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Diastereoselective Addition Reactions of Furyl Aldehydes Using Chiral Boronates as Auxiliary: Application to the Enantioselective Synthesis of 2,3-Disubstituted Furyl Alcohols[†]

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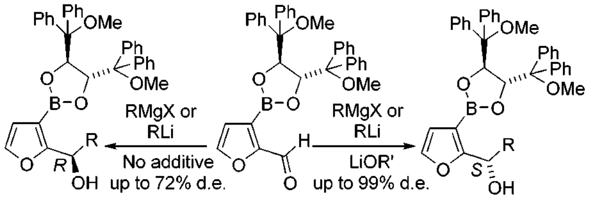
ABSTRACT



The addition reactions of various nucleophiles to a furyl aldehyde bearing a chiral boronate at the C-3 position furnished chromatographically separable diastereomers. The *R* diastereoselection was more favorable when no additive was added. Surprisingly, when lithium alkoxides were selected as additives, the *S* diastereoselection is superior instead. Further transformation of C–B bonds to C–C bonds was achieved by using standard Suzuki coupling conditions to give optically active 2,3-disubstituted furyl alcohols.

6-Hydroxy-2*H*-pyran-3(6*H*)-one (**1**) contains several functionalities that could allow facile introductions of other functional groups. In this way, derivatives of **1** have become important building blocks for the synthesis of biologically active natural products (Figure 1).[1] The easiest way to access this type of compounds is through the oxidative rearrangement of furyl alcohols by peracid.[1b] Conventional methods developed for the synthesis of furyl alcohols include Sharpless asymmetric aminohydroxylation of vinylfuran,[2a] kinetic resolution,[2b] enzymatic resolution of racemic 2-furyl alcohols,[2c] asymmetric allylation,[2d] and aldol reaction[2e] of furyl aldehyde

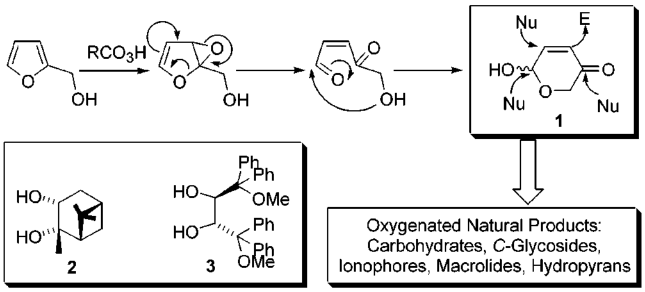


Figure 1. Oxidative rearrangement of furfuryl alcohol and structures of diols **2** and **3**.

[†] Dedicated to Professor Qi-Yi Xing of Peking University on the occasion of his 90th birthday.

[‡] An area of Excellence of the University Grants Committee (Hong Kong).

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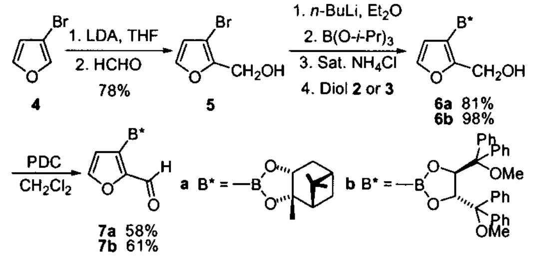
as well as asymmetric catalytic hydrogenation of furyl ketone.[2f] Despite the high yield and high enantioselectivity, all the synthesized furyl alcohols possess only C-2 substituents. 2,3-Disubstituted furyl alcohols, on the other hand, have attracted less attention.

Boronic esters of (*S*)-pinanediol (**2**)[3] and (2*R*,3*R*)-1,4-dimethoxy-1,1,4,4-tetraphenyl-2,3-butanediol (**3**)[4] (Figure 1) have been used as efficient chiral auxiliaries in asymmetric synthesis. Moreover, the diastereoselective aldol reactions of chiral 3-(*p*-tolylsulfinyl)furfural with silyl ketene were also reported recently.[5] In connection with our interest in the realization of highly functionalized pyranone **1**, we wish to report our employment of boronic esters as chiral auxiliaries for the synthesis of optically pure 2,3-disubstituted furyl alcohols.

Employing our own experience on the regiospecific synthesis of substituted furans,[6] pyrroles,[7] and thiophenes,[8] furyl aldehydes **7** were designed as our initial target molecules, which in turn were synthesized from commercially available 3-bromofuran (**4**) via the regiospecific route as shown in Scheme 1.

Scheme 1. Synthesis of Furyl Aldehydes **7**



Regiospecific depotonation[9] of **4** with LDA at −78 °C in THF gave α-lithiated furan, which was further quenched by gaseous formaldehyde to furnish furyl alcohol **5**. Transformation of the C−Br bond of **5** to the C−B bond of **6** was successful after a series of reactions, including metalation with 2 equiv of *n*-BuLi, boronation with triisopropyl borate, hydrolysis of borate salt, and dehydration of furyl boronic acid with the corresponding diols. Mild oxidation[10] of **6** with PDC in CH_2Cl_2 furnished furyl aldehydes **7** without destroying the chiral boronate moiety.

From the X-ray crystallographic analysis of **7a** (Figure 2a) and **7b** (Figure 2b), it is evident that, compared to the diol **2** as chiral auxiliary, the bulky diol **3** with C_2 symmetry more effectively occupies the space around the carbonyl group on the furan ring. As the *Si*-face of the carbonyl group was blocked by a bulky substituent, the less hindered *Re*-face attack of nucleophiles to the carbonyl group was expected, leading possibly to high diastereoselectivity. An AM1 calculation also confirms this conformation.[11] Moreover, the huge geometric differentiation between the resulting diastereomers should also allow for a successful separation of both diastereomers by flash column chromatography.

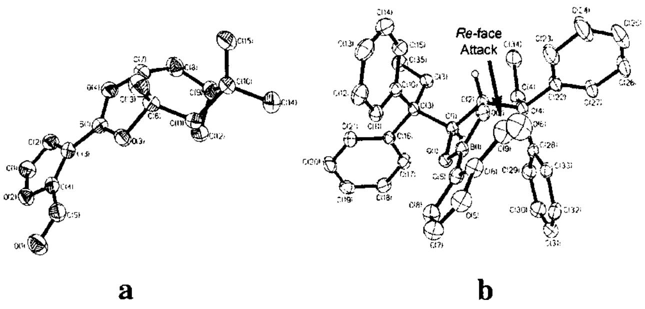


Figure 2. (a) X-ray crystal structure of **7a**; (b) X-ray crystal structure of **7b** with a predicted more favorable *Re*-face nucleophilic attack.

We first investigated the addition reactions of furyl aldehyde **7a** (entry 1, Table 1). The addition reaction of **7a** with *n*-BuLi furnished **8a** and **9a**, which are not separable on column chromatography, in moderate yield and low diastereoselectivity. The newly created chiral centers of the diastereomers were confirmed by their conversions to the corresponding Mosher ester.[12] This unsatisfactory outcome may be attributed to the less pronounced stereochemical environment of the chiral auxiliary around the carbonyl group. We then turned our focus to the addition reactions of **7b**. Thus, addition reactions of **7b** with various nucleophiles afforded diastereomers **8b**−**h** and **9b**−**h** in good yields and moderate diastereoselectivities (entries 2−8, Table 1). As expected, these diastereomers can be efficiently separated by flash column chromatography leading to pure diastereomers. Further increasing the nucleophile's bulkiness allows an easier separation of both diastereomers (entries 5−8, Table 1). The newly created chiral centers were also confirmed by conversion to the corresponding Mosher ester, by Riguera's method,[13] and by X-ray crystallographic analysis.[14]

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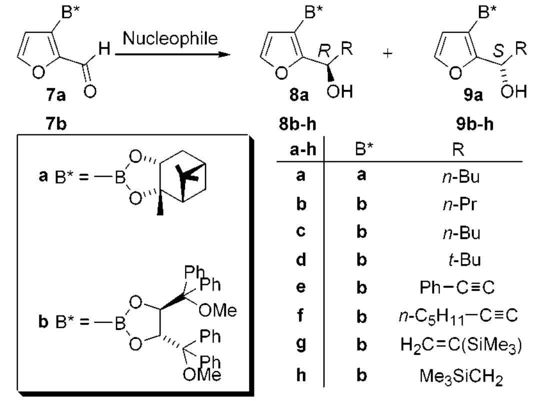
Table 1. Addition Reactions of **7a** and **7b**[a]



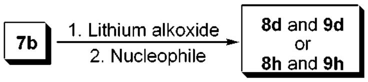
a-h	B*	R
a	**a**	*n*-Bu
b	**b**	*n*-Pr
c	**b**	*n*-Bu
d	**b**	*t*-Bu
e	**b**	$Ph{-}C{\equiv}C$
f	**b**	$n\text{-}C_5H_{11}{-}C{\equiv}C$
g	**b**	$H_2C{=}C(SiMe_3)$
h	**b**	Me_3SiCH_2

entry	nucleophile	conditions	products		yield, %[b]	de, %[c]
1	*n*-BuLi	Et_2O, −78 °C	**8a**	**9a**	47	23 (*R*)
2	*n*-PrMgBr	THF, −78 °C	**8b**	**9b**	45	23 (*R*)
3	*n*-BuLi	Et_2O, −78 °C	**8c**	**9c**	64	33 (*R*)
4	*t*-BuLi	THF, −78 °C	**8d**	**9d**	29	33 (*R*)
5	$PhC{=}CLi$	THF, 0 °C	**8e**	**9e**	79	38 (*R*)
6	$n\text{-}C_5H_{11}C{=}CLi$	THF, 0 °C	**8f**	**9f**	75	23 (*R*)
7	$CH_2{=}C(SiMe_3)MgBr$	THF, −78 °C	**8g**	**9g**	81	20 (*R*)
8	Me_3SiCH_2MgCl	Et_2O, −78 °C	**8h**	**9h**	85	71 (*R*)
9	Me_3SiCH_2MgCl	DME, −60 °C	**8h**	**9h**	84	72 (*R*)
10	Me_3SiCH_2MgCl	PhMe, −78 °C	**8h**	**9h**	81	56 (*R*)
11	Me_3SiCH_2MgCl	DCM, −78 °C	**8h**	**9h**	86	6 (*R*)
12	Me_3SiCH_2MgCl	Hex, −78 °C	**8h**	**9h**	94	3 (*R*)
13	Me_3SiCH_2MgCl	THF, −78 °C	**8h**	**9h**	92	0 (−)

[a] All reactions were carried out by adding nucleophiles (4 equiv) to furyl aldehydes **7**. [b] Total isolated yield of **8** and **9**. [c] Determined by ^1H NMR analysis of crude mixture. The major diastereomer is indicated in the parentheses.

It was found that the *R* diastereomers **8b**−**d** and **8h** were more polar than the *S* diastereomers **9b**−**d** and **9h**. For the nucleophiles with *β*-hydrogens (entries 1−4, Table 1), reduction of **7** to give furyl alcohol **6** was the main reason for the low reaction yields. To overcome the yield limitation, nucleophiles without *β*-hydrogens were employed. Encouraging results were obtained by employing Me_3SiCH_2MgCl as nucleophile, giving **8h** and **9h** in 85% isolated yield with 71% de. This satisfactory result prompted us to further investigate its scope and limitation. It is important to note that solvents greatly influence the diastereoselectivity of the addition reactions of **7b** with Me_3SiCH_2MgCl. When cyclic ether THF was used, no diastereoselectivity was observed (entry 13, Table 1). Surprisingly, however, when the less Lewis basic DME or Et_2O was employed as solvent, the diastereoselectivity was tremendously increased to over 70% (entries 8 and 9, Table 1). Such phenomena can be briefly explained in term of the Grignard reagent's reactivity. A more strongly Lewis basic solvents such as THF would increase the number of monomeric, solvated species of the Grignard reagent, leading to enhanced nucleophilicity of the C−Mg bond, thereby increases its reactivity but decreases its diastereoselectivity toward the aldehyde group. The possibility of the formation of a tetrahedral borate intermediate between the chiral boronate and the organometallic nucleophile and a subsequent intramolecular delivery of the alkyl group to the aldehyde could not be ruled out.[15] However, this intramolecular alkyl transfer process does not seem to lead to a good diastereomeric control. Moreover, initial treatment of **7b** with 1 equiv of *t*-BuLi followed by subsequent addition of 1 to 3 equiv of $PhC{\equiv}CLi$ gave better diastereoselectivity.[16] This indicates that the first equivalent of nucleophile is likely to attack the trigonal planar boronate before the alkylation of the carbonyl group.

Table 2. Addition Reaction of 7b with Nucleophiles Using Lithium Alkoxides as Additive[a]



entry	nucleophile	additive	^{11}B *δ* [b]	products		yield, %[c]	de, %[d]
1	*t*-BuLi	MeOLi	7.6	**8d**	**9d**	54	50 (*S*)
2	*t*-BuLi	EtOLi	7.0	**8d**	**9d**	64	67 (*S*)
3	Me_3SiCH_2MgCl	EtOLi	7.0	**8h**	**9h**	57	71 (*S*)
4	*t*-BuLi	*n*-PrOLi	7.6	**8d**	**9d**	49	99 (*S*)
5	Me_3SiCH_2MgCl	*n*-PrOLi	7.6	**8h**	**9h**	51	73 (*S*)
6	*t*-BuLi	*n*-BuOLi	7.5	**8d**	**9d**	37	95 (*S*)
7	Me_3SiCH_2MgCl	*n*-BuOLi	7.5	**8h**	**9h**	40	82 (*S*)
8	*t*-BuLi	*n*-AmOLi	7.5	**8d**	**9d**	46	99 (*S*)
9	*t*-BuLi	*n*-AmOLi 12-C-4[e]	7.5	**8d**	**9d**	70	58 (*S*)
10	*t*-BuLi	*n*-AmOLi 12-C-4[f]	7.5	**8d**	**9d**	85	33 (*S*)

[a] All reactions were carried out by mixing lithium alkoxides (1.3 equiv) with furyl aldehyde **7b** in suitable solvents at −78 °C; then nucleophiles (10 equiv) were added. THF and Et_2O were used for nucleophiles *t*-BuLi and Me_3SiCH_2MgCl, respectively. [b] BF_3 as reference. [c] Total isolated yield of **8** and **9**. [d] Determined by ^1H NMR analysis of crude mixture. The major diastereomer is indicated in parentheses. [e] 12-Crown-4 (1.3 equiv). [f] 12-Crown-4 (15 equiv).

Tetrahedral borate species have been known for decades.[17] The idea of forming tetrahedral borate species from trigonal planar boronates, in which the chiral director is closer to the aldehyde, led us to select alkoxides as additives. By simply using ^{11}B NMR spectroscopy,[18] an upfield shift to about *δ* 7 ppm was observed when **7b** (*δ* 30.8 ppm) was mixed with lithium alkoxides, indicating the formation of tetrahedral borate species (Table 2). ^1H NMR analysis of a mixture, which was obtained by mixing lithium *d*-methoxide with **7b** in *d*-methanol, also gave strong evidence that the aldehyde group remained intact. *t*-BuLi and Me_3SiCH_2MgCl were selected to react with the tetrahedral borate species. Surprising, the diastereoselectivity changed from *R* diastereomeric selection to *S* diastereomeric selection. Further increasing the alkyl chains of the alkoxides resulted in much higher diastereoselectivity. This observed diastereoselectivity

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(14) See Supporting Information.

(15) A ^{11}B signal at *δ* 9 ppm was detected upon addition of an organometallic reagent to the chiral furanylboronate.

(16) Employing 1 to 3 equiv of $PhC{=}CLi$ gave **8e** and **9e** in 53%, 50%, and 42% yields in 47% (*R*), 22% (*R*) and 71% (*R*) de, respectively.

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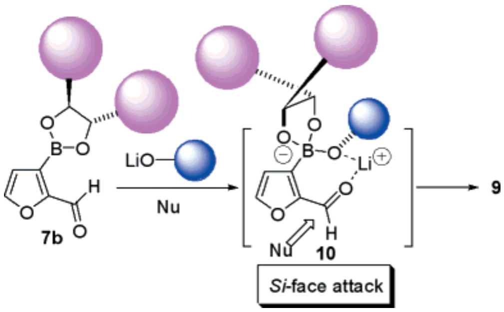
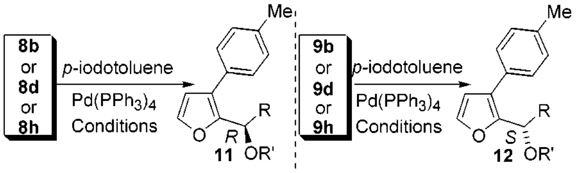


Figure 3. Proposed transition state for the addition reactions of **7b** with lithium alkoxides as additives.

is explained by assuming the following reaction mechanism (Figure 3).[19] The alkoxides first added to the trigonal planar boronate center to form a tetrahedral borate, which is a transition stage, **10**, with a seven-membered ring linked by the lithium ion. Due to the conformational congestion, the alkyl chain of the alkoxides must point downward, which blocks the *Re*-face of carbonyl group. Thus, nucleophiles must attack the carbonyl group from the less hindered *Si*-face. Addition of 12-crown-4, which traps the Li^+ ions and destroys the seven-membered ring transition stage, confirms our assumption (entries 9−10, Table 2).

The Suzuki coupling reaction is regarded as one of the most important transformations of the C−B to C−C bond. We were not surprised to find that the direct coupling of our stable furyl boronic ester of diol **3** with aryl iodide was successful, giving optically pure 2,3-disubstituted furyl alcohols **11** and **12** (Table 3).[20] Also, as mentioned in the introduction, these compounds can serve as important precursors for 6-hydroxy-2*H*-pyran-3(6*H*)-one **1**. Thus treatment of **12b** with *m*-chloroperbenzoic acid in CH_2Cl_2 afforded **1a** in 91% yield (Figure 4).

Table 3. Suzuki Coupling Reactions of **8** and **9** with Aryl Iodide



starting	condition^a	R	R′	yield, %
8b	A	*n*-Pr **11a**	Me	65^b
8d	B	*t*-Bu **11b**	H	63
8h	A	Me_3SiCH_2 **11c**	H	75
9b	A	*n*-Pr **12a**	Me	65^b
9d	B	*t*-Bu **12b**	H	57
9h	A	Me_3SiCH_2 **12c**	H	82

^{a} A = 2 M Na_2CO_3, PhMe/MeOH (1:1), reflux, 2 h; B = $Ba(OH)_2$, DME/H_2O (4:1), reflux, 2 h. ^{b} Total yield of coupling and protection.

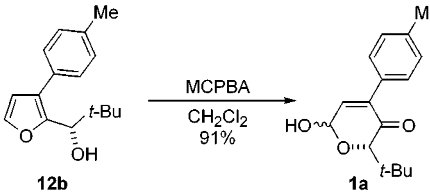


Figure 4. Oxidative rearrangement of **12b**.

In conclusion, we have described efficient procedures for the realization of furyl aldehydes **7** and their addition reactions with different nucleophiles such as Grignard reagents and alkyllithiums. Conversion of furyl aldehydes **7** to imine derivatives and their addition reactions are currently underway in our group.

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Supporting Information Available: Complete experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Diol **3** cannot be recovered after the Suzuki coupling reaction. However, prior reduction of **8d** by $LiAlH_4$ gave diol **3** in a nearly quantitative yield without lose of optical purity, as well as the corresponding furanboronic acid, which was then subjected to Suzuki coupling conditions to give furyl alcohol **11b**.