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Preliminary communication

The Kharasch reaction revisited: CuX_3Li_2-catalyzed conjugate addition reactions of Grignard reagents ☆

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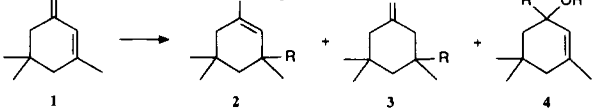
Abstract

The conjugate addition of Grignard reagents RMgX to α,β-unsaturated ketones and esters is effectively catalyzed by soluble copper ate-complexes of the type CuX_3Li_2, e.g. CuI · 2LiCl. In the presence of Me_3SiCl the corresponding ketone enolsilanes are formed in high yield and selectivity. Diasteroselectivity in the case of chiral ketones is similar to that observed by using stoichiometric amounts of cuprates R_2CuLi. Thus CuX_3Li_2-catalyzed 1,4-additions of Grignard reagents may be an industrially viable process.

Keywords: Copper; Magnesium; Lithium; Silicon; Ketone; Ensolsilanes

The 1,4-addition of cuprates R_2CuLi to α,β-unsaturated carbonyl compounds is a widely used reaction in organic chemistry [1]. In the case of sterically hindered substrates, higher order cuprates [2] and/or additives such as Me_3SiCl must be employed which exert an accelerating effect [3]. Whereas all these variations are based on stoichiometric amounts of copper reagents, the CuX-catalyzed conjugate addition of Grignard reagents RMgX as described by Kharasch requires only catalytic amounts of copper [1,4]. However, reproducibility with respect to 1,4- vs. 1,2-selectivity is influenced by impurities in the magnesium and by the nature of the halogen in the copper salt [5]. The use of CuBr · SMe_2 [6], which is more soluble in ethereal medium than CuX, appears to be considerably more efficient [1,7]. Nevertheless, it has been claimed that the combination of CuBr · SMe_2, Me_3SiCl (200 mol.%) and hexamethylphosphoric acid trisamide (HMPA) (250 mol.%) is the ideal reagent system [3d,8]. Recently we reported the use of CuX_3Li_2 (X = halide) [9] as a cheap and highly efficient homogeneous catalyst in the conjugate addition of dialkylmagnesium reagents R_2Mg to α,β-unsaturated ketones and esters, a process that can be carried out with or without Me_3SiCl as an additive [10]. We now show that these Cu(I) salts are also excellent catalysts in the classical Kharasch reaction.

Upon reacting the sterically hindered isophorone **1** with CH_3MgI (110 mol.%) in the presence of CuI · 2LiCl (10 mol.%) and Me_3SiCl (100 mol.%) at 0°C in tetrahydrofuran (THF), a smooth reaction occured within 30 min, providing the enolsilane **2a**. 1,4-Selectivity is greater than 99%, the ratio of silylated product **2a** to ketone **3a** also being excellent (99 : 1). Similar results were obtained with PhMgBr (Table 1). The preparation of the catalyst involves simple mixing of CuI and LiCl in THF which results in a homogeneous solution. Special care such as recrystallization of CuI is not necessary. Carbonyl compounds **5–10** were also tested successfully (Table 1). Although a systematic comparison with the use of the traditional CuBr · SMe_2 catalyst was not made in all cases, Table 1 (entries 1, 2, 8, 10, 14 and 15) shows that the CuI · 2LiCl-catalyzed processes are just as efficient or slightly better. Indeed, CuBr ·



a) R = CH_3
b) R = C_6H_5

☆ Dedicated to Professor Henri Brunner on the occasion of his 60th birthday.

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Table 1
Copper-catalyzed conjugate addition reactions in THF in the presence of Me_3SiCl [a]

Entry	Carbonyl compound	RMgX	Catalyst [b]	Temperature (°C)	Conversion [c] (%)	1,4 : 1,2 addition	Silylated : desilylated
1	**1**	CH_3MgI	$CuI \cdot 2LiCl$	0	99(93)	99 : 1	99 : 1
2	**1**	CH_3MgI	$CuBr \cdot SMe_2$	0	96(71)	99 : 1	93 : 7
3	**1**	^{n}BuMgCl	$CuI \cdot 2LiCl$	−40	85(65)	> 99 : > 1	99 : 1
4	**1**	PhMgBr	$CuI \cdot 2LiCl$	0	95(71)	> 99 : > 1	97 : 3
5	**5**	CH_3MgI	$CuI \cdot 2LiCl$	−40	87(70)	98 : 2	77 : 23
6	**5**	^{n}BuMgCl	$CuI \cdot 2LiCl$	−78	99(80)	99 : 1	97 : 3
7	**6**	CH_3MgI	$CuI \cdot 2LiCl$	0	88(75)	> 99 : > 1	97 : 3
8	**6**	^{n}BuMgCl	$CuI \cdot 2LiCl$	−40	98(96)	> 99 : > 1	99 : 1
9	**6**	^{n}BuMgCl	CuI	−78	75	62 : 38	72 : 28
10	**6**	^{n}BuMgCl	$CuBr \cdot SMe_2$	−78	95	96 : 4	83 : 17
11	**6**	$CH_2{=}CHMgBr$	$CuI \cdot 2LiCl$	0	95(87)	> 99 : > 1	94 : 6
12	**6**	PhMgI	$CuI \cdot 2LiCl$	0	99(80)	> 99 : > 1	95 : 5
13	**6**	$PhCH_2MgBr$	$CuI \cdot 2LiCl$	0	99(60)	> 99 : > 1	97 : 3
14	**7**	CH_3MgI	$CuI \cdot 2LiCl$	0	99(78)	> 99 : > 1	> 99 : > 1
15	**7**	CH_3MgI	$CuBr \cdot SMe_2$	0	89	99 : 1	90 : 10
16	**7**	CH_3MgI	$CuBr \cdot SMe_2$–2LiCl	0	97	> 99 : > 1	97 : 3
17	**7**	^{n}BuMgCl	$CuI \cdot 2LiCl$	−40	90(84)	> 99 : > 1	> 99 : > 1
18	**8**	CH_3MgI	$CuI \cdot 2LiCl$	−40	90(80)	> 99 : > 1	88 : 12
19	**8**	^{n}BuMgCl	$CuI \cdot 2LiCl$	−78	90(60)	> 99 : > 1	> 99 : > 1
20	**9**	CH_3MgI	$CuI \cdot 2LiCl$	0	89(86)	> 99 : > 1	> 99 : > 1 [d]
21	**10**	CH_3MgI	$CuI \cdot 2LiCl$	0	97(92)	> 99 : > 1	— [e]
22	**10**	^{n}BuMgCl	$CuI \cdot 2LiCl$	0	66(62)	> 99 : > 1	— [e]

[a] Reaction time, 0.5 h.
[b] 10 mol.%.
[c] Isolated yield in parentheses.
[d] Only one diasteromer (*Z*).
[e] Desilylative work-up.

SMe_2-catalyzed reactions can be improved by adding LiCl to the reaction mixture (entries 15 and 16).

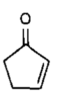
Experiments directed toward diastereoselective conjugate additions were performed with *R*-carvone (**11**) [11]. Complete 1,4-selectivity with exclusive formation of the silylated products **12**–**13** was observed, diastereoselectivity being 94% in favor of **12** (greater than 93% conversion; 62% isolated). Essentially the same result was obtained upon using $(CH_3)_2CuLi$ (140 mol.%)–Me_3SiCl (100 mol.%) at −78°C (→ 22°C for 6 h) (100% conversion, 68% isolated; *ds* = 93%).

The CuX_3Li_2-catalyzed 1,4-addition also works well without Me_3SiCl, although the yields of isolated products are somewhat lower (Table 2). A limitation of this variation became visible in the case of the very reactive cyclopentenone (**5**), the main products being oligomers.

Table 2
Copper-catalyzed conjugate addition reactions in THF in the absence of Me_3SiCl [a]

Entry	Carbonyl compound	RMgX	Catalyst [b]	Temperature (°C)	Conversion [c] [%]	1,4 : 1,2 addition
1	**1**	CH_3MgI	$CuI \cdot 2LiCl$	0	95(72)	95 : 5
2	**6**	CH_3MgI	$CuI \cdot 2LiCl$	0	98(84)	99 : 1
3	**6**	^{n}BuMgCl	$CuI \cdot 2LiCl$	−40	99(65)	99 : 1
4	**6**	^{n}BuMgCl	CuCl	−78	87	65 : 35
5	**6**	^{n}BuMgCl	$CuBr \cdot SMe_2$	−78	83	85 : 15
6	**6**	^{n}BuMgCl	$CuBr \cdot SMe_2$–2LiCl	−78	94	99 : 1
7	**7**	CH_3MgI	$CuI \cdot 2LiCl$	0	99(97)	99 : 1
8	**7**	CH_3MgI	$CuI \cdot 2LiCl$ [d]	0	84	95 : 5
9	**7**	^{n}BuMgCl	$CuI \cdot 2LiCl$	−40	99(70)	99 : 1
10	**8**	CH_3MgI	$CuI \cdot 2LiCl$	−40	84(60)	99 : 1
11	**9**	CH_3MgI	$CuI \cdot 2LiCl$	0	96(47)	98 : 2

[a] Reaction time, 0.5 h.
[b] 10 mol.%.
[c] Isolated yield in parentheses.
[d] Only 1 mol.% catalyst.



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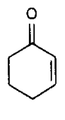

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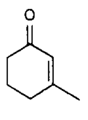

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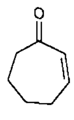

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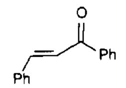

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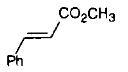

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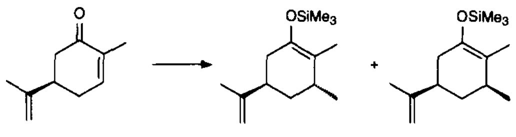

11 12 13

94 6

What is the nature of the LiX effect in these reactions? The high solubility of these salts in THF is certainly an important factor. Indeed, these salts are more soluble in this medium than CuBr · SMe_2 (which sometimes forms suspensions at low temperatures). Preliminary results show that CuBr or CuCl can be used in place of CuI without significantly influencing the results [12]. It is currently unclear whether the structure of the intermediate magnesiocuprates [13] are influenced by the presence of LiX [14]. Whatever the precise mechanism may be, CuX_3Li_2 salts are as efficient or in some cases more efficient than CuBr · SMe_2 in catalyzing the Kharasch reaction. They are readily prepared by mixing CuX and LiX and require no dimethylsulfide as a ligand or HMPA as an additive during the conjugate addition reactions [15].

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[15] Typical procedure: under an inert gas atmosphere THF (6 ml) was charged with LiCl (8.4 mg, 0.2 mmol) and CuI (19 mg, 0.1 mol), which resulted in a homogeneous solution. At 0°C, isophorone (150 μl, 1.0 mmol) and $(CH_3)_3SiCl$ (154 μl, 1.1 mmol) were added and the solution stirred for 10 min. A Grignard solution in THF (1.2 mmol) was slowly added via a syringe. After stirring for 0.5 h, the solution was poured onto 20 ml of saturated aqueous NH_4Cl, extracted with ether and dried over $MgSO_4$. The solvent was removed and the crude product analyzed by gaschromatography and/or purified by flash chromatography over silica gel (ether–pentane).