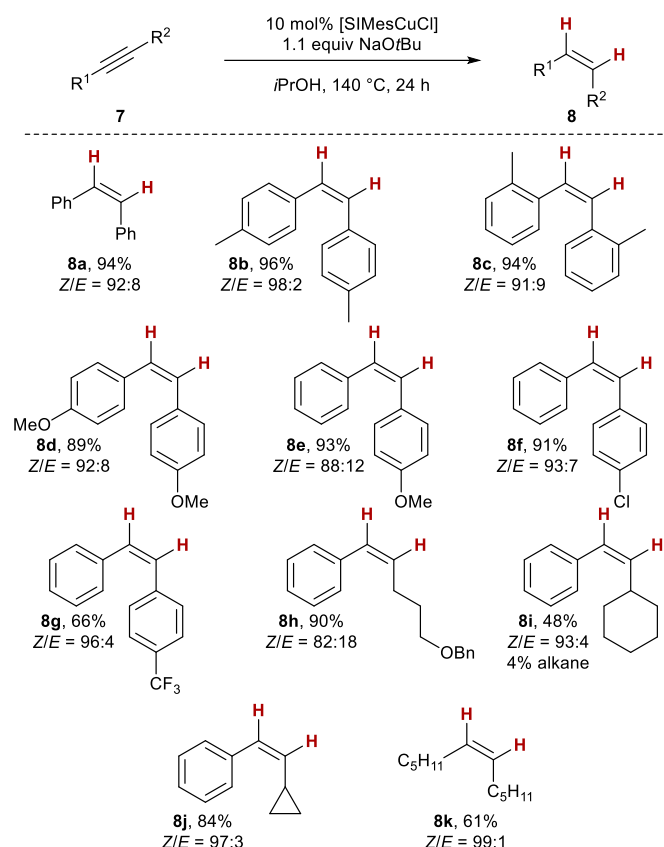
As the conduction of the reaction outside the microwave leads to a simpler overall procedure, we investigated the substrate scope of the copper(I)-catalysed transfer semihydrogenation with conventional heating next (Scheme 2). A variety of tolane derivatives gave the corresponding products **8a-c** in very good yields and *Z*-stereoselectivity ($\geq 94\%$, *Z/E* $\geq 91:9$). Both electron-rich as well as electron-poor stilbene derivatives **8d** to **8g** were obtained with similarly good results in terms of yield and *Z/E*-selectivity, albeit that trifluoro-substituted stilbene was isolated with a somewhat lower yield of 66%. Moving on to aryl alkyl-substituted alkynes as substrates, we were able to isolate benzyl-protected hexenol-derivative **8h** with *Z/E* = 88:12 and in 94% yield. This result is noteworthy, as no benzyl ether deprotection was detected, albeit the overall reducing conditions of the overall process.¹⁹ The sterically more demanding cyclohexyl derivative **8i** was the only compound studied which was accompanied by a negligible amount of the corresponding alkane (4%). The clean isolation of cyclopropyl styrene **8j** with very good results (84% *Z/E* = 97:3), and no evidence for a ring-opening gives an important indication that no radical intermediates are involved in the overall process.²⁰ Finally, the production of *Z*-6-dodecene **8k** in acceptable yields shows that isopropanol can also be used as H₂ equivalent with dialkyl alkynes as substrates, which are relatively unreactive in copper-based semihydrogenations.³

Table 1. Copper-catalysed transfer semihydrogenation, optimisation.^a

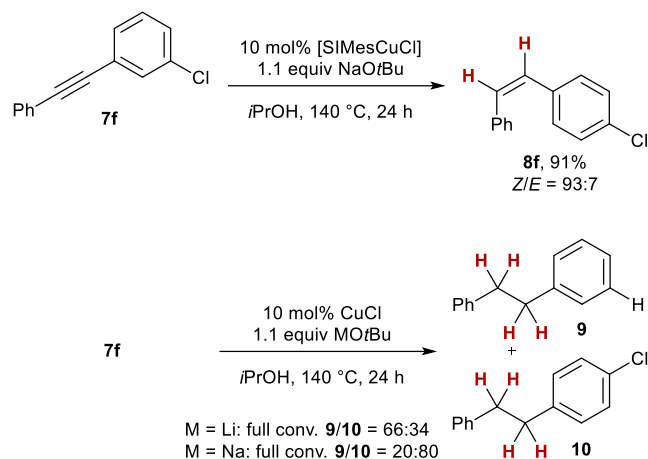
Entry	Catalyst, Loading	Base	Alcohol/Solvent ^b	Conv. [%]	<i>Z/E</i> -5	6 [%]
1	[SiMesCuCl], 5 mol%	NaOtBu	<i>i</i> PrOH	49%	90:10	<1%
2	[SiMesCuCl] , 10 mol%	NaOtBu	<i>i</i>PrOH	100%	92:8	<1%
3	[IPrCuCl], 10 mol%	NaOtBu	<i>i</i> PrOH	90%	92:8	<1%
4	[IMesCuCl], 10 mol%	NaOtBu	<i>i</i> PrOH	100%	90:10	<1%
5	[SiMesCuCl], 10 mol%	NaOtBu ^c	<i>i</i> PrOH	100%	84:16	<1%
6	[SiMesCuCl], 10 mol%	NaOtBu	BnOH/1,4-dioxane ^d	100%	70:30	<1%
7	[SiMesCuCl], 10 mol%	NaOtBu	glycerol/1,4-dioxane ^e	69%	93:7	<1%
8	[SiMesCuCl], 10 mol%	NaOtBu	EtOH	29%	86:14	<1%
9	CuCl, 20 mol%	NaOtBu	<i>i</i> PrOH	100%	80:20	6%
10	CuCl, 20 mol%	LiOtBu	<i>i</i> PrOH	100%	>1%	>99%
11 ^f	[SiMesCuCl] , 10 mol%	NaOtBu	<i>i</i>PrOH	100%	95:5	<1%

^a Reactions were carried out on a 0.2 mmol scale. Conversion and selectivity determined by GC and ¹H NMR analysis. ^b If not noted otherwise, 1 mL of the corresponding alcohol was employed as solvent. ^c 50 mol% NaOtBu was employed. ^d 2.0 equiv BnOH in 1 mL 1,4-dioxane was used. ^e 1 mL of a glycerol/1,4-dioxane mixture (1:10 v/v) was employed. ^f Reaction was performed with microwave heating at 120 °C for 16 h.

It should be noted that generally, no overreduction to the corresponding alkane was observed, underscoring the ability of the NHC ligand to control chemoselectivity in the transfer hydrogenation. This feature is in stark contrast to related transfer hydrogenations employing catalytic amounts of copper nanoparticles which cleanly deliver the corresponding alkanes from alkyne starting materials.^{7a} The present protocol thus achieves hitherto unreached chemoselectivity for copper-catalysed transfer semihydrogenations, which can be related back to the key influence of NHC ligands.

Scheme 2. Copper-catalysed transfer semihydrogenation, substrate scope.

To underscore the significant presence of the SiMes ligand on the selectivity of the transfer semihydrogenation, we have re-investigated chlorotolane **7f** as substrate. In the presence of SiMesCuCl under standard conditions, clean and stereoselective formation of the corresponding chlorostilbene **8f** was observed (91%, Z/E = 93:7, see Scheme 2). Under identical reaction conditions but employing only copper(I) chloride as catalyst, no alkene formation was observed, instead high conversion to the corresponding dechlorinated and chlorinated overreduced alkane **9** and **10** was detected (**9/10** = 66:34). The amount of dechlorination also depended on the counterion of the base employed: with lithium tert-butoxide, a higher percentage of the dechlorinated alkane **9** was found. (**9/10** = 66:34 vs. **9/10** = 20:80 with NaOtBu) This result serves as additional evidence for the fact that the active catalyst present in the transfer semihydrogenations comprises an NHC ligand which is vital for high selectivities.²¹

Scheme 3. Influence of the NHC ligand on chemoselectivity.

Conclusions

To address the need for readily available and cheap H₂ equivalents for transfer hydrogenations, we have demonstrated that simple alcohols can be employed in copper-catalysed transfer hydrogenations. The results show that in the realm of copper hydride catalysis both, high pressure equipment (when using H₂) as well as waste-generating hydrosilanes can be circumvented, offering a cheap access to copper hydrides and a practical overall protocol. The use of NHCs as key ligands leads to high chemoselectivity (little or no overreduction to the corresponding alkanes) and stereoselectivity (very high Z/E ratios observed). The present first entryway to copper hydride catalysis in a transfer hydrogenation setting from alcohols thus has implications for a potential broader application in copper hydride catalysis. The extension of this methodology to other common copper hydride-based transformations is currently ongoing.

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Conflicts of interest

There are no conflicts to declare.

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