THE CONJUGATE ADDITION OF HIGHER-ORDER ORGANOCUPRATES TO $\alpha\mbox{-}Methoxyenones$

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Abstract: The conjugate addition of higher-order organocuprates (Lipshutz reagents) at low temperature (-78°C) to α -methoxyenones (4) provides the corresponding β -substituted α -methoxy ketones (5) in 74-90% isolated yields.

Some time ago, we reported the Pd-catalyzed cross-coupling of α -methoxyvinyltin compounds (e.g. 3) with acid chlorides (Stille reaction)² to provide a simple entry to α methoxyenones (4).³ The ready availability of 3^4 from α -methoxyvinyllithium (2) via Baldwin's deprotonation of methyl vinyl ether with $Li(t-Bu)^5$ makes this route to 4 both simple and highly efficient. In an effort to more fully develop the chemistry of these interesting systems, we observed that 4 failed to undergo the expected 1,2-asymmetric carbonyl reduction with chlorodiisopinocampheylborane, but rather, was reduced in a 1,4 manner.⁶ Although mechanistically quite different, this result suggested that 4 might also act as a Michael acceptor for organocuprate additions. With this process, it was felt that this elaboration of the carbon skeleton at the beta position in 4 would considerably enhance the synthetic value of these intermediates. Impressed with the superior results that were realized with higher-order organocuprates,⁷ compared to other reagents, in the ring-openings of α -silvl epoxides,⁸ we chose to examine these reagents for the $4\rightarrow 5$ conversion. We were initially apprehensive as to the success potential of these additions because electron-transfer processes of type believed to be involved in organocuprate additions to enones, are known to be slowed by methoxy substitution.9 Fortunately, our concerns proved unfounded, and the addition of higher-order organocuprate reagents to 4 at -78 °C occurs smoothly to result in excellent isolated yields of the desired α -methoxy ketones (5) (cf. Table 1).



Entry	4	R	R'	5	Yield*	bp (Torr)
1	a	n-C ₆ H ₁₃	n-Bu	a	90	73-6 (0.03)
2	a	$n - C_6 H_{13}$	Vi	b	81	80-2 (0.45)
3	b	Ph	Me	с	83	77-8 (0.05)
4	b	Ph	<i>n</i> -Bu	đ	86	105-7 (0.5)
5	Ъ	Ph	Vi	e	82	74-5 (0.2)
6	с	2-furanyl	n-Bu	f	74	77-80 ^b
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Table 1. α -Methoxy Ketones (5) from the Addition of Li₂Cu(CN)R'₂ to 4.

* Isolated yields of analytically and spectroscopically pure material. * mp.

The additions are operationally simple to carry out, and the products are easily isolated in pure form.¹⁰ For **4b**, we also found Yamamoto's R'Cu-BF₃ procedure¹¹ to provide **5d** with comparable efficiency to that obtained with the corresponding Lipshutz reagent. Through the $1\rightarrow 5$ sequence, it has been demonstrated that the normal mode of addition to a vinyl ether by RCO^{\oplus} and R'^{\oplus} can be completely reversed to result in the formation of two new carbon-carbon bonds. In effect, this chemistry allows **1** to function as the dipolar form, **B**, rather than from its normal polarity, **A**.



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10. To CuCN (0.9 g, 10 mmol) in THF (40 mL) at -78 °C, was added LiBu (8.06 mL, 2.48 M, 20.0 mmol) dropwise. The mixture was stirred for 10 min and the cold bath was removed to result in a light-yellow solution. The mixture was recooled to -78 °C and **4b** (1.64 g, 10.0 mmol) was added dropwise. After 1 h, the reaction was complete and was quenched at room temperature with 1:1 mixture of saturated NH₄Cl and concentrated NH₄OH (50 mL). Pentane (25 mL) was added and the organic phase was dried (Na₂SO₄), concentrated and distilled to give 1.89 (86%) of **5d** (bp 105-7 °C, 0.5 Torr, 99% GC purity).

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