

1,4-Additions of the Highly Functionalized Copper Reagents $\text{RCu}(\text{CN})\text{ZnI} \cdot 2 \text{BF}_3$ to Trisubstituted Enones. A New BF_3 Promoted Cyclization Reaction

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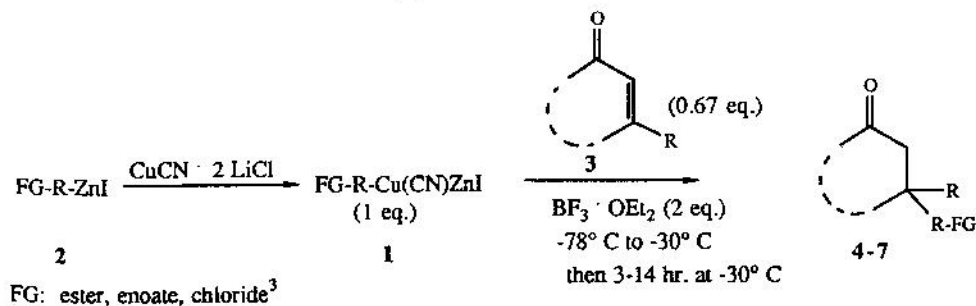
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Summary: The new copper reagents $\text{RCu}(\text{CN})\text{ZnI} \cdot 2 \text{BF}_3$ **1** containing various functional groups like esters, nitriles, chlorides or enoates react with β, β' -disubstituted enones to afford the Michael adducts **4-7** in high yields (81-98%). Cyano-substituted 1,4-adducts undergo a new cyclization reaction leading to the very stable bicyclic difluoroboron enolates **11a-11c** which could be converted into the bicyclic diketones **12** under mild basic conditions. The X-ray structure of **11b** is reported.

Recently, we reported¹ that the highly functionalized copper, zinc organometallics $\text{FG-R-Cu}(\text{CN})\text{ZnI}$ **1** obtained from the corresponding alkylzinc iodides **2** react with various electrophiles like acyl chlorides, allylic halides, aldehydes or enones to afford polyfunctional molecules in high yields. However a β, β' -disubstituted enone like 3-methyl-2-cyclohexen-1-one gave the desired 1,4-adduct in only a moderate yield^{1a}.

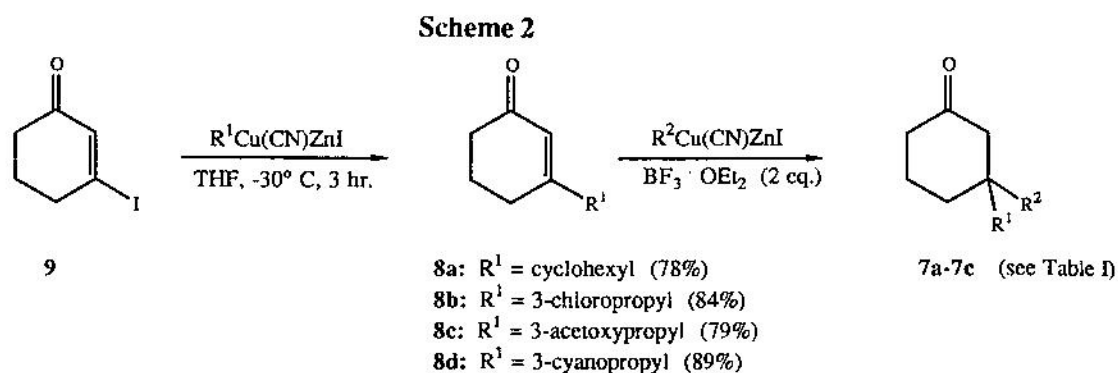
We wish now to report that the presence of $\text{BF}_3 \cdot \text{OEt}_2$ allows us to perform Michael additions of the organo-copper reagents **1** to highly substituted enones **3** in excellent yields (81-98%). See Scheme 1 and Table 1.

Scheme 1

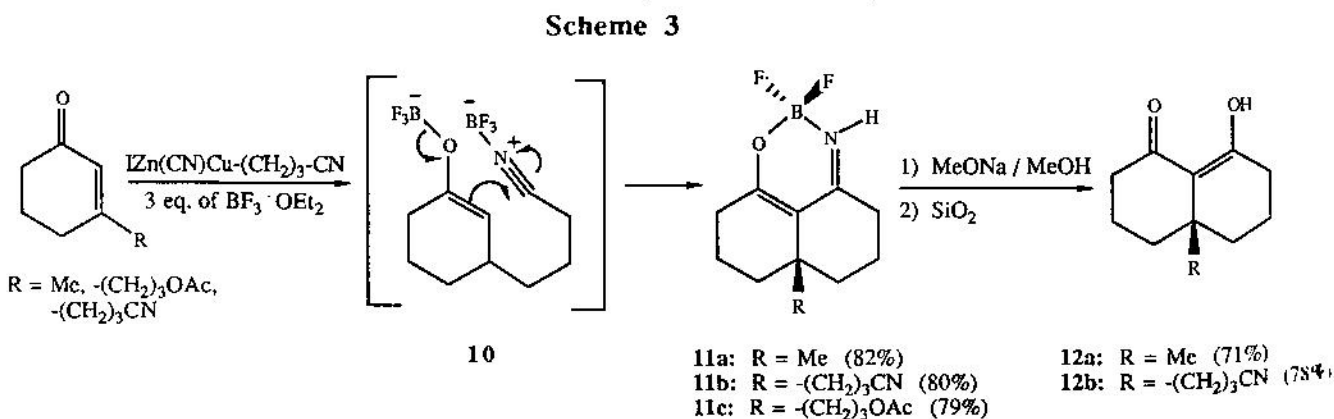


In a typical procedure, 2.5 ml (20 mmol) of $\text{BF}_3 \cdot \text{OEt}_2$ was added at -78°C to a THF solution of 10 mmol of the copper reagent **1**, followed by 6.67 mmol (0.67 eq.) of the enone **3**. The reaction mixture was allowed to reach -30°C and was stirred 3 to 14 hours at this temperature. An additional 2 hours of stirring at 0°C was necessary in some

cases. (See Table I). After the usual work-up, the resulting oil was purified by flash chromatography. Since no 1,4-addition reaction occurs without the presence of $\text{BF}_3 \cdot \text{OEt}_2$, a selective synthesis of highly functionalized enones of type **8** and of the β, β' -disubstituted ketones **7a-c** was possible respectively by the reaction of 3-iodo-2-cyclohexen-1-one⁴ **9** with $\text{R}^1\text{Cu}(\text{CN})\text{ZnI}$ (THF, 3 hrs., -30°C ; 78-89%) and by the reaction of enones **8** with $\text{R}^2\text{Cu}(\text{CN})\text{ZnI} \cdot 2\text{BF}_3$ (see Scheme 2 and Table I).

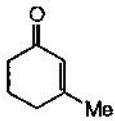
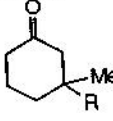
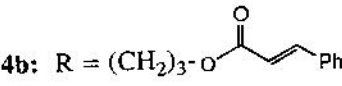
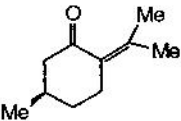
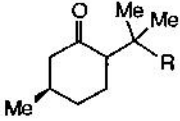
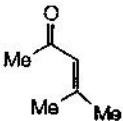
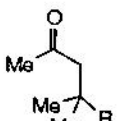
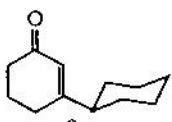
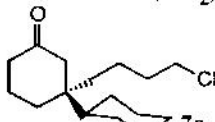
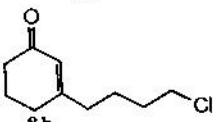
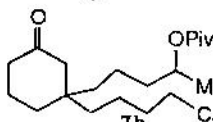
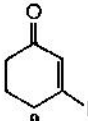
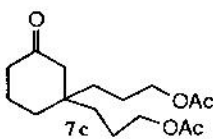


Noteworthy in all these BF_3 -promoted reactions is the tolerance of various oxygen containing functional groups. 1,4-Adducts containing a cyano group show a different behavior. After the initial Michael addition leading to **10**, a ring closure reaction occurs and affords the bicyclic difluoroboron enolates **11** which could be isolated in good yields (79-82%) and converted under mild basic conditions (i) MeONa/MeOH , 0°C , 30 min. (ii) SiO_2 (flash chromatography)) to the bicyclic ketones **12** in 71-78% yield (see Scheme 3).



The boron enolates **11** are remarkably stable compounds which could be purified by flash chromatography (solvent: $\text{AcOEt}/\text{Hexane}$). An X-ray analysis⁵ of **11b** ($\text{R} = -(\text{CH}_2)_3\text{CN}$) disclose a very symmetrical structure with a C-N double bond (1.31 Å) and with a C10-C9 bond and a C9-O bond of 1.36 Å and 1.33 Å length respectively which is typical for an enolate⁶. Interestingly the tetrahedral boron is not in the plane of the organic chelate but is slightly bent toward the same side as the substituent at C5 (see Fig. 1).

Table I. Products 4-7 Obtained by the Reaction of Enones with Organo-Copper Reagents 1

RCu(CN)Zn I 1	Enone	Products of 4-7	Yield(%) ^a
Cl-(CH ₂) ₄ -Cu(CN)ZnI		 4a: R = -(CH ₂) ₄ -Cl	88
Ph-CH=CH-CO-O-(CH ₂) ₃ -Cu(CN)ZnI		 4b: R = (CH ₂) ₃ -O-CO-CH=CH-Ph	98b
AcO-(CH ₂) ₃ -Cu(CN)ZnI		4c: R = -(CH ₂) ₃ OAc	87
Cl-(CH ₂) ₄ -Cu(CN)ZnI		 5a: R = -(CH ₂) ₄ -Cl	94b,c
EtO ₂ C-(CH ₂) ₃ -Cu(CN)ZnI		5b: R = -(CH ₂) ₃ CO ₂ Et	94b,c
Ph-CH=CH-CO-O-(CH ₂) ₃ -Cu(CN)ZnI		5c: R = -(CH ₂) ₃ -O-CO-CH=CH-Ph	84c
EtO ₂ C-(CH ₂) ₃ -Cu(CN)ZnI		 6a: R = -(CH ₂) ₃ -CO ₂ Et	88
Ph-CH=CH-CO-O-(CH ₂) ₃ -Cu(CN)ZnI		6b: R = -(CH ₂) ₃ O-CO-CH=CH-Ph	88b
PivO-CH(CH ₃)-(CH ₂) ₃ -Cu(CN)ZnI		6c: R = -(CH ₂) ₃ -CH(CH ₃)-OPiv	88b
Cl-(CH ₂) ₄ -Cu(CN)ZnI		 7a	81d
PivO-CH(CH ₃)-(CH ₂) ₃ -Cu(CN)ZnI		 7b	86b,c
AcO-(CH ₂) ₃ -Cu(CN)ZnI		 7c	86

^a All indicated yields are isolated yields. Satisfactory spectral data (IR, ¹H and ¹³C-NMR, mass spectra), high resolution mass spectra or elemental analysis were obtained for all compounds.

^b The reaction was stirred 14 hrs. at -30° C then 2 hr. at 0° C.

^c A 1:1 mixture of diastereoisomers was obtained.

^d The reaction was stirred 22 hrs. at -30° C, then 6 hrs. at 0° C.

m.p. 177-179°C

$^1\text{H-NMR}$: $\delta(\text{H-N})$ 6.85 ppm

$^{13}\text{C-NMR}$: $\delta(\text{C1})$ 172.4 ppm

$\delta(\text{C10})$ 111.5 ppm

$\delta(\text{C9})$ 175.90 ppm

IR (CDCl_3): $\nu(\text{NH})$ 3147 cm^{-1}

$\nu(\text{C=C or C=N})$ 1614 cm^{-1}

Elemental analysis:

Calcd: C: 60.03; H: 6.81; N: 10.00

Found: C: 60.02; H: 6.84; N: 9.99

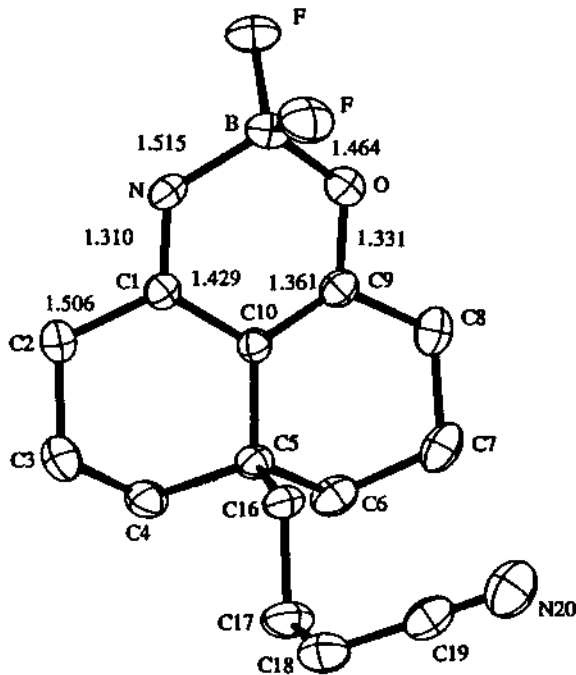


Fig. 1. ORTEP representation of the structure of **11b** determined by X-ray analysis and significant analytical data of **11b**.

Further synthetic applications of this new BF_3 -mediated cyclization are currently underway in our laboratory.

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- Crystallographic data for compound **11b**: crystal system: orthorhombic space group: $Pbca$ [$a = 7.069(2)$ Å, $b = 16.123(5)$ Å, $c = 24.497(8)$ Å] $D_{\text{calc.}} = 1.333$ g/cm^3 ; λ (Mo $K\alpha$) = 0.71069 Å; $V = 2792$ (1) Å³; $Z = 8$; crystal size (mm): 0.23 x 0.208 x 0.426 no. of data, $I > 3\sigma(I)$: 951; no. of refined parameters: 184; $R = 0.040$; $R_w = 0.035$.
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