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Stereoselective Synthesis of Trifluoromethylated Vicinal Ethylenediamines with α-Amino *N-tert*-Butanesulfinimines and $TMSCF_3$

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The initial discovery[1] of Fried that the 9α-fluorohydrocortisone acetate is 11 times more biologically active than the corresponding nonfluorinated analogue has been the motivation for chemists to incorporate fluorine to modulate the biological properties of organic molecules. The inability of enzymes to distinguish fluorinated compounds from their nonfluorinated analogues has been the basis for rational drug design, resulting in a large number of fluorinated compounds as anticancer, antiviral, and antibacterial agents. Moreover, the fluorinated compounds, especially the fluorinated ketones and the amino alcohols, function as protease inhibitors. Lack of availability of the fluorinated building blocks and our broad interest in the fluorination chemistry inspired us to explore new approaches in this field.

Earlier, we discovered[2] that trifluoromethyltrimethylsilane ($TMSCF_3$) acts as an efficient nucleophilic trifluoromethylating agent, exemplified by its use for the direct preparation of trifluoromethylated alcohols, esters, amines, and amino alcohols.[2,3] Ubiquity of the 1,2-diamino moiety in the natural products as well as their wide applications as ligands in the transition metal catalyzed asymmetric synthesis have brought about numerous studies for their efficient stereoselective synthesis.[4] Profound change exhibited by the amino moiety when it is placed α to a "CF_3" group prompted us to design and execute the preparation of trifluoromethylated vicinal diamines as novel surrogates for their nonfluorinated analogues. Herein we report a convenient method for the preparation of trifluoromethylated vicinal diamines using our nucleophilic trifluoromethylation strategy, i.e. direct stereoselective transfer of "CF_3" to a preformed α-amino imines. Although several such imines were prepared and used for various nucleophile transfer reactions,[5] our digression from these conventional methodologies is due to the fact that only activated imines participate in our nucleophilic trifluoromethylation reaction, and in general strongly activated imines, such as sulfonylimines and nitrones are very unstable. Our previous success[3] together with the ready availability of *N-tert*-butanesulfinamide[6] encouraged us to seek the possibility of preparing α-amino *N-tert*-butanesulfinimines for our nucleophilic trifluoromethylation reactions. Although the initial attempts to condense α-amino aldehydes with the *N-tert*-butanesulfinamide using $MgSO_4$ or $CuSO_4$ was disappointing, soon we found that the stronger dehydrating-Lewis acidic reagent, $Ti(OEt)_4$, gave quantitative yields of the imines without any racemization. Four equivalents of $Ti(OEt)_4$ were necessary to complete the reaction. A variety of amino aldehydes derived from L-amino acids (**1c**−**f**) condensed smoothly. Steric crowding had no affect on the yields of the imine products. Amino aldehydes (**1g**) derived from D-amino acids also condensed similarly without any stereochemical loss. The *E* stereochemistry of the imine function was determined through single-crystal X-ray analysis (see the Supporting Information). Having obtained these imines in the stereochemically pure form we investigated their nucleophilic trifluoromethylation. By using TBAT (tetrabutylammonium difluorotriphenylsilicate)[7] as the fluoride source for the activation of $TMSCF_3$ for trifluoromethylation, **2a** gave the adduct **3a** in only 20% isolated yield. On the basis of our previous observation,[3] the low yield of the reaction appears to be due to the steric bulk of the tetrabutylammonium counterion. We changed the fluoride source to the less bulky TMAF (tetramethylammonium fluoride).[8] With the use of TMAF, the adduct **3a** was obtained in 86% yield under similar reaction conditions. A single diastereomer was observed by ^{19}F and ^{1}H NMR spectroscopy. By using TMAF as the fluoride source, imines **2b**−**f** were trifluoromethylated to the corresponding vicinal ethylenediamine adducts (**3b**−**f**) in good to excellent yields with high diastereoselectivities (>99:01). On the other hand, the

Table 1. Condensation of Reetz's Amino Aldehydes with Ellman's (*R*)-*N-tert*-Butanesulfinamide

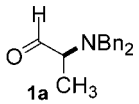
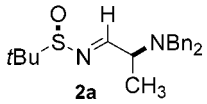
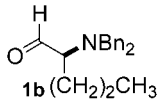
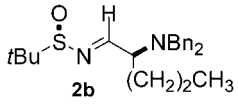
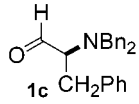
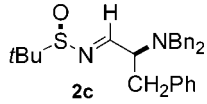
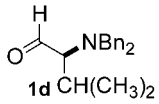
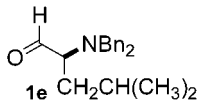
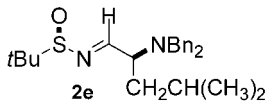
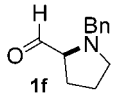
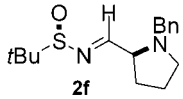
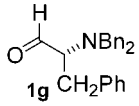
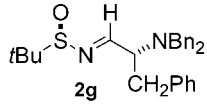
aldehyde	product	yield(%)
 **1a**	 **2a**	**91**
 **1b**	 **2b**	**89**
 **1c**	 **2c**	**93**
 **1d**	 **2d**	**87**
 **1e**	 **2e**	**92**
 **1f**	 **2f**	**80**
 **1g**	 **2g**	**95**

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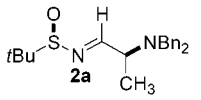
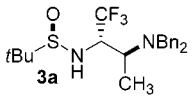
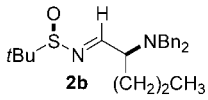
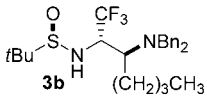
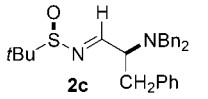
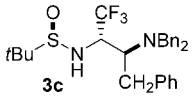
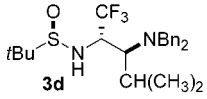
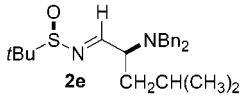
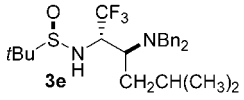
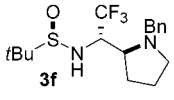
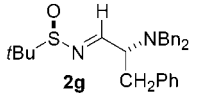
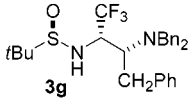
Table 2. Nucleophilic Trifluoromethylation of **2a**−**g**

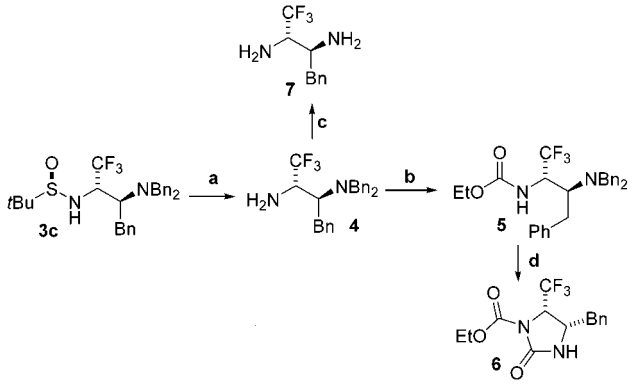
imine	product	yield(%)	de
 **2a**	 **3a**	**86**	**>99 : 01**
 **2b**	 **3b**	**85**	**>99 : 01**
 **2c**	 **3c**	**81**	**>99 : 01**
 **2d**	 **3d**	**66**	**>99 : 01**
 **2e**	 **3e**	**71**	**>99 : 01**
 **2f**	 **3f**	**79**	**>99 : 01**
 **2g**	 **3g**	**60**	**80 : 20**

imine derived from the D-amino aldehyde (**2g**) gave the corresponding adduct in 80:20 diastereomeric ratio with a 60% yield of the major diastereomer. The very high diastereoselectivities observed in the case of the imines derived from the L-amino acids suggest that both the chiral centers present in the molecule direct the incoming nucleophile to the *re* face of the imines. The absolute configuration of the sulfinamide **3a** was also determined by single-crystal X-ray analysis (see the Supporting Information) and the configurations of **3b**−**f** were assigned by analogy. The configuration of the major diastereomer obtained from the imine **2g** was determined by hydrolyzing the minor diastereomer and comparing its NMR spectra to that of **4** (see the Supporting Information).

As a demonstration, **4** has been further elaborated to the related derivatives (Scheme 1). Attempts to protect the free amino group of **4** as its BOC derivative were not successful. However, the reaction with ethyl chloroformate under Bauman conditions gave the corresponding carbamate **5** in excellent yield. Debenzylation of **5**, followed by treatment with triphosgene, proceeded smoothly to yield the 2-oxa-1-imidazolidinyl derivative **6**. Moreover, catalytic hydrogenation of **4** gave the free amine **7** in good yield.

In conclusion we have showed for the first time that isolable α-amino *N-tert*-butanesulfinimines could be prepared without any stereochemical loss. Their subsequent nucleophilic trifluoromethylation reaction gave high yield of the trifluoromethylated vicinal ethylenediamines in high stereoselectivity, particularly in the case of imines derived from L-amino acids.

Scheme 1 [a]



[a] Conditions: (a) 1. 10 equiv of HCl in dioxane, MeOH, 70 °C, 3 h. 2. Saturated $NaHCO_3$ washing; 92% yield. (b) EtOCOCl, 50% K_2CO_3, dioxane; 95% yield. (c) Pd/C, H_2, MeOH/DCM, 24 h. (d) 1. Pd/H_2, MeOH/DCM, 24 h; 2. $(Cl_3CO)_2CO$, Et_3N, THF; 60% yield.

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Supporting Information Available: ^1H, ^{13}C, and ^{19}F NMR spectra for all new compounds as well as X-ray ORTEP and related data for **2a** and **3a** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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