Tetrahedron Letters,Vol.24,No.49,pp 5521-5524,1983 0040-4039/83 \$3.00 + .00
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1,5-ADDITION OF DIALKYLCUPRATE REAGENTS TO ALKYLCYCLOPROPYL KETONES

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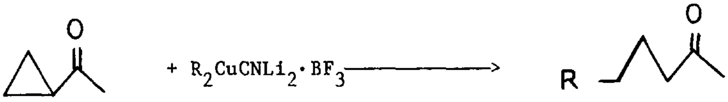
Summary: Cyclopropyl ketones undergo 1,5-addition at the less substituted carbon using the complex reagent $R_2CuCNLi_2 \cdot BF_3$.

Nucleophilic ring-cleavage of diactivated cyclopropanes has found many applications in the total synthesis of natural products[1]. On the other hand, comparable homoallylic additions to monoactivated cyclopropanes are rare and normally restricted to highly strained systems[2], powerful nucleophiles (PhS^-, $PhSe^-$)[3,4],or electrophile assisted reactions[5]. For example, Wender[6], in the total synthesis of Modhephene, reported that Me_2CuLi failed to react with a cyclopropyl ketone, but did undergo 1,5-addition with a related vinylcyclopropyl ketone in 76% yield. With methylcyclopropyl ketone, Me_2CuLi gives only enolization[7]. In this communication we describe the first homoconjugate addition to monoactivated cyclopropanes with concomitant C-C bond formation by exploitation of Lewis acid complexed cuprates under mild conditions.

The reluctance of monoactivated alkylcyclopropyl ketones to accept cuprates by homoconjugate addition is consistent with House's correlation[8] between enone reduction potential and proclivity towards 1,4-addition. Methylcyclopropyl ketone has a polarographic reduction potential of $E_{1/2} = -2.87$v whereas enone conjugate addition usually occurs if $E_{1/2} = -1.4$ to -2.35v.[8] The report by Yamamoto[9] of enhanced reactivity of organocopper reagents when complexed with Lewis acids and several recent applications of Lewis acid assisted cleavage[5] of cyclopropanes under very mild conditions prompted us to examine the effect of Lewis acids on organocopper homoconjugate addition to cyclopropyl ketones.

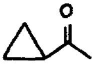
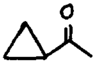
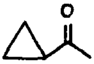
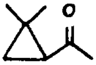
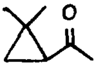
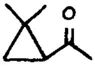
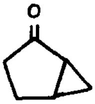
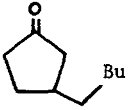
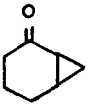
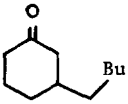
Addition of n-BuCu.BF_3 to methylcyclopropyl ketone 1 affords mainly the 1,2-carbonyl adduct whereas $R_2CuCNLi_2.BF_3$ smoothly furnishes the 1,5-adducts in moderate to good yields at -78°/-60°C (Table I). Preparation of the latter reagent from CuI or Grignard reagent results in lower yields. n-Butyl and t-butyl are transferred in 80% and 35% yield, respectively, but the corresponding phenyl cuprate fails to react. With 2,2-dimethylcyclopropyl ketone 2, n-butyl and sec-butyl are regiospecifically transferred to the less substituted carbon (entries 4 and 5). This contrasts with other nucleophilic reagents, e.g., $Me_3SiCl/NaCl$, which preferentially attack monoactivated cyclopropanes at the more substituted carbon[5c]. Diactivated systems also react at the more substituted carbon[11] which led Cram[12] to conclude that diactivated cyclopropanes have a high degree of zwitterionic character and thus tend to favor SN_1-type products. The present results suggest that $R_2CuCNLi_2.BF_3$ reacts in a concerted SN_2 reaction. Although t-butyl (entry 3) can be transferred in modest yield, the added congestion of a gem-disubstituted cyclopropyl (entry 6) could not be overcome. Finally, entries 7 and 8 demonstrate that the geometrical constraints in bicyclic systems which reduce cyclopropyl-carbonyl π overlap have an adverse effect on the yield.



Representative Procedure : In a 50 ml flask, equipped with a magnetic stirrer and maintained under argon, were placed 0.358 g of CuCN (4 mmole) and 12 ml of dry ether. n-Butyllithium in hexane (1.6 M, 8 mmole) was slowly added at -30°C and the suspension stirred for 5 min. The resultant colorless, homogeneous solution was cooled to -78°C and $BF_3.Et_2O$ (47%, 0.51 ml, 4 mmole) was slowly added. After 2 min, the cyclopropyl ketone (2 mmole, neat or in a small amount of ether) was added and the stirring maintained at -78°C by addition of H_2O, warmed to room temperature and the product obtained by extractive isolation and chromatographic purification (SiO_2).

Acknowledgment : This work was supported in part by the Robert A. Welch Foundation (I-782) and NATO (RG 158.80).

Table I. Homoconjugate Addition of $R_2CuLi_2 \cdot BF_3$ to Cyclopropyl Ketones.

Entry	Ketone	R	Equivalent of Cuprate	Time H	Temp[a] °C	Product	Yield
1		nBu	3 1.2	1	-70		78% 50%
2		sBu	2	3	-70		62%
3		tBu	2	6	-60		35%
4		nBu	2	1	-70		55%
5		sBu	2	2	-70		35%
6		tBu	2	6	-60		0%
7		nBu	2	3	-70		5%
8		nBu	2	3	-70		8%

[a] At temperatures above -50°C, decomposition and/or 1,2-carbonyl addition is favored.

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(Received in France 1 September 1983)