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SELECTIVE γ-1,4 ADDITION OF METHOXYALLYLCOPPER TO ENONE.

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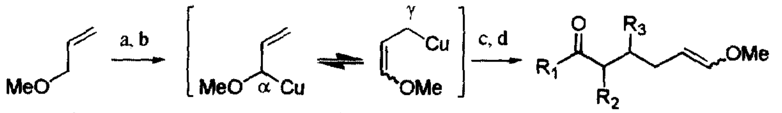
Abstract: Methylallylether is deprotonated by *sec*-butyllithium and treated with copper$^{(I)}$ iodide in dimethylsulfide to afford the corresponding allylcopper reagent. This ambident nucleophile adds in highly γ-1,4 selectivity to several enones and the corresponding ketoenolethers are obtained in good yields. © 1999 Elsevier Science Ltd. All rights reserved.

Oxygen substituted allylic carbanions are known as homoenolate equivalents[1]. These ambident nucleophiles can react with electrophiles in α or γ position of oxygen. High degrees of selectivity have been observed depending on solvents, cationic counterions and also the type of electrophiles. When reacting with enones, a supplementary problem of regioselectivity occurs (i.e. 1,2 or 1,4 addition). Nucleophilic attack of trimethylsilyloxyallyllithium species to enones has been reported by Still to be highly α-1,2 selective[2]. Same results have been obtained by Evans with methoxyallylzinc and cadmium reagents[3,4]. While this has been further extended to numerous other alkoxyallylmetallic species with the same α-1,2 selectivity[5,6,7,8,9,10], little works have focused on γ-1,4 selectivity. Attempts with methoxyallylcuprate gave first unsatisfactory results because of lack of regioselectivity[4]. Later, Kuwajima found very difficult to control conjugate addition of several silyloxyallylcopper reagents to enones, except for trimethylsilylacetylide heterocuprate which showed high γ-1,4 selectivity[11]. To our knowledge, methoxyallylcopper reagents have never been tested.

We report herein that methoxyallylcopper reagent **2** (scheme 1) reacts with enones **3a-e** in the presence of TMSCl exclusively with γ-1,4 selectivity to afford in good yields ketoenolethers **4a-e** after desilylation (table I). Compounds **4a-c** have been previously prepared in lower yields by α-1,2 addition of methoxyallylzinc reagents to enones followed by oxy-Cope rearrangement[4].



1 **2** **4a-e**

a) sec-BuLi (1eq), THF, -78°C. b) CuI (1 eq), DMS. c) TMSCl then enone **3a-e**, -78°C. d) TBAF.3H_2O, THF, rt.

Scheme 1

Enolethers **4a-e** are obtained as a mixture of *E* and *Z* isomers indicating that poor chelation exists between the methoxy group and copper which would have favored a *Z* configuration of methoxyallylcopper **2**[3]. The use of TMSCl was necessary to ensure total conjugate addition[12]. Reaction of **2** with MVK in the absence of TMSCl gave 7 % of α-1,2 adduct. Deprotection of initially formed silylenolethers was easily performed with TBAF. One can note that lithiumdiallylcuprate reagent generated in the same conditions with 0.5 equivalent of CuI showed lower γ/α selectivity with MVK (γ-1,4 / α-1,4 : 6 / 1).

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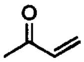
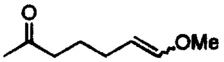
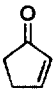
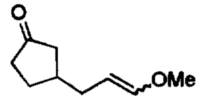
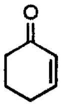
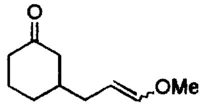
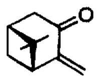
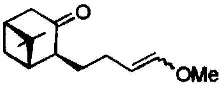
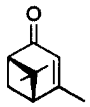
Table I : Conjugate addition of methoxylallylcopper reagent **2** on enones **3a-e**[a]

Entry	Enones 3a-e	γ-1,4 adduct 4a-e[b]	Selectivity[c,d] γ-1,4 / α-1,4	Z / E[c]	Yields %
a			100 / 0	65 / 35	95[c]
b			100 / 0	75 / 25	74[e]
c			100 / 0	75 / 25	96[e]
d		 [f]	100 / 0	70 / 30	75[e]
e		 [f]	100 / 0	90 / 10	81[e]

a) All reactions were performed with two equivalents of reagent 2. b) All products gave satisfactory spectral data and elemental analysis. c) Determined on crude ^{1}H NMR. d) 1,2 addition products were not detected. e) Yields refer to flash chromatography purified product, as *E* and *Z* isomers mixture. f) Total diastereoselectivity was observed.

In a general experiment, 2.31 mL (3.0 mmol) of 1.6 M *sec*-BuLi were added at - 78°C to an argon degased anhydrous solution of methylallylether **1** (285 μL, 3.0 mmol) in THF (15 mL). After 5 mn, a degased solution of CuI (570 mg, 3.0 mmol) in dimethylsulfide (1.5 mL) was slowly injected and the reaction mixture was stirred for 15 mn. To this dark brown solution was slowly added 245 μL (3.0 mmol) of TMSCl and then 1.5 mmol of enone. After 90 mn stirring at - 78°C, the reaction mixture was hydrolysed with 20 mL of aqueous NH_4OH buffered with NH_4Cl. A 20 mL portion of Et_2O was then added and the organic layer was decanted, washed with buffered NH_4OH solution until blue color disappeared, dried over $MgSO_4$ and the solvents were evaporated under reduced pressure. The oily residue was stirred 20 mn in THF (20 mL) with TBAF.$3H_2O$ (0.95 g, 3.0 mmol). A 20 mL portion of Et_2O was then added and the organic layer was decanted, washed with water, dried over $MgSO_4$ and the solvents were evaporated under reduced pressure to give after purification by chromatography on silicagel the ketoenol ethers **4a-e**.

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