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Asymmetric addition reactions of Grignard reagents to chiral 2-trifluoromethyl *tert*-butyl (Ellman) sulfinimine–ethanol adducts

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Abstract—The addition of Grignard reagents to chiral trifluoromethyl *tert*-butyl sulfinimine–ethanol adducts affords protected trifluoromethylamines in high yields with good to excellent diastereoselectivities. The stereochemical outcome of the addition is opposite to that expected via a chelation controlled transition state.

The development of effective means for the synthesis of fluorinated organic compounds is of considerable interest as there are many examples wherein fluorine dramatically alters the chemical and biological properties of a molecule.[1] In particular, trifluoromethyl-containing molecules represent an especially interesting example due to the profound properties conferred by the CF_3 group.[2]

In connection with a current research program, we recently required an efficient route for the preparation of a suitably protected form of chiral 1,1,1-trifluorobut-3-en-2-amine **1**. Despite the potential synthetic utility of the multiple functionalities present in **1**, little synthetic effort has been reported so far for its preparation.[3] Accordingly, an effective method for the introduction of the chiral amine center was paramount.

One method we considered was the addition of a vinyl Grignard reagent to a non-racemic trifluoromethylimine (Fig. 1).[4,5] Ellman has established that chiral *tert*-butyl sulfinimines are excellent substrates for the addition of a variety of nucleophiles, yielding the desired adducts in high diastereoselectivities.[6] The *tert*-butyl sulfinyl functionality also serves as a useful amine protecting group, which can be cleaved under mildly acidic conditions in high yield.[7] Accordingly, we sought to adapt this procedure to our specific requirements.

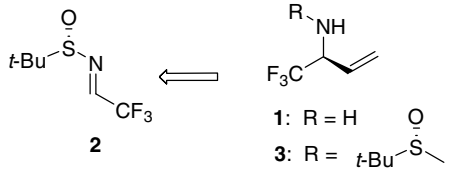

Figure 1.

Due to the strong electron withdrawing effects of fluorine, trifluoromethylimines would be expected to exist as their hydrated forms. We decided to take advantage of this property by isolating the alcohol adduct of imine **2**. It was hoped that this sulfinamine-acetal would be a stable intermediate from which the imine could be liberated in situ by treatment with base.

Initial attempts to condense trifluoroacetaldehyde ethyl hemiacetal **4** with (*S*)-*tert*-butanesulfinamide **5** using $CuSO_4$ or $MgSO_4$ as the promoters gave very low conversions after extended reaction periods. The condensation could be effectively mediated by heating a mixture of **4** and **5** neat in $Ti(OEt)_4$ overnight at 70 °C to afford a crude mixture of diastereomeric products.[8,9] These diastereomers could be easily separated by normal silica gel chromatography to provide **6a** and **6b** as stable crystalline solids in 74% isolated yield (Scheme 1). The absolute stereochemistry of **6b** was confirmed by single crystal X-ray analysis.[10]

The reactivity of **6a/b** with 2.5 equiv of vinylmagnesium bromide was investigated as shown in Table 1.[11] Reaction of diastereomer **6a** or **6b** in toluene at 0 °C

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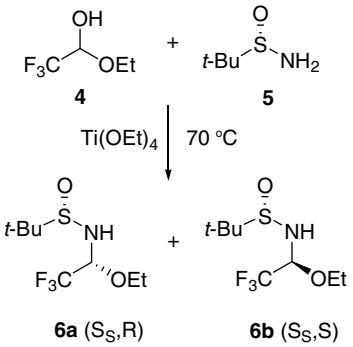


Scheme 1.

for 30 min provided major diastereomer **3a** in high yield and promising selectivity (entries 1 and 2). To the best of our knowledge, this represents the first example of addition of a vinylmetallic reagent to a trifluoromethyl imine.[12,13] Lowering the temperature improved the selectivity to 16:1, but incomplete conversion at −40 °C was noted even after 2 h (entry 4). Changing the solvent to THF (entry 5) provided no improvement in selectivity, but CH_2Cl_2 improved the diastereoselectivity to 22:1, although the conversion was again incomplete at −40 °C (entry 6). As noted in entry 7, adding the vinylmagnesium bromide at −30 °C allowed for complete consumption of the starting material, but a lower selectivity was observed (14:1). However, when addition of the Grignard reagent was carried out at −40 °C and the reaction mixture was allowed to slowly warm to −20 °C (entry 8), complete conversion was observed and the diastereoselectivity restored to 22:1.

It should be noted that entries 3–8 were carried out for diastereomer **6a**. When **6b** was treated with vinylmagnesium bromide in CH_2Cl_2 at −40 °C, complete conversion was realized with a lower selectivity (14:1, entry 9). Adding the Grignard to **6b** at −60 °C and allowing the reaction to slowly warm to −40 °C (entry 10) afforded **3a** with similar selectivity to **6a** (entries 6 and 8).

We propose that the selectivity difference between diastereomers **6a**/**b** is dependent on the temperature at which imine **2** is generated. As illustrated in Figure 2, it is postulated that metallated intermediate **6b′** can eliminate efficiently to **2** at low temperature (>−60 °C), while **6a′** requires higher temperature for imine formation (>−40 °C). This was supported by variable temperature ^{1}H NMR studies in which **6a′** (formed via addition of 1 equiv of vinylmagnesium bromide at −78 °C) did not lead to formation of significant levels of **2** until the temperature approached −35 °C, consistent with the reactivity profile observed in Table 1.[14] In comparison, NMR analysis of **6b′** began to show imine formation at ∼−55 °C. Once liberated, imine **2** undergoes efficient addition of vinylmagnesium bromide to provide **3**.

It should be noted that the stereochemistry of the newly formed center is *S*,[15] which is opposite of what was predicted via a chelation controlled transition state **A** (Fig. 3).[16] It is likely that the bromomethoxymagnesium species, which is produced by the additional equivalent of Grignard reagent used to liberate the imine, coordinates to the oxygen of the sulfoxide. Addition then proceeds through an acyclic transition state **B**, in accord with that proposed by Davis.[17]

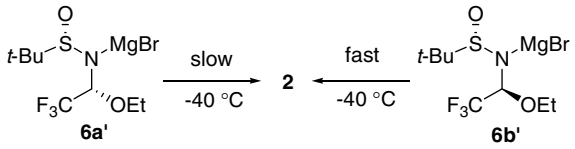
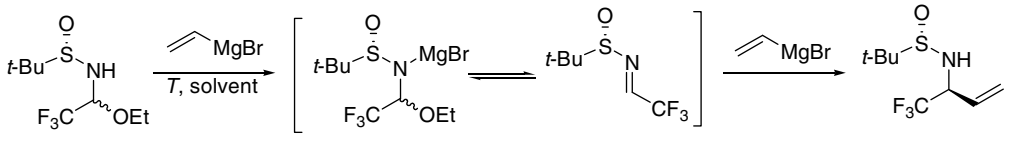


Figure 2.

Table 1.



Entry	Substrate	Solvent	*t* (h)	*T* (°C)	Ratio (S_SS:S_SR)[a]	Yield (%)[b]
1	**6a**	Toluene	0.5	0	7:1	80
2	**6b**	Toluene	0.5	0	6:1	85
3	**6a**	Toluene	2	−23	11:1	78
4	**6a**	Toluene	2	−40	16:1	58 (71)
5	**6a**	THF	2	−40	13:1	64 (74)
6	**6a**	CH_2Cl_2	2	−40	22:1	58 (70)
7	**6a**	CH_2Cl_2	2	−30	14:1	68
8	**6a**	CH_2Cl_2	3	−40 to −20	22:1	71
9	**6b**	CH_2Cl_2	1	−40	14:1	70
10	**6b**	CH_2Cl_2	2	−60 to −20	22:1	75

[a] Ratio determined by ^{19}F NMR of the unpurified product.
[b] Isolated yields of analytically pure material. Yields in parentheses are based on the recovered starting material.

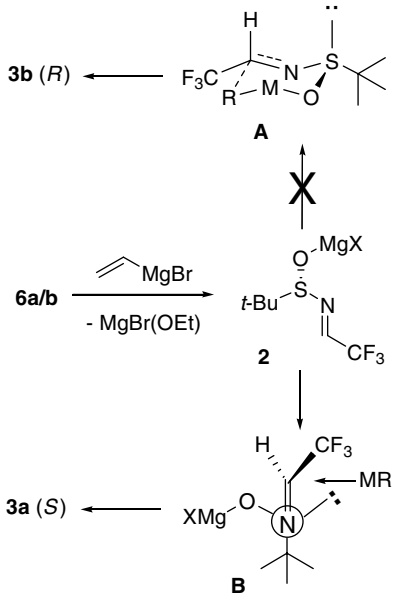
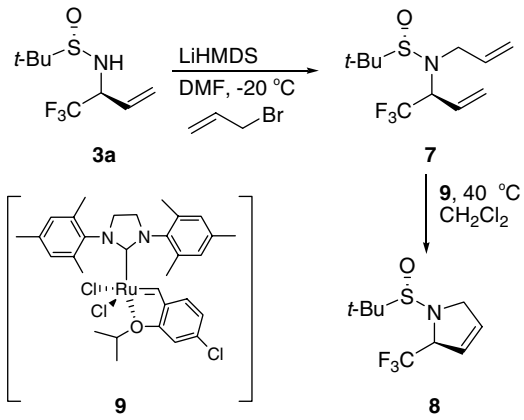


Figure 3.



Scheme 2.

As an example of the utility of **3**, we sought to prepare dihydropyrrolidine **8** via a ring-closing metathesis reaction.[18] Careful allylation of **3a** provided **7**, which underwent smooth ring closure employing catalyst **9** to afford **8** in 95% yield (Scheme 2).

In order to further examine the scope of the addition reaction of **6a**, we substituted vinylmagnesium bromide with other commonly available Grignard reagents (Table 2). While the product yields were uniformly high, the diastereoselectivity was dependent on the size of the Grignard reagent (entries 1–4). For example, phenylmagnesium bromide provided a dr of 6:1, while straight chain 3-butenylmagnesium bromide afforded product in >30:1 diastereoselectivity.[19] The low diastereoselectivity observed with allylmagnesium bromide (entry 2) may be attributed to an alternative intramolecular pathway.[20] Surprisingly, phenyllithium (entry 6) did not yield any desired product.

In summary, we have developed an efficient synthesis of chiral allyltrifluoromethylamine **1** utilizing the Ellman *tert*-butyl sulfinimine methodology. Sulfinamino acetals **6a/b** serve as stable precursors for the in situ generation of imine **2**, which undergoes addition with Grignard reagents in good yields with moderate to excellent selectivity.

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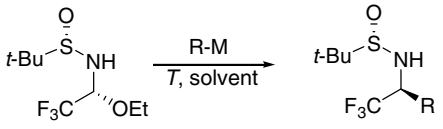
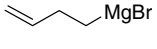
Table 2.



Entry	RM	Solvent	t (h)	T (°C)	Product	Ratio (S_SS:S_SR)[a]	Yield (%)[b]
1		CH_2Cl_2	2	−40 to −20	**10a**	11:1	81
2		CH_2Cl_2	2	−40 to −20	**10b**	5:1	98
3		CH_2Cl_2	2	−40 to −10	**10c**	>30:1	74
4		CH_2Cl_2	2	−40 to −20	**10d**	6:1	98
5		THF	0.5	−40 to −20	**10d**	3.5:1	97
6		CH_2Cl_2	3	−40 to 0	**10d**	—	—

[a] Ratio determined by ^{19}F NMR of the unpurified product.
[b] Isolated yields of analytically pure material.

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9. Representative procedure: To a mixture of **4** (4.70 g, 32.6 mmol) and **5** (4.34 g, 35.9 mmol) was added titanium tetraethoxide (11.16 g, 48.9 mmol) and the mixture was heated to 70 °C for two days. The mixture was diluted with EtOAc and was poured into a flask containing 250 mL of brine and stirred vigorously for several minutes. The suspension was filtered through celite rinsing liberally with EtOAc. The mixture was extracted with EtOAc and washed with additional brine. The organic extracts were dried over Na_2SO_4, filtered and concentrated. Chromatography of the crude reaction mixture on silica gel (20–50% EtOAc/Hexane) afforded the less polar diastereomer **6a** (3.6 g, 45%) and polar diastereomer **6b** (2.3 g, 29%). **6a**: mp = 50–51 °C; ^{19}F NMR ($CDCl_3$, 500 MHz) δ −81.29 (d, $J = 4.9$ Hz); **6b**: mp = 101 °C; ^{19}F NMR ($CDCl_3$, 500 MHz) δ −80.51 (d, $J = 4.9$ Hz); HRMS calcd for $C_8H_{16}F_3NO_2$ (M+Na): 270.0746. Found: 270.0746.
10. Perspective view (ORTEP) of **6b** showing crystallographic numbering scheme. Non-hydrogen atoms are represented by ellipsoids corresponding to 50% probability envelopes. Hydrogen atoms have been drawn at an arbitrary size.
11. Representative procedure: To a solution of **6b** (3.30 g, 13.34 mmol) in 100 mL of CH_2Cl_2 at −60 °C was added dropwise 33.4 mL of a 1 M solution of vinylmagensium bromide in THF (Aldrich). After 10 min, the reaction was allowed to slowly warm to −20 °C over ~2 h. The reaction mixture was quenched by the addition of 30 mL of saturated aqueous ammonium chloride and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. Chromatography of the crude reaction mixture on silica gel (0–30% EtOAc/hexane) afforded a 22:1 mixture of **3a**:**3b** (2.3 g, 75%). **3a**: ^1H NMR ($CDCl_3$, 500 MHz) δ 8.55 (d, $J = 4.9$ Hz, 1H), 7.66 (t, $J = 7.6$ Hz, 1H), 7.29–7.16 (m, 2H), 4.82 (bd, $J = 4.9$ Hz, 1H), 4.82–4.57 (m, 1H), 1.51 (d, $J = 6.8$ Hz, 3H), 1.26 (s, 9H); ^{19}F NMR ($CDCl_3$, 500 MHz) δ −76.01 (d, $J = 7.0$ Hz); LRMS (electrospray): *m/z* 230.2 (MH^+).
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13. Alternatively, the direct trifluoromethylation of α,β-unsaturated *N-tert*-butyl sulfinimes has been reported: see: Surya Prakash, G. K.; Mandal, M.; Olah, G. A. *Org. Lett.* **2001**, *3*, 2847–2850.
14. Only one geometric isomer of **2** was observed.
15. The stereochemistry was determined by ozonolysis followed by reductive workup with sodium borohydride to provide alcohol **11**. X-ray analysis confirmed the stereochemistry to be (S_S,*S*).
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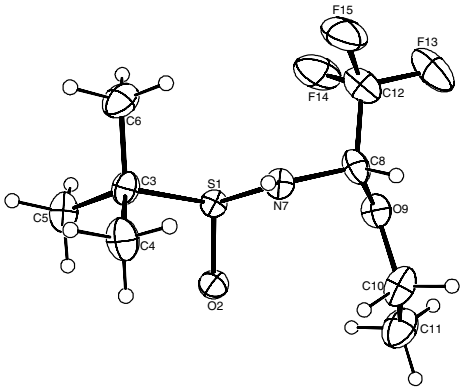
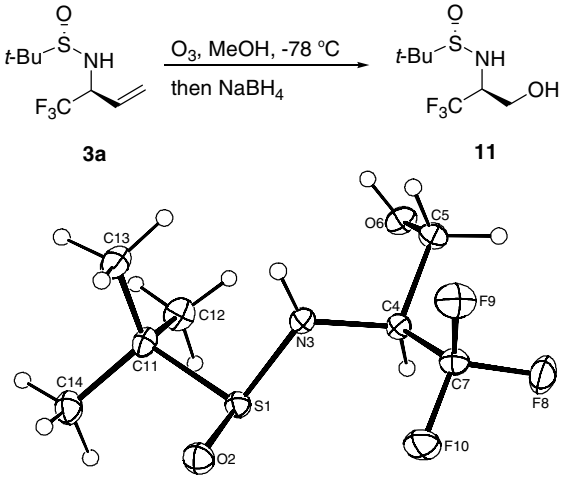
18. While the synthesis of related α-trifluoromethyl nitrogen heterocycles has been reported by the RCM approach, this represents the first example in which a five membered ring





Perspective view (ORTEP) of **11**, showing crystallographic numbering scheme. Non-hydrogen atoms are represented by ellipsoids corresponding to 50% probability envelopes. Hydrogen atoms have been drawn at an arbitrary size.

CCDC 296065 (**6b**) and 296066 (**11**) contain the supplementary crystallographic data for this letter. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

is formed: see: Gille, S.; Ferry, A.; Billard, T.; Langlois, B. *J. Org. Chem.* **2003**, *68*, 8932–8935.
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