Tetrahedron Letters,Vol.25,No.10,pp 1079-1082,1984 0040-4039/84 \$3.00 + .00
Printed in Great Britain

ADDITION OF BORON TRIFLUORIDE COMPLEXES OF ORGANOCOPPER REAGENTS TO ALDIMINES CONTAINING α-HYDROGENS

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Abstract : $RCu \cdot BF_3$, generated in situ from Grignard reagents, CuI, and $BF_3 \cdot OEt_2$, added to aldimines containing α-hydrogens to afford secondary amines in good yields. Boron trifluoride complex of dialkylcuprate gave essentially the same result with wider application.

Reactions of organometallic reagents with imines show complex behavior depending on the species of each reagent and the structure of imines, i. e., (i) alkyl Grignard reagents afford metalloenamines from aldimines and ketimines containing α-hydrogens,[1] (ii) alkyl- and aryllithiums add to aldimines in low to moderate yields,[2] (iii) allylic or propargylic Grignard reagents add to ketimines in moderate yields,[3] (iv) reductive dimerization often competes with the desired addition.[4]

It is desirable to circumvent these problems and to device an efficient method for addition of organometallic reagents to imines with α-hydrogens. We tried to find out some organometalloids with low basicity which can activate imines by coordination and make simultaneous addition possible. Now we describe addition of $RCu \cdot BF_3$[5] to aldimines containing α-hydrogens.

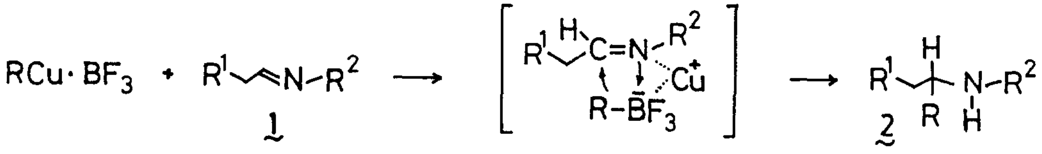
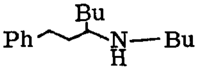
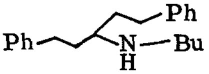
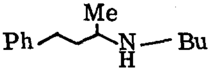
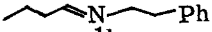
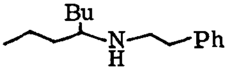
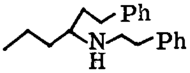
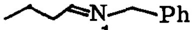
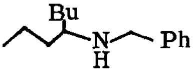


Table Synthesis of Secondary Amines via Addition of $RCu \cdot BF_3$ to Aldimines

Entry	Aldimine 1	Nucleophile[1)] (2 equiv.)	Product[4)] 2	Yield[5)] (%)
1	 1a	BuMgBr		0
2		BuCu		0
3		BuLi	 2a-i	54
4		$BuCu \cdot BF_3$[2)]		47
5		$BuCu \cdot BF_3$[3)]		64
6		$BuCu \cdot BF_3$		78
7		$PhCH_2CH_2Cu \cdot BF_3$	 2a-ii	85
8		$MeCu \cdot BF_3$	 2a-iii	60
9	 1b	$BuCu \cdot BF_3$	 2b-i	57
10		$PhCH_2CH_2Cu \cdot BF_3$	 2b-ii	79
11	 1c	$BuCu \cdot BF_3$	 2c-i	78

1) $RCu \cdot BF_3$ was prepared *in situ* from RMgX, CuI, and $BF_3 \cdot OEt_2$ except entry 4 and 5.

2) One equiv. of the reagent prepared from BuLi was used.

3) Two equiv. of the reagent prepared from BuLi was used.

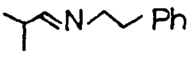
4) Satisfactory IR, NMR, and MS data were obtained for these compounds. All 2 are hygroscopic, 2a-i, 2a-ii, and 2b-i gave correct elemental analyses, but 2a-iii, 2b-ii, and 2c-i gave correct result only when ca. 0.1 mole of water is assumed to be contained. N-acetyl and benzoyl derivatives of 2c-i were prepared for identification.

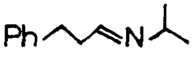
5) Isolated yield by thin layer chromatography (isopropylamine : hexane = 1 : 30), based on aldimines.

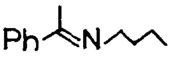
A typical experimental procedure follows (entry 6) : A solution of butylmagnesium bromide was prepared from butyl bromide (0.80 ml, 7.44 mmol) and magnesium (0.20 g, 8.18 mmol) in THF (13 ml) under argon with stirring at room temperature and CuI (1.41 g, 7.44 mmol) was added to the solution after cooling to -30°C. After stirring for 10 min at that temperature, the mixture was cooled to -70°C and $BF_3 \cdot OEt_2$ (0.91 ml, 7.44 mmol) was added slowly. The resulting mixture was stirred for 5 min and N-β-phenylpropylidene-butylamine (1a, 0.74 ml, 3.72 mmol) was added. The reaction mixture was stirred for 10 min at -70°C and allowed to warm slowly to room temperature with stirring. After addition of aqueous 10% NaOH (10 ml), extraction with ether (20 ml × 3), drying (anhydrous $MgSO_4$), and evaporation of the solvent, the residue was purified by preparative TLC with isopropylamine : hexane = 1 : 30 as an eluent to afford 2a-i (0.72 g, 2.90 mmol) in 78% yield.

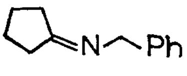
Addition of two equiv. of $RCu \cdot BF_3$, prepared from Grignard reagents, CuI, and $BF_3 \cdot OEt_2$, to aldimines (1) usually gave good results (entry 6 - 11), wheareas Grignard or copper (I) reagent did not give the addition product at all (entry 1 and 2) and the starting aldimine (1a) was recovered. It is necessary to prepare $RCu \cdot BF_3$ before the reaction, because the product (2a-i) was obtained only in low yield (10~20%) when two equiv. of BuCu was added to a premixed THF solution of 1a and two equiv. of $BF_3 \cdot OEt_2$.

It should be noted here that there is definitely a limitation to the present method. $RCu \cdot BF_3$ prepared from phenyl- or 1-propenylmagnesium bromide under otherwise the same conditions added to 1a only in low yield (4~8%). Moreover, the desired products could not be obtained at all by the reaction of $BuCu \cdot BF_3$ with ketimines (1f and 1g), nor isolated with branched aldimines (1d and 1e) due to low yields. We further tried to overcome the limitation and used boron trifluoride complex of lithium dibutylcuprate (3a : $Bu_2CuLi \cdot BF_3$)[6] which may be more reactive than $BuCu \cdot BF_3$. By the reaction of one equiv. of 3a with 1b, 2b-i was obtained in 64% yield, and moreover, one equiv. of 3a gave the desired addition


1d


1e


1f


1g

products with 1d and 1e in 63 and 84% yield, respectively. The same type of ate complex (3b : $Bu_2CuMgBr \cdot BF_3$) prepared from butylmagnesium bromide gave essentially the same result as 3a. Complexation with boron trifluoride is again essential, because Bu_2CuLi did not give addition product with 1b nor 1e at all. Even 3a and 3b could not react with a ketimine (1f). These severe steric demand implies that the coordination of the Lewis acid part of the reagent to the nitrogen is necessary to pass rather tight transition state.

Thus, at present, we beleive that the boron trifluoride complexes of cuprates are the best choice to effect the addition of alkyl groups to aldimines. Quite recent publication by Volkmann et al. prompted us to write up our results, because they stated essentially the same idea to activate 3-thiazolines by $BF_3 \cdot OEt_2$ for addition of several nucleophiles.[7] Their success, however, may certainly be limited, because butylmagnesium bromide did not add to aldimines (1) activated by Lewis acids such as $SnCl_4$, $TiCl_4$, and $BF_3 \cdot OEt_2$.

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8. Partial support of this work was provided by Grant-in-Aid for Special Project Research (No. 57218017) and for Scientific Research (No. 58540317) administered by Ministry of Education, Science, and Culture.

(Received in Japan 10 December 1983)