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Unexpected highly diastereoconvergent Grignard additions to D-xylofuranose-derived *t*-butanesulfinyl aldimines

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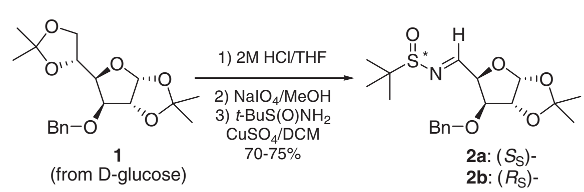
ABSTRACT

Unexpected high levels of diastereoconvergence (*dr* >15:1) were observed in the addition of a series of Grignard reagents in THF to D-xylose-derived *t*-BS aldimines **2a**,**b** affording (S_S,5*R*)- and (R_S,5*R*)-adducts. This anomaly was absent when using ethereal solutions of organometallic reagents, revealing the subtle solvent effects. This study illustrates the scope and limitations of *N*-*t*-BS imine chemistry in complex systems.

Recent development in the chemistry of *t*-butanesulfinyl imines has greatly advanced the asymmetric synthesis of chiral α-branched amines, amino alcohols, amino acids, vicinal diamines, aziridines, etc.[1] For simple substrates, the sense of asymmetric induction was solely dictated by the sulfinyl auxiliary, whereas in substrates with multiple stereogenic centers, the effect of this chiral auxiliary also predominated.[2] To date, only a few clear-cut exceptions have been noted, in which a diastereomeric pair of *N*-*t*-BS imines exhibited the same diastereofacial selectivity toward the C═N bond regardless of the sulfinyl chirality.[3] As a part of our ongoing projects concerning alkaloids[4] and nucleosides,[5] we planned to exploit the powerful and predictable chiral induction of *t*-butanesulfinyl for stereodivergent synthesis based on carbohydrate scaffolds. However, an unexpected result was encountered, and herein we report our preliminary findings.

Compared to analogous nitrones[6] and oximes,[7] sugar-derived *N*-*t*-BS imines have rarely been explored.[8] The *t*-butanesulfinyl imines in interest were easily prepared from D-glucose in five routine steps (Scheme 1). 3-*O*-Benzyl-1,2:5,6-diacetonide **1**[9] was selectively deprotected at the less hindered site,[10] and the resulting 5,6-diol was oxidatively cleaved by $NaIO_4$. The crude aldehyde was condensed with R_S- and S_S-*t*-butanesulfinamides, respectively, to afford a diastereomeric pair of Ellman's imines **2a** and **2b** with a carbohydrate backbone in good yields.[11]



Scheme 1. Preparation of D-xylofuranose-derived *t*-butanesulfinyl imines.

Initially, the addition of vinyl Grignard reagent to **2a** and **2b** was examined.[12] Both reactions appeared to be highly diastereoselective, affording *N*-*t*-BS allylic amines which were virtually diastereopure (*dr* >50:1) in high yields, as judged by NMR of the crude adducts. The absolute configuration of **3a**, the adduct derived from S_S-sulfinimine **2a**, was unambiguously established by single crystal X-ray crystallography to be (S_S,5*R*).[13] The other adduct **3b**, derived from R_S-sulfinimine **2b**, was an oil. Under the assumption that the chiral sulfinyl dictated the diastereoselectivity, we reasoned that **3b** was of the (R_S,5*S*) configuration. In order to prepare a crystalline derivative for rigorous structural determination by X-ray analysis, the chiral auxiliary was selectively removed using 2 M HCl without affecting the 1,2-acetonide, and the amine was derivatized as the corresponding 3,5-dinitrobenzamide **4b** (Scheme 2). Unfortunately, it was still an oil, and this prompted us to prepare the analogous *N*-3,5-dinitrobenzoylated **4a** from **3a** for a comparison of their NMR spectra. Indirect assignment of the C-5 configuration of **4b** can thus be made. To our surprise, the conceived epimers **4a** and **4b** were identical in all respects.[14] Thus we concluded that the C-5 configuration of **3b** was also *R*. More importantly, this

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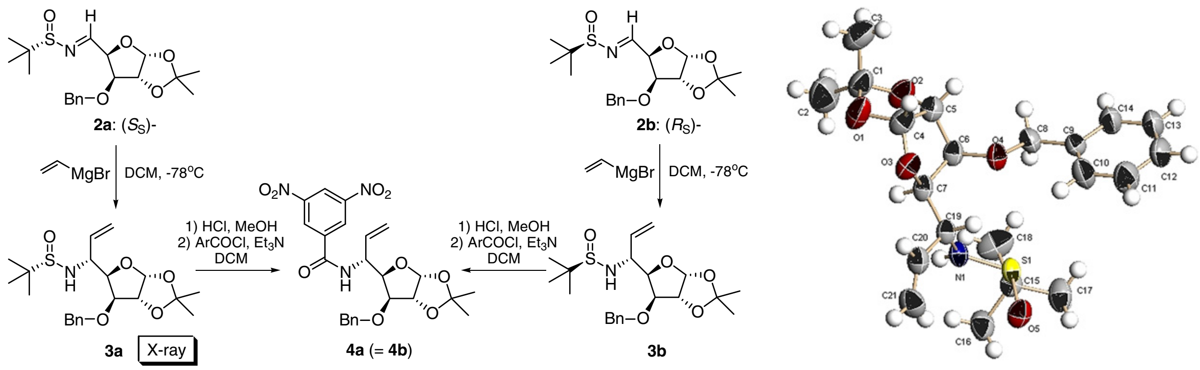


Scheme 2. Vinyl Grignard addition to **2a**,**b** and correlation of C-5 absolute configurations of **3a** and **3b**. ORTEP drawing for **3a**.

means that the addition of vinylmagnesium bromide to **2a** and **2b** proceeded in an unexpected highly diastereoconvergent fashion, both from the *Re* face of the C=N double bond.

Stimulated by this unusual phenomenon, we then investigated the diastereoselectivities for the additions of other carbanions to determine whether this was general in scope (Table 1). Initially, when using (for convenience) commercial 3.0 M ethereal solutions of PhMgBr or EtMgBr, the stereochemical outcome diverged with that of vinyl addition, especially for the S_S-imine **2a**. Phenyl addition to **2a** afforded predominantly (5*S*)-adduct **3d** (entry 3), whose structure was established by X-ray analysis (Fig. 1).[15] The analogous ethyl addition to **2a** was almost non-selective (entry 5). Additions to **2b** proceeded with lower *dr*s (7.5–12:1) as compared to the vinyl addition (entries 4 and 6). When using TMSC≡CMgBr in Et_2O as a nucleophile, no desired adducts were detected (entries 7 and 8). It occurred to us that the apparent irregular behaviors of different Grignard species might be attributed to their respective co-solvents, although the volume of these ethereal Grignard solutions was just a fraction of CH_2Cl_2 used as the solvent for **2**.

Indeed, after shifting the co-solvent to THF, all these additions proceeded in a diastereoconvergent manner, yielding the 5*R*-adducts in high *dr*s (>15:1) regardless of the sulfur chirality (Table 2). Notably, addition of TMSC≡CMgBr prepared in THF afforded the propargylic adducts **3k**,**l** in good yields and high *dr*s (entries 9 and 10), with the exception that these reactions were carried out at −20 °C overnight. In view of the importance of co-solvent, we also tested on substrate **2a** using THF as the sole solvent, as

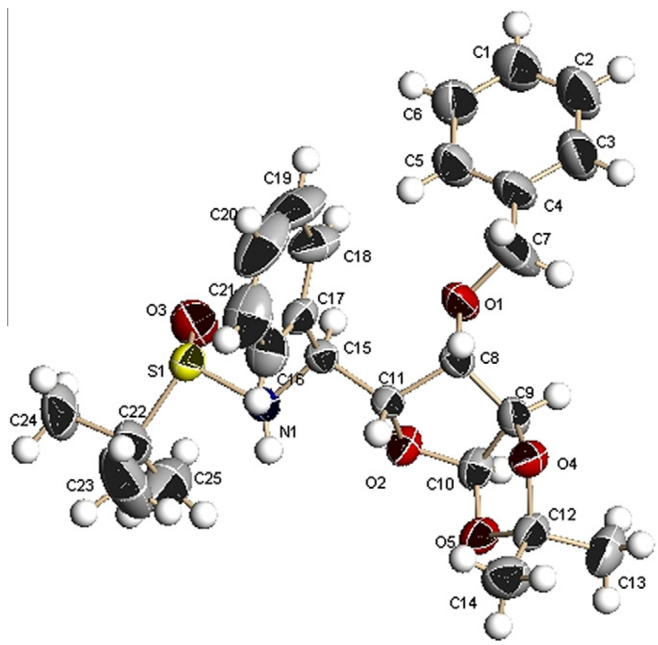


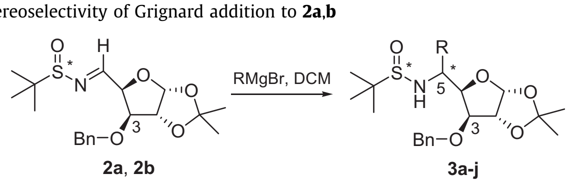
Figure 1. ORTEP drawing for **3d**.

well as inverse order of addition. In the former case, no reaction was observed, and **2a** was recovered (entry 5). When a solution of **2a** in CH_2Cl_2 was added to 0.7 M PhMgBr in THF under −78 °C, the high *dr* was maintained, albeit the conversion dropped to ~50% (entry 6). These results clearly indicated a pronounced effect of the co-solvent: Grignard species dissolved in THF afforded high levels of diastereoconvergence, while ethereal solutions of the same nucleophiles produced widely varying and often unsatisfactory *dr*s. Such solvent effect has not been emphasized in previous studies.[16]

The methods of stereochemistry determination for the adducts **3a**–**l** were outlined in Table 3. Diimide reduction[17] of the vinyl group of **3a** and **3b** afforded ethyl analogs **3g** and **3i**, respectively. Similarly, removal of TMS (K_2CO_3/MeOH) in **3k** and **3l** followed by saturation of the triple bond produced **3g** and **3i**, respectively. In this manner, the C-5 configuration of **3g**–**l** was established. Removal of *t*-BS and *N*-benzoylation of **3d** and **3f** gave the same benzamide **4d** to establish the C-5 configuration of **3c**–**f**. Thus, with the aid of X-ray and chemical correlation, the structures of all adducts were unambiguously assigned.

Although it has been reported that carbanion addition to the analogous carbohydrate-derived nitrones[6b] and *N*-benzyl imines[18] proceeded in moderate to high stereoselectivity, the uniformly

Table 1
Diastereoselectivity of Grignard addition to **2a**,**b**



Entry	Imine	R, concn, co-solvent	**3** (%)[a]	*dr*[b]
1	**2a**	Vinyl, 0.7 M, THF	**3a**, 87	50:1[c]
2	**2b**	Vinyl, 0.7 M, THF	**3b**, 85	50:1[c]
3	**2a**	Ph, 3.0 M, Et_2O	**3c**, **3d**, 92	1:16[c]
4	**2b**	Ph, 3.0 M, Et_2O	**3e**, **3f**, 85	7.5:1[c]
5	**2a**	Et, 3.0 M, Et_2O	**3g**, **3h**, 93	1.3:1[d]
6	**2b**	Et, 3.0 M, Et_2O	**3i**, **3j**, 87	12:1[c]
7	**2a**	TMS-C≡C, 0.7 M, Et_2O	Complex	nd
8	**2b**	TMS-C≡C, 0.7 M, Et_2O	Complex	nd

[a] Combined isolated yields of both diastereomers.
[b] Diastereomeric ratio of (5*R*)- to (5*S*)-.
[c] Determined by NMR.
[d] Determined by the isolated yields of each diastereomer.

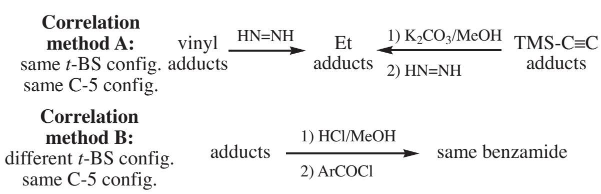
Table 2
Diastereoconvergent Grignard additions to **2a**,**b**

2a, **2b** **3a-l**

Entry	Imine	R, concn, co-solvent	**3** (%)[a]	*dr*[b]
1	**2a**	Vinyl, 0.7 M, THF	**3a**, 87	50:1
2	**2b**	Vinyl, 0.7 M, THF	**3b**, 85	50:1
3	**2a**	Ph, 0.7 M, THF	**3c**, **3d**, 90	15:1
4	**2b**	Ph, 0.7 M, THF	**3e**, **3f**, 88	25:1
5[c]	**2a**	Ph, 0.7 M, THF	NR	nd
6[d]	**2a**	Ph, 0.7 M, THF	**3c**, **3d**, 42	15:1
7	**2a**	Et, 0.7 M, THF	**3g**, **3h**, 83	20:1
8	**2b**	Et, 0.7 M, THF	**3i**, **3j**, 75	20:1
9[e]	**2a**	TMS-C≡C, 0.7 M, THF	**3k**, 65	18:1
10[e]	**2b**	TMS-C≡C, 0.7 M, THF	**3l**, 80	30:1

[a] Combined isolated yields of both diastereomers.
[b] Ratio of (5*R*)- to (5*S*)-, determined by ^{1}H NMR of the crude adducts.
[c] THF as the solvent for substrate.
[d] Inverse addition of **2a** in CH_2Cl_2 to PhMgBr-THF, 50% conversion.
[e] At −20 °C, 12 h.

Table 3
Summary of C-5 configuration determination



Adduct	*t*-BS	R	C-5	Determination method
3a	S_S-	Vinyl	*R*	X-ray
3b	R_S-	Vinyl	*R*	Correlate with **3a** (B)
3c	S_S-	Ph	*R*	Infer from **3d**
3d	S_S-	Ph	*S*	X-ray
3e	R_S-	Ph	*R*	Infer from **3f**
3f	R_S-	Ph	*S*	Correlate with **3d** (B)
3g	S_S-	Et	*R*	Correlate with **3a** (A)
3h	S_S-	Et	*S*	Infer from **3g**
3i	R_S-	Et	*R*	Correlate with **3b** (A)
3j	R_S-	Et	*S*	Infer from **3i**
3k	S_S-	TMS-C≡C	*R*	Correlate with **3g** (A)
3l	R_S-	TMS-C≡C	*R*	Correlate with **3i** (A)

high *dr*s observed for Grignard additions to **2a**,**b** are still remarkable and synthetically useful. In addition, compared to *N*-benzyl, the *N*-*t*-BS group also enjoyed the benefit of easy removal. The origin of this unexpected diastereoconvergence is yet to be rationalized; nevertheless, it cannot be attributed solely to the carbohydrate moiety, for the stereo-induction of the latter cannot overcome that of the chiral sulfinyl completely. The present case suggested subtle interplay between the two chiral auxiliaries.

To summarize, we report a rare example of the diastereoconvergent addition of Grignard reagents to a pair of D-xylofuranose-based *t*-butanesulfinyl aldimines **2a** and **2b**. Both the R_S- and S_S-imines afforded predominantly (5*R*)-adducts. The use of THF as the co-solvent for the Grignard reagents is essential to achieve high and consistent diastereoselectivity. On the other hand, precaution should be paid in assigning the stereochemistry of nucleophilic additions to polysubstituted *N*-*t*-BS imines. In view of the versatile synthetic potentials of the vinyl and alkynyl groups, the adducts can be exploited in the asymmetric synthesis of azasugars or related chiral scaffolds. Work along this line is currently in progress in this laboratory.

Acknowledgments

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Supplementary data

Supplementary data (Experimental procedures and spectral data.) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.11.002.

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12. *General procedures:* To a cooled (−78 °C) solution of **2a** (353 mg, 0.93 mmol) in CH_2Cl_2 (5 mL) under Ar was added dropwise vinylmagnesium bromide (3.3 mL, 0.7 M in THF, 2.31 mmol), and the solution was stirred at the same temperature for 1 h. The reaction was quenched by satd aq NH_4Cl, diluted with ether (50 mL), the organic layer was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography eluated with EtOAc/Hexane. Compound **3a**: $[\alpha]_D^{23}$ +6.1 (*c* 1.13, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.26 (m, 5H), 6.00 (ddd, 1H, *J* = 17.2, 10.5, 5.4 Hz), 5.93 (d, 1H, *J* = 3.8 Hz), 5.49 (d, 1H, *J* = 17.2 Hz), 5.29 (d, 1H, *J* = 10.5 Hz), 4.66–4.45 (AB, 2H, J_{AB} = 11.0 Hz), 4.64 (m, 1H), 4.32–4.25 (m, 1H), 4.24 (dd, 1H, *J* = 7.5, 3.2 Hz), 4.11 (d, 1H, *J* = 3.2 Hz), 3.92 (d, 1H, *J* = 8.2 Hz), 1.50 (s, 3H), 1.32 (s, 3H), 1.09 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.7, 136.3, 128.5, 128.1, 127.9, 117.7, 111.6, 105.0, 82.7, 81.4, 81.3, 71.9, 57.7, 56.0, 26.7, 26.2, 22.5. HR-ESI-MS *m/z* Calcd for $C_{21}H_{31}NO_5SNa$ (M+Na$^+$) 432.1821. Found 432.1813. Compound **3b**: $[\alpha]_D^{23}$ −46.4 (*c* 2.23, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.26 (m, 5H), 5.98 (d, 1H, *J* = 3.5 Hz), 5.91 (ddd, 1H, *J* = 17.2, 10.4, 6.3 Hz), 5.35 (d, 1H, *J* = 17.2 Hz), 5.24 (d, 1H, *J* = 10.4 Hz), 4.68–4.61 (AB, 2H, J_{AB} = 11.2 Hz), 4.64 (m, 1H), 4.32–4.26 (m, 1H), 4.16 (d, 1H, *J* = 3.3 Hz), 4.13 (dd, 1H, *J* = 7.6, 3.3 Hz), 3.66 (d, 1H, *J* = 7.5 Hz), 1.48 (s, 3H), 1.31 (s, 3H), 1.11 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.1, 136.2, 128.4, 128.0, 127.9, 117.2, 111.5, 105.0, 81.9, 81.8, 81.3, 71.6, 57.0, 55.7, 26.7, 26.1, 22.4. HR-ESI-MS *m/z* Calcd for $C_{21}H_{31}NO_5SNa$ (M+Na$^+$) 432.1821. Found 432.1814.
13. CCDC 720014 contains the crystallographic data for **3a**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
14. Compound **4a**: $[\alpha]_D^{21}$ +23.1 (*c* 0.72, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.03 (t, 1H, *J* = 2.0 Hz), 8.61 (d, 2H, *J* = 2.1 Hz), 7.92 (d, 1H, *J* = 8.1 Hz), 7.30–7.26 (m,

2H), 7.21–7.16 (m, 3H), 6.03 (d, 1H, *J* = 3.8 Hz), 5.84 (ddd, 1H, *J* = 17.2, 10.4, 6.0 Hz), 5.36 (d, 1H, *J* = 17.2 Hz), 5.32 (d, 1H, *J* = 10.4 Hz), 5.24 (m, 1H), 4.76–4.46 (AB, 2H, J_{AB} = 10.4 Hz), 4.75 (m, 1H), 4.36 (m, 1H), 4.21 (d, 1H, *J* = 3.2 Hz), 1.52 (s, 3H), 1.36 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.1, 148.4, 138.2, 135.8, 133.2, 128.7, 128.6, 128.5, 126.8, 120.5, 117.8, 111.9, 104.8, 84.0, 81.1, 78.8, 72.8, 52.6, 26.6, 26.0. HR-ESI-MS *m*/*z* Calcd for $C_{24}H_{26}N_3O_9$ (M+H$^+$) 500.1669. Found 500.1676.
15. CCDC 730904 contains the crystallographic data for **3d**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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