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1,4-Additions of the Highly Functionalized Copper Reagents RCu(CN)ZnI · 2 BF_3 to Trisubstituted Enones. A New BF_3 Promoted Cyclization Reaction

Ming Chang P. Yeh, Paul Knochel*, William M. Butler and Scott C. Berk

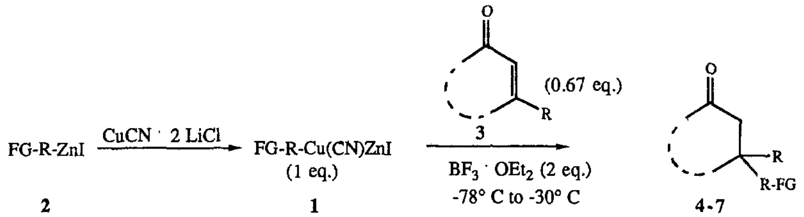
Department of Chemistry, The University of Michigan, Ann Arbor, Michigan 48109

Summary: The new copper reagents RCu(CN)Zn I · 2 BF_3 **1** containing various functional groups like esters, cyanides, 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 reported[1] that the highly functionalized copper, zinc organometallics FG-R-Cu(CN)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 $BF_3 \cdot OEt_2$[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.

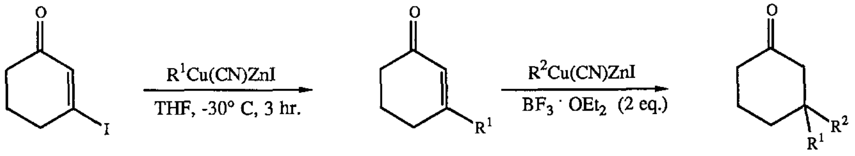
Scheme 1



FG: ester, enoate, chloride[3]

In a typical procedure, 2.5 ml (20 mmol) of $BF_3 \cdot OEt_2$ was added at -78° C to a THF solution of 10 mmol of the copper reagent[1] **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 $BF_3 \cdot OEt_2$, 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-one[4] **9** with $R^1Cu(CN)ZnI$ (THF, 3 hrs., -30° C; 78-89%) and by the reaction of enones **8** with $R^2Cu(CN)ZnI \cdot 2\,BF_3$ (see Scheme 2 and Table I).

Scheme 2



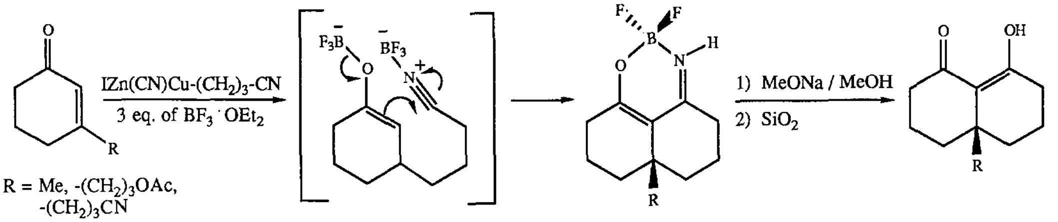
9

8a: R^1 = cyclohexyl (78%)
8b: R^1 = 3-chloropropyl (84%)
8c: R^1 = 3-acetoxypropyl (79%)
8d: R^1 = 3-cyanopropyl (89%)

7a-7c (see 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).

Scheme 3



R = Me, $-(CH_2)_3OAc$, $-(CH_2)_3CN$

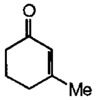
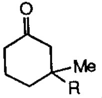
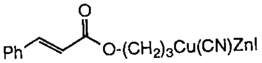
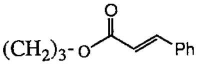
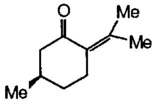
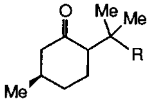
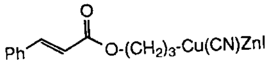
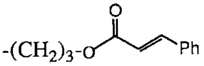
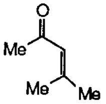
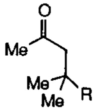
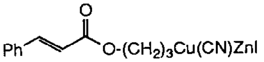
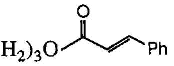
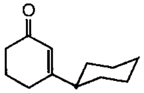
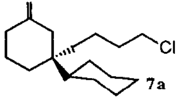
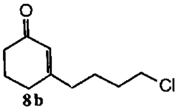
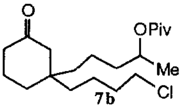
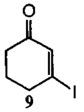
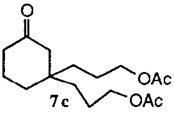
10

11a: R = Me (82%)
11b: R = $-(CH_2)_3CN$ (80%)
11c: R = $-(CH_2)_3OAc$ (79%)

12a: R = Me (71%)
12b: R = $-(CH_2)_3CN$ (78%)

The boron enolates **11** are remarkably stable compounds which could be purified by flash chromatography (solvent: AcOEt / Hexane). An X-ray analysis[5] of **11b** (R = $-(CH_2)_3CN$) 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 enolate[6]. 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
		**4b**: R = 	98[b]
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	94[b,c]
EtO_2C-$(CH_2)_3$-Cu(CN)ZnI		**5b**: R = -$(CH_2)_3CO_2Et$	94[b,c]
		**5c**: R = 	84[c]
EtO_2C-$(CH_2)_3$-Cu(CN)ZnI		 **6a**: R = -$(CH_2)_3$-CO_2Et	88
		**6b**: R = 	88[b]
PivO-CH(CH_3)-$(CH_2)_3$-Cu(CN)ZnI		**6c**: R = -$(CH_2)_3$-CH(CH_3)-OPiv	88[b]
Cl-$(CH_2)_4$Cu(CN)ZnI	 **8a**	 **7a**	81[d]
PivO-CH(CH_3)-$(CH_2)_3$-Cu(CN)ZnI	 **8b**	 **7b**	86[b,c]
AcO-$(CH_2)_3$-Cu(CN)ZnI	 **9**	 **7c**	86

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[a] All indicated yields are isolated yields. Satisfactory spectral data (IR, ^1H and ^{13}C-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}H-NMR: δ (H-N) 6.85 ppm

^{13}C-NMR: δ (C1) 172.4 ppm
δ (C10) 111.5 ppm
δ (C9) 175.90 ppm
IR ($CDCl_3$): ν (NH) 3147 cm^{-1}
ν (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

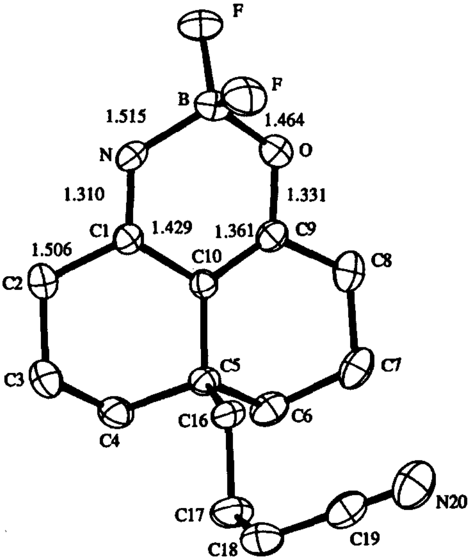

Fig. 1. ORTEP representation of the structure of **11b** determined by X-ray analysis and significant analytical data of **11b**.

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

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References

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2. (a) Yamamoto, Y. Angew. Chem. Int. Ed. Engl. **1986**, 25, 947; ibid. Angew. Chem. **1986**, 98, 945; (b) Lipshutz, B.H. Synthesis **1987**, 325.
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5. 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] $D_{calc.}$ = 1.333 g/cm^3; λ (Mo Kα) = 0.71069 Å; V = 2792 (1) Å^3; Z = 8; crystal size (mm): 0.23 x0.208 x 0.426 no. of data, I > 3σ (I) : 951; no. of refined parameters: 184; R = 0.040; R_W = 0.035.
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