An Effective Method for the Regio- and Stereo-selective 1,4-Addition to β-Cyclopropyl-α,β-enones using Organocopper(I)–Aluminium Trichloride Reagents

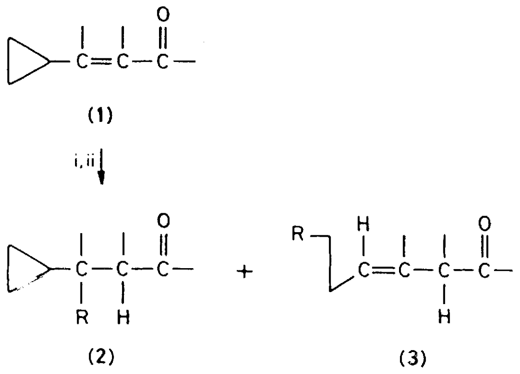
Toshiro Ibuka* and Eiji Tabushi

Faculty of Pharmaceutical Sciences, Kyoto University, Kyoto, Japan

An efficient regio- and stereo-selective 1,4-addition to β-cyclopropyl-α,β-enones using RCu–AlCl$_3$ is described.

The 1,4-addition of ordinary organocopper(I) reagents, such as the Gilman reagent (R$_2$CuLi), to α,β-unsaturated carbonyl compounds has proved highly useful in organic synthesis.[1,2] With β-cyclopropyl-α,β-enones, however, the conventional organocopper(I) reagent has a serious limitation. While the conjugate addition to an α,β-enone proceeds well, addition to a β-cyclopropyl-α,β-enone (**1**) [to yield compound (**2**)] is in significant competition with cyclopropane ring opening [yielding the product (**3**)], in particular when steric factors cause the cyclopropyl group to be approximately perpendicular to the plane of the enone system, and this latter reaction may even dominate (Scheme 1).[3-8]

Although 1,4-adducts (**2**) of β-cyclopropyl-α,β-enones are promising intermediates for the synthesis of many cyclopropane ring-containing natural products, scanning the literature revealed that no general method for the efficient regio- and stereo-selective 1,4-addition to such enones was available.



Scheme 1. *Reagents:* i, R$_2$CuLi; ii, H$_3$O$^+$.

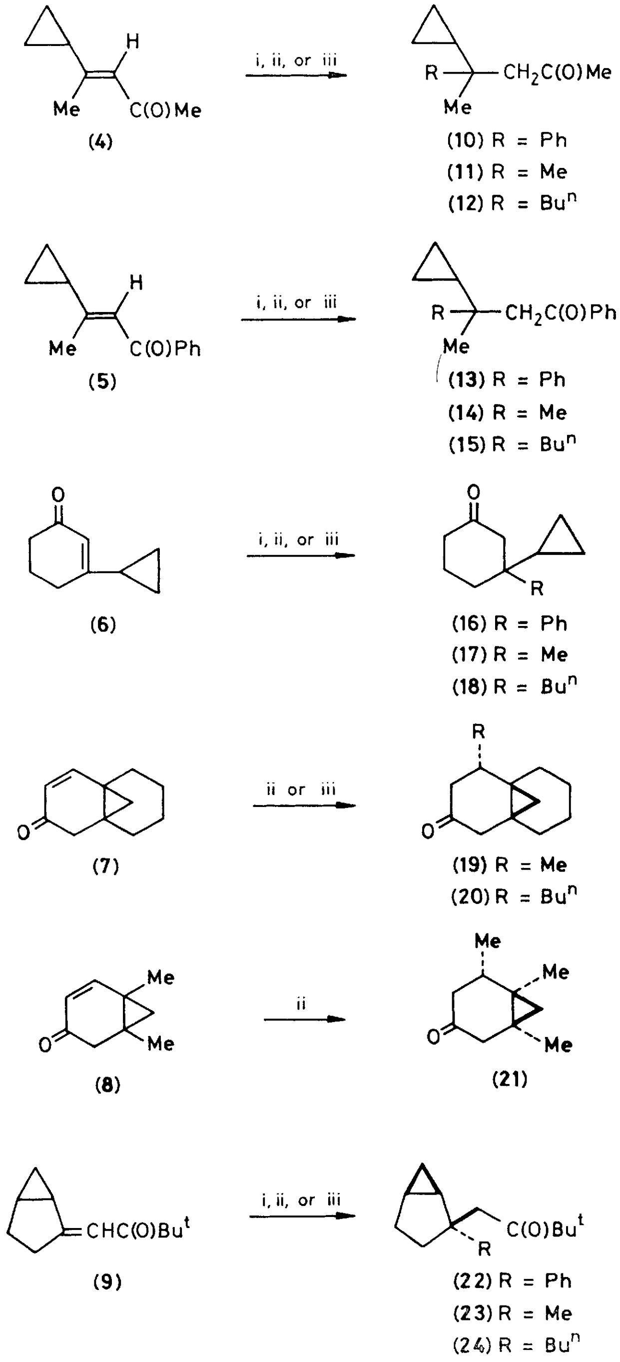
We report that an equimolar mixture of an organocopper(I) compound and aluminium trichloride (RCu–AlCl$_3$) is an effective reagent for the regio- and stereo-selective 1,4-addition to β-cyclopropyl-αβ-enones. In the absence of AlCl$_3$, stoicheiometric organocopper reagents (RCu) are inactive for 1,4-addition to β-cyclopropyl-α,β-enones. The results in

Table 1 show that RCu–AlCl$_3$ gives 1,4-adducts in satisfactory yields. It has been reported that the enones **(7)** and **(8)** give a mixture of the 1,4-adduct and by-product(s) formed after cyclopropane ring-opening on treatment with Me$_2$CuLi.[4,5] In contrast, both the enones **(7)** and **(8)** gave the regio- and stereo-selective adducts **(19)** and **(21)**, respectively, after treatment with 5 mol. equiv. of MeCu–AlCl$_3$. In these reactions, we did not detect any cyclopropane ring-opening by gas chromatographic analysis and ^{1}H n.m.r. measurements of the products. The stereochemistry of the adducts **(19)** and **(21)** was ascertained by comparison of observed spectral data with those of authentic spectra.[4,5] The difference in reactivity of Me$_2$CuLi and MeCu–AlCl$_3$ was also worthy of remark. Whereas Me$_2$CuLi was quite reluctant to undergo the 1,4-addition with the enone **(9)**, MeCu–AlCl$_3$ readily reacted with **(9)** at −70 °C to yield the adduct **(23)** as the sole product in a high yield.†

Table 1. Yields of products in the reactions of β-cyclopropyl-α,β-enones with RCu–AlCl$_3$.[a]

Expt.	Substrate	Reagent[b]	1,4-Adduct, yield/%
1	**(4)**	i	**(10)** 84
2	**(4)**	ii	**(11)** 82
3	**(4)**	iii	**(12)** 86
4	**(5)**	i	**(13)** 87
5	**(5)**	ii	**(14)** 98
6	**(5)**	iii	**(15)** 92
7	**(6)**	i	**(16)** 84
8	**(6)**	ii	**(17)** 98
9	**(6)**	iii	**(18)** 95
10	**(7)**	ii	**(19)** 75
11	**(7)**	iii	**(20)** 57
12	**(8)**	ii	**(21)** 72
13	**(9)**[c]	i	**(22)** 70
14	**(9)**[c]	ii	**(23)** 89[d]
15	**(9)**[c]	iii	**(24)** 87[d]

[a] Because the RCu–AlCl$_3$ reagent is a heterogeneous suspension, complete formation of the 1,4-adduct was obtained by using 5 mol. equiv. of RCu–AlCl$_3$. All reactions were carried out at least in duplicate and the following procedure for the 1,4-addition is typical. To a stirred suspension of MeCu (2.8 mmol) in dry ether (10 ml) under Ar at −70 °C was added dropwise a solution of AlCl$_3$ (2.8 mmol) in ether (2 ml) and the mixture was stirred for 1 h. The enone **(9)** (100 mg, 0.56 mmol) in dry ether (6 ml) at −70 °C was added to the mixture with stirring, and the temperature was gradually raised to −50 °C. After the usual work-up, the product was purified, if necessary, by silica gel column chromatography to yield the pure adduct **(23)** (96 mg, 89% yield after Kugelrohr distillation). [b] Reagents are designated as in Scheme 2. Other organocopper(I) reagents such as RCu–Bu$_3^n$P gave unsatisfactory results for the present 1,4-addition. [c] The enone **(9)** is a *ca.* 1 : 1 mixture of (*E*)- and (*Z*)-stereoisomers. [d] The stereochemistry of **(23)** and **(24)** was inferred from ^{1}H n.m.r. spectra.



Scheme 2. *Reagents:* i, PhCu–AlCl$_3$; ii, MeCu–AlCl$_3$; iii, Bu^{n}Cu–AlCl$_3$.

The present methodology for the 1,4-addition to β-cyclopropyl-α,β-enones using RCu–AlCl$_3$ has several advantages over the ordinary organocopper(I) reagent in terms of stereo- and regio-selectivity, and of efficiency.

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† All new compounds exhibited satisfactory spectroscopic and analytical data consistent with the proposed structures.