A Practical and Highly Chemoselective Hydrogenation of Aldehydes with a Copper Catalyst

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Abstract: A practical hydrogenation of aldehydes mediated by an inexpensive and easily available base metal, copper, is reported. A copper complex associated with 1,4-bis(diphenylphosphino)butane (DPPB) hydrogenates α,β-unsaturated aldehydes in a highly chemoselective fashion to give allylic alcohols with improved catalytic productivities. The reaction system was also effective for the conversion of simple aldehydes to the corresponding alcohols.

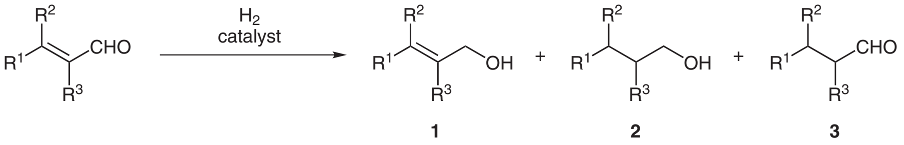
Key words: hydrogenation, aldehydes, copper, homogeneous catalysis, chemoselectivity

The reduction of aldehydes is a fundamental method for preparing primary alcohols. Among the many methods that are available for reduction, hydrogenation is desirable, especially for reactions beyond a laboratory scale, because of good atom economy, low waste, and ease of workup.

In the hydrogenation of α,β-unsaturated aldehydes, chemoselectivity is crucial. In many cases, only allylic alcohol **1** is desired among three potential products (**1**, saturated alcohol **2**, and saturated aldehyde **3**; Scheme 1).[1] Thus, high chemoselectivity in favor of the carbonyl group is indispensable.

Various heterogeneous[2] and homogeneous[3] hydrogenation systems have been investigated for this purpose, and in most cases platinum group metals (such as Ir and Ru) have been used as a catalyst. However, with a few exceptions,[4] this subject remains challenging, since many of the reported examples suffer from overreduction and/or limited substrate scope. The most successful results were obtained with a homogeneous diamine-modified Ru catalyst developed by Noyori and co-workers.[5] The use of $RuCl_2(PPh_3)_3$ in the presence of $NH_2(CH_2)_2NH_2$ and KOH gave rise to highly carbonyl-selective hydrogenation to give **1** virtually without any generation of **2** or **3**.

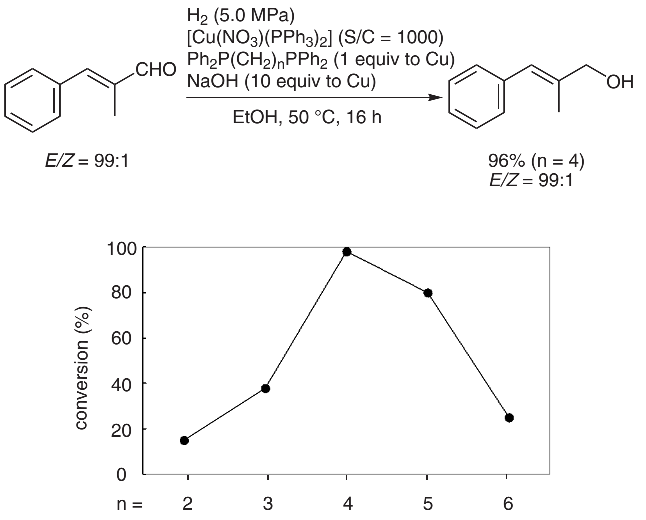
On the other hand, Stryker and co-workers pioneered a base-metal-catalyzed hydrogenation using a Cu complex.[6] They demonstrated that $[CuH(PPh_3)]_6$, together with $PhPMe_2$ and an excess amount of *t*-BuOH, catalyzed hydrogenation with excellent 1,2-selectivity to give **1**. Although the use of an inexpensive base metal was very attractive, the downside was a somewhat low turnover number.[7] Obviously, higher catalytic productivity was needed for Cu catalysis to be more practical.



Scheme 1 Hydrogenation of α,β-unsaturated aldehydes

Recently, we reported an asymmetric hydrogenation of aromatic ketones mediated by a copper catalyst.[8] In that study, we found that the catalytic productivity greatly depended on the ligand used. Specifically, bisphosphine ligands with C3–C4 alkylene linkers tend to give higher turnover numbers (up to 3000). Thus, we envisioned that, for aldehydes, a similar system with a proper choice of bisphosphine ligand could drastically improve the catalytic productivity to a practical level.

We started our study by screening bisphosphine ligands with alkyl linkers of various lengths, with



Scheme 2 Hydrogenation of (*E*)-2-methyl-3-phenylprop-2-enal

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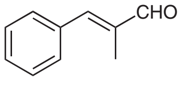
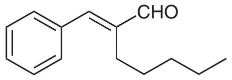
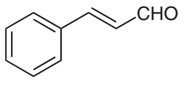
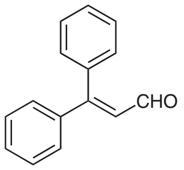
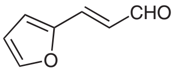
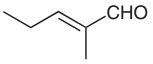
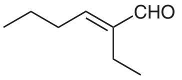
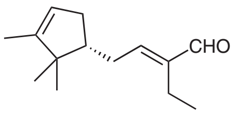
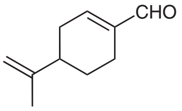
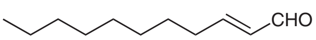
$[Cu(NO_3)(PPh_3)_2]$[9] and NaOH as components of a catalyst precursor and EtOH as a solvent. As expected, conversion was greatly influenced by the linkers, and in the case of (*E*)-2-methyl-3-phenylprop-2-enal as a substrate, a C4 entity, 1,4-bis(diphenylphosphino)butane (DPPB), was the ligand of choice, and the reaction was complete at a reasonable catalyst loading [molar ratio of substrate to catalyst (S/C) = 1000]. The reaction proceeded with excellent chemoselectivity and virtually only (*E*)-2-methyl-3-phenylprop-2-en-1-ol was generated (Scheme 2). Herein, the use of $PhPMe_2$ (2 equiv to Cu) as ligand resulted in 13% conversion.

We then investigated the substrate generality and some reaction conditions using the Cu–DPPB system at S/C = 500 (Table 1).[10] We found that the protocol can be applied to other α,β-unsaturated aldehydes with excellent conver-

Table 1 Hydrogenation of α,β-Unsaturated Aldehydes[a]

Entry	Substrate (*E*/*Z*)[b]	Conversion (%)[b]	Yield of **1** + **2** (%)[c]	**1**/**2**[b]	*E*/*Z* of **1**[b]
1	 (99:1)	>99	99	>99:1	99:1
2[d]		>99	95	>99:1	99:1
3[e]		>99	91	>99:1	98:2
4	 (95:5)	>99	98	>99:1	95:5
5	 (>99:1)	>99	68	>99:1	>99:1
6		98	96	>99:1	n.a.
7[f]	 (>99:1)	>99	92	>99:1	>99:1
8[f,g]		>99	96	>99:1	>99:1
9	 (99:1)	>99	72	32:1	96:4
10	 (94:6)	98	87	16:1[h]	91:9
11	 (93:7)	98	94	35:1	92:8
12		98	92	51:1	n.a.
13		>99[i]	–	–	–

[a] Unless otherwise noted, reactions were carried out at 50 °C for 16 h in EtOH (1.1–1.5 M) in the presence of $[Cu(NO_3)(PPh_3)_2]$ (S/C = 500), DPPB (1 equiv to Cu) and NaOH (10 equiv to Cu). The initial hydrogen pressure was 5.0 MPa.

[b] Determined by GC analysis using a BC-WAX column or HP-1 column.

[c] Isolated yield.

[d] Hydrogen pressure of 1.0 MPa was adopted.

[e] $Cu(NO_3)_2 \cdot 3H_2O$ was used in place of $[Cu(NO_3)(PPh_3)_2]$.

[f] S/C = 566.

[g] $[CuH(PPh_3)]_6$ (S/C = 500 based on Cu metal) and Ph_3P (3 equiv to Cu) were used in place of $[Cu(NO_3)(PPh_3)_2]$ and NaOH.

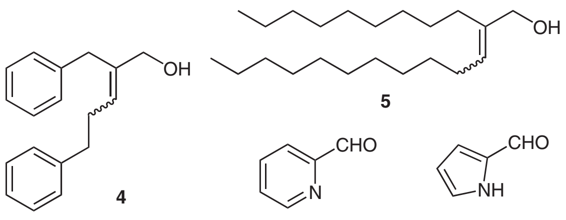
[h] Substrate contained ca. 3% of 2-ethylhexan-1-ol.

[i] A complex mixture.

sion and with high chemoselectivities for 1,2-reduction. Specifically, with cinnamic aldehyde type substrates, virtually only allylic alcohols **1** were obtained without any disorder in geometry (entries 1–8). On the other hand, in the case of substrates with only alkyl substituents, saturated alcohol **2** was obtained in a yield of several percent, although the chemoselectivity to give **1** remained high (entries 9–12). In the latter case, a small drop in the *E*/*Z* ratio was observed. In every case, little (<1%) or no saturated aldehyde **3** was observed. With a few substrates, the reaction was accompanied by the generation of unidentified byproducts, presumably oligomeric compounds, which led to a decrease in isolated yields (entries 5 and 9). On the other hand, the reaction with a simply substituted substrate, (*E*)-undec-2-enal, gave a complex mixture and only trace amount of the allylic alcohol was detected (entry 13).

While the reactions were routinely conducted at an initial hydrogen pressure of 5.0 MPa, comparable results were obtained when this level was lowered to 1.0 MPa (entry 2). With regard to the catalyst precursor, $Cu(NO_3)_2{\cdot}3H_2O$ could be used in place of $[Cu(NO_3)(PPh_3)_2]$ (entry 3). $[CuH(PPh_3)]_6$ with additional Ph_3P also worked equally well even in the absence of NaOH (entry 8).

The protocol was also effective with other aldehydes such as aryl, heteroaryl, and alkyl compounds (Table 2). In most cases, hydrogenation proceeded smoothly to give the corresponding alcohols in high yield (entries 1–7). However, the protocol had some limitations with aldehydes without a substituent at the α-position; the reactions of 3-phenylpropanal and undecanal resulted in low yields (entry 8 and 9) due to the generation of respective byproducts **4** and **5** derived from aldol-type reactions (Figure 1). With 2-pyridinecarboaldehyde as substrate, the reaction resulted in incomplete conversion, giving a mixture of several products. With 1*H*-pyrrole-2-carbaldehyde, no reaction was observed (Figure 1).



4

5

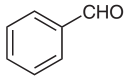
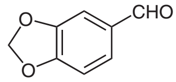
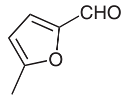
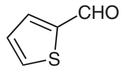
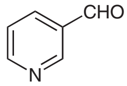
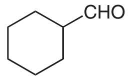
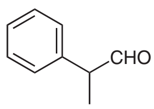
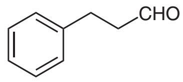
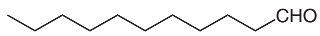
conv. 56%
mixture of several products

no reaction

Figure 1

In summary, we have developed a method for hydrogenating aldehydes using an inexpensive and easily available Cu catalyst with a practical level of catalytic productivity. The protocol generally gives the corresponding alcohols in high yield, although it has some limitations with a few substrate types. In the case of α,β-unsaturated aldehydes, the reaction led to the exclusive formation of allylic alcohols. The reaction infrequently produced a small amount of Cu metal, which need to be solved for industrial application. The influence of linkers of phosphine ligand on catalytic productivity, as well as the cause of small drop in *E*/*Z* ratio in some cases, will require further investigation. A mechanistic study is currently under way. Also, extension of this protocol to α,β-unsaturated ketones is in progress and will be reported in due course.

Table 2 Hydrogenation of Aldehydes[a]

Entry	Substrate	Conversion (%)[b]	Yield (%)[c]
1		>99	91
2		>99	98
3		>99	87
4		>99	96
5		>99	85
6		>99	90
7		97	76
8		88	10
9		97	9

[a] Reactions were carried out at 50 °C for 16 h in EtOH (1.3–1.5 M) in the presence of $[Cu(NO_3)(PPh_3)_2]$ (S/C = 500), DPPB (1 equiv to Cu) and NaOH (10 equiv to Cu). The initial hydrogen pressure was 5.0 MPa.

[b] Determined by GC using a BC-WAX column.

[c] Isolated yield.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

References and Notes

(1) (a) Chapuis, C.; Jacoby, D. *Appl. Catal., A* **2001**, *221*, 93. (b) *Common Fragrance and Flavor Materials*; Surburg, H.; Panten, J., Eds.; Wiley-VCH: Weinheim, **2006**. (c) Saudan, L. A. *Acc. Chem. Res.* **2007**, *40*, 1309.

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(6) (a) Chen, J.-X.; Daeuble, J. F.; Brestensky, D. M.; Stryker, J. M. *Tetrahedron* **2000**, *56*, 2153. (b) Chen, J.-X.; Daeuble, J. F.; Stryker, J. M. *Tetrahedron* **2000**, *56*, 2789.

(7) Our attempt to hydrogenate (–)-4-(prop-1-en-2-yl)cyclohexen-1-carbaldehyde [(–)-perilaldehyde] at S/C = 500 with the condition described in ref. 6b, resulted in trace conversion. The reaction reportedly completed at S/C = 20, which was reproduced by us.

(8) Shimizu, H.; Igarashi, D.; Kuriyama, W.; Yusa, Y.; Sayo, N.; Saito, T. *Org. Lett.* **2007**, *9*, 1655.

(9) [$Cu(NO_3)(PPh_3)_2$] can be prepared from $Cu(NO_3)_2·3H_2O$ and Ph_3P. See: Gysling, H. J. *Inorg. Chem.* **1979**, *19*, 92.

(10) **Representative Procedure (Table 1, Entry 1)**
To a 100 mL stainless steel autoclave equipped with a glass inner lining and a Teflon-coated stirring bar were added [$Cu(NO_3)(PPh_3)_2$] (11.7 mg, 0.018 mmol) and DPPB (7.7 mg, 0.018 mmol). The atmosphere was replaced with N_2, and an EtOH solution (0.03 M) of NaOH (6.0 mL, 0.18 mmol) and (*E*)-2-methyl-3-phenylprop-2-enal (*E*/*Z* = 99:1; 1.26 mL, 9.0 mmol) were then added. Hydrogen gas was initially introduced into the autoclave at a pressure of 1.0 MPa before being reduced to 0.1 MPa by carefully releasing the stop valve. After this procedure was repeated three times, H_2 was introduced at 5.0 MPa and the solution was stirred at 50 °C for 16 h. Silica gel chromatography (Et_2O–hexane = 1:1) after removal of the solvent gave (*E*)-2-methyl-3-phenylprop-2-en-1-ol (1.32 g, 99%, *E*/*Z* = 99:1).