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Asymmetric Syntheses of 1-Aryl-2,2,2-trifluoroethylamines via Diastereoselective 1,2-Addition of Arylmetals to 2-Methyl-*N*-(2,2,2-trifluoroethylidene)propane-2-sulfinamide

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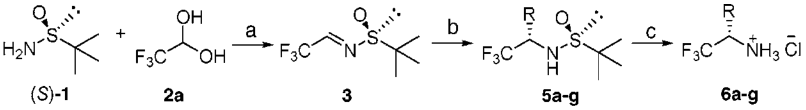
ABSTRACT



(a) Molecular sieves, toluene, 40 °C, (b) RLi, THF, -78 °C, (c) HCl, MeOH, rt

Condensation of *N-tert*-butanesulfinamide (*S*)-1 with trifluoroacetaldehyde hydrate 2a afforded 2-methyl-*N*-(2,2,2-trifluoroethylidene)propane-2-sulfinamide 3. Without isolation and purification, imine 3 was added to various aryllithium reagents to give highly diastereomerically enriched adducts 5a–g. Acidic methanolysis of 5a–g provided the desired 1-aryl-2,2,2-trifluoroethylamine hydrochloride compounds 6a–g.

1-Aryl-2,2,2-trifluoroethylamines are becoming increasingly important in the pharmaceutical industry because fluorine lowers the basicity of amines and improves the metabolic stability of the bioactive agents.[1] Consequently, they have attracted considerable attention as synthetic targets, especially in the area of asymmetric syntheses.[2] Previously, Olah and co-workers[3] reported the stereoselective synthesis of 1-aryl-2,2,2-trifluoroethylamines using $TMSCF_3$ as CF_3 source. Enders and co-workers[4] have also disclosed the asymmetric synthesis of 1-aryl-2,2,2-trifluoroethylamines via nucleophilic 1,2-addition of alkyllithium reagents to trifluoroacetaldehyde SAMP- or RAMP-hydrazone as a key step. More recently, Gosselin et al.[5] reported the asymmetric reduction of ketimines to form the corresponding 1-aryl-2,2,2-trifluoroethylamines. Our objective was to develop a more practical method suitable for the rapid syntheses of analogues of **6**.

The commercially available *N-tert*-butanesulfinamide **1** has been widely used as a chiral reagent in the synthesis of a variety of amines by virtue of its excellent diastereocontrol

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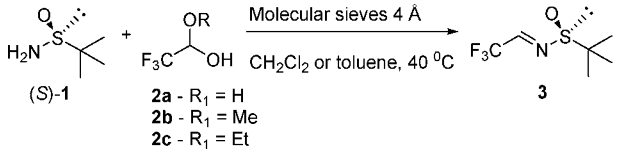
and the mild conditions for its cleavage.[6] Consequently, we decided to apply this chiral reagent to the asymmetric syntheses of the 1-aryl-2,2,2-trifluoroethylamines **6** using 2-methyl-*N*-(2,2,2-trifluoroethylidene)propane-2-sulfinamide **3** as a key precursor. The advantage of this approach is that a variety of chiral 1-aryl-2,2,2-trifluoroethylamine analogues can be rapidly produced by simply changing the organometallic reagents in the 1,2-addition step.

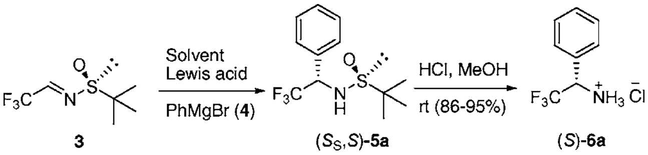
The representative preparation conditions for key intermediate **3** are shown in Scheme 1. Variation of the source of trifluoroacetaldehyde, solvent, temperature, and condensation mediator identified 1.1 equiv of trifluoroacetaldehyde hydrate **2a** in dichloromethane or toluene at 40 °C in the presence of 4 Å molecular sieves as the optimal conditions for the preparation of **3**[7] from **1**. Imine **3** was converted to an aminal upon aqueous quenching, and a poor yield (22%) was obtained by distillation due to decompositon.

Scheme 1. Preparation of Imine **3**



In order to avoid isolation and purification of **3**, we decided to investigate a one-pot, two-step process for the preparation of sulfinamide **5**. Our initial efforts were focused on the effect of solvent on the addition of phenylmagnesium bromide **4** to substrate **3** and the establishment of the absolute stereochemistry of the major isomer of **5a** (Table 1). Reaction of 1 equiv of phenylmagnesium bromide **4** with the crude imine **3** in toluene at −78 °C for 1 h gave a 52% yield of **5a** from **1**. The chiral reagent of **5a** was cleaved with HCl in methanol[6a,b,8] to afford the corresponding amine salt **6a**, which was subjected to chiral HPLC analysis. The enantiomeric ratio of **6a** was found to be 72:28. On the basis of the comparison to an authentic standard,[3,5] the absolute configuration of the major enantiomer **6a** was assigned as *S*. As it has previously been established that the sulfinamide auxiliary cleavage usually occurs without any erosion of chirality,[3,9] this indicated that the absolute configuration of the major diastereomer **5a** at the newly formed stereocenter, generated from the 1,2-addition, is also *S* (entry 1). This provided us with a reliable method for determining the diastereomeric ratio of different analogues of **5** in this report. After establishment of the absolute stereochemistry of each diastereomer in the mixture of sulfinamides, we then investigated the solvent effect on the 1,2-addition reaction. When the reaction was performed in THF, a similar diastereomeric ratio of **5a** was observed (entry 2). However, when dichloromethane was used as solvent, a modest improvement in diastereoselectivity was observed (entry 3).

Table 1. Diastereoselective 1,2-Addition of Phenylmagnesium Bromide to Imine **3**



entry	solvent	Lewis acids	yield of **5a**[d] (%)	dr[e]
1	PhMe	none	52	72:28
2	THF[a]	none	31	74:26
3	CH_2Cl_2	none	54	85:15
4	CH_2Cl_2	$AlMe_3$[b]	55	88:12
5	CH_2Cl_2	$AlMe_3$[c]	51	90:10
7	CH_2Cl_2	$AlEt_3$[c]	46	88:12
8	CH_2Cl_2	$BF_3{\cdot}Et_2O$[c]	36	88:12
9	CH_2Cl_2	$TiCl_4$[c]	11	93:07
10	CH_2Cl_2	$Zn(OTf)_2$[b]	7	89:11
11	CH_2Cl_2	$Mg(OTf)_2$[b]	34	89:11

[a] CH_2Cl_2 was removed by distillation and replaced by THF. [b] Precomplexation of imine **3** with Lewis acid at 0 °C, cooled to −78 °C, addition of phenylmagnesium bromide solution. [c] Precomplexation of imine **3** with Lewis acid at 0 °C; added to phenylmagnesium bromide solution at −78 °C. [d] Isolated yield. [e] Diastereomeric ratio (dr) was determined by chiral HPLC of the unpurified amine salt **6a**.

Since Lewis acids usually improve both the yield and diastereoselectivity of the 1,2-additon reaction,[6e,10] we screened a variety of Lewis acids in the phenylmagnesium bromide addition to imine **3** using dichloromethane as solvent. Table 1 highlights some Lewis acids which afforded a slight improvement in the diastereoselectivity of **5a**. The best diastereoselectivity was achieved with $TiCl_4$ as additive. Unfortunately, these conditions afforded **5a** in a very low yield (entry 9). The order of addition had no effect on the yield and diastereoselectivity of the reaction (entries 4 and 5).

As we were not successful in improving the diastereoselectivity of the phenylmagnesium bromide **4** addition to imine **3** using Lewis acids as promoter, we explored the 1,2-addition reaction using lithium reagents (Table 2).[11] After optimization of the solvent, temperature, order of addition, and number of equivalents, it was found that the addition of **3** in toluene to 2.5 equiv of phenyllithium (freshly generated from phenyl bromide and 2.5 M *n*-BuLi in THF) at −78 °C

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(7) Only one isomer was observed by ^{1}H, ^{13}C, and ^{19}F NMR spectrometry. The stereochemistry of **3** was assigned as *E* based on NOE between the proton of imine and the proton of *tert*-butyl and by analogy (see Davis, F. A.; Reddy, R. E.; Szewczyk, G.; Reddy, V.; Portonovo, P. S.; Zhang, H.; Fanelli, D.; Reddy, R. T.; Zhou, P.; Carroll, P. J. *J. Org. Chem.* **1997**, *62*, 2555−2563 and ref 5e).

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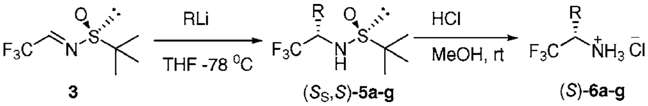
Table 2. Diastereoselective 1,2-Addition of Aryllithium Reagents to Imine **3**



enty	RLi	5	yield of **5**^{e} (%)	dr^{f}	6	yield of **6**^{e} (%)
1	PhLi[a]	**5a**	66	98:2	**6a**	86−95
2	PhLi[b]	**5a**	42	98:2	**6a**	86−95
3	PhLi[c]	**5a**	58	96:4	**6a**	86−95
4	4-MeOPhLi	**5b**	55	97:3	**6b**	86
5	4-MeSPhLi	**5c**	53	98:2	**6c**	85
6	4-FPhLi	**5d**	50	100:1	**6d**	84
7	3,5-diFPhLi[d]	**5e**	36	83:17	**6e**	56
8	2-MePhLi	**5f**	40	99:1	**6f**	52
9	pyridin-2-yllithium	**5g**	15	98:2	**6g**	69

[a] 2.5 equiv of PhLi was used. [b] 1.1 equiv of PhLi was used. [c] Precomplexation of imine with $AlMe_3$ at 0 °C, added to PhLi solution at −78 °C. [d] Unoptimized conditions. [e] Isolated yield. [f] Determined by chiral HPLC of the unpurified amine salts **6**.

rapidly generated **5a** in 66% overall yield with an excellent 98:2 diastereomeric ratio (entry 1). However, the yield was significantly decreased when 1.1 equiv of phenyllithium was employed (entry 2). The use of Lewis acids such as $AlMe_3$ did not improve the diastereoselectivity of the reaction and resulted in a lower yield of **5a** (entry 3).

Encouraged by the above results, we then examined the scope of the diastereoselective 1,2-addition of a various aryllithium reagents to imine **3** using the optimized reaction conditions. The results are shown in Table 2. In general, various aryllithium reagents participated successfully in the 1,2-addition reaction to provide the corresponding sulfinamides **5a**−**g** in moderate to good yields and good to excellent diastereoselectivities. All sulfinamides **5a**−**g** were then hydrolyzed to provide the corresponding amine hydrochloride salts **6a**−**g**, which were subjected to chiral HPLC analysis. It was determined that the addition of phenyllithium to imine **3** also generated sulfinamide **5a** with the *S* absolute configuration at the newly formed stereocenter. By analogy, the stereocenter of the remaining products **5b**−**g** is tentatively assigned as *S*.

Consistent with the literature,[6e,12] the addition of phenyllithium to imine **3** appears to have proceeded via a nonchelated transition-state model where phenyllithium preferably added to the imine from the less hindered face to predominantly afford the major diastereomer adduct (S_s,*S*)-**5a** (Figure 1). When Grignard reagents are used, previous reports proposed a six-membered chelating transition state where magnesium coordinates to the oxygen of the sulfinyl group and dictates the addition from the same face. However, contrary to this model, addition of the phenylmagnesium bromide to imine **3** also appeared to proceed via a nonchelated transition-state model to give the sulfinamide (S_s,*S*)-**5a** as the major diastereomer. To our knowledge, this is the first example of Grignard reagent addition to imine **3** in dichloromethane in the absence of Lewis acid that proceeded via a nonchelated transition state.

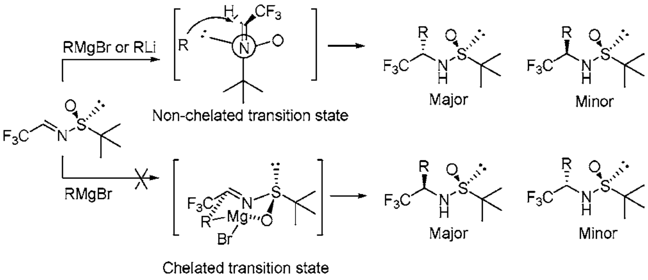


Figure 1. Speculative models for diastereoselectivity.

In conclusion, we have developed a very practical method for the syntheses of a variety of 1-aryl-2,2,2-trifluoroethylamine analogues in moderate to good yields with high optical purities using 2-methyl-*N*-(2,2,2-trifluoroethylidene)propane-2-sulfinamide **3** as a key precursor. Further application of **3** in the preparation of a variety of chiral amine analogues are under investigation and will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization data for **5a**−**g** and **6a**−**g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) **Experimental Procedure for 5a.** To a solution of *N*-*tert*-butanesulfinamide (*S*)-**1** (200 mg, 1.65 mmol) in toluene (3.3 mL) were added trifluoroacetaldehyde hydrate **2a** (75% in aqueous solution, 200 μL, 1.82 mmol) and molecular sieves pellets 4 Å (1 g) from Acros. The reaction mixture was stirred at 40 °C for 6 h under nitrogen to provide the crude imine **3**. A solution of bromobenzene (530 μL, 4.95 mmol) in THF (3.3 mL) in a flame-dried round-bottom flask under nitrogen was cooled to −78 °C, and a solution of *n*-BuLi (2.5 M in hexanes, 1.65 mL, 4.13 mmol) was added dropwise. The reaction mixture was aged at −78 °C for 1 h. The crude imine **3** was cooled to −78 °C and transferred via cannula to the reaction mixture. The resulting mixture was aged at −78 °C for 5 min and transferred to a cooled (0 °C) saturated aqueous NH_4Cl. The aqueous layer was extracted three times with ethyl acetate. The organic extracts were combined, washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel using ethyl acetate−hexanes (25:75) to afford **5a** in 66% yield (302 mg).

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