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Diastereoselective Addition Reactions of Furyl Sulfonylimine Using Chiral Boronates as Auxiliary: Application to the Enantioselective Synthesis of 2,3-Disubstituted Furyl Sulfonylamides†

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Received December 23, 2003

Abstract: The addition reactions of various nucleophiles to a furyl sulfonylimine bearing a chiral boronate at the C-3 position furnished chromatographically separable diastereomers. The *R* diastereoselection was found to be more favorable. 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 sulfonylamides.

1,6-Dihydro-2*H*-pyridin-3-one (**1**) is a useful intermediate for the synthesis of bioactive natural products.[1] It contains several functionalities that allow its conversion to many potential precursors or valuable natural products (Figure 1).[2] Although there are many possible ways to synthesize derivatives of **1**, the easiest and simplest method is based on the aza-Achmatowicz reaction, an oxidative rearrangement of furylamines.[3]

Although various methods have been developed for the synthesis of optically active furylamines,[4] the nucleophilic addition to imino group has not been too actively investigated as compared to those for carbonyl compounds, the major difference being the poor electrophilicity of the imino group. Generally, this difficulty could be overcome by activation of the imino group through the introduction of an electron-withdrawing substituent. Despite the high yield and high enantioselectivity, all the synthesized

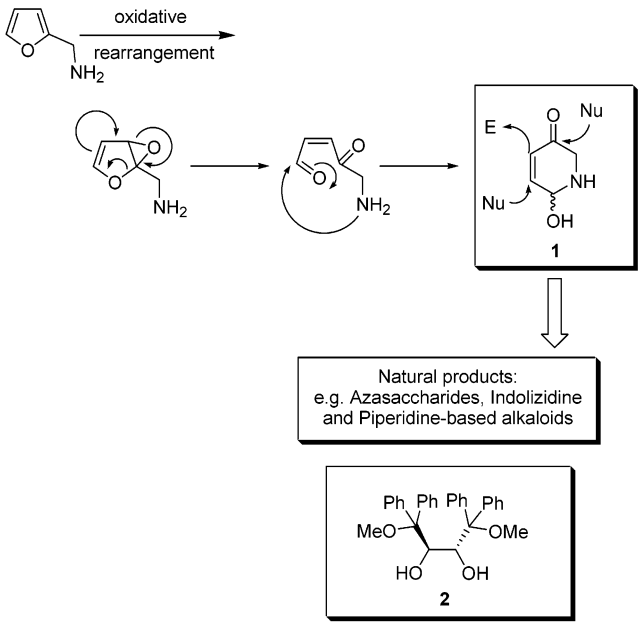

FIGURE 1. Oxidative rearrangement of furylamine and structure of diol **2**.

furylamines possess only C-2 substituents. 2,3-Disubstituted furylamines, on the other hand, have attracted much less attention.

The boronic ester of (2*R*,3*R*)-1,4-dimethoxy-1,1,4,4-tetraphenyl-2,3-butanediol (**2**)[5] has been used as an efficient chiral auxiliary in asymmetric synthesis.[6] Moreover, in our earlier work, we have successfully employed a similar strategy to synthesize various optically active 2,3-disubstituted furyl alcohols from furyl aldehyde **3** with high diastereoselectivities.[7] In connection with our interest in the realization of highly functionalized dihydropyridone **1**, we herewith wish to report our employment of boronic ester as chiral auxiliary for the synthesis of optically pure 2,3-disubstituted furylamines.

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

In earlier work, we disclosed that for the addition reactions to furyl aldehyde **3**, the *Re*-face attack of nucleophiles to the carbonyl group of **3** was found to be more favorable.[7a] This result was consistent with information being obtained from both X-ray crystallography (solid state) and AM1 calculations (solution state).[9] From the X-ray crystallographic analysis of **7**, it can be clearly

† Dedicated to Professor Sunney I. Chan on the occasion of his retirement.

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

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10.1021/jo030385e CCC: $27.50
Published on Web 03/13/2004

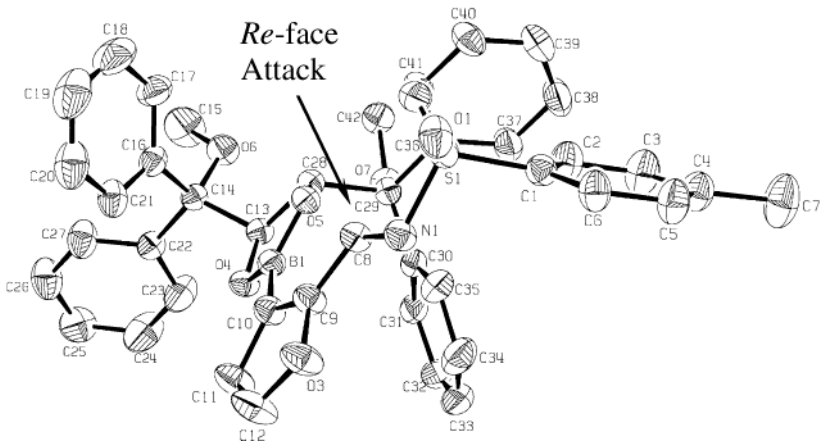
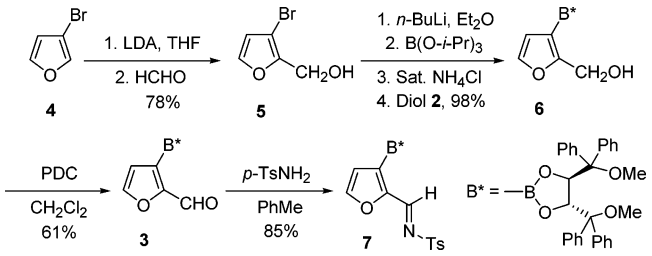


FIGURE 2. X-ray crystal structure of **7**. The black arrows show the predicted more favorable *Re*-face attack.

SCHEME 1. Synthesis of Furyl Sulfonylimine 7

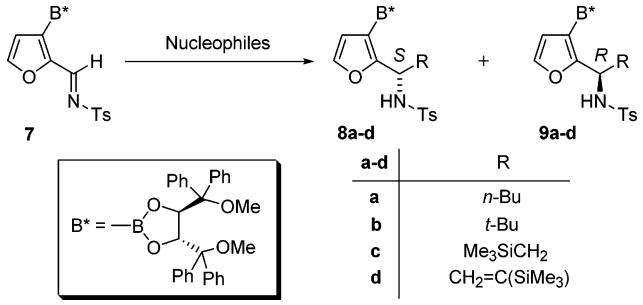


seen that furyl sulfonylimine **7** (Figure 2) retains a geometry similar to that of furyl aldehyde **3** with furan and borolane rings arranging on the same side. In this way, the *Si*-face of the imino group of furyl sulfonylimine **7** is blocked by the bulky substituents, and as a result the less hindered *Re*-face attack of nucleophiles to the imino group is therefore expected. Moreover, the huge geometric differentiation and conformational difference between the resulting diastereomers should also allow a successful separation of both diastereomers by common flash column chromatography.

The addition reactions of various nucleophiles to **7** afforded diastereomers **8a**−**d** and **9a**−**d** in good yields and good diastereoselectivities (Table 1). As anticipated, all these diastereomers could be efficiently separated by flash column chromatography and the newly created chiral centers were confirmed directly or indirectly by X-ray crystallographic analyses.[10] It was found that the *R* diastereomers **8a**−**d** were more polar than *S* diastereomers **9a**−**d**.

The difficulty of performing an addition reaction to imines is a result of the poor electrophilicity of imines, which proved to be rather inert to alkyl Grignard reagents.[11] Fortunately, encouraging results were obtained by employing Me_3SiCH_2MgCl and $CH_2{=}C(SiMe_3)$-MgBr as nucleophiles. As shown in Table 1, the addition reactions to **7** with Me_3SiCH_2MgCl furnished furyl sulfonylamides **8c** and **9c** in high yields (Table 1, entries 5−10). It is surprising that the choice of solvent greatly affects the diastereoselectivity of the addition reaction. When THF was employed, low diastereoselectivity was observed (Table 1, entry 5). However, when the less Lewis basic DME was employed as solvent, the diastereoselectivity was tremendously increased to over 80% (Table 1, entry 6). It should be mentioned that Et_2O was not employed as solvent because of the poor solubility of the starting material. Surprisingly, however, when a mixture

TABLE 1. Addition Reactions of Various Nucleophiles to 7[a]



a-d	R
a	*n*-Bu
b	*t*-Bu
c	Me_3SiCH_2
d	$CH_2{=}C(SiMe_3)$

entry	nucleophile	conditions (solvent, *T* (°C))	products		yield[b] (%)	de[c] (%)
1	*n*-BuLi	THF, −78	**8a**	**9a**	45	33 (*R*)
2	*n*-BuLi	DME, −60	**8a**	**9a**	58	33 (*R*)
3	*n*-BuLi	PhMe, −78	**8a**	**9a**	64	33 (*R*)
4	*t*-BuLi	THF, −78	**8b**	**9b**	35	33 (*R*)
5	Me_3SiCH_2MgCl	THF, −40	**8c**	**9c**	94	20 (*R*)
6	Me_3SiCH_2MgCl	DME, −30	**8c**	**9c**	81	83 (*R*)
7	Me_3SiCH_2MgCl	THF/Et_2O 1:4	**8c**	**9c**	88	80 (*R*)
8	Me_3SiCH_2MgCl	THF/Et_2O 1:8	**8c**	**9c**	85	86 (*R*)
9	Me_3SiCH_2MgCl	DCM, −40	**8c**	**9c**	82	25 (*R*)
10	Me_3SiCH_2MgCl	PhH, −40	**8c**	**9c**	78	56 (*R*)
11	$CH_2{=}C(SiMe_3)MgBr$	THF, −40	**8d**	**9d**	90	25 (*R*)
12	$CH_2{=}C(SiMe_3)MgBr$	DME, −30	**8d**	**9d**	75	74 (*R*)
13	$CH_2{=}C(SiMe_3)MgBr$	THF/Et_2O 1:4	**8d**	**9d**	80	78 (*R*)
14	$CH_2{=}C(SiMe_3)MgBr$	THF/Et_2O 1:8	**8d**	**9d**	76	80 (*R*)

[a] All reactions were carried out by adding nucleophiles (4 equiv) to furyl sulfonylimine **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.

(9) Courtesy of Prof. Yundong Wu, The Hong Kong University of Science and Technology.

(10) See the Supporting Information.

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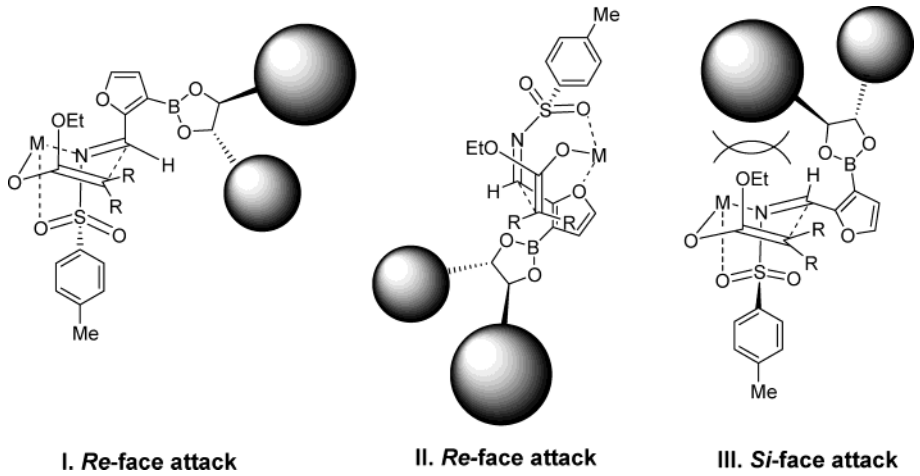
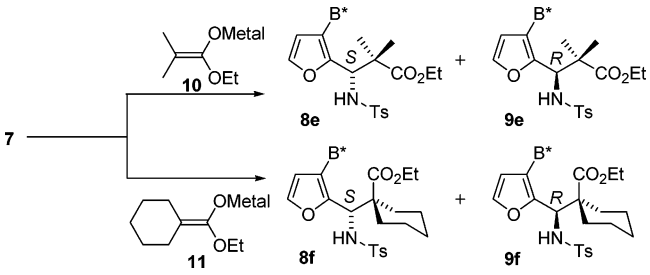


FIGURE 3. Proposed transition states for the addition reaction of metal enolates to **7**.

TABLE 2. Addition Reaction of Enolates 10 and 11 to 7[a]



entry	enolate	metal[b]	conditions (solvent, *T* (°C))	products		yield[b] (%)	de[c] (%)
1	**10a**	Li	THF, −78	**8e**	**9e**	76	46 (*R*)
2	**10b**	Na	THF, −78	**8e**	**9e**	54	20 (*R*)
3	**10c**	$Ti(O^iPr)_3$	THF, −78	**8e**	**9e**	92	83 (*R*)
4	**10d**	Et_2Al	THF, −78	**8e**	**9e**	95	92 (*R*)
5	**10d**	Et_2Al	DME, −78	**8e**	**9e**	96	94 (*R*)
6	**11a**	Li	THF, −78	**8f**	**9f**	68	36 (*R*)
7	**11b**	Na	THF, −78	**8f**	**9f**	56	38 (*R*)
8	**11c**	$Ti(O^iPr)_3$	DME, −78	**8f**	**9f**	88	86 (*R*)
9	**11d**	Et_2Al	THF, −78	**8f**	**9f**	85	96 (*R*)
10	**11d**	Et_2Al	DME, −78	**8f**	**9f**	88	99 (*R*)

[a] All reactions were carried out by adding enolates (4 equiv) to furyl sulfonylimine **7**. [b] For transmetalation, metal halides such as Et_2AlCl and $Ti(O^iPr)_3$ were added to the lithium enolates at −78 °C, and the resulting enolate was stirred for 30 min. [c] Total isolated yield of **8** and **9**. [d] Determined by ^1H NMR analysis of crude mixture. The major diastereomer is indicated in the parentheses.

of THF and Et_2O in a ratio of 1:4 was employed as solvent, the diastereoselectivity was greatly increased to 80% (Table 1, entry 7). Further increasing the solvent ratio of THF and Et_2O to 1:8 gave the best result with 85% yield and 86% de. Similar results were observed when $CH_2{=}C(SiMe_3)MgBr$ was used instead as the nucleophile (Table 1, entries 11−14). This phenomenon can be briefly explained in terms of the Grignard reagent's reactivity.[12] A more strongly Lewis basic solvents such as THF would increase the number of monomeric, solvated species of the Grignard reagent, as well as leading to enhanced polarity of the C−Mg bond, thereby

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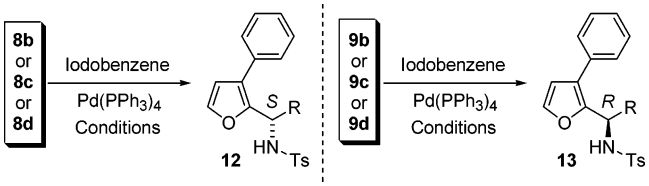
TABLE 3. Suzuki Coupling Reactions of 8 and 9



starting	condition[a]	R	product	yield (%)
8b	A	*t*-Bu	**12a**	62
8c	B	Me_3SiCH_2	**12b**	88
8d	B	$CH_2{=}C(SiMe_3)MgBr$	**12c**	82
9b	A	*t*-Bu	**13a**	64
9c	B	Me_3SiCH_2	**13b**	90
9d	B	$CH_2{=}C(SiMe_3)MgBr$	**13c**	82

[a] A = $Ba(OH)_2$, PhMe/MeOH (1:1), reflux, 2 h. B = 2 M K_3PO_4, DME/H_2O (4:1), reflux, 2 h.

increases its reactivity. This combined effect, nevertheless, would at the same time decrease its diastereoselectivity toward the imino group.

Asymmetric Mannich-type reactions are known to provide useful routes for the synthesis of optically active *β*-amino ketones or esters, which are versatile chiral building blocks in the preparation of many nitrogen-containing biologically important compounds.[13] Encouraging results were obtained from the addition reactions of metal enolates **10** to **7**. As shown in Table 2, the addition products **8e** and **9e** were obtained in good yield and excellent diastereoselectivity. Aluminum and titanium enolates (Table 2, entries 3−5) gave significantly better results than lithium and sodium enolates (Table 2, entries 1−2).

When the reaction was carried out in DME, the best result was observed with 96% isolated yield and with 94% de (Table 2, entry 5). More bulky enolates **11** were also examined for the addition reactions to **7** (Table 2, entries 6−10), and similar results were also observed. The diastereoselectivity could be predicted by employing a chelation-control model. In the case of aluminum and titanium enolates, a six-membered chairlike transition

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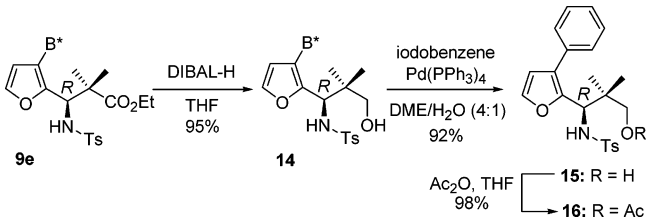

FIGURE 4. Suzuki coupling reaction of **14**.

state **I** and/or a seven-membered counterpart **II** may likely be involved (Figure 3). It should be mentioned that in the transition state **II**, the chelation between the metals with the oxygen of sulfonyl group and the oxygen of furan ring might be involved. Moreover, the transition states **I** and **II** are both responsible for the formation of *R*-diastereomers because the *Si*-face of the imine group is sterically hindered by the bulky group of the boronic ester so that the enolates approach from a less sterically congested *Re*-face, forming the C−C bond with high diastereoselectivity.

The Suzuki coupling reactions of chiral furyl sulfonylamides **8** and **9** with organic halides provide an efficient method to realize optically pure 2,3-disubstituted furyl sulfonylamides. It is not surprising that all Suzuki coupling reactions between the furyl sulfonylamides and iodobenzene proceeded smoothly to furnish furyl sulfonylamides **12**, **13** (Table 3), and **15** (Figure 4) in high yields. In addition, the optically pure 2,3-disubstituted furyl sulfonylamides could serve as important precursors for dihydropyridone **1**. Thus, treatment of furyl sulfonylamide **13b** and **16** with *m*-chloroperbenzoic acid in CH_2Cl_2 at room temperature furnished dihydropyridone **1a** in 94% yield and **1b** in 83% yield, respectively (Figure 5).

In conclusion, we have described the addition reactions of **7** with different nucleophiles such as Grignard reagents and alkyllithiums. The transformation of the carbon−boron bond of chiral furyl sulfonylamides was

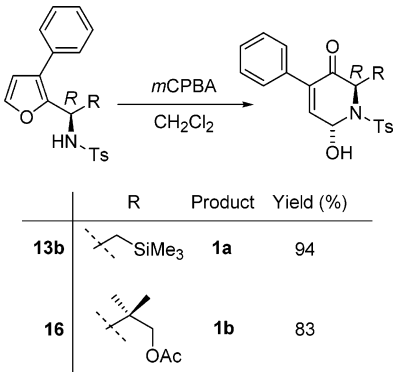

FIGURE 5. Oxidative rearrangement of **13b** and **16**.

achieved by employing palladium-catalyzed Suzuki coupling with various halides to furnish optically active 2,3-disubstituted furyl sulfonylamides. Oxidative rearrangement of these optically active 2,3-disubstituted furyl sulfonylamides afforded highly functionalized dihydropyridone **1**, which is a useful building block for natural product synthesis.

Acknowledgment. The work described in this paper was supported by a grant from the Research Grants Council of the Hong Kong SAR, China (Project No. CUHK 4178/97P), a Direct Grant (A/C No. 2060186) administered by the Chinese University of Hong Kong, and the Areas of Excellence scheme established under the University Grants Committee of the Hong Kong SAR, China (Project No. AoE/P-10/01).

Supporting Information Available: Complete experimental procedures and characterization of all new compounds and ORTEP drawings of compounds **7**, **8a**, and **9c**,**e**,**f**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO030385E