Pergamon

Tetrahedron Letters, Vol. 38, No. 38, pp. 6705-6708, 1997
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0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01570-0

Highly Stereoselective S_N2' Reactions of Grignard Reagents towards CF_3-Containing Allylic Acetates

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Abstract: γ-Trifluoromethylated allylic acetates were found to quite smoothly proceed S_N2' type reaction with various Grignard reagents in the presence of a catalytic amount of CuCN and TMS-Cl, without any trace amount of the corresponding S_N2 products in all cases examined due to the electronic effect of a CF_3 group. © 1997 Elsevier Science Ltd.

The enhancement of biological activity by modification of organic materials with fluorine atom(s)[1] has been one of the principal driving forces for development of novel methods for the introduction of fluorine-containing methyl or methylene groups. Considerable difficulty has usually accompanied the preparation of CF_3-containing compounds by way of the classical fluorination techniques[2a] compared to the much easier synthetic pathways to mono- or difluorinated substances.[2b] Manipulation of appropriately functionalized building blocks that contain a CF_3 group is therefore the major strategy to access such specific targets at present.

On the other hand, because extensive recent work has allowed the construction of chiral trifluorinated secondary alcohols **A** in high optical purities *via* optical resolution of racemates[3] or asymmetric synthesis,[4] one might conclude that such molecules could be versatile chiral units for the construction of type **C** molecules by the S_N2 reaction *via* the corresponding sulfonate **B** (Fig. 1) However, in sharp contrast to the nonfluorinated prototypes, the desired substitution of **B** by carbon nucleophiles is especially difficult, which is usually explained as the result of the strongly electron-withdrawing nature of a CF_3 group[5] i) causing the electronic repulsion with the incoming anionic species, and ii) strengthening the C-O bond to be cleaved. To the best of our knowledge, there is only one successful precedent in the literature for this transformation.[6]

We have recently disclosed the convenient construction of the chiral propargylic alcohols **E** from readily available 2-bromo-3,3,3-trifluoropropene **F**,[7] more advantageous than the use of the quite expensive gas 3,3,3-trifluoropropyne. Allylic derivatives **D**, easily accessible from **E**,[7] seems to have reduced steric crowding around the CF_3 group and a weaker C-O bond than the one in **B**. If **D** undergoes new C-C bond formation at the position γ to the leaving group, this process becomes an alternative route for the synthesis of **C**.[8] Here, we would like to report the Grignard reaction towards **D** in the presence of CuCN and TMS-Cl as catalysts,

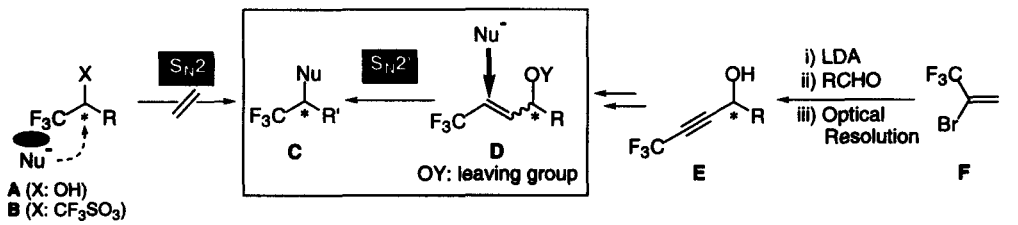

Fig. 1 Preparative Routes of the General Structure **C** *via* S_N2 and S_N2' Processes

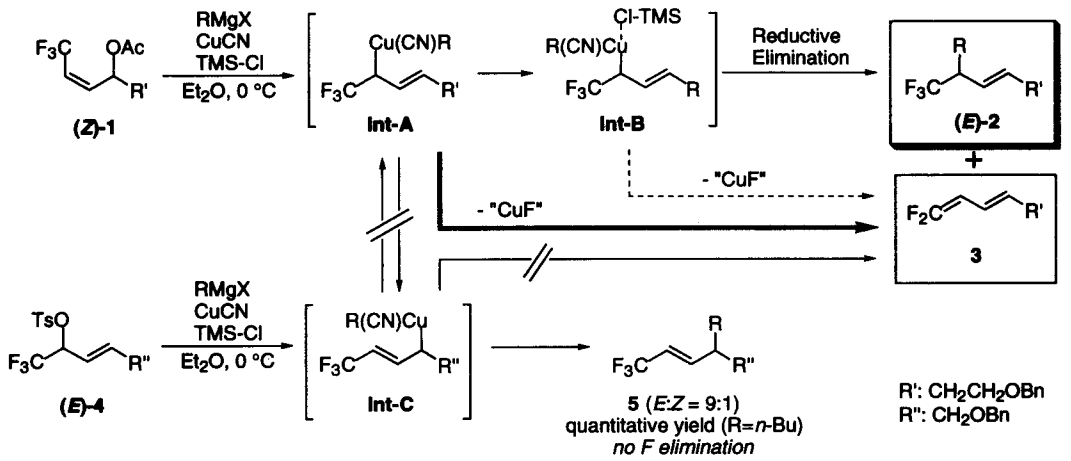

Fig. 2 Reaction Mechanism of the Present S_N2' Process

proceeding with γ regiospecificity and high *E* stereoselectivity when starting from *Z* substrates.[9]

(*Z*)-1, the model substrate throughout the present work, was reacted with 2 equiv of *n*-BuMgCl[10] in the presence of 0.1 equiv of CuCN,[11,12] and optimization of other factors was carried out (Table 1). Without any additives (entry 1), the desired product **(*E*)-2** was obtained only in a moderate yield along with the formation of the unexpected difluorinated diene **3** as the major product. Addition of Lewis acids such as $BF_3 \cdot OEt_2$ or $TiCl_4$ (entries 2 and 3) did not affect the reaction. However, TMS-Cl[13] was found to play a significantly important role in accelerating the reaction[14] and **(*E*)-2** was obtained in 85% yield with the complete regio- (α vs γ) and stereoselectivity (*E* vs *Z*, entry 4). Employment of THF as a solvent was turned out to completely suppress the desired reaction path (entry 6). We eventually determined the usage of 0.2 and 0.6 equiv of CuCN and TMS-Cl, respectively, in Et_2O at 0 ℃ as the standard conditions. Various Grignard reagents were also revealed to react smoothly with **(*Z*)-1** in an S_N2' manner to produce **(*E*)-2** in high yields with complete *E* stereoselectivity. On the other hand, the isomeric **(*E*)-1** resulted only in the low olefinic stereoselectivity; the difference can be understood from the conformational preference based on the allylic 1,3-strain concept.[15,16] Thus, **(*Z*)-1** usually possesses only one energetically important structure with the leaving group approximately perpendicular to the C-C double bond, while, in the case of **(*E*)-1**, there exist two such conformations producing different isomers at the olefinic bond of **2** in a comparable ratio.

As a comparison, **(*E*)-4**[17] was also subjected to the same reaction condition (*n*-BuMgCl) to furnish **5** quantitatively (*E*:*Z* = 9:1), which led us to conclude that **1** and **4** were the special substrates specifically giving the S_N2' products **(*E*)-2** and **5**, respectively,[18] whose mechanism was explained as follows. In the absence of TMS-Cl, intramolecular interaction of the neighboring fluorine atom(s) to Cu in **Int-A**[11b] is considered to be responsible for the formation of the unexpected product, difluorinated diene **3**,[19] which would lead to the acceleration of the "Cu-F" elimination rather than the expected reductive elimination or the isomerization to **Int-C** under the π-electron assistance. However, because coordination of TMS-Cl to copper effectively decreases the transition state energy barrier of the reductive elimination,[13a,20] the much smoother production of **(*E*)-2** occurred. Since Grignard reagents employed in entries 7 and 18 possess inherently lower reductive elimination ability,[21] the unfavorable route to **3** was still the major pathway even under the action of TMS-Cl but utilization of diethylphosphates instead of acetates was found to increase the yields of **(*E*)-2** to an acceptable level. On the other hand, in the case of the regioisomeric **(*E*)-4**, the quantitative conversion to **(*E*)-5** was understood as the combined results of the difficult isomerization of **Int-C** to **Int-A** by the electron deficient C-C double bond and no chance of the Cu···F interaction. Regiospecific preparation of the S_N2' products described above was thus attributed to the electron-withdrawing effect of the CF_3 moiety and coordination

Table 1 Reaction of (*Z*)-**1** with Various Grignard Reagents

entry	Equivalent of CuCN	Equivalent of additives[b]	Substrate **1** *E* or *Z*	RMgX	Isolated yield[a] (%) **2**	[*E*:*Z*]	**3**
1	0.1	none	*Z*	*n*-BuMgCl	(39)	[>99/1]	(54)
2	0.1	B, 0.3	*Z*	*n*-BuMgCl	(38)	[>99/1]	(50)
3	0.1	Ti, 0.3	*Z*	*n*-BuMgCl	(42)	[>99/1]	(18)
4	0.1	Si, 0.3	*Z*	*n*-BuMgCl	(85)	[>99/1]	(7)
5	0.2	Si, 0.6	*Z*	*n*-BuMgCl	91	[>99/1]	(3)
6[c]	0.2	Si, 0.6	*Z*	*n*-BuMgCl	(1)	---------	(99)
7	0.2	Si, 0.6	*Z*	MeMgBr	(17)	[>99/1]	(83)
8[d]	0.2	Si, 0.6	*Z*	MeMgBr	88	[>99/1]	(<1)
9	0.2	Si, 0.6	*Z*	*n*-C_7H_{15}MgBr	95	[>99/1]	(<1)
10	0.2	Si, 0.6	*Z*	allylMgBr	0[e]	---------	(0)
11[d]	0.2	Si, 0.6	*Z*	allylMgBr	67	[>99/1]	(9)
12	0.2	Si, 0.6	*Z*	*i*-PrMgCl	99	[>99/1]	(<1)
13	0.2	Si, 0.6	*E*	*i*-PrMgCl	88	[60/40]	(1)
14	0.2	Si, 0.6	*Z*	*c*-C_6H_{11}MgCl	91	[>99/1]	(<1)
15	0.2	Si, 0.6	*E*	*c*-C_6H_{11}MgCl	89	[59/41]	(3)
16	0.2	Si, 0.6	*Z*	*t*-BuMgCl	86	[>99/1]	(5)
17	0.2	Si, 0.6	*E*	*t*-BuMgCl	33	[79/21]	(15)
18	0.2	Si, 0.6	*Z*	PhMgI	(8)	[>99/1]	(92)
19[d]	0.2	Si, 0.6	*Z*	PhMgI	49	[>99/1]	(18)

a: Yields in parentheses and *E*/*Z* ratios were determined by 470 MHz ^{19}F NMR. b: Si: TMS-Cl, Ti: $TiCl_4$, B: $BF_3{\cdot}OEt_2$. c: THF was used as the solvent. d: The corresponding diethylphosphate was used. e: No reaction (93% recovery of (*Z*)-**1**).

ability of a fluorine atom.

At the next stage, we extended this process to the asymmetric version, which was expected to give us further mechanistic information on the present reaction. (*S*)-(*Z*)-**1**[7,22] after acetylation of (*S*)-(*Z*)-**6** was treated as above, and (*S*)-(*E*)-**2** was obtained in 93% yield whose stereochemistry at the CF_3-attached carbon atom was clarified by chemical correlation to the product (*R*)-(*E*)-**7** starting from (*S*)-(*Z*)-**6** by way of the mechanistically established Johnson-Claisen rearrangement (Fig. 3). Chiral capillary GC analysis of the alcohol after cleavage of the terminal benzyl group of (*S*)-(*E*)-**2** showed 2 peaks in a ratio of 77.4:22.6, which unambiguously demonstrated the complete chirality transmission *via* the *anti*-S_N2' mechanism.

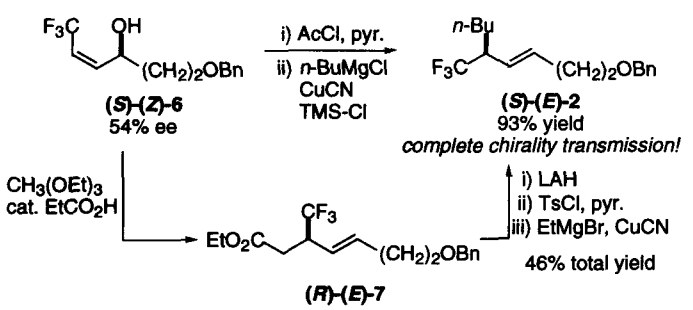

Fig. 3 Asymmetric S_N2' Reaction with *n*-BuMgCl

As depicted above, we have found that the copper(I)-catalyzed Grignard reaction towards α or γ CF_3-containing allylic alcohol derivatives smoothly proceeded by the addition of TMS-Cl, and this reaction was proved to follow the *anti*-S_N2' mechanism by the strong electronic effect of the CF_3 group as the controlling factor. We believe this procedure will open the novel route to access the important class of materials like **C** in Fig. 1, whose

scope and limitation as well as further utilization of the S_N2' products is now investigating in this laboratory.

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(*Received in Japan* 5 *June* 1997; *accepted* 28 *July* 1997)