

Conjugate Addition of Methyl Groups to $\alpha\beta$ -Unsaturated Aldehydes: Use of $\text{Me}_5\text{Cu}_3\text{Li}_2^\dagger$

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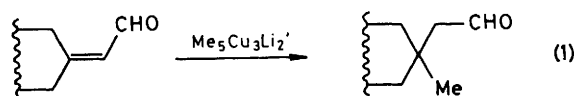
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Summary $\text{Me}_5\text{Cu}_3\text{Li}_2$ converts $\alpha\beta$ -unsaturated aldehydes efficiently into β -methyl aldehydes and, unlike Me_2CuLi , it usually gives a negligible amount of the 1,2-adduct even when a quaternary carbon is generated in the reaction.

CONJUGATE addition of methyl groups to $\alpha\beta$ -unsaturated carbonyl systems is a common step in organic synthesis.² In the domain of unsaturated ketones and aldehydes, however, the conventional reagent Me_2CuLi has a serious limitation: while conjugate methylation of unsaturated ketones proceeds well, the reaction is not synthetically useful with unsaturated *aldehydes*, particularly those bearing alkyl groups on the sp^2 -hybridised carbons, since substantial amounts (*ca.* 5–60%) of 1,2-addition takes place.³

We report that a little known, but readily accessible species, tentatively assigned¹ the composition $\text{Me}_5\text{Cu}_3\text{Li}_2$, is an effective reagent for making carbon–carbon bonds by conjugate addition to $\alpha\beta$ -unsaturated aldehydes and that, unlike Me_2CuLi , it is generally synthetically useful in this

respect. The process is well suited to generating quaternary centres⁴ (equation 1). Our results are listed in the Table, which gives the yields and relative proportions of 1,4- to 1,2-addition resulting from experiments with $\text{Me}_5\text{Cu}_3\text{Li}_2$ and Me_2CuLi .



$\text{Me}_5\text{Cu}_3\text{Li}_2$ has been assigned¹ tentatively the specified stoichiometry (in ether) but little is known of its chemical properties. Its reactions with alkyl halides proceed poorly.⁵ It does add efficiently to enones, however, and the reaction is faster than that of Me_2CuLi ,⁶ but such experiments do not reveal the relative synthetic potential of the penta-methyl species because Me_2CuLi itself is a most satisfactory reagent for conjugate methylation of enones.²

[†] This stoichiometry is tentative, see ref. 1.

TABLE

Starting material ^a	Reaction solvent; T/°C ^b (quench)	Reagent	% Yield ^c	% 1,4-Methylation ^d	% 1,2-Methylation ^d
(1)	Et ₂ O; -40 (AcOH)	Me ₅ Cu ₃ Li ₂ Me ₂ CuLi	90 71 ^f	99.0 87.0	1.0 ^e 13.0
(2) ^g	Et ₂ O; -40 (AcOH)	Me ₅ Cu ₃ Li ₂ Me ₂ CuLi	90 90	>99.5 ^h 91.5	<0.5 ⁱ 8.5
(3) ^g	Et ₂ O; 0 (AcOH)	Me ₅ Cu ₃ Li ₂ Me ₂ CuLi	80 78	>99.5 90.0	<0.5 ⁱ 10.0
(4)	Et ₂ O; -20 (Me ₃ SiCl)	Me ₅ Cu ₃ Li ₂ Me ₂ CuLi	92 92	98.5 94.5	1.5 5.5
(5)	Et ₂ O-pentane; 0 (Me ₃ SiCl)	Me ₅ Cu ₃ Li ₂ Me ₂ CuLi	88 91	>99.5 80.0	<0.5 20.0
(6)	Et ₂ O; 0 (Me ₃ SiCl)	{ Me ₅ Cu ₃ Li ₂ Me ₂ CuLi	85 86 ^j	77.5 36 ^j	22.5 64 ^j
(6)	Et ₂ O-pentane; 0		Me ₅ Cu ₃ Li ₂	88	85.0
(7)	Et ₂ O; -20 (AcOH)	{ Me ₅ Cu ₃ Li ₂ Me ₂ CuLi	88 88	94.5 ^h 83.0	5.5 17.0
(7)	Et ₂ O; 0 (AcOH)		Me ₅ Cu ₃ Li ₂	81	92.6 ^e
(7)	Et ₂ O-pentane; -10 (AcOH)	Me ₅ Cu ₃ Li ₂	80	95.1 ^e	4.9 ^e
(8)	Et ₂ O; 0 (AcOH)	Me ₅ Cu ₃ Li ₂ Me ₂ CuLi	73 42	0.0 0.0	100.0 100.0

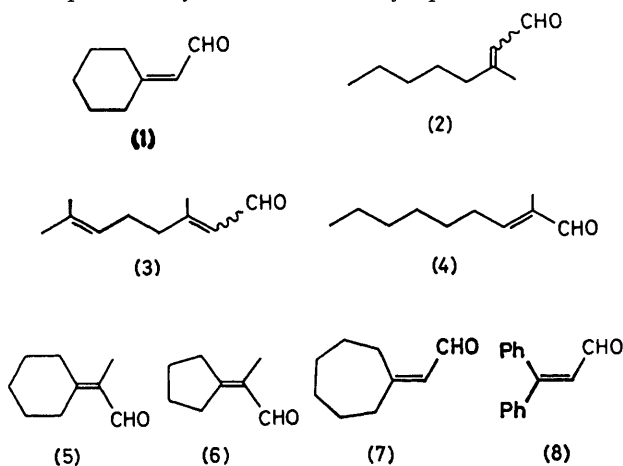
^a Except for (3), which is commercially available, the starting aldehydes were made by the method of E. J. Corey, D. Enders, and M. G. Bock (*Tetrahedron Lett.*, 1976, 6), using t-butyylimines. ^b The temperature refers to the highest temperature reached by the reaction mixture before the reaction was quenched (at -75 °C) with AcOH or Me₃SiCl. In the latter case the product isolated was the trimethylsilyl enol ether. ^c Yields refer to isolated and distilled material of >97% purity (g.l.c.). ^d The proportions were determined from 200 MHz n.m.r. spectra, except where indicated. ^e Ratio determined by g.l.c. ^f In this experiment the mixture was quenched with saturated aqueous NH₄Cl solution. ^g Mixture of geometric isomers. ^h For combustion analysis the 2,4-dinitrophenylhydrazone was used. ⁱ None was detected (by n.m.r. or g.l.c.). ^j Data from ref. 3.

The results in the Table show that Me₅Cu₃Li₂ gives products in high yield and, usually, the amount of 1,2-adduct is less than 1.5%. A fully substituted double bond [compounds (5) and (6)] is an especially unfavourable case and the tabulated results serve to emphasize the superiority of the pentamethyl- over the dimethyl-species.

In a typical experiment, ethereal MeLi-LiCl (5 equiv.) was added to a slurry of CuI (3 equiv.) in ether at 0 °C to afford a solution (ca. 0.08 M) of Me₅Cu₃Li₂. In some cases (see Table) the solution was diluted with about an equal volume of pentane. The aldehyde (1 equiv.) in ether (ca. 1.0 M) was added dropwise at -75 °C and, after 1–2 h, the mixture was allowed to warm to the indicated temperature (see Table). It was then quenched at -75 °C with AcOH or with Me₃SiCl-Et₃N-HMPA⁷ (HMPA = hexamethylphosphoramide). Aqueous work-up and kugelrohr distillation gave the products directly in >97% purity (g.l.c.). Experiments with Me₂CuLi were done in the same way using 1.2–1.4 equiv. of the organocuprate.

All new aldehydes gave satisfactory spectroscopic and combustion analytical (of the 2,4-dinitrophenylhydrazone or silyl enol ether derivatives) data.

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