Asymmetric synthesis of either diastereomer of trifluoromethylated allylic amines by the selective reduction of trifluoromethyl α,β-unsaturated *N*-*tert*-butanesulfinyl ketoimines†

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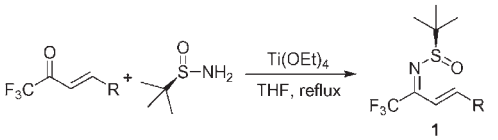
Regio- and diastereoselective reduction of chiral trifluoromethyl α,β-unsaturated *N*-*tert*-butanesulfinyl ketoimines 1 was achieved by choosing appropriate reducing agent and either diastereomer of the corresponding trifluoromethylated allylic amines was obtained with good yield and excellent diastereoselectivity (up to >99 : 1 dr).

Allylic amines represent an important class of compounds not only for their key function as precursors or intermediates in organic synthesis,[1] but also for their presence in some biologically active compounds and pharmaceuticals.[2] Therefore, many methods have been developed for their asymmetric synthesis.[3] Despite the fact that the introduction of fluorine into bioactive molecules may bring profound changes on their properties,[4] few methods are available for the asymmetric synthesis of trifluoromethylated allylic amines. In 2001, Prakash *et al.*[5] reported a stereoselective synthesis of trifluoromethylated allylic amines using $TMSCF_3$ as CF_3 source, but only one diastereomer was obtained in moderate yields and the substituent at γ-position was limited to aryl. Although the addition of vinylmetallic reagents to chiral trifluoromethylated imines provides a viable approach,[6] the method is restricted by the availability of vinylmetallic derivatives. Another approach involved multiple steps with low yields.[7] Consequently, highly efficient asymmetric synthesis of enantiopure trifluoromethylated allylic amines still remains a significant synthetic challenge.

The commercially available *N*-sulfinamides have been widely used as highly efficient chiral auxiliaries in the synthesis of a variety of optically active amines by virtue of their excellent diastereocontrol and the mild conditions for their cleavage.[8]

Recently, much attention has been paid to the synthesis of chiral CF_3-substituted *N*-sulfinyl imines and their applications in the diastereoselective synthesis of trifluoromethylated amine derivatives.[9] However, most of the reported CF_3-substituted *N*-sulfinyl imines are easily hydrolyzed or decomposed during work-up and unstable at room temperature. This greatly restricts their applications. During the course of our studies on the reactions of CF_3-substituted ketones,[10] we found that unlike the usual CF_3-substituted *N*-sulfinyl imines,[9a,b,d-f] trifluoromethyl α,β-unsaturated *N*-*tert*-butanesulfinyl ketoimines, derived from trifluoromethyl α,β-unsaturated ketones, could be stored at room temperature for several months without any decomposition. Herein, we wish to report their preliminary applications in the asymmetric synthesis of either diastereomer of trifluoromethylated allylic amines with high diastereoselectivity.



Scheme 1 Preparation of trifluoromethyl α,β-unsaturated *N*-*tert*-butanesulfinyl ketoimines.

Our research began with the synthesis of new chiral CF_3-substituted α,β-unsaturated (*R*)-*N*-*tert*-butanesulfinyl ketoimines **1** from (*R*)-*tert*-butanesulfinyl amide (Scheme 1).[11] The optimized reaction was performed in dry THF in the presence of 2.0–2.5 equiv. of $Ti(OEt)_4$ under reflux and ketoimines **1** were obtained in moderate to good yields (see ESI† Table S1). In all cases, the products were easily isolated in pure form by flash chromatography. The high stability of **1** was tentatively ascribed to the conjugative stabilizing effect of the C–C double bond on the C–N double bond. Moreover, ^1H, ^{19}F and ^{13}C NMR analysis revealed that ketoimines **1a–1l** existed in a single isomeric form. An X-ray diffraction study of **1c**‡ indicated that it had the *E*-geometry with the C–N double bond, and a reasonable assumption was made that all ketoimines **1** had a similar geometry.

With these ketoimines in hand, we next investigated the reduction of **1a** with $NaBH_4$ in THF.[12] To our delight, the reaction took place very smoothly at −78 °C and gave only 1,2-adducts in 90% overall yield with a 89 : 11 dr (**2a**/**3a**) after 3 h (Table 1, entry 1). To achieve better results, a series of metal hydrides were screened to improve the diastereoselectivity and test the possibility of stereoselectivity reversal.[13] The results were promising, as revealed in entries 2–13. When DIBAL-H was used instead of $NaBH_4$ as the reductant, a significant improvement in diastereoselectivity was observed and a 99 : 1 dr could be obtained (entry 3). Catecholborane and $NaBH_3CN$ were less reactive and longer reaction time was needed for the full conversion of **1a** (entries 2 and 5). $LiAlH_4$

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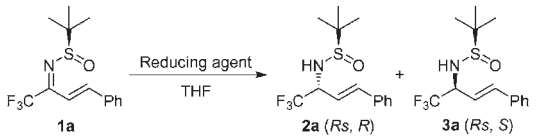
† Electronic supplementary information (ESI) available: Experimental details, spectroscopic data, and scans of NMR spectra. CCDC 691649 (**1c**) and 691650 (**3d**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b810459j

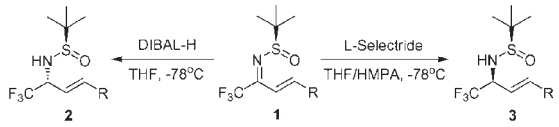
Table 1 The reduction of **1a** with various metal hydrides



Entry[a]	Reducing agent	Time (h)	Conversion[b] (%)	**2a** : **3a**[b]
1	$NaBH_4$	3	100	89 : 11
2[c]	Catecholborane	22	96	89 : 11
3	DIBAL-H	0.5	100	99 : 1
4	$LiAlH_4$	3	100	63 : 37
5[c]	$NaBH_3CN$	48	100	85 : 15
6	Red-Al	1	100	71 : 29
7	$LiBH_4$	3	100	43 : 57
8	$LiBHEt_3$	2	100	23 : 78
9	L-Selectride	2	100	16 : 84
10[d]	L-Selectride	2	100	14 : 86
11[e]	L-Selectride	2	100	17 : 83
12[f]	L-Selectride	0.5	100	6 : 94
13[g]	L-Selectride	0.5	100	1 : 99

[a] All reactions were performed using 3.0 equiv. of reducing agent in dry THF at −78 °C unless otherwise indicated. [b] Conversion and diastereomeric ratios were determined by ^{19}F NMR of crude reaction mixture. [c] The reaction were performed at −78 °C to rt. [d] The reaction was performed at −98 °C. [e] 20 mol% $Ti(OEt)_4$ was added. [f] 300 mol% HMPA was added. [g] The reaction was performed in THF/HMPA (5 : 1).

Table 2 The reduction of **1** with DIBAL-H and L-Selectride



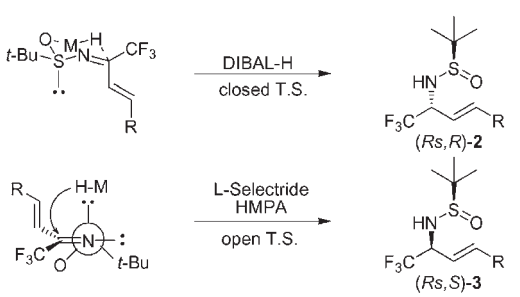
			DIBAL-H[a]		L-Selectride[b]	
Entry	**1**	R	Product	Yield[c] (%) (dr)[d]	Product	Yield[c] (%) (dr)[d]
1	**1a**	C_6H_5	**2a**	99 (99 : 1)	**3a**	99 (99 : 1)
2	**1b**	4-$MeOC_6H_4$	**2b**	98 (99 : 1)	**3b**	92 (98 : 2)
3	**1c**	4-MeC_6H_4	**2c**	97 (>99 : 1)	**3c**	95 (98 : 2)
4	**1d**	4-ClC_6H_4	**2d**	98 (99 : 1)	**3d**	88 (99 : 1)
5	**1e**	4-BrC_6H_4	**2e**	97 (99 : 1)	**3e**	96 (98 : 2)
6	**1f**	2-$MeOC_6H_4$	**2f**	97 (99 : 1)	**3f**	96 (97 : 3)
7	**1g**	3-BrC_6H_4	**2g**	93 (97 : 3)	**3g**	90 (99 : 1)
8	**1h**	1-Naphthyl	**2h**	96 (99 : 1)	**3h**	94 (99 : 1)
9	**1i**	2-Furyl	**2i**	94 (>98 : 2)	**3i**	97 (98 : 2)
10	**1j**	$C_6H_5C{\equiv}C$	**2j**	93 (>96 : 4)	**3j**	81 (95 : 5)
11	**1k**	n-C_8H_{17}	**2k**	87 (>99 : 1)	**3k**	60 (96 : 4)
12	**1l**	$C_6H_5(CH_2)_3$	**2l**	81 (>99 : 1)	**3l**	62 (99 : 1)

[a] All reactions were carried out on a 0.25 mmol scale using 3.0 equiv. of DIBAL-H in THF at −78 °C (0.5 h). [b] All reactions were carried out on a 0.25 mmol scale using 3.0 equiv. of L-Selectride in THF : HMPA = 5 : 1 at −78 °C (0.5–1 h). [c] Isolated yield. [d] Diastereomeric ratios were determined by ^{19}F NMR of crude reaction mixture.

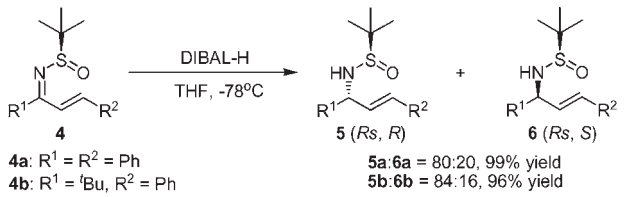
and Red-Al gave poor diastereoselectivity for isomer **2a** (entries 4 and 6). We were gratified to find the reversal of the diastereofacial selectivity when $LiBH_4$ was used as the reducing agent (entry 7). With $LiBHEt_3$, a diastereomeric ratio of 78 : 23 (**3a**/**2a**) was obtained (entry 8). More excitingly, performing the reaction with L-Selectride resulted in a much better selectivity for **3a** (*Rs*, *S*)[14] (**3a** : **2a** = 86 : 14, entry 9). Further attempt by performing the reaction at −98 °C or adding 20 mol% $Ti(OEt)_4$[12,13a,b] to the reaction mixture did not improve the diastereoselectivity (entries 10–11). Fortunately, an enhanced diastereoselectivity (**3a** : **2a** = 94 : 6) was observed when Lewis base HMPA[15] was used as the additive (entry 12). Finally, the diastereomeric ratio was improved to 99 : 1 (**3a** : **2a**) when the reaction was performed in a mixed solvent of THF and HMPA (THF–HMPA = 5 : 1, entry 13). These results indicated that the presence of excess HMPA was necessary for achieving high stereoselectivity.

Under the two optimized conditions (Table 1, entries 3 and 13), a variety of trifluoromethyl α,β-unsaturated *N*-*tert*-butanesulfinyl ketoimines were employed as the substrates to probe the generality of the reversal in diastereofacial selectivity upon using DIBAL-H *versus* L-Selectride. As summarized in Table 2, all the reactions took place readily and afforded the corresponding trifluoromethylated allylic amines in good to excellent yields with very high diastereoselectivities. *N*-Sulfinyl ketoimines with aromatic, heteroaromatic, or alkynyl substitutions at the *β*-position were proved to be excellent substrates in both systems (entries 1–10). The reaction also tolerated alkyl substitutions at the β-position, giving 92 to >98% de (entries 11–12). Although the L-Selectride system gave moderate yield probably due to the electronic effect, to our knowledge, this is the first example about the asymmetric synthesis of γ-alkyl trifluoromethylated allylic amines. It is of note that no 1,4-adducts were formed in all reactions,[16] indicating that the reaction is regiospecific under these conditions. The stereochemistry of trifluoromethylated allylic amines **3** was further confirmed as (*Rs*, *S*) by X-ray crystallography of product **3d**.‡ Therefore, we deduced the absolute configuration of **2** was (*Rs*, *R*).

Referring to the literature,[13a] the origin of the reversal in diastereofacial selectivity upon changing reducing agent from DIBAL-H to L-Selectride can be explained *via* a cyclic transition state in the former reduction (DIBAL-H) and an open transition state in the latter one (L-Selectride) based on the *E*-geometry of the ketoimines (Scheme 2). The CF_3 group might play an important role in the regio- and diastereoselectivity in both systems. The electron-withdrawing nature of CF_3 group increases the reactivity of sulfinimines and facilitates the 1,2-hydride reduction. Furthermore, the steric hindrance of CF_3 group is between those of ^{i}Pr and ^{t}Bu,[17] and therefore an *e* bond for CF_3 group is more stable than an *a* bond in the six-membered chairlike models in the DIBAL-H



Scheme 2 Proposed transition state for the reduction of **1**.



Scheme 3 Reduction of ketoimines **4** with DIBAL-H.

reduction. On the other hand, electrostatic repulsion between the lone pair of sulfur atom and the electron-rich CF_3 group makes CF_3 far away from sulfur atoms in both systems. Hence, the six-membered transition state in which the sulfinyl oxygen participates in the delivery of hydride in the DIBAL-H system gives (*Rs*, *R*)-**2** as the major product, while an open transition state in the L-Selectride (poorly coordinating metal hydrides) system affords the major product (*Rs*, *S*)-**3**. This model may also explain why the addition of excess HMPA tends to give higher selectivity. The probable role of HMPA in the reaction system is to coordinate with lithium(I) ion and disrupts the chelation of Li(I) with sulfinyl oxygen.

To demonstrate the importance of CF_3 group in these selective reduction reactions, non-CF_3-substituted α,β-unsaturated *N*-*tert*-butylsulfinyl ketoimines with a similar steric hindrance to that of CF_3 group **4a** and **4b** were synthesized and subjected to both reduction reactions (Scheme 3). Using the conditions of entry 3 in Table 1 for the DIBAL-H system, the reaction proceeded well for both ketoimines and gave the corresponding allylic amines in excellent overall yields, but only moderate diastereoselectivity was obtained (de 60–68%). With the optimized L-Selectride system, however, the reaction became complicated in the case of **4a** and no reaction was observed for **4b**.

In summary, we have developed a highly efficient method for the asymmetric synthesis of either stereoisomer of trifluoromethylated allylic amines with good yield and high diastereoselectivity by the selective reduction of chiral trifluoromethyl α,β-unsaturated *N*-*tert*-butanesulfinyl ketoimines **1** with DIBAL-H and L-Selectride, respectively. Further studies on the application of **1** in the preparation of a variety of chiral amine analogues are in progress.

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Notes and references

‡ *Crystal data*: for **1c**, $C_{15}H_{18}F_3NOS$, M = 317.36, orthorhombic, space group $P2_12_12_1$, a = 6.0128(9), b = 8.4458(13), c = 32.013(5) Å, V = 1625.7(4) Å^3, T = 293 K, Z = 4, 8907 reflections measured, 3183 unique (R_{int} = 0.1349), R_1 = 0.0545 [$I > 2\sigma(I)$], wR_2 = 0.1175; for **3d**, $C_{14}H_{17}ClF_3NOS$, M = 339.80, orthorhombic, space group $P2_12_12_1$, a = 5.8166(6), b = 14.9426(16), c = 18.2981(19) Å, V = 1590.4(3) Å^3, T = 293 K, Z = 4, 8401 reflections measured, 2948 unique (R_{int} = 0.1417), R_1 = 0.0510 [$I > 2\sigma(I)$], wR_2 = 0.1108.

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