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Unique Property of Copper(I) Chloride as a Radical Initiator as well as a Lewis Acid: Application to CuCl-Catalyzed Aldol Reaction of α,β-Unsaturated Ketones with Bu_3SnH

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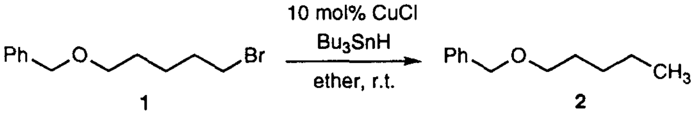
Abstract
Copper (I) chloride in combination with tributyltin hydride showed unique character as an initiator of certain radical reactions. Hydrostannation of α,β-unsaturated ketones with Bu_3SnH was initiated by CuCl and the resulting tin enolates underwent subsequent aldol reaction with aldehydes under the influence of CuCl as a Lewis acid catalyst. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Copper and compounds; Tin and compounds; Radicals and radical reactions; Aldol reactions.

During the recent couple of decades, the application of free radical reactions has grown enormously in organic synthesis providing a wealth of useful new methodologies [1-3]. Further, there has been intensive development in the control of stereoselectivity, which has expanded the scope of these reactions [4-13]. The great success of enantio- and/or diastereoselective radical reactions can be partially ascribed to the introduction of new radical initiators such as triethylborane making it feasible to perform these stereoselective reactions at or below room temperature [14,15]. Recently, Yamamoto and co-workers reported the successful utilization of zinc chloride as a radical initiator as well as a chelating agent for the stereoselective allylation of α-bromoglycine derivatives [16,17]. In addition to these findings, we wish to report that copper (I) chloride exhibits unique character as an initiator of certain radical reactions in combination with tributyltin hydride [18].

Scheme 1



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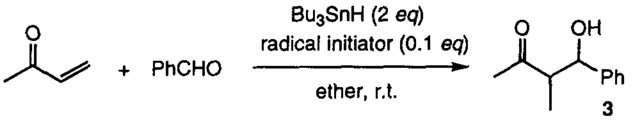
First, we carried out the radical reduction of alkyl bromide **1** with Bu_3SnH. Simple treatment of **1** with Bu_3SnH (1.1 equiv) in dry ether at room temperature gave none of the reduction product **2** after stirring for several hours. In contrast, however, when the reaction was carried out in the presence of catalytic CuCl (10 mol%) under otherwise similar reaction conditions, the corresponding reduction product **2** was obtained in 69% isolated yield. Attempted addition of galvinoxyl (5 mol%) completely halted the reaction, implying the intervention of a radical mechanism for the reduction.

The interesting feature of our approach is a facile one-pot hydrostannation-aldol reaction sequence, where CuCl can initiate the radical addition of Bu_3SnH to α,β-unsaturated ketones and also catalyze the subsequent aldol reaction of the resulting tin enolates with aldehydes [19]. For instance, treatment of the reaction mixture of methyl vinyl ketone (1 equiv), Bu_3SnH (2 equiv) and benzaldehyde (3 equiv) in dry ether with catalytic CuCl (10 mol%) at room temperature for 2 h resulted in formation of 4-hydroxy-3-methyl-4-phenylbutan-2-one (**3**) in 72% yield [20]. Notably, the yield of the aldol product was dramatically lowered without CuCl. Use of catalytic Et_3B as a radical initiator afforded **3** in only 3% yield under similar reaction conditions mainly due to its feeble Lewis acidity.



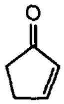
3

radical initiator : none : 2%
Et_3B : 3%
CuCl : 72% (*syn*/*anti* = 3:1)

Other selected examples listed in Table 1 clearly demonstrate the effectiveness of CuCl as a radical initiator in hydrostannation of α,β-unsaturated carbonyl compounds as well as a Lewis acid catalyst for aldol reactions, thereby allowing the present one-pot synthesis of β-hydroxy ketones under mild conditions. Aldol products were uniformly obtained in good yield with alkyl and aryl vinyl ketones (entries 1, 4 and 6). β-Substituent significantly lowered the reaction rate and only a trace amount of the product was isolated in the case of 2-cyclopenten-1-one (entries 7 and 8). Aliphatic and α,β-unsaturated aldehydes can be employed for the present transformation, giving the corresponding β-hydroxy ketones (entries 2, 3 and 5). Unfortunately, diastereoselectivity was moderate regardless of the structure of substrates.

The typical experimental procedure is as follows [21]: To a solution of methyl vinyl ketone (41.6 μL, 0.5 mmol) and benzaldehyde (153 μL, 1.5 mmol) in dry ether (5 mL) were added Bu_3SnH (269 μL, 1.0 mmol) and CuCl (5 mg, 0.05 mmol) sequentially at room temperature under argon. The reaction mixture was stirred at room temperature for 2 h and poured into saturated NH_4Cl solution. Extractive workup was performed with ether and the organic extracts were dried over Na_2SO_4. Evaporation of the solvents and purification of the residual oil by column chromatography on silica gel (ether/hexane = 1:1 as eluant) gave 4-hydroxy-3-methyl-4-phenylbutan-2-one (3) (64.4 mg, 0.36 mmol; 72% yield) as a colorless oil.

Table 1. CuCl-Catalyzed One-Pot Hydrostannation-Aldol Reactions of α,β-Unsaturated Ketones with Aldehydes [a]

entry	enone	aldehyde	time (h)	% yield, [b] (*syn*/*anti*) [c]
1	$CH_3COCH{=}CH_2$ (MVK)	PhCHO	2	72 (3 : 1)
2		$C_7H_{15}CHO$	3	69 (2.4 : 1)
3		$PhCH{=}CHCHO$	3	65 (1.3 : 1)
4	$PhCOCH{=}CH_2$	PhCHO	2	85 (2.8 :1)
5		$C_7H_{15}CHO$	2	54 (3.3 : 1)
6	$Ph(CH_2)_2COCH{=}CH_2$	PhCHO	2	91 (2.6 : 1)
7	$PhCOCH{=}CHBu$	PhCHO	5	15 (1.5 : 1)
8		PhCHO	3	trace

[a] The reaction was carried out with aldehyde (3 equiv), Bu_3SnH (2 equiv) and CuCl (10 mol%) in dry ether at room temperature. [b] Isolated yield of aldol products. [c] Determined by ^1H NMR analysis (Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Chapter 2.).

Acknowledgments

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[20] Use of stoichiometric amount of CuCl significantly decreased the yield of 3, probably because of the predominant formation of CuH which could easily decompose under the reaction conditions. See: Hajos A. Complex Hydrides. Amsterdam: Elsevier, 1979.

[21] Toluene can be also used as solvent.