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LETTERS

Copper(II) Mediated Regioselective Acetoxylation of Allylic Acetates and 1,4-Diacetoxylation of Alkenes

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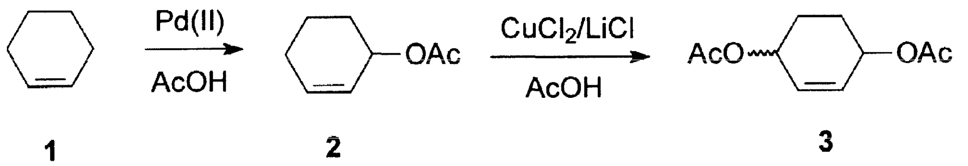
Summary. Copper(II) chloride in presence of lithium chloride in acetic acid oxidizes allylic acetates with high regioselectivity. Tandem allylic C-H bond functionalization of unsubstituted alkenes could be accomplished by using copper(II) chloride / lithium chloride reagent together with catalytic amounts of palladium(II) salts.

Allylic C-H bond functionalization of alkenes is a reaction of considerable value in organic synthesis.[1] An important type of these reactions provides allylic alcohols and acetates by allylic oxidation of alkenes. Although, one of the most widely used reagents employed in allylic oxidations is SeO_2, transition metal (e.g. palladium and copper) based procedures are receiving increasing attention due to their simplicity and efficiency.[1-4] There are two major deficiencies that often obscure the usefulness of these oxidative transformations: (1) a poor regioselectivity due to a facile allylic rearrangement; (2) the oxidation rate is slow in presence of electron withdrawing substituents, such as acetate or hydroxy group. However, we have now found that copper(II) chloride in the presence of lithium chloride is suitable for regioselective oxidation of various alkenes bearing electron-withdrawing allylic substituents. Furthermore, the copper(II) chloride / lithium chloride reagent together with catalytic amounts of palladium(II) salts can be employed for 1,4-diacetoxylation of unsubstituted alkenes.



(1)

Oxidation of Allylic Acetates. Although the usual reaction conditions of palladium catalysed allylic oxidation of alkenes provide monooxidized products, analysis of the reaction mixture by ^1H NMR spectroscopy or GC indicates regioselective formation of 1,4-oxidized alkenes as minor products (1-2 %). Thus, when cyclohexene (**1**) was oxidized with $Pd(OAc)_2$ in acetic acid using the reaction conditions reported by Åkermark and co-workers,[2] traces of 1,4-diacetoxy-2-cyclohexene (**3**) was also formed together with the main product 1-acetoxy-2-cyclohexene (**2**). The amount of the 1,4-diacetoxy product (**3**) could be considerably

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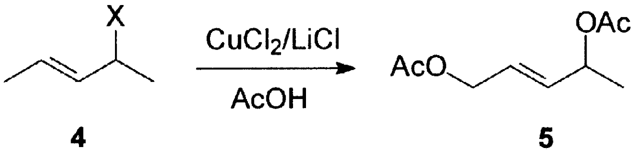
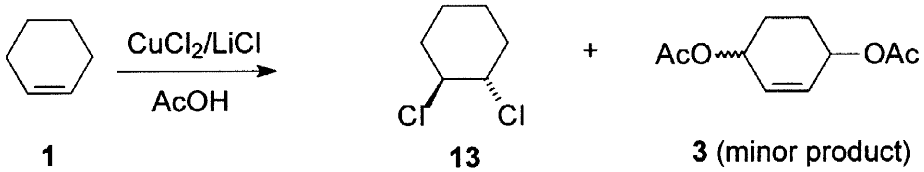
increased by adding $CuCl_2$ and LiCl to the reaction mixture (eq 1). Subsequent studies showed that the first oxidation step is catalysed by palladium(II) and $CuCl_2$ reoxidizes the quinone co-catalyst. However, we found that oxidation of **2** can be carried out by the $CuCl_2$/LiCl reagent alone without the assistance of palladium. Optimization of the reaction conditions (Method A)[5] afforded **3** with a fairly good yield (Table 1, entry 1). Using copper(II) chloride was crucial for oxidation of **2**. Employment of other copper(II) salts, such as $Cu(OAc)_2$, or using Cu(I)Cl did not result in the formation of 1,4-diacetate **3**. Radical initiators, which are used in Cu(I) catalysed monooxidation of alkenes[4] had no effect on the Cu(II) mediated oxidation reaction. We have also studied the dependence of the reaction rate on the LiCl concentration. It was found that the rate of oxidation was considerably increased by increasing the LiCl concentration. High Cl^- concentration improves the solubility of $CuCl_2$ (probably due to the formation of $CuCl_4^{2-}$) in acetic acid, and it also prevents the formation of $Cu(OAc)_2$, which is poorly soluble in the reaction medium.



X = OAc,OH, Cl, NH-Tos (2)

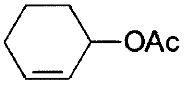
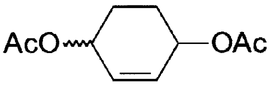
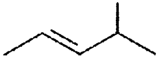
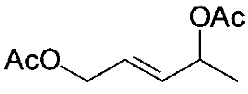
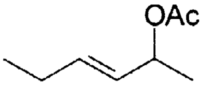
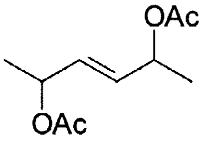
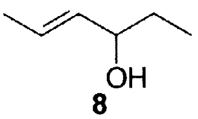
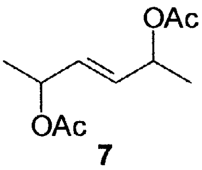
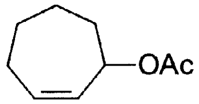
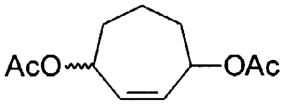
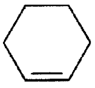
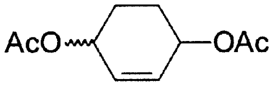
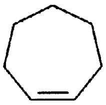
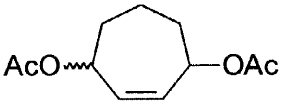
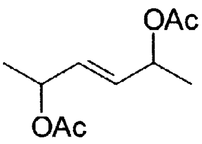
The observation that $CuCl_2$/LiCl is suitable for oxidation of **2** led us to investigate the oxidation of other allylic acetates. Various allylic acetates could be oxidized to 1,4-diacetates by $CuCl_2$/LiCl in acetic acid. In the case of the pentenyl system **4** several polar allylic substituents involving OH, Cl and NH-Tos were tested (eq 2), however the reactions using Method A[5] afforded allylic diacetates (**5**) in all cases. The yields of these reactions were approximately the same as in the case of substrate **4** (entry 2). We found that under the ususal reaction conditions, or at lower temperature (40°C), the polar substituents (X) were easily exchanged to the acetoxy group, thereby the direct substrate of the oxidation was always the acetate (X = OAc, entry 2). This also implies that the oxidation reactions can also be carried out from allylic halides and alcohols providing 1,4-acetates as final products. It is well known that **6** and the acetate of **8** can easily be converted to each other by palladium catalysed allylic rearrangement.[2] We found that $CuCl_2$ also induced allylic isomerization of these compounds, thus oxidation of **6** and **8** by $CuCl_2$/$LiCl_2$ afforded the same final product **7** (entries 3, 4). *Cis-trans* isomerization was not observed in oxidation of the acyclic substrates (**4**, **6** and **8**). Cycloheptenyl acetate **9** could also be oxidized leading to the 1,4-oxidized compound **10** (entry 5). The regiochemistry of the reaction was excellent, however the stereoselectivity was rather poor.

Diacetoxylation of Alkenes. Considering the above results, a tandem allylic oxidation of alkenes is expected by using the $CuCl_2$/LiCl reagent. However, the $CuCl_2$/LiCl system was not suitable for direct oxidation of simple alkenes, such as **1**, **11** and **12**. Attempted oxidation of **1** under the reaction conditions A resulted in extensive Cl^- addition (eq 3), which was certainly faster than the oxidation, since this reaction yielded only about 10 % of **3**. Addition of NaOAc prohibited the Cl^- addition, but it also slowed down the oxidation reaction, because of the formation of $Cu(OAc)_2$. However, monooxidation of alkenes can easily be carried out under similar reaction conditions by Pd(II) catalysed transformations.[2]



(3)

Table 1. Copper(II) Assisted Oxidation Reactions

entry	substrate	method[a]	t [°C]	time [h]	product	yield [%]	cis/trans
1	 **2**	A	70	16	 **3**	66	70/30
2	 **4**	A	80	24	 **5**	56	
3	 **6**	A	60	6	 **7**	48	
4	 **8**	A	60	6	 **7**	50	
5	 **9**	A	80	16	 **10**	54	62/38
6	 **1**	B	100	48	 **3**	49	61/39
7	 **11**	C	60, 80	28, 16	 **10**	28	62/38
8	 **12**	C	65, 60	46, 16	 **7**	39	

[a] Method A: 2.6 equiv. of $CuCl_2$ and 11.3 equiv. of LiCl in AcOH; Method B: 2.6 equiv. of $CuCl_2$, 4.9 equiv. of LiCl, 4.9 equiv. of NaOAc, 0.1 equiv. of DDQ and 0.05 equiv. of $PdCl_2$ in AcOH. Method C: first step: 0.2 equiv. of benzoquinone, 2 equiv. of MnO_2 and 0.05 equiv. of $Pd(OAc)_2$ in AcOH, second step: 2.6 equiv. of $CuCl_2$, 11.3 equiv. of LiCl.

Accordingly, employment of $CuCl_2$/LiCl reagent together with a catalytic amount of $PdCl_2$ gave the 1,4-diacetoxy compound **3** from cyclohexene (Method B). For other substrates (**11**, **12**), however, Method B could not be applied, because of extensive side reactions. Therefore the first oxidation step was carried out under the usual reaction conditions of the Pd(II) catalysed allylic oxidation,[2] which was followed by subsequent addition of the $CuCl_2$/LiCl reagent (Method C) without isolation of the monooxidized products (**6**, **8** and **9**). Thus, the good compatibility of the Pd(II) catalysed and Cu(II) mediated oxidation processes allows a tandem 1,4-acetoxylation of **11** and **12** (entries 7 and 8). Interestingly, the Cu(II) mediated second oxidation step (6-16 hours) was faster than the Pd(II) catalyzed first allylic oxidation (28-46 hours).

In summary, in this study we describe a new Cu(II) assisted oxidation procedure affording regioselective oxidation of allylic acetates and their analogs bearing a polar allylic substituent. In combination with catalytic amounts of Pd(II) salts this procedure is suitable for tandem C-H bond functionalization of unsubstituted olefins. As far as we know this is the first example reported for Cu(II) mediated acetoxylation of alkenes bearing electron withdrawing substituents in the allylic position. The regioselectivity of this process is excellent, however further studies are necessary to improve the stereoselectivity of the reaction.

References and Notes:

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(5) **Method A**: To the allylic substrate (0.8 mmol) dissolved in acetic acid (10 ml) LiCl (9 mmol, 0.38 g) and $CuCl_2$ (2 mmol, 0.28 g) was added in this order. The reaction mixture was stirred for 6-16 hours at the given temperature (Table 1). After cooling to room temperature the reaction mixture was diluted with water (25 ml) and extracted with 1:4 mixture of ether and pentane. The organic phase was extracted with water and 1 M NaOH solution and dried over $MgSO_4$. After evaporation the crude product was purified by silica-gel chromatography. **Method B**: To cyclohexene (5 mmol, 0.41 g) dissolved in acetic acid (40 ml) LiCl (25 mmol, 1.06 g), $CuCl_2$ (13 mmol, 1.75 g), $PdCl_2$ (0.3 mmol, 0.04 g), DDQ (0.5 mmol, 0.11 g) and NaOAc (25.2 mmol, 2.07 g) was added in this order. The reaction mixture was stirred at 100 °C for 48 hours, thereafter it was worked up (see above). **Method C**: To the corresponding alkene (7 mmol) dissolved in acetic acid (50 ml) $Pd(OAc)_2$ (0.4 mmol, 0.08 g), benzoquinone (1.4 mmol, 0.15 g) and MnO_2 (14 mmol, 1.2 g) was added in this order. The reaction mixture was stirred at the given temperature until the alkene consumed.[2] Thereafter, LiCl (80.4 mmol, 3.4 g) and $CuCl_2$ (18.4 mmol, 2.5 g) dissolved in acetic acid (30 ml) was added at the appropriate temperature and the reaction mixture was stirred for an additional 16 h, followed by work up.