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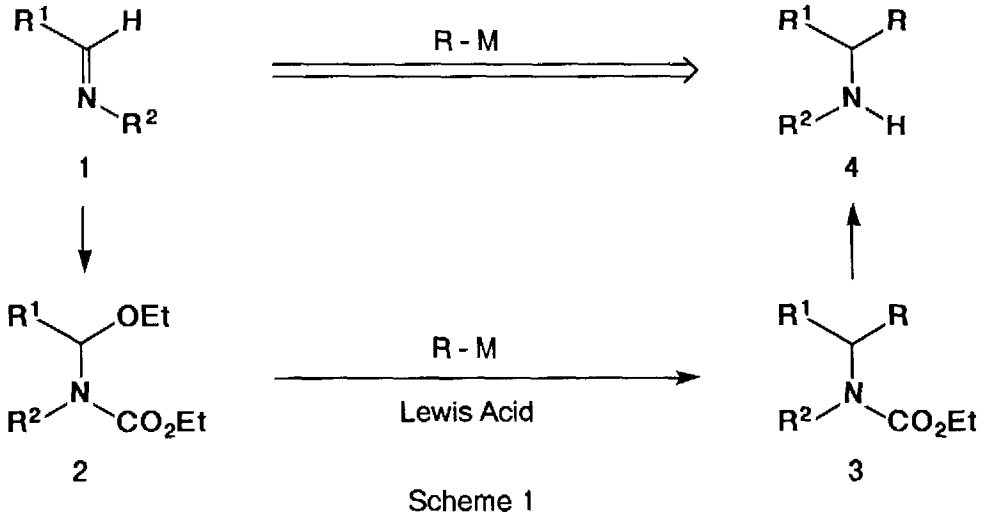
THE ALKYLATION OF α-ETHOXYCARBAMATES WITH ORGANO-LEAD, -ZINC, AND -COPPER REAGENTS. HIGH CRAM SELECTIVITY AND FORMAL NONBASIC ALKYLATION OF IMINES

Jun-ichi Yamada, Hisashi Satô, and Yoshinori Yamamoto*
Department of Chemistry, Faculty of Science, Tohoku University, Sendai 980, Japan

Summary: The alkylation of α-ethoxycarbamates is accomplished with organo-lead, -zinc, and -copper reagents in the presence of Lewis acids. The reaction proceeds with high diastereoselectivity in good to high yields.

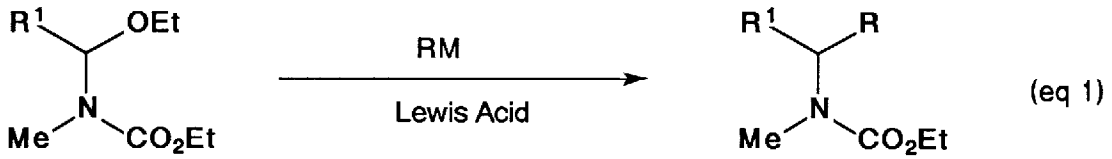
The alkylation of imines 1 with ordinary organometallic reagents does not proceed in high yield. Most of basic organometallic compounds like Grignard and organolithium reagents abstract α-hydrogen of the imines, and thus the alkylation is frequently accompanied by a number of side reactions.[1] To overcome this difficulty, Wada, Akiba, and their coworkers have employed $RCu{\cdot}BF_3$, $R_2CuLi{\cdot}BF_3$, $RLi{\cdot}CeCl_3$, and $RMgBr{\cdot}CeCl_3$.[2] We report an alternative way to solve this problem (Scheme 1); (1) imines 1 are easily converted to α-ethoxycarbamates 2; (2) treatment of 2 with alkyl-lead, -zinc, and -cuprate compounds in the presence of Lewis acids gives the desired alkylation derivatives 3 in good yields; (3) deprotection of the ethoxycarbonyl group with TMSI[3] produces 4 in very high yields. The alkylation of α-ethoxycarbamates proceeds in higher yields than the alkylation of imines themselves, but more importantly very high 1,2-asymmetric induction is accomplished by the present procedure.

The results on the alkylation of 5 with organo-leads, -zincs, and -cuprates in the presence of Lewis acids are summarized in Table 1. α-Ethoxycarbamates 5 were prepared in high yields from the corresponding imines



Scheme 1

according to the literature.[4a] We examined the alkylation of **5a** with various organometallic reagents (eq 1). Although it has been reported that methyl and cyclohexyl Grignard reagents alkylate the α-alkoxycarbamate which has a hydrogen on the nitrogen atom (R^2=H in **2**),[5] the reaction of **5a** with n-BuMgBr alone did not give the desired



(eq 1)

5 **a**:R^1=Ph
b:R^1=C_7H_{15}
c:R^1=C_6H_{11}

6 **a**:R^1=Ph
b:R^1=C_7H_{15}
c:R^1=C_6H_{11}

Table 1. Reaction of **5** with Organo-Pb, -Zn, and -Cu Compounds.[a]

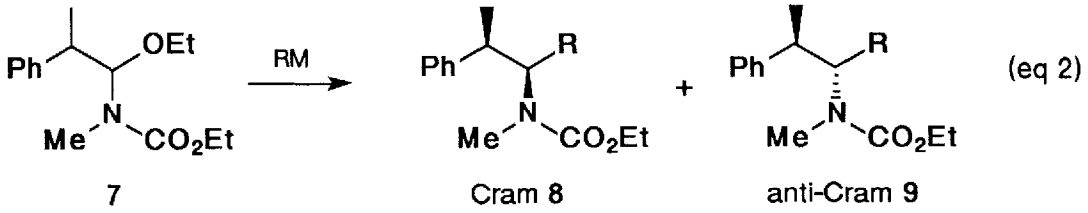
entry	5	RM (equiv)	temp (°C)	yield of **6** (%)
1	5a	Et_4Pb(1.2)/$TiCl_4$	-78 → 0	64
2	5a	Et_4Pb(2.0)/$TiCl_4$	-78 → rt	88
3	5a	$^nBu_4Pb$(2.0)/$TiCl_4$	-78 → rt	70
4	5a	Et_2Zn(1.2)/$TiCl_4$	-78 → 0	72
5	5b	Et_4Pb(2.0)/$TiCl_4$	-78 → rt	82
6	5b	Et_2Zn(1.2)/$TiCl_4$	-78 → 0	90
7	5b	$^nBu_2CuLi{\cdot}BF_3$(2.0)[b]	-78 → rt	88
8	5c	Et_4Pb(2.0)/$TiCl_4$	-78 → 0	47
9	5c	Et_4Pb(3.0)/$TiCl_4$	-78 → 0	60

[a]To a solution of **5** (1.0 or 0.5 mmol) in CH_2Cl_2 was added at -78°C a solution of $TiCl_4$ in CH_2Cl_2 (1M, 1.2 equiv) except where otherwise indicated, and then the organometallic reagents were added. The reaction was gradually warmed to either room temperature (rt) or 0°C, and then quenched with sat. $NaHCO_3$ aq. solution. The product was isolated through a silica gel column chromatography. In entry 3, a column chromatography on alumina was used. [b]Instead of $TiCl_4$, $BF_3{\cdot}OEt_2$ was used to generate the acyliminium ion.

alkylation product. Lewis acid mediated reactions with Grignard and organolithium reagents, n-BuMgBr/$TiCl_4$ and n-BuLi/$TiCl_4$, also resulted in failure. Fortunately, however, the reactions with $R_4Pb/TiCl_4$[6] and $Et_2Zn/TiCl_4$ afforded **6a** in good yields (entries 1-4). The corresponding aldimine did not undergo alkylation with these reagents, suggesting that the intermediate acyliminium ion generated from **5a** is more electrophilic than the aldimine-$TiCl_4$ complex. The α-ethoxycarbamate **5b** having hydrogens alpha to the ethoxy group also reacted smoothly with $Et_4Pb/TiCl_4$ and $Et_2Zn/TiCl_4$ to give **6b** in high yields (entries 5 and 6). The cuprate•BF_3 mediated alkylation of **5b** afforded **6b** similarly (entry 7). The alkylation of sterically hindered **5c** was somewhat sluggish even with $Et_4Pb/TiCl_4$ (entries 8 and 9).

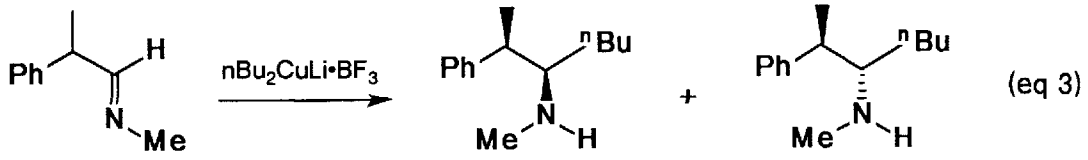
It is well known that treatment of α-alkoxycarbamates with Lewis acids produces acyliminium ions,[7] which react with organometallic compounds having easily transferable functional groups such as allylsilanes,[4b,4c,5] propargylsilanes,[4a,b] silyl enol ethers,[4d] acetylenyl silanes,[5] and γ-oxygenated allylic tin.[4e] The alkyl transfer with R_3Al is limited to methylidene acyl iminium ions (R^1=H in **2**).[8] Although it is reported that BuMgBr/cat BF_3•OEt_2 reagent alkylates a certain α-methoxycarbamate,[4d] this reagent system does not work in our substrates. Consequently, $R_4Pb/TiCl_4$ and $R_2Zn/TiCl_4$ are reagents of choice for the alkylation of acyliminium ions.

Next, we investigated 1,2-asymmetric induction in the alkylation of **7** (eq 2). The reaction with $Et_2Zn/TiCl_4$ gave a mixture of Cram **8** and anti-Cram **9** in a ratio of 74 : 26 in 50% yield. Et_4Pb/BF_3 produced similar



7 Cram 8 anti-Cram 9

$Et_2Zn/TiCl_4$	74	:	26
Et_4Pb/BF_3•OEt_2	75	:	25
$Et_4Pb/TiCl_4$	91	:	9
$nBu_4Pb/TiCl_4$	94	:	6



10 Cram 11 anti-Cram 12

69 : 31

diastereoselectivity (**8**:**9**=75:25 in 56% yield), whereas high Cram selectivity was accomplished with $Et_4Pb/TiCl_4$; **8**:**9**=91:9 in 50% yield. Similarly, n-$Bu_4Pb/TiCl_4$ produced very high diastereoselectivity. Treatment of **7** with n-$Bu_2CuLi{\cdot}BF_3$ induced the elimination of ethanol, giving the corresponding enamine derivative. As shown in eq 3, the alkylation of imine **10** with n-$Bu_2CuLi{\cdot}BF_3$ gave a 69:31 mixture of **11** and **12**. The carbamates **8** and **9** were transformed into the amines **11** and **12** in essentially quantitative yield upon treatment with TMSI.[3]

In conclusion, introduction of alkyl groups to the α-position of α-alkoxycarbamates **2** has become feasible with R_4Pb/Lewis acid or R_2Zn/Lewis acid. Further, it is revealed that $R_4Pb/TiCl_4$ is a useful reagent for high 1,2-asymmetric induction of certain α-alkoxycarbamate, as well as of an aldehyde.[6] We are now in a position to convert **1** into **4** via the α-alkoxycarbamate route.

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