One-Pot Sequential 1,4- and 1,2-Reductions of α,β-Unsaturated δ-Lactones to the Corresponding δ-Lactols with CuCl and $NaBH_4$ in Methanol

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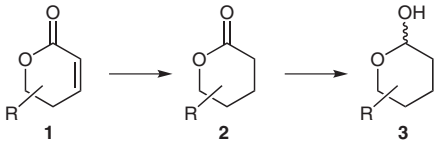
Abstract: An efficient, one-pot method for the highly chemoselective synthesis of δ-lactols from α,β-unsaturated δ-lactones using CuCl and $NaBH_4$ in methanol was developed.

Key words: copper, hydrides, lactones, lactols, reduction

δ-Lactols, which are the cyclic equivalents of δ-hydroxy aldehydes, are useful synthons for a broad range of intermediates for the synthesis of natural products and biologically active compounds.[1] δ-Lactols **3** can be generally prepared by a two-step reduction of α,β-unsaturated lactones **1** (Scheme 1), which will be easily prepared by ring-closing metathesis.[2]



Scheme 1 Reduction of α,β-unsaturated lactones **1** to lactols **3**

Typically, the conjugated double bond of lactones **1** is hydrogenated, and then the carbonyl group of α,β-saturated lactones **2** is reduced with diisobutylaluminum hydride (DIBAL-H).[1b,e,f,i,p] However, both of these reduction reactions suffer from poor functional-group tolerance. In the hydrogenation reaction, other double bonds, as well as triple bonds and benzyl ether groups, can also be reduced. In addition, DIBAL-H has the potential to reduce ester, acetate, and cyano groups. To our knowledge, no effective methods leading to lactols **3** from α,β-unsaturated lactones **1** with high functional-group tolerance have previously been reported. Furthermore, obtaining lactols **3** directly from α,β-unsaturated lactones **1** in one pot is challenging. In this letter, we report that CuCl and $NaBH_4$ in MeOH is a simple, effective reagent system for highly chemoselective sequential 1,4- and 1,2-reductions of α,β-unsaturated lactones **1** to lactols **3** in one pot.

We chose α,β-unsaturated benzyl-substituted lactone **4** as a representative substrate to optimize the reaction conditions for the sequential reductions (Table 1). We found that reduction of **4** with three molar equivalents of $NaBH_4$ alone in MeOH at room temperature for three hours gave five products, along with recovered starting material; the main product was diol **5e**, which was produced by overreduction (Table 1, entry 1). The use of ten equivalents of $NaBH_4$ at a lower temperature (–50 °C) resulted in the recovery of most of the starting material (70%, Table 1, entry 2). Surprisingly, the use of 0.5 equivalents of CuCl along with three equivalents of $NaBH_4$ gave the desired lactol **5b** in moderate yield (Table 1, entry 3). This combination of reagents is known to effectively reduce α,β-unsaturated esters to saturated esters via 1,4-reduction by CuH generated in situ,[3] but the application of this combination to sequential reductions of α,β-unsaturated lactones has not previously been reported. Further optimization experiments revealed that 0.5 equivalents of CuCl and ten equivalents of $NaBH_4$ in MeOH provided lactol **5b** in high yield almost without overreduction (Table 1, entry 4). Under these reaction conditions, we observed that upon addition of the CuCl, the reaction temperature briefly rose from –50 to ca. –20 °C, owing to the exothermic nature of the reaction. When the amount of CuCl was decreased to 0.2 equivalents, some amount of **5a** remained (Table 1, entry 5). Interestingly, the combination of 0.5 equivalents of CuCl and one equivalent of $NaBH_4$ gave mostly saturated lactone **5a** (Table 1, entry 6). When ten equivalents of $NaBH_4$ were used with $NiCl_2 \cdot 6H_2O$ instead of CuCl, a good yield of **5b** was obtained (Table 1, entry 7),[1a] whereas $CoCl_2$ gave only a moderate yield (Table 1, entry 8).[1a,4] The order of the addition of CuCl and $NaBH_4$ was important: In the optimized protocol, $NaBH_4$ was added to the solution of α,β-unsaturated lactone in MeOH at –50 °C, and the solution was stirred at this temperature for 15 minutes; then CuCl was added to the reaction mixture, at which point the reaction began immediately, as indicated by the evolution of H_2 gas.

Using the optimized reaction conditions, we explored the substrate scope and generality of the CuCl–$NaBH_4$/MeOH reagent system by carrying out sequential reductions of various substituted α,β-unsaturated lactones (Table 2). Substitution at the α-, β-, or γ-position had no deleterious effects; the desired lactols **7a**–**c** were obtained in high yields. Experiments with δ-lactones with a substituted phenyl group at the δ position indicated that electron-donating and electron-withdrawing substituents on the benzene ring had little effect on the yields of the de-

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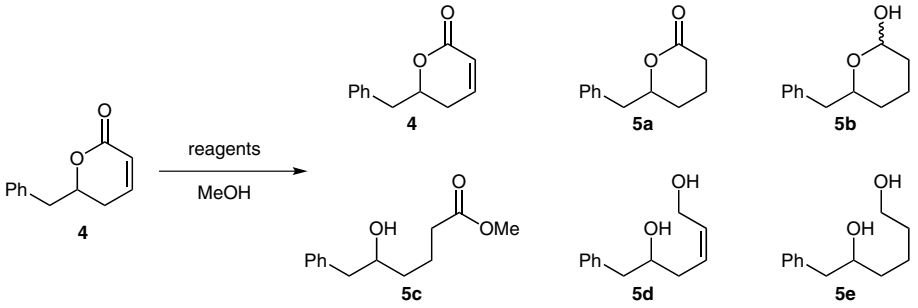
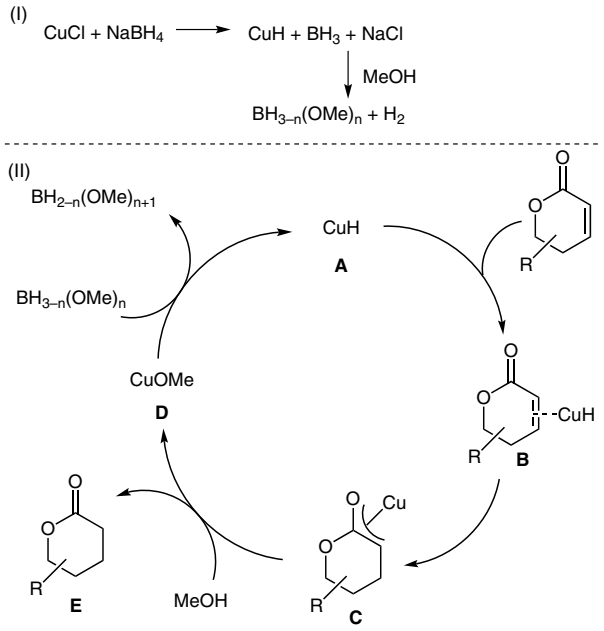
Table 1 Optimization of the Reaction Conditions[a]



Entry	Reagents (equiv)	Bath temp (°C)	Time (h)	Yield of **4** (%)[b]	Yield of **5a** (%)[b]	Yield of **5b** (%)[b]	Yield of **5c** (%)[b]	Yield of **5d** (%)[b]	Yield of **5e** (%)[b]
1	$NaBH_4$ (3)	r.t.	3	6	<1	7	3	1	71
2	$NaBH_4$ (10)	–50	1	70	4	–[c]	–[c]	<1	13
3	CuCl (0.5), $NaBH_4$ (3)	0	1	–[c]	5	68	<1	–[c]	16
4	CuCl (0.5), $NaBH_4$ (10)	–50 to –20	1	–[c]	<1	90	<1	–[c]	<1
5	CuCl (0.2), $NaBH_4$ (10)	–50 to –20	1	<1	7	79	–[c]	–[c]	<1
6	CuCl (0.5), $NaBH_4$ (1)	–50 to –20	1	<1	90	<1	–[c]	–[c]	–[c]
7	$NiCl_2·6H_2O$ (0.5), $NaBH_4$ (10)	–50 to –20	1	–[c]	<1	86	–[c]	–[c]	<1
8	$CoCl_2$ (0.5), $NaBH_4$ (10)	–50 to –20	1	–[c]	35	58	<1	–[c]	–[c]

[a] General conditions: α,β-unsaturated lactone **4** (0.5 mmol), MeOH (5 mL).
[b] Because **4**, **5a**, and **5c** were inseparable, their yields were determined by NMR spectroscopy; the other yields are isolated yields.
[c] Not detected.

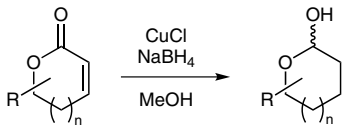


Scheme 2 Mechanism of 1,4-reduction of α,β-unsaturated lactones by CuCl–$NaBH_4$ in MeOH

sired lactols **7d**–**g**. Furthermore, the carboxylate ester group of **6f** and the cyano group of **6g** were unaffected under these reduction conditions. An ethyl ester and an acetate functional group, which are sensitive to DIBAL-H reduction, were tolerated well, as were an isolated double bond and triple bonds, including a terminal triple bond; the desired lactols **7h**–**l** were obtained without hydroboration.[5] However, we found that α,β-unsaturated γ-lactone **6m** and ε-lactone **6n** gave the corresponding saturated lactones in 90% and 85% yields, respectively. That is, the five- and seven-membered ring lactones underwent only 1,4-reduction without subsequent 1,2-reduction.

We propose that our one-pot sequential reductions of α,β-unsaturated δ-lactones with CuCl and $NaBH_4$ in MeOH proceeds via successive CuH-catalyzed reduction reactions. CuH-catalyzed 1,4-reduction of α,β-unsaturated carbonyl compounds by CuCl and $NaBH_4$ is known to occur,[3,6] and the first step of our reaction can be expected to proceed by a similar mechanism. Specifically, reducing species CuH and $BH_{3-n}(OMe)_n$ are generated by reaction of CuCl, $NaBH_4$, and MeOH (Scheme 2, I). CuH (**A**) then reacts with the α,β-unsaturated lactone, a Michael acceptor, to form π-complex **B**, which reacts with MeOH to form lactone **E** via copper enolate **C** (Scheme 2, II). Reduction of generated copper alkoxide **D** by $BH_{3-n}(OMe)_n$ regenerates CuH.

Table 2 Sequential 1,4- and 1,2-Reductions of α,β-Unsaturated Lactones with CuCl and $NaBH_4$ in MeOH[a]



6a–n **7a–n**

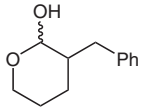
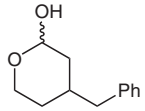
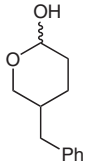
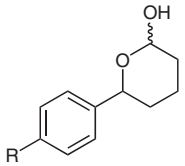
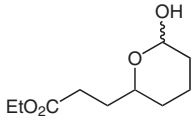
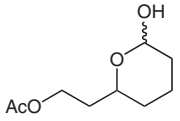
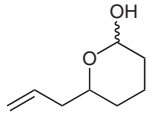
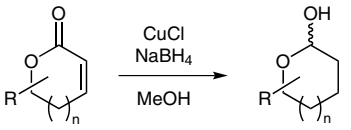
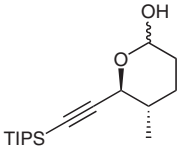
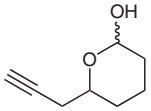
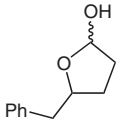
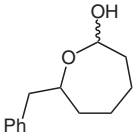
Entry	Product **7**	Yield of **7** (%)
1	 **7a**	92
2	 **7b**	83
3	 **7c**	79
4	 **7d** R = H **7e** R = OMe **7f** R = CO_2Me **7g** R = CN	90 91 85 80
5	 **7h**	88
6	 **7i**	83
7	 **7j**	70

Table 2 Sequential 1,4- and 1,2-Reductions of α,β-Unsaturated Lactones with CuCl and $NaBH_4$ in MeOH[a]



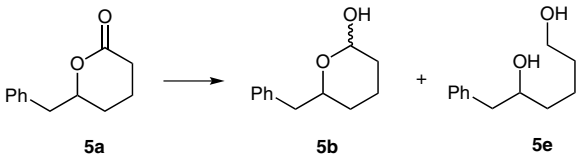
6a–n **7a–n**

Entry	Product **7**	Yield of **7** (%)
8	 **7k**	91
9	 **7l**	78
10	 **7m**	0[b]
11	 **7n**	0[b]

[a] General conditions: α,β-unsaturated lactones **6a–n** (1.0 mmol), CuCl (0.5 mmol), $NaBH_4$ (10 mmol), MeOH (10 mL), –50 to –20 °C, 1 h. Yields are isolated yields.
[b] The corresponding saturated lactones were isolated in 90% and 85% yields, respectively (data not shown).

We propose that the second step of the reaction sequence involves 1,2-reduction of saturated lactone **E** by the same reducing species, as indicated by the fact that saturated lactone **5a** can be reduced to lactol **5b** under the optimized reaction conditions (Table 3, entry 1).[7] This result indicates that $BH_{3-n}(OMe)_n$ and CuH generated in situ were the reducing species that provided the lactol. In addition, in the absence of CuCl, reduction with ten equivalents of $NaBH_4$ gave only overreduction product diol **5e**. Under these conditions, unreacted excess $NaBH_4$ overreduced the hydroxyl aldehyde that was in equilibrium with the lactol during the workup with aqueous NH_4Cl (Table 3, entry 2). We speculate that in the presence of CuCl, excess $NaBH_4$ is rapidly transformed to $B(OMe)_3$, which prevents overreduction after the successive 1,4- and 1,2-reductions by CuH and $BH_{3-n}(OMe)_n$. Additionally, we propose that activation of the carbonyl group by CuH (**F**) facilitates conversion of saturated lactone **E** into lactol **G** (Scheme 3).

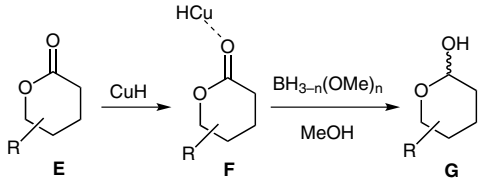
Table 3 1,2-Reduction of Saturated Lactone **5a**



5a **5b** **5e**

Entry	Conditions	Yield of **5b** (%)[a]	Yield of **5e** (%)[a]
1	CuCl (0.5 equiv), $NaBH_4$ (10 equiv), MeOH, –50 to –20 °C, 1 h	88	<1
2	$NaBH_4$ (10 equiv), MeOH, –50 to –20 °C, 1 h	<1	90

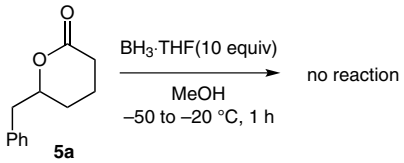
[a] Yields are isolated yields.



E **F** **G**

Scheme 3 1,2-Reduction of saturated lactones **E** by CuCl and $NaBH_4$ in MeOH

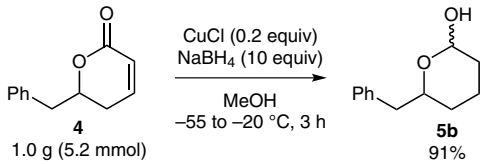
To confirm the participation of CuH in the 1,2-reduction, we conducted an experiment using BH_3·THF as a reducing agent in the absence of CuH (Scheme 4). Specifically, saturated lactone **5a** was treated with ten equivalents of BH_3·THF in MeOH at –50 °C, and then the reaction temperature was raised to –20 °C. That no reaction occurred under these conditions supports the idea that CuH is involved in the 1,2-reduction.



5a

Scheme 4 Treatment of saturated lactone **5a** with BH_3·THF in MeOH

Next, we scaled the reaction up to 1.0 g (5.2 mmol) of α,β-unsaturated lactone **4** as a substrate (Scheme 5). At this scale, we could decrease the amount of CuCl from 0.5 equivalents to 0.2 equivalents, and we obtained the desired lactol **5b** in excellent yield (91%). However, as shown in entry 5 of Table 1, it turned out that at least 0.5 equivalents of CuCl were required in a 0.5 mmol scale reaction, and we suppose the regeneration of CuH and



4 1.0 g (5.2 mmol) **5b** 91%

Scheme 5 Scale-up experiment

lifetime of $BH_{3-n}(OMe)_n$ were not enough to complete the second-step 1,2-reduction.

Comparison of the reactivities of the five-, six-, and seven-membered ring lactones shown in Table 2 revealed that unlike the six-membered ring lactones, the five- and seven-membered ring lactones gave only 1,4-reduction products; that is, the 1,2-reduction to the corresponding lactols did not occur. To explore the origin of these reactivity differences, we performed density functional theory calculations. Previously, Wiberg et al. reported that the calculated proton affinity of a δ-lactone is 8 kcal/mol greater than that of a γ-lactone.[8] Although CuH is a soft Lewis acid in comparison to a proton, in a similar concept, we thought the reactivity of these lactones might be explained by their coordinating affinity to CuH. However, our density functional theory calculations of the energies of complexes between CuH and model γ-, δ-, and ε-lactones did not provide any clear evidence to support the involvement of CuH affinity in the observed reactivity differences between these lactones (see Supporting Information).

In summary, we have described a new highly chemoselective one-pot method to prepare δ-lactols in high yields from α,β-unsaturated δ-lactones using CuCl and $NaBH_4$ in methanol.[9] This simple and convenient protocol constitutes a new method for the preparation of useful synthons for synthetic chemistry.

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Supporting Information for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083.

References and Notes

(1) For example, see: (a) Bhattacharjee, A.; Soltani, O.; De Brabander, J. K. *Org. Lett.* **2002**, *4*, 481. (b) Statsuk, A. V.; Liu, D.; Kozmin, S. K. *J. Am. Chem. Soc.* **2004**, *126*, 9546.

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(7) It is noteworthy to mention that the reduction of an saturated lactone to a lactol with CuCl and $NaBH_4$ in MeOH has not been reported previously.

(8) Wiberg, K. B.; Waldron, R. F. *J. Am. Chem. Soc.* **1991**, *113*, 7705.

(9) **General Procedure**

$NaBH_4$ (10 mmol, 10 equiv) was added in three roughly equal portions to a stirred solution of an α,β-unsaturated δ-lactone (1.0 mmol) in MeOH (10 mL; lactone concentration, 0.1 M) at –50 °C in a reaction flask connected to a drying tube containing $CaCO_3$. After the solution was stirred for 15 min at –50 °C, the drying tube was removed, and CuCl (0.5 mmol, 0.5 equiv) was added to the reaction mixture, which immediately turned into a black suspension and evolved H_2 gas (the flask was kept open to let out the gas). The reaction temperature was warmed to –20 °C over the course of 1 h, and the reaction was quenched at that temperature with sat. aq NH_4Cl. Then EtOAc and H_2O were added to the mixture, which was vigorously stirred for 30 min at r.t. The resulting clear solution was extracted with EtOAc, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude mixture of products was purified by silica gel flash column chromatography with gradient of EtOAc and *n*-heptane as eluents to afford the desired δ-lactol.

6-Benzyltetrahydro-2*H*-pyran-2-ol (5b)

White solid (90%, *cis*/*trans* = 1.4:1). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.30–7.27 (m, 4 H, *cis trans*), 7.22–7.20 (m, 6 H, *cis trans*), 5.28 (br s, 1 H, *trans*), 4.66 (m, 1 H, *cis*), 4.19 (m, 1 H, *trans*), 3.64 (m, 1 H, *cis*), 3.06 (d, *J* = 4.0 Hz, 1 H, *cis*-OH), 2.95 (dd, *J* = 14.0, 7.0 Hz, 1 H, *cis*), 2.81 (dd, *J* = 14.0, 7.0 Hz, 1 H, *trans*), 2.73 (dd, *J* = 14.0, 7.0 Hz, 1 H, *cis*), 2.67 (dd, *J* = 14.0, 7.0 Hz, 1 H, *trans*), 2.55 (br s, 1 H, *trans*-OH), 1.87–1.80 (m, 3 H, *cis trans*), 1.71–1.42 (m, 6 H, *cis trans*), 1.35–1.28 (m, 2 H, *cis trans*), 1.25–1.18 (m, 1 H, *cis*). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 138.7 (*trans*), 138.5 (*cis*), 129.4 (*cis*), 129.4 (*trans*), 128.2 (*cis*), 128.2 (*trans*), 126.2 (*cis*), 126.1 (*trans*), 96.5 (*cis*), 92.0 (*trans*), 77.3 (*cis*), 69.7 (*trans*), 42.8 (*trans*), 42.6 (*cis*), 32.5 (*cis*), 30.9 (*trans*), 30.0 (*cis*), 29.6 (*trans*), 21.9 (*cis*), 17.3 (*trans*). IR (ATR): ν = 3318, 2942, 2861, 1353, 1142, 1047, 1010, 903, 746, 700 cm^{-1}. HRMS (ESI$^+$): *m/z* calcd for: $C_{12}H_{20}NO_2$ $[M + NH_4]^+$: 210.1489; found: 210.148.

