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Using alcohols as simple H_2-equivalents for copper-catalysed transfer semihydrogenations of alkynes†

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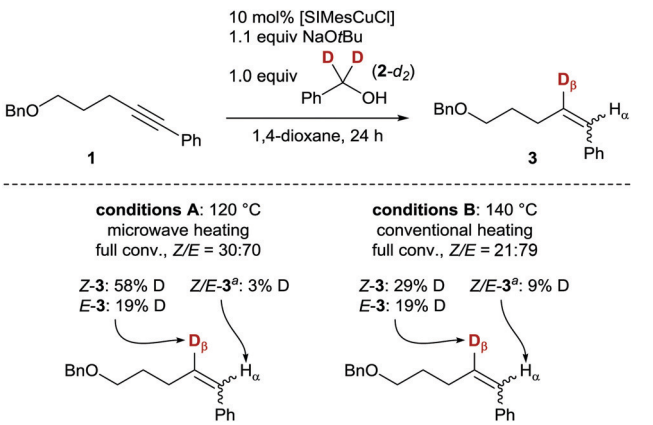
Copper(I)/N-heterocyclic carbene complexes enable a transfer semihydrogenation of alkynes employing simple and readily available alcohols such as isopropanol. The practical overall protocol circumvents the use of commonly employed high pressure equipment when using dihydrogen (H_2) on the one hand, and avoids the generation of stoichiometric silicon-based waste on the other hand, when hydrosilanes are used as terminal reductants.

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 (H_2) 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 above-mentioned 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 H_2) as investigated by us and others[3–5] generally require elevated H_2 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 H_2 equivalents have not been reported so far, as this would manifest an atom economic and practical access to copper hydride chemistry, addressing the abovementioned limitations.[7–9] Herein, we show that simple alcohols (such as isopropanol) can be employed as H_2 equivalents for a prototypical copper hydride-based catalytic transformation, namely the semi-reduction 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**-d_2, Scheme 1). Employing readily available [SIMes-CuCl][13] in catalytic amounts (10 mol%) and NaO*t*Bu as base, full conversion either with microwave or conventional heating to the corresponding alkene **3** was found. Furthermore, significant ^{2}H-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]

No formation of the overreduced alkane was observed in this initial experiment, which encouraged us to further develop the



Scheme 1 Deuterated alcohol as formal HD source in a copper-catalysed transfer hydrogenation. Reaction was carried out on a 0.2 mmol scale. Conversion monitored by GC analysis. Deuterium incorporation determined by ^{1}H/^{2}H NMR spectroscopy. [a] The H_α resonances could not be resolved by ^{2}H NMR spectroscopy.

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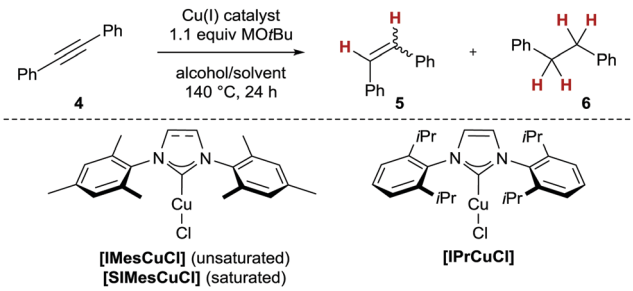
copper-catalysed transfer semihydrogenation of alkynes. Therefore, the viability of alcohols as H_2 sources for copper hydride catalysis in a transfer hydrogenation setting was established.

To optimise the conditions of the catalytic protocol, we opted for tolane (**4**) as model substrate (Table 1). We first demonstrated that 10 mol% of well-defined copper(I) complexes of standard N-heterocyclic carbene (NHC) ligands[17] (SIMes, IMes and IPr, respectively)[18] sufficed to achieve high or full conversion in the catalytic transfer semihydrogenation of **4** employing readily available isopropanol as H_2 equivalent (Table 1, entries 1–5). Along these lines, [SIMesCuCl] as catalyst delivered the highest conversion and stereoselectivity to give stilbene *Z*-**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 H_2 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. Indeed, when other secondary alcohols (2-pentanol and 2-hexanol) were tested, also, unselective reactions in terms of stereo- and chemoselectivity were observed (see the ESI,† Section S2). The omission of NHC ligands led to diminished or complete loss of chemoselectivity, as with CuCl itself either 6% (with NaO*t*Bu as base) or complete conversion to undesired alkane **6** (using LiO*t*Bu) was detected (Table 1, entries 9 and 10). These results indicate the presence of heterogeneous copper catalysts when no ligand is employed (see also Scheme 3 for more details). 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 (≥94%, *Z*/*E* ≥ 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 **8g** 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* = 82 : 18 and in 90% 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 fully stereoselective production of *Z*-6-dodecene (*Z*-**8k**) in acceptable yields shows that isopropanol can also be used as H_2 equivalent with dialkyl alkynes as substrates, which are relatively unreactive in copper-based semihydrogenations.[3]

It should be noted that generally, no overreduction to the corresponding alkane was observed, underscoring the ability of

Table 1 Copper-catalysed transfer semihydrogenation, optimisation[a]

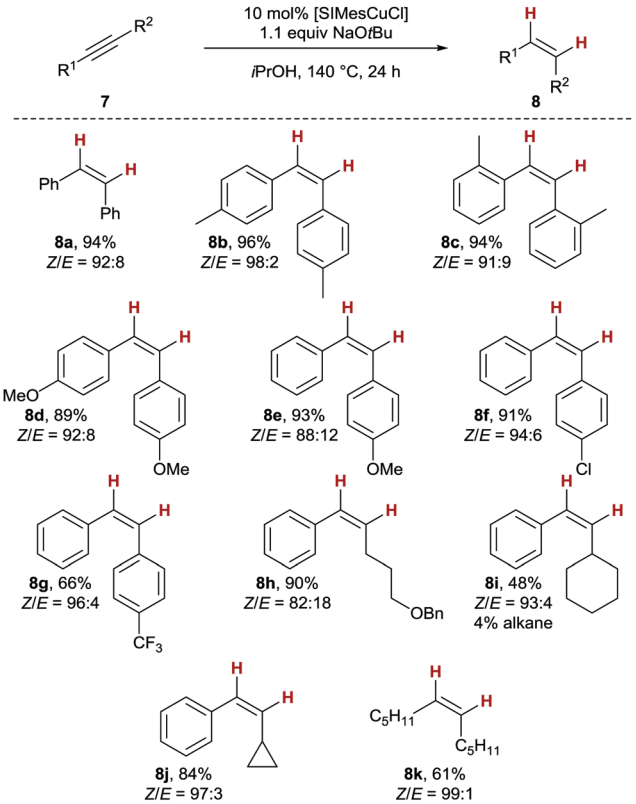


Entry	Catalyst, loading	Base	Alcohol/solvent[b]	Conv. [%]	*Z*/*E*-**5**	**6** [%]
1	[SIMesCuCl], 5 mol%	NaO*t*Bu	iPrOH	49	90 : 10	<1
2	**[SIMesCuCl], 10 mol%**	**NaO*t*Bu**	**iPrOH**	**100**	**92 : 8**	**<1**
3	[IPrCuCl], 10 mol%	NaO*t*Bu	iPrOH	90	92 : 8	<1
4	[IMesCuCl], 10 mol%	NaO*t*Bu	iPrOH	100	90 : 10	<1
5	[SIMesCuCl], 10 mol%	NaO*t*Bu[c]	iPrOH	100	84 : 16	<1
6	[SIMesCuCl], 10 mol%	NaO*t*Bu	BnOH/1,4-dioxane[d]	100	70 : 30	<1
7	[SIMesCuCl], 10 mol%	NaO*t*Bu	Glycerol/1,4-dioxane[e]	69	93 : 7	<1
8	[SIMesCuCl], 10 mol%	NaO*t*Bu	EtOH	29	86 : 14	<1
9	CuCl, 20 mol%	NaO*t*Bu	iPrOH	100	80 : 20	6
10	CuCl, 20 mol%	LiO*t*Bu	iPrOH	100	>1%	>99
11[f]	**[SIMesCuCl], 10 mol%**	**NaO*t*Bu**	**iPrOH**	**100**	**95 : 5**	**<1**

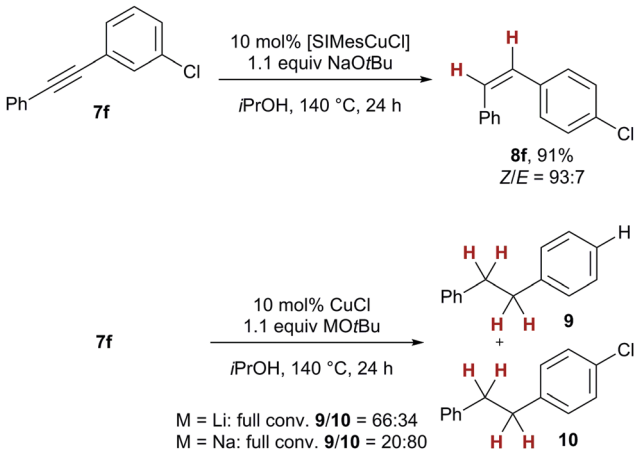
[a] Reactions were carried out on a 0.2 mmol scale. Conversion and selectivity determined by GC and ^{1}H NMR analysis. [b] If not noted otherwise, 1 mL of the corresponding alcohol was employed as solvent. [c] 50 mol% NaO*t*Bu was employed. [d] 2.0 equiv. BnOH in 1 mL 1,4-dioxane was used. [e] 1 mL 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.

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. The high *Z* selectivity reached for most alkynes deserves some more comments: When following the reaction with **8h**, a relatively fast aforegoing alkyne semihydrogenation takes place (100% conversion reached after **4h**), followed by a period in which no alkane was formed but the *Z*/*E* ratio diminished, indicating a secondary isomerisation process (see the ESI† for details). These results show that close optimization of the reaction time for an alkyne of interest can lead to even higher *Z*/*E* ratios.

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



Scheme 2 Copper-catalysed transfer semihydrogenation, substrate scope.



Scheme 3 Influence of the NHC ligand on chemoselectivity.

percentage of the dechlorinated alkane **9** was found. (**9**/**10** = 66 : 34 *vs.* **9**/**10** = 20 : 80 with NaO*t*Bu) 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]

To address the need for readily available and cheap H_2 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 H_2) 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 entry way to copper hydride catalysis in a transfer hydrogenation setting from alcohols thus has implications for a potential broader application in reductive copper-catalysed transformations. 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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16 No significant induction period for either heating method (A or B) was observed (~30% conversion of 1 after 30 min), indicating a homogeneous catalyst (see the ESI† for more details). Over the course of time, the ratio of *Z*-**3**/*E*-**3** diminished, suggesting a rapid *Z*-selective semihydrogenation followed by a Z → E isomerisation process. Literature precedence exists for these combined mechanisms, see for example: (*a*) D. Srimani, Y. Diskin-Posner, Y. Ben-David and D. Milstein, *Angew. Chem., Int. Ed.*, 2013, **52**, 14131–14134; (*b*) K. Tokmic and A. R. Fout, *J. Am. Chem. Soc.*, 2016, **138**, 13700–13705; (*c*) K. Murugesan, C. B. Bheeter, P. R. Linnebank, A. Spannenberg, J. N. H. Reek, R. V. Jagadeesh and M. Beller, *ChemSusChem*, 2019, **12**, 3363–3369.

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