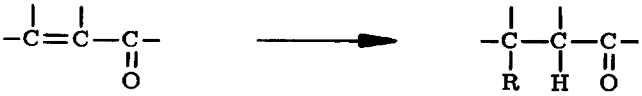
Tetrahedron Letters Vol. 21, pp 1247 - 1250
0040-4039/80/0322-1247$02.00/0

ORGANOCOPPER CONJUGATE ADDITION REVISITED

M. Suzuki, T. Suzuki, T. Kawagishi, and R. Noyori*
Department of Chemistry, Nagoya University, Chikusa, Nagoya 464, Japan

Summary: An efficient organocopper conjugate addition based on the use of equimolar amounts of an enone and an entering group is described.

The most noteworthy feature of organocopper reagents illustrating synthetic utility is the capability of undergoing conjugate addition to α,β-unsaturated ketones.[1] Among various organocopper compounds, lithium organocuprates (Gilman reagents) resulting from a copper(I) salt and 2 equiv of an organolithium compound are employed for this purpose. However, this method suffers from the severe disadvantages that one equiv of the organic group is inevitably wasted. Therefore persistent efforts to circumvent this problem have been continued and some modified procedures using mixed cuprate reagents have been elaborated.[2] During the reinvestigation of such processes, we found a simple, general solution to this problem.



The present method is based on the use of an organocopper reagent derived from equimolar amounts of copper(I) iodide and an organolithium compound and 2—3 equiv of tri-*n*-butylphosphine. Reaction of this reagent and an enone (1:1 ratio) in ether proceeds at -78 to 0 °C to give after quenching with aqueous ammonium chloride solution the desired conjugate addition product in a satisfactory yield. In usual the tertiary phosphine ligand was easily separated from the products by column chromatography. Examples of the reaction are given in Table I, indicating the wide utility for a large range of enone substrates and entering groups.[3] We noted that efficiency of the conjugate addition is highly dependent on the amount of added tertiary phosphine ligand (for example, entries 10—14 in Table I). When >2 equiv of the tertiary phosphine ligand was present, the reaction system remained homogeneous throughout the reaction.[4] Reactivity of the organocopper compounds is influenced by the nature of organic groups. Interestingly, the methylcopper reagent,[5] even with the added phosphine ligand, is the least reactive among the organocoppers so far examined; isopropenyl group transfers quite smoothly. As might be expected, introduction of a substituent to the β-position of enones

Table I. The Reaction of Enones with Organocopper Phosphine Complexes[a]

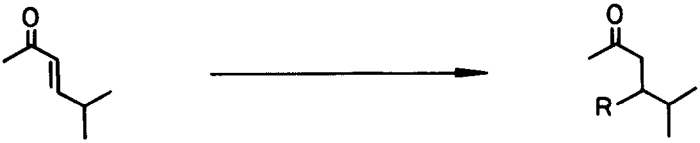
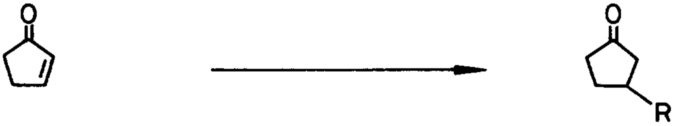
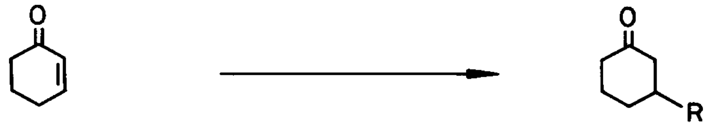
entry	substrate	R[b]	n-Bu_3P/CuI ratio	product	%yield[c]
					
1		n-C_4H_9	2.6		94
2		$(CH_3)_2CH$	22		95
3		$(CH_3)_3C$	20		86
4		C_6H_5	2.2		84[d]
					
5		n-C_4H_9	22		88[e]
6		$(CH_3)_2CH$	22		99[e]
7		C_6H_5	2.2		70[d,e]
8		$CH_2=C(CH_3)$	22		66
					
9		CH_3	22		73[e]
10		n-C_4H_9	0		18
11			10		73
12			2.0		93
13			3.0		91
14			40		65
15		$(CH_3)_2CH$	22		90
16		$(CH_3)_3C$	20		66
17		$CH_2=C(CH_3)$	26		98

Table I (Continued)

entry	substrate	R[b]	n-Bu_3P/CuI ratio	product	% yield[c]
					
18		CH_3	2.2		95[e]
19		n-C_4H_9	22		100, 82[d]
20		$(CH_3)_2CH$	22		94
21		$(CH_3)_3C$	20		91
22		$CH_2=C(CH_3)$	26		100
					
23		n-C_4H_9	3.0		86
24		$(CH_3)_2CH$	22		100[e,f]
25		$CH_2=C(CH_3)$	26		100

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[a] The organocopper phosphine complex was prepared in situ by mixing copper(I) iodide, organolithium, and tri-*n*-butylphosphine in 1:1:2—3 mol ratio in ether. Unless otherwise stated, the conjugate addition was carried out at -78 °C for 0.5—1 h and -40 °C for 1—3 h. All new compounds gave consistent NMR and IR characteristics and correct elemental analysis and/or mass spectral data. [b] *n*-Butyllithium in hexane, isopropyllithium in pentane, and *t*-butyllithium in pentane were obtained from Nakarai Chemical Co., K&K laboratories Inc., and Aldrich Chemical Co., respectively, and were used directly from the bottle. Methyllithium and phenyllithium were prepared by the reaction of methyl bromide and phenyl bromide with lithium metal in ether. Isopropenyllithium was prepared in situ by mixing isopropenyl bromide with *t*-butyllithium at -78 °C for 1.5 h in ether. [c] Determined by GLC analysis. [d] Isolated yield after silica gel column chromatography. [e] This reaction was performed at 0 °C for 5—10 min. [f] Yield based on consumed substrate. Conversion was 44%.

retarded the alkyl transfer reaction.

The following procedure is representative. To a suspension of copper(I) iodide (2.00 g, 10.5 mmol) in dry ether (150 mL) was added tri-*n*-butylphosphine (5.76 mL, 23.1 mmol) at room temperature under argon atmosphere. After stirring for 10 min, the suspension became a clear solution. To this solution cooled at -78 °C was added a 1.86 M solution of *n*-butyllithium in hexane (5.65 mL, 10.5 mmol) and the mixture was stirred for an additional 20 min at the same temperature. A solution of 2-cyclohexenone (961 mg, 10.0 mmol) in dry ether (50 mL) was then added at -78 °C and the mixture was stirred at this temperature for 1 h and at -40 °C for 2.5 h. The reaction mixture was quenched by adding a saturated ammonium chloride solution (100 mL) at -40 °C with vigorous stirring. The organic layer was separated and the aqueous layer was extracted with ether (50 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated. The residual oil was chromatographed on silica gel (200 g) using a mixture of hexane and ether (20:1 to 5:1, gradient) to give 3-*n*-butylcyclohexanone as a colorless oil (1.27 g, 82% yield).

The organocopper-generated enolate intermediates were complex in nature[6] and displayed behavior different from that of simple lithium enolates.[7] For instance, attempted benzaldehyde trapping of an enolate formed from 2-cyclohexenone and the butylcopper reagent (-78 to -40 °C) gave the aldol product in only 19% yield accompanied by serious side reaction products.

Acknowledgment. This work was generously supported by the Yamada Science Foundation.

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(Received in Japan 28 December 1979)