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Access to 2,5-disubstituted tetrahydrofurans from Grignard reagents and hemiacetal derivatives

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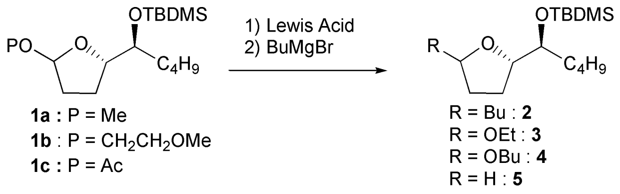
The first diastereoselective addition of Grignard reagents onto cyclic oxocarbenium ions, obtained from glycosyl acetates, to afford 2,5-disubstituted tetrahydrofurans, is reported.

Substituted tetrahydrofurans are widely used as synthetic intermediates and are often encountered in natural products (*e.g.* polyether antibiotics[1] and acetogenins of Annonaceae[2]). Synthesis of 2,5-disubstituted tetrahydrofurans *via* organometallic reagents is usually achieved by addition of alkylsilanes[3] onto a cyclic oxocarbenium ion, derived from 5-membered cyclic hemiacetals, in a Lewis acid-promoted reaction, but limited to allyl- and propargylsilanes. Only scarce examples of use of other metals such as Al, Zn, Ti, Mg and Li are reported[4] but the two latter ones failed to give the desired products.[5] During the course of the study of total synthesis of natural products, we were interested in functionalizing a tetrahydrofuran moiety and wondered if a Grignard reagent would be able to add onto a cyclic oxocarbenium ion generated from hemiacetals to afford 2,5-disubstituted tetrahydrofurans (Scheme 1).

When butylmagnesium bromide (2 equiv.) in Et_2O was added to a mixture of **1a**[6] and $BF_3{\cdot}OEt_2$ (2 equiv.) in Et_2O at −20 °C, the expected tetrahydrofuran **2** was obtained in low yield (20%) after 30 min, along with starting material **1a** (23%) and the unexpected butoxy derivative **4** (44%) (Table 1, entry 1). Moderate diastereoselectivity was observed (34:66 mixture of *cis*- and *trans*- compounds **2**, respectively).[7] However, when CH_2Cl_2 was used as solvent in place of Et_2O for generating the oxocarbenium ion and butylmagnesium bromide in Et_2O added, **2** was then obtained in 55% yield along with **1a** (10%), ethoxy derivative **3** (13%) and a reduced amount of **4** (6%) (entry 2), and the *trans*-diastereoselectivity was increased (dr = 75:25). The formation of **3** and **4**, which is reported herein for the first time, is not yet explained but a Lewis-acid mediated transetherification may be invoked. When the organomagnesium reagent was prepared in THF, the reaction is inhibited (entry 3). Adding first the Grignard reagent onto **1a**, followed by $BF_3{\cdot}OEt_2$, resulted in only 34% of **2** (entry 4). When the reaction was performed in CH_2Cl_2 at −20°C, the use of only 1 equiv. of $BF_3{\cdot}OEt_2$ and 2 equiv. of Grignard reagent led to 59% yield of **2** (compare with 55% yield with 2 equiv. of Lewis acid) whereas by using 2 equiv. of $BF_3{\cdot}OEt_2$ and 3 equiv. of butylmagnesium bromide, a slightly better yield of **2** was obtained (65%) along with reduced compound **5** (which probably arised from β-elimination of the Grignard reagent) (entries 5, 6). When the reaction was performed at −78 °C, **2** was formed in only 27% yield (entry 7). Use of other Lewis acids such as $TiCl_4$, $SnCl_4$, $Sc(OTf)_3$ and $Y(OTf)_3$ gave either low yields or no product (entries 8, 9, 10, 11). Use of methoxyethoxy derivative **1b** gave no better yields of **2** whereas use of acetoxy derivative **1c** allowed us to increase the yield of **2** up to 72%, the same diatereoselectivity being observed whatever the leaving group was (entries 6, 12 and 13). The use of a catalytic amount of trityl perchlorate, as Lewis acid, resulted in a lower yield of **2** (44%) but better selectivity (entry 14). Toluene may be used without significant loss of yield but the selectivity is slightly lower (entry 15). It is noteworthy that the lack of any catalyst did not allow us to obtain any disubstituted product, $MgBr_2$ being a too weak Lewis acid (results not shown). Traces of more polar compounds were sometimes observed when substrate **1c** was used, however compounds **3** and **4** were never observed in that case. The nature of the organometallic species involved in this



Scheme 1

Table 1 Addition of butylmagnesium bromide onto hemiacetal derivatives **1a–c** in the presence of a Lewis acid

Entry	Substrate	Solvent[a]	BuMgBr (equiv.)/solvent[b]	Lewis Acid (equiv.)	*T*/°C	**2a** (%)[c] (*trans*:*cis*)	**1**[c] (%)	**3**[c] (%)	**4**[c] (%)	**5**[c] (%)
1	**1a**	Et_2O	2/Et_2O	$BF_3{\cdot}OEt_2$ (2)	−20	20 (66:34)	23	—	44	—
2	**1a**	CH_2Cl_2	2/Et_2O	$BF_3{\cdot}OEt_2$ (2)	−20	55 (75:25)	10	13	6	—
3	**1a**	CH_2Cl_2	2/THF	$BF_3{\cdot}OEt_2$ (2)	−20	—	80	13	Traces	—
4	**1a**	CH_2Cl_2	2/Et_2O	$BF_3{\cdot}OEt_2$ (2)[d]	−20	34 (72:28)	30	16	15	—
5	**1a**	CH_2Cl_2	2/Et_2O	$BF_3{\cdot}OEt_2$ (1)	−20	59 (70:30)	6	7	Traces	—
6	**1a**	CH_2Cl_2	3/Et_2O	$BF_3{\cdot}OEt_2$ (2)	−20	65 (75:25)	5	—	—	17
7	**1a**	CH_2Cl_2	2/Et_2O	$BF_3{\cdot}OEt_2$ (1)	−78	27 (75:25)	33	Traces	16	17
8	**1a**	CH_2Cl_2	2/Et_2O	$TiCl_4$ (1)	−20	37 (68:32)	37	Traces	12	—
9	**1a**	CH_2Cl_2	2/Et_2O	$SnCl_4$ (1)	−20	—	50	25	7	—
10	**1a**	CH_2Cl_2	2/Et_2O	$Sc(OTf)_3$ (0.1)	−20	—	99	—	—	—
11	**1a**	CH_2Cl_2	2/Et_2O	$Y(OTf)_3$ (0.1)	−20	—	99	—	—	—
12	**1b**	CH_2Cl_2	2/Et_2O	$BF_3{\cdot}OEt_2$ (1)	−20	60 (76:24)	—	19	12	15
13	**1c**	CH_2Cl_2	2/Et_2O	$BF_3{\cdot}OEt_2$ (1)	−20	72 (75:25)	—	—	—	28
14	**1c**	CH_2Cl_2	2/Et_2O	$TrClO_4$ (0.1)	−20	44 (78:22)	—	22[e]	—	—
15	**1c**	Toluene	2/Et_2O	$BF_3{\cdot}OEt_2$ (1)	−20	56 (71:29)	—	Traces	—	22

[a] Of the reaction.[b] Of the Grignard reagent.[c] Isolated yield.[d] Lewis acid added to a mixture of **1a** and Grignard reagent.[e] With 21% of product resulting from dimerization of **1c** (bis-tetrahydrofuran-acetal).

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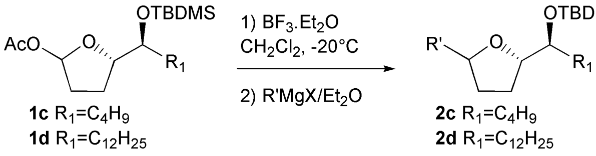
reaction is not determined, and depends on the solvent used. Indeed, studies have shown that solvents play a role both on the Schlenk equilibrium and on the organometallic aggregates.[8] Transmetallation through organoboron species (*e.g.* R_3B) should be discarded at −20 °C in Et_2O[9] although $BF_3·OEt_2$ may participate with the reactive species. However the true organometallic species remain unknown at this time, and further experiments are needed.

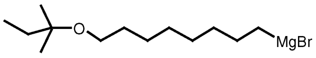
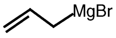
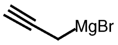
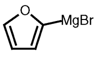
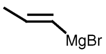
We then applied the best reaction conditions[10] (Table 1, entry 13) to various organomagnesium reagents (Scheme 2, Table 2).

Addition of *n*-butylmagnesium bromide to **1d** resulted in 64% of tetrahydrofurans **2d** (structural analogues of 2,5-dialkyltetrahydrofurans isolated from *Lepidoptera*[11]) with almost the same diastereoselectivity (78:22 in favour of the *trans* isomer) as with substrate **1c** (see Table 1 entry 13, Table 2 entry 1). Furthermore, additions of either the bulky *n*-dodecylmagnesium bromide or the Grignard reagent derived from 1-*tert*-amyloxy-8-bromooctane[12] did not increase the diastereoselectivity (Table 2, entries 2, 3). It seems that the diastereoselectivity is not very dependant on the nucleophile but may be controlled by substitution at the 5-position. The diastereoselectivities can be rationalized by involving attack of the lower energy conformer of the oxocarbenium ion, as already reported by Reissig with alkylsilanes.[3a] Addition of allylmagnesium bromide as well as propargylmagnesium bromide gave poor stereoselectivity and in the latter case, a 68:32 mixture of 2-propargyl- and 2-allenyl-tetrahydrofurans was obtained, respectively. It is interesting to note that vinylic, aromatic and heteroaromatic Grignard reagents can be used with moderate yields and diastereoselectivity (entries 6, 7 and 8). Application to functionalized Grignard reagents, obtained by halogen–metal exchanges, is now in progress, and will further extend the scope of this transformation.



Scheme 2

Table 2 Addition of various Grignard reagents[10]

Entry	Substrate	Grignard reagent	**2** (%) (dr)
1	**1d**	C_4H_9MgBr	64[a] (78:22)
2	**1c**	$C_{12}H_{25}MgBr$	61 (78:22)
3	**1c**		45 (78:22)
4	**1c**		64 (63:37)
5	**1c**		56[b] (65:35)
6	**1c**	PhMgBr	60 (77:23)
7	**1c**		47 (74:26)
8	**1d**		59 (67:33)

[a] With 13% of **5d**. [b] Mixture of allenyl- propargyl-tetrahydrofurans in a 32:68 ratio, respectively.

In conclusion we have developed a stereoselective method for the synthesis of functionalized 2,5-disubstituted tetrahydrofurans using Grignard reagents. The use of these readily available nucleophiles is noteworthy, since a large variety of such organometallic species are now easily prepared.[13] This methodology constitutes a new C-glycosylation reaction which may certainly be applied to tetrahydropyrans as well (studies in course in our laboratory) or 4-acetoxy-1,3-dioxanes.[14] It is an altenative solution to the addition of an organometallic reagent onto a lactone ring followed by Et_3SiH reduction of the resulting hemiacetal to lead to the major *cis* isomer.[15]

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