

# **ORIGINAL PAPER**

## Copper hydride-catalyzed reduction of electron-deficient olefins

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Copper hydride derived from CuF(PPh<sub>3</sub>)<sub>3</sub>·2MeOH-bis[(2-diphenylphosphino)phenyl] ethersilane can reduce electron-deficient olefins selectively and efficiently. © 2013 Institute of Chemistry, Slovak Academy of Sciences

**Keywords:** copper hydride, conjugate reduction,  $\alpha,\beta$ -unsaturated carbonyl, catalysis, bis[(2-diphenylphosphino)phenyl] ether

#### Introduction

Selective conjugate reduction of electron-deficient olefins, e.g.  $\alpha,\beta$ -unsaturated carbonyl compounds, is an important transformation in organic synthesis. Versatility of this reaction has been well demonstrated in the synthesis of some molecules with complex structures (Nicolaou et al., 2005; Li et al., 2008). Although several methods can be used for this transformation (Magnus et al., 2000; Blackwell et al., 2002; Jung & Krische, 2006; Hirasawa et al., 2007; Monguchi et al., 2008),  $[CuHPPh_3]_6$  has been recognized as the reagent of choice for this kind of reactions due to its high regioselectivity, mild conditions and tolerance of other functional groups including isolated C=C bond (Mahoney et al., 1988; Brestensky & Stryker, 1989; Chiu, 1998; Rendler et al., 2007; Sass et al., 2011). A combination of  $[CuHPPh_3]_6$  as the catalyst and other reducing reagents, e.g. Bu<sub>3</sub>SnH (Lipshutz et al., 1998), make this reduction very attractive from the economic point of view. The use of silanes instead of tin hydrides as the reducing reagents makes this reaction economical and environmentally benign (Lipshutz et al., 2000). Employment of the [CuHPPh<sub>3</sub>]<sub>6</sub> catalyst generated in situ from stable copper compounds and silane as the reducing reagent makes this method more feasible and practical than that using [CuHPPh<sub>3</sub>]<sub>6</sub>, as it avoids long-time storage of airunstable  $[CuHPPh_3]_6$  and its high cost. Ito (1997) reported the formation of copper hydride from CuCl

and hydrosilane in 1,3-dimethylimidazolidinon, and its application in conjugate reduction. Mori et al. (1997) reported that silanes are able to reduce enones in 1,4selectivity in the presence of a catalytic amount of  $CuF(PPh_3)_3 \cdot 2EtOH$  or  $CuCl-PPh_3-Bu_4NF$  in N,Ndimethylacetamide (Mori et al., 1999) affording saturated ketones in high yields. However, these copper hydrides are not very reactive with bulky ketones and some latent polarized olefins. Optimization of the ligand has led to the discovery that copper hydride ligated with 1,2-bis(diphenylphosphino)benzene (DP-Ben, Fig. 1) is a more efficient catalyst for conjugate reduction of enones or unsaturated esters, and interestingly, more stable than  $[CuHPPh_3]_6$  (Baker et al., 2008). CuH–DPBen has been used to catalyze conjugate reduction of isophorone and unsaturated esters (including thioesters) (Baker et al., 2008; Li et al., 2011; Ou et al., 2012) which are inert to  $[CuHPPh_3]_6$ .

Even though copper hydride is regarded as a suitable reagent/catalyst for conjugate reduction of  $\alpha,\beta$ ketones and esters, there are a number of reports showing that the choice of phosphine ligands is of great importance for the selectivity for the reduction of unsaturated carbonyls. For  $\alpha,\beta$ -unsaturated aldehydes, 1,2-reduction is the predominant reaction using the copper catalyst; for  $\alpha,\beta$ -unsaturated ketones, 1,4-reduction with triphenylphosphine or DPBen as the ligand occurs, whereas 1,2-reduction proceeds using some aryldialkylphosphines as the ligands (Chen, et al., 2000; Lee & Lipshutz, 2008). In most cases,

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Fig. 1. Structures of DPBen and DPEphos.

the two reduced products are formed simultaneously (Mori et al., 1999; Lee & Lipshutz, 2008; Moser et al., 2010). There are also abundant examples of copper hydride–phosphine complexes catalyzing the reduction of ketones (Lee & Yun, 2004). Very recently, Moser et al. (2010) have reported asymmetric ligandaccelerated copper hydride-catalyzed 1,2-reduction of enones yielding non-racemic allylic alcohols.

On the other hand, copper hydride-catalyzed reduction of  $\alpha,\beta$ -unsaturated carbonyl compounds has been dominantly investigated from the point of view of organic chemistry. The progress is monitored by TLC and the final isolated products are verified by NMR. This process requires a long operation time. Moreover, the yields of minor products were neglected in most cases or they can be inaccurate due to the isolation process and the sensitivity of the detection method.

Our study on intramolecular conjugate reductive aldol addition, a domino reaction promoted by copper hydride, has proved that copper hydride ligated to the bis[(2-diphenylphosphino)phenyl] ether (DPEphos, Fig. 1) ligand is an efficient reagent in the reaction (Zheng et al., 2012). Since conjugate reduction is a part of the domino reaction, we turned our attention to simple conjugate reduction, investigating the products' distribution, and the selectivity of the reduction. Herein, these results, including the highly selective reduction of some 'inert' substrates, are reported.

#### Experimental

All reagents were purchased from Alfa Aesar (China), A Johnson Matthey (USA), and the solvents were bought from Sinoreagent (China).

GC analyses were performed on a Shimadzu GC-2010 GC chromatograph (Shimadzu Corporation, Japan) using an SE-54 capillary column (30 m × 0.32 mm × 0.4 µm). Mass spectra were recorded on a HP 6890/5973 GC-MS mass spectrometer (Agilent Technologies, USA) at 70 eV. Infrared spectra were recorded on a Nicolet 550 FT-IR spectrometer (Thermo Fisher Scientific, USA) in nujol from 4000 cm<sup>-1</sup> to 400 cm<sup>-1</sup>, and NMR spectra were recorded on a Varian Mercury Plus-400 NMR spectrometer (Varian, USA) in CDCl<sub>3</sub> at 400 MHz and 100 MHz for <sup>1</sup>HNMR and <sup>13</sup>CNMR, respectively, chemical shifts are given in parts per million (ppm).

Under nitrogen atmosphere, a mixture of  $CuF(PPh_3)_3 \cdot 2MeOH$  (2.8 mg, 3.0 µmol), and DPEphos (1.6 mg,  $3.0 \mu mol$ ) in toluene in a Schlenk tube was stirred for 15 min at room temperature followed by an addition of poly(methylhydrosiloxane) (PMHS) (55 µL, 0.90 mmol), the mixture was then stirred for another 15 min, resulting in an orange-red color solution. A solution of ethyl cyclohexylideneacetate (53  $\mu$ L, 0.30 mmol) in toluene (0.5 mL) was added via a cannula, and the residue was washed with toluene (0.50 mL) and added to the reaction mixture. After the addition of 2-methyl-2-propanol (81  $\mu$ L, 0.90 mmol), the reaction mixture was stirred for 19 h, followed by an addition of a solution of ammonium fluoride (0.30 M, 10 mL) to quench the reaction and hydrolyze the silyl ether formed. General work-up and column chromatography separation provided ethyl cyclohexylacetate (50 mg, purity: 96.9 mass %, yield: 95 %). Structures of simple conjugate reduction, carbonyl reduction products were deduced from the MS spectra and the retention time in GC with authentic samples prepared by the reduction of substrates using palladium-catalyzed hydrogenation or sodium borohydride reduction.

### **Results and discussion**

The presented study started with the reduction of 3-methylcyclohex-2-enone (I), a  $\beta$ , $\beta$ -disubstituted enone. Theoretically, three products, 3-methyl-cyclohexone (II), 3-methylcyclohex-2-enol (III), and 3methylcyclohexanol (IV), can be produced (Fig. 2). As shown in Table 1, the reduction using  $CuF(PPh_3)_3$  $\cdot 2MeOH-Ph_2SiH_2$  was highly chemoselective for the formation of II, even though formation of both III and IV was also observed. Previously,  $Ph_2SiH_2$  has been reported in clean formation of copper hydride (Chiu et al., 2003) and highly reactive to copper-catalyzed conjugate reduction (Jurkauskas et al., 2003). However, thus generated copper hydride has low reactivity in our conditions, as only a 68.3 % conversion of I was achieved within 1 h in the presence of 5 mol % of the copper complex (entry 1). Increasing the reaction time to 5 h led to an 80 % conversion (entry 2), which is still far from the quantitative conversion. Previously, it has been found that higher yields of  $[CuHPPh_3]_6$  can be achieved using an excess of PPh<sub>3</sub> (Chiu et al., 2003), therefore, an equivalent of  $PPh_3$  (based on copper salt) was added to the reaction system. Nevertheless, this resulted in lower reactivity, where only a 64.8 % conversion of I was achieved in 20 h (entry 3). In this case, the formation of III was not observed while the relative amount of IV increased, although the yield was still very low.

PMHS is commonly used as a reducing reagent due to its suitable reactivity, low price and low toxicity. However, replacing  $Ph_2SiH_2$  with PMHS leads to lower conversion of I and lower selectivity of II (en-



Fig. 2. Reduction of 3-methylcyclohex-2-enone (I), a  $\beta$ ,  $\beta$ -disubstituted enone can provide three possible products: 3-methylcyclohexone (II), 3-methylcyclohex-2-enol (III), and 3-methylcyclohexanol (IV).

**Table 1.** Reaction conditions and yield of the reduction of 3-methylcyclohex-2-enone (I) using different silanes and ligands. Reaction<br/>conditions: I: 0.500 mmol; molar ratio I :  $CuF(PPh_3)_3 \cdot 2MeOH$  : ligand = 1 : 0.05 : 0.05; THF: 2.0 mL, temperature:<br/>25 °C

	0.1	T · 1		<b>T</b> : /1	Q	Yield/%		
Entry	Silane, eq	Ligand	2-Metnyl-2-propanol	Time/h	Conversion/%	II	III	IV
1	$Ph_2SiH_2, 1.2$			1	68.3	65.4	0.3	0.8
2	$Ph_2SiH_2, 1.2$	—	_	5	80.0	76.6	0.5	0.9
3	$Ph_2SiH_2, 1.2$	$PPh_3$	_	20	64.8	62.8	-	2.0
4	PMHS, 3	—	_	2	46.8	32.8	0	14.0
5	PMHS, 3	DPEphos	_	1	95.8	95.2	-	0.7
6	PMHS, 3	DPEphos	$3  \mathrm{eq}$	1	98.7	94.1	-	4.6
7	PMHS, 3	DPEphos	3 eq	1.5	100	94.2	_	5.8

**Table 2.** Products distribution for the reaction (Fig. 2). Reaction conditions: I: 0.500 mmol; molar ratio I: PMHS = 1: 3; solvent:2.0 mL; temperature:  $25 \,^{\circ}\text{C}$ 

Enters	CriE(DDh) 2MaOU/mail 97	Linond	Colourt	Time/h	$\operatorname{Conversion}/\%$	Yield/%		
Entry	Cur (FPII3)3 · 2MeOn/moi %	Ligand	Solvent			II	III	IV
1	2	DPEphos	THF	2	74.4	73.5	-	0.8
2	2	DPEphos	THF	7	98.1	94.6	-	3.4
3	1	DPEphos	Toluene	7	100	97.0	_	3.0
4	0.5	DPEphos	Toluene	18	100	98.3	-	1.7
5	0.1	DPEphos	Toluene	30	63.0	58.6	_	4.4
6	1	DPBen	Toluene	1	95.3	91.5	-	3.7

try 4). The low cost of PMHS made us to explore the possibility of using PMHS as a reducing reagent despite the above facts. Fortunately, an addition of DPEphos to  $CuF(PPh_3)_3 \cdot 2MeOH$  gave a catalyst for PMHS reduction of I in a shorter reaction time and with a higher selectivity. A 95.8 % conversion of I and a 95.2 % yield of *II* were achieved within 1 h (entry 5). It has been reported that an addition of alcohol can increase the reactivity of copper-catalyzed silanes reduction of  $\alpha,\beta$ -unsaturated nitriles (Kim et al., 2005) and of  $\alpha,\beta$ -unsaturated esters (Hughes et al., 2003), which is attributed to the promotion of the metathesis of silvl ether and the regeneration of the copper hydride catalyst. Accordingly, 2-methyl-2-propanol was added to the reduction of I. The reaction proceeded faster than that in the absence of the alcohol. The conversion of I achieved in 1 h was 98.7 %, providing II in an 94.1 % yield. Unsurprisingly, the relative amount of IV increased and, fortunately, the yield of IV was just 4.6 % (entry 6). Prolonging the reaction time to

1.5 h led to complete conversion of I (entry 7) and, as expected, the yield of the over-reduction to saturated alcohol IV increased again. The yield of II reached 94.2 %, which is comparable with the yields obtained using 5 mol % of [CuHPPh<sub>3</sub>]<sub>6</sub> in 24 h reported in literature (Lipshutz et al., 1998, 2000). Thus, it can be concluded that CuH–DPEphos is more efficient than [CuHPPh<sub>3</sub>]<sub>6</sub> in catalyzing the conjugate reduction.

After a successful selective reduction of 3-methylcyclohex-2-enone, reaction (I) was carried out using different catalyst loadings attempting to minimize the amount of the catalyst used; the results are summarized in Table 2. When employing 2 mol % of DPEphos, the reaction time of 7 h was needed to achieve nearly quantitative conversion of I (entries 1– 2) with II as the dominant product displaying high selectivity for conjugate reduction. Baker et al. (2008) found that CuH–DPBen shows much higher reactivity in toluene than in THF as the catalyst in conjugate reduction of  $\alpha,\beta$ -unsaturated enones. Consequently,

	Substrate	Catalyst	Time	Yield <sup>a</sup>	
Entry	Substrate	mol %	h	%	
1	n-C <sub>5</sub> H <sub>11</sub>	0.5	15	93	
2	Ph	0.5	21	99	
3	°	0.5	18	92	
4	o	5 (+ 5 % 2-Methyl-2-propanol)	7	95 <sup>c</sup>	
5		$0.5^b$	11	$43^c$	
6	OEt	1	19	95	
7	CO <sub>2</sub> Et	2	8	89	
8	O CN	2 + (+ 2 % 2-Methyl-2-propanol)	3.5	99	

**Table 3.** Reduction of the C=C bonds in  $\alpha,\beta$ -enones, esters, and nitriles. Reaction conditions: substrate: 0.500 mmol; toluene: 2.0 mL; temperature: 25 °C

a) Isolated C=C bond reduced the product yield unless otherwise stated; b) DPBen as the ligand; c) GC yield.

toluene was used as the solvent for this reduction, and a 97.0 % yield of II was obtained along with a 3.0 % yield of IV. The loading of DPEphos can be lowered to 0.5 %, but longer reaction time is needed to achieve high conversion of I. When using 0.1 mol % of DPEphos, the reduction was very slow. In addition, the relative amount of IV increased, resulting in a less selective reduction. For comparison, DPBen was also tested in this reaction (Fig. 2), and complete conversion of I and a 95.2 % yield of II were achieved within 1 h (entry 6). When employing DPEphos as the ligand, the selectivity to II was slightly higher compared to that obtained with DPBen as the ligand.

After a successful conjugate reduction of 3-methylcyclohex-2-enone, reduction reactions of various  $\alpha,\beta$ unsaturated carbonyl compounds (including esters and nitriles) were performed; the isolated yields are given in Table 3. For less bulky  $\beta$ -monosubstituted enones, yields exceeding 90 % were obtained using 0.5 mol % of the copper–DPEphos catalyst (entries 1 and 2). However, for isophorone, a very bulky enone, the reaction was so slow that higher catalyst loading was needed to achieve a reasonable yield of the product. With 5 mol % of the catalyst, a 95 %yield of the corresponding saturated ketone was obtained (entry 4). A combination of 0.5 mol % of  $CuF(PPh_3)_3 \cdot 2MeOH$  and 0.5 mol % of DPBen as the catalyst afforded the reduced product in only a 43 %yield determined by GC in 11 h (entry 5). Replacement of  $CuF(PPh_3)_3 \cdot 2MeOH$  with  $Cu(OAc)_2 \cdot H_2O$ led to much lower conversion of I. This is very different from the results presented in literature (Baker et al., 2008). Chiu et al. (1998) found that  $\alpha,\beta$ -unsaturated enone is more reactive than  $\alpha,\beta$ -unsaturated ester, while  $\alpha,\beta$ -unsaturated nitrile is the least reactive among the  $\alpha,\beta$ -unsaturated compounds in tandem reductive aldol reactions with a copper hydride catalyst. A recent report on complete reduction of unsaturated ketones and esters clearly demonstrates that the reactivity of unsaturated esters is lower than that of unsaturated ketones (Pelšs et al., 2009). A 95 % yield of saturated ester was obtained from ethyl cyclohexylideneacetate, a  $\beta$ , $\beta$ -disubstituted unsaturated ester, using the CuF(PPh<sub>3</sub>)<sub>3</sub> · 2MeOH–DPEphos catalyst (entry 6). For diethyl 2-benzylidenemalonate, an  $\alpha$ -substituted unsaturated ester, 2 mol % of the catalyst was required to obtain the reduced ester in a 89 % yield within a reasonable reaction time (entry 7). The catalytic system is also applicable for the reduction of  $\alpha$ , $\beta$ -unsaturated mononitrile (entry 8).

#### Conclusions

In summary, copper hydride derived from  $CuF(PPh_3)_3 \cdot 2MeOH-DPEphos-PMHS$  can catalyze the reduction of electron-deficient olefins, e.g.  $\alpha,\beta$ -unsaturated ketones, esters, and nitriles, providing high product yields. The catalyst system might be applied for the reduction of other polar electron-deficient C=C bonds which conjugate to nitro, sulfonate and phosphite electron-withdrawing groups.

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