CuX₃Li₂-catalysed Conjugate Addition of Dialkylmagnesium Reagents to α,β-Unsaturated Carbonyl Compounds

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Copper salts of the type CuX_3Li_2 (X = halogen) catalyse the conjugate addition of dialkylmagnesium compounds to α,β-unsaturated carbonyl compounds in the presence or absence of Me_3SiCl as an additive, the organomagnesium compounds being prepared from α-olefins, hydrogen and magnesium according to the procedure of Bogdanović.

The conjugate addition of Gilman reagents R_2CuLi to α,β-unsaturated carbonyl compounds is a standard reaction in synthetic organic chemistry.[1] If the reaction is sluggish due to steric and/or electronic reasons, either additives such as Me_3SiCl[2] or higher order cuprates[1,3] need to be employed. The CuCl-catalysed 1,4-addition of Grignard reagents RMgX as originally described by Kharasch and Tawney[1,4] requires only catalytic amounts of copper, but problems regarding reproducibility with respect to yield and 1,4- *versus* 1,2-selectivity have been reported.[1,5] Catalytic amounts of $CuBr·SMe_2$ seem to be more efficient, especially in combination with Me_3SiCl (200 mol%) and hexamethylphosphoric triamide (HMPA, 250 mol%).[2d,6] We now report a new conjugate addition reaction which is based on the use of dialkylmagnesium reagents[7] and catalytic amounts of CuX_3Li_2 (X = halide) in the presence or absence of Me_3SiCl. Since the organomagnesium reagents R_2Mg are readily available in a nearly quantitative one-pot catalytic reaction from α-olefins, hydrogen and magnesium as described by Bogdanović *et al.*,[8] the overall two-step sequence constitutes an exceptionally simple process (Scheme 1).

Exploratory experiments were first carried out with cyclohexenone 1 and samples of Et_2Mg prepared conventionally from EtBr and magnesium (shift of the Schlenk equilibrium by $MgBr_2$–dioxane precipitation). Such solutions of R_2Mg do not contain transition metal salts, in contrast to the crude solutions of the same reagents obtained by the Bogdanović procedure. Table 1 shows that in the absence of the Cu catalyst and Si additive, 1,2-selectivity is essentially complete (entry 1), and that LiCl as an additive leads to an increased amount of 1,4-adduct (entry 2). Upon repeating these experiments in the presence of stoichiometric amounts of Me_3SiCl, regioselectivity was reversed, although not completely (entries 3 and 4). Furthermore, the ratio of enolsilane 2 to the corresponding ketone 3 is only about 3:1. The use of $CuBr·SMe_2$ improves the situation, although the results are not completely satisfactory (entries 5 and 6). The addition of two parts of LiCl to the $CuBr·SMe_2$ catalyst has a beneficial effect (entry 7), but the best selectivities were obtained upon employing a catalyst prepared by mixing CuI with two equivalents of LiCl. Although its structure is currently not known, this THF-soluble catalyst can be represented by $CuI·2LiCl$ (or CuX_3Li_2).[9] In the absence of Me_3SiCl, complete 1,4-selectivity results (entry 8). In the presence of Me_3SiCl, 1,4-selectivity remains complete, and enolsilane–ketone selectivity amounts to >97% (entries 9 and 10). The reaction was then repeated using this optimal catalyst
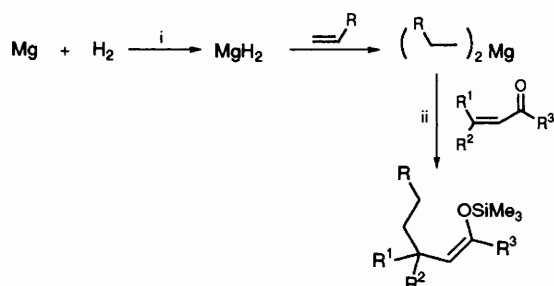
and Et_2Mg prepared by the Bogdanović procedure. In doing so, no purification of the organomagnesium reagent was performed, *i.e.* the crude THF solution was used.† The results turned out to be identical, which means that trace amounts of transition metals necessary in the synthesis of R_2Mg do not influence the CuX_3Li_2-catalysed conjugate addition reaction. Without the Cu catalyst, mixtures of products are obtained. Preliminary studies show that CuX_3Li_2 catalysts prepared from other salts (*e.g.* CuBr, LiBr, LiI)[9] perform in a similar manner. Also, no special precautions such as recrystallization of the commercial forms of the copper or lithium halides prior to use are necessary. The success of these catalysts has to do with their high solubility in the reaction medium used, amongst other possible reasons. Although mechanistic studies have not been carried out, the intermediacy of magnesiocuprates is likely.[1,10]

Using enones 1 and 5–7 as well as the α,β-unsaturated ester 8, the sequence shown in Scheme 1 was applied in the standard way. Good to excellent results were uniformly observed, except in the reaction of chalcone 7 (Table 2). In that case 1,4-selectivity is excellent, but conversion to the desired product and its isolation are moderate to poor (entries 7 and 8). It is likely that the two phenyl groups in 7 cause side reactions such as electron transfer and/or radical coupling. Noteworthy is the smooth 1,4-addition to the sterically hindered isophorone 5 (entries 3 and 4). In the case of Et_2Mg addition to this ketone, lower amounts of Cu catalyst were also tested. The use of 5 mol% $CuI·2LiCl$ led to identical results. A further reduction to 2.5 mol% also had no negative effect on 1,4-selectivity or yield, but a small amount of nonsilylated product was observed (*ca.* 5%). It should be noted that in some cases the enolsilane is sensitive to hydrolysis during chromatographic purification. Dry workup
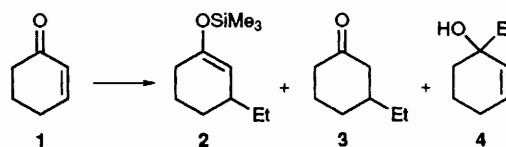

Table 1 Addition reactions of Et_2Mg with cyclohexenone 1 in THF at −20 °C

Entry	Equivs. Et_2Mg	Equivs. Me_3SiCl	Catalyst[a]	2:3:4[b]	Conversion to products 2/3/4 (%)[c]
1	0.5	—	—	— 2:98	80
2[d]	0.5	—	—	— 31:69	80
3[d]	0.5	1.0	—	57:19:24	92
4[e]	0.5	1.0	—	55:21:24	98
5	0.5	—	$CuBr·SMe_2$	— 91:9	75
6	0.5	1.0	$CuBr·SMe_2$	20:68:12	75
7	0.5	1.0	$CuBr·SMe_2$ +2LiCl	92: 8:0	89
8	0.5	—	$CuI·2LiCl$	— 99:1	83
9	0.5	1.0	$CuI·2LiCl$	97: 3:0	93
10	1.0	1.0	$CuI·2LiCl$	99: 1:0	93

[a] 10 mol%. [b] Determined by gas chromatography. [c] 1 was completely consumed in all cases. [d] 10 mol% LiCl as additive. [e] 100 mol% LiCl as additive.

Scheme 1 *Reagents and conditions*: i, cat. anthracene, cat. $CrCl_3$, $ZrCl_4$ or $TiCl_4$; ii, cat. CuX_3Li_2

Table 2 CuI·2LiCl catalysed[a] addition reactions of R_2Mg^b with α,β-unsaturated carbonyl compounds in THF

Entry	Carbonyl compound	Reagent	$T/°C$	1,4:1,2 addition	Enolsilane:Ketone	% conversion (% isolated)
1	1	Et₂Mg	−20	99: 1	99:1	95 (92)
2	1	Oct₂Mg	−40	99: 1	—	96 (89)[c]
3	5	Et₂Mg	−20	99: 1	99:1	97 (95)
4	5	Oct₂Mg	−40	99: 1	99:1	89 (76)[c]
5	6	Et₂Mg	−20	99: 1	—	93 (37)[c]
6	6	Oct₂Mg	−40	99: 1	—	94 (64)[c]
7	7	Et₂Mg	−20	99: 1	85:15	68 (20)
8	7	Oct₂Mg	−40	93: 7	96:4	59 (48)
9	8	Et₂Mg	−20	>90:<10[d]	—	90 (73)[c]
10	8	Oct₂Mg	−40	99: 1	—	85 (75)[c]

[a] 10 mol%. [b] Prepared by the Bogdanović procedure.[8] [c] Isolated as ketone following chromatography on SiO₂. [d] The precise value could not be determined due to analytical problems.

5 6 7 8
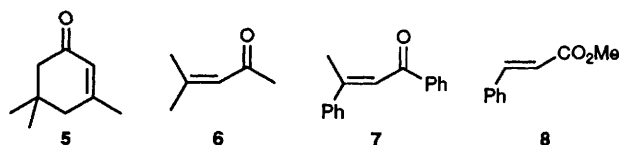
as used traditionally in the synthesis of sensitive O-silyl ketene ketals was not tested.

In summary, CuX₃Li₂ (X = Cl, Br, I) are excellent homogeneous catalysts in the conjugate addition of dialkylmagnesium compounds prepared either classically from Grignard reagents RMgX or from α-olefins via hydromagnesiation. The salient features include: (i) ready preparation of the Cu catalysts without the need for ligands such as dimethylsulfide or stoichiometric amounts of additives such as HMPA; (ii) transfer of both alkyl groups in the organomagnesium reagents; (iii) avoidance of extremely low temperatures; (iv) excellent 1,4-selectivity; and (v) in the case of Me₃SiCl as an additive, essentially complete enolsilane formation. The catalytic and economical access to dialkylmagnesium reagents from α-olefins coupled with the CuX₃Li₂ catalysed conjugate addition reaction may well constitute an industrially viable two-step sequence.

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Footnote

† Typical procedure: LiCl (42 mg, 1 mmol) is flame-dried *in vacuo* in a 50 ml flask. CuI (95 mg, 0.5 mmol) and dry THF (15 ml) are added under an Ar atmosphere, and the mixture is stirred until a clear solution is formed. An enone (5 mmol) and Me₃SiCl (700 μl, 5 mmol) are added and the solution is cooled to −20 or −40 °C (Table 2). A 1 mol dm⁻³ solution of R₂Mg in THF (2.6 mmol) is added dropwise within 4 min. After stirring for 0.5 h, the mixture is quenched with 25 ml of a sat. NH₄Cl solution, ether (10 ml) added and the aqueous solution extracted three times with ether. The combined organic phases are washed with brine and dried over MgSO₄. The solvent is stripped off and the residue, analysed by gas chromatography if necessary, is chromatographed over silica gel (hexane–ether 20:1).

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