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Highly Stereoselective Trichloromethylation of *N*-(*tert*-Butylsulfinyl)aldimines: Facile Synthesis of Chiral α-Trichloromethylamines

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The first highly stereoselective and facile synthesis of α-trichloromethylamines is described by using a nucleophilic trichloromethylation strategy. With tetrabutylammonium triphenyldifluorosilicate (TBAT) as the mediator, the trichloromethyl anion (CCl_3^-) from $TMSCCl_3$ can be transferred to *N*-(*tert*-butylsulfinyl)aldimines in excellent yields and with high diastereoselectivity (≥99:1 *dr*).

Introduction

The trichloromethyl unit is a structural feature present in a vast number of bioactive natural products and pharmaceutical drugs, and it was found to be the key component for potent activity and low toxicity in some cases.[1] In this context, α-trichloromethylamines are attracting enormous recent attention in the field of medicinal chemistry as well as synthetic chemistry.[2] It was believed that incorporation of the α-trichloromethylamine subunit can result in higher metabolism and improved biological properties of a target drug candidate.[2a,2b] Moreover, the α-trichloromethylamine subunit is highly valuable synthetic intermediate in organic synthesis, which has frequently served as a precursor for the synthesis of α-amino acids,[3] 2,2-dichloroaziridines,[4] α-di- and monochloromethylamines,[5] 3,3-dichloropyrrolidines,[6] along with trichloromethylated heterocyclic compounds.[7]

Despite its importance for applications related to life sciences, the synthesis of α-trichloromethylamines has not been well explored. The few known methods are mainly based on the use of a trichloromethyl anion equivalent ("CCl_3^-"), including trichloroacetic acid,[8] trichloromethane,[9] carbon tetrachloride,[10] or 2,2,2-trichloroethanimine derivatives[11] as precursors. The earliest reported method for the preparation of α-trichloromethylamines involved the addition reaction between trichloroacetic acid and imines.[8a,8b] Friedel–Crafts-type reaction of *N*-(2,2,2-trichloroethylidene)benzenesulfonamide with pyrrole or pyrazole afforded the expected addition products.[11a,12] However, these methods suffer from low yields and lack generality. More recently, Abbaspour Tehrani reported a facial synthesis of α,β-unsaturated α-trichloromethylamines by Lewis acid promoted Petasis-type reaction of 2,2,2-trichloroethanimines with styryl- or phenylethynyltrifluoroborates.[13] As to the asymmetric synthesis of α-trichloromethylamines, only two examples have been disclosed: one was using the addition reaction between in situ generated *N*-acyl-*N*-(2,2,2-trichloroethylidene)amines and the cyclic enamine (*S*)-1-(cyclohexenyl)-2-(methoxymethyl)pyrrolidene,[14] and the other involved ring opening of 3-trichloromethyl β-sultam by using alcohols or amines to afford β-trichloromethyl β-amino sulfonates or sulfonamides.[2c] To the best of our knowledge, there is no general method available for the highly stereoselective synthesis of α-trichloromethylamines by using a direct trichloromethylation strategy, and the general and efficient asymmetric synthesis of α-trichloromethylamines still remains an unexplored research area. As part of our continuing efforts in the development of efficient methodologies for the synthesis of chiral α-(halogenated methyl)amines,[15] herein we report the first stereoselective synthesis of α-trichloromethylamines by using readily accessible trimethyl(trichloromethyl)silane ($TMSCCl_3$, **1**).

Results and Discussion

In previous reports, $TMSCCl_3$ (**1**) turned out to be an especially useful trichloromethylating reagent for carbonyl compounds,[16] commonly accomplished under various fluoride (F^-) sources [tris(diethylamino)sulfonium difluoromethylsilicate (TASF), potassium fluoride (KF), and tetrabutylammonium fluoride (TBAF)] or weak Lewis bases

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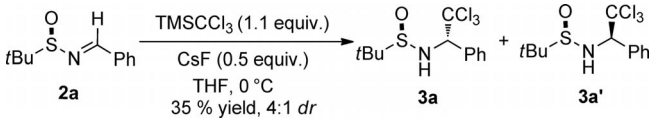
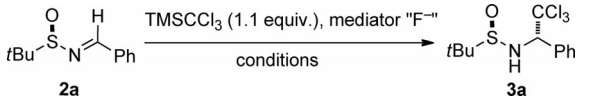
[potassium carbonate (K_2CO_3), sodium formate (HCOONa), and so on]. It was observed that the trichloromethyl anion (CCl_3^-), generated in situ from **1** and a base showed both higher thermal stability and better nucleophilicity in comparison to trichloromethyllithium (CCl_3Li).[17] Although its addition reaction to carbonyl compounds has been extensively explored, only one report dealing with its addition to imines has appeared in the literature (trichloromethylation of salicylaldimines through initial formation of an intramolecular boron complex followed by interaction with $TMSCCl_3$ gave the trichloromethylated adducts in only 34% yield).[18] We envisioned that the reactions between $TMSCCl_3$ and chiral imines, such as widely used *N*-(*tert*-butylsulfinyl)aldimines, would provide an excellent approach to obtain chiral α-trichloromethylamines by taking advantage of the reasonable stability of the CCl_3^- anion and its the high electrophilic properties and the powerful chiral directing ability of *N*-(*tert*-butylsulfinyl)aldimines. With these in mind, first we tried the diastereoselective nucleophilic trichloromethylation of (*R*)-(*tert*-butylsulfinyl)aldimine **2a** with reagent **1**. When compound **1** (1.1 equiv., in THF) was added to a solution of aldimine **2a** (1 equiv.) and CsF (0.5 equiv.) in THF at 0 °C, a facial addition reaction occurred, and corresponding products **3a** + **3a′** can be obtained in 35% yield (Scheme 1). More interestingly, analysis of the crude reaction mixture and the obtained product by ^1H NMR spectroscopy showed that the reaction proceeded diastereoselectively with 4:1 *dr*.



Scheme 1. Trichloromethylation of **2a** by using CsF as the mediator.

Encouraged by the above results, we then carried out a series of experiments to improve both the yield and diastereoselectivity. Aldimine **2a** was used as a model compound, and the reaction conditions were carefully tuned as shown in Table 1. It is apparent that the reaction was significantly influenced by the fluoride source, the reaction solvent, and the reaction temperature. Using CsF as the fluoride source, and less polar to polar solvents, such as diglyme, THF, and DMF, expected product **2a** can only be obtained in 30–67% yield (Table 1, Entries 1–3). After several trials, we found that the combination of THF and TBAT (tetrabutylammonium triphenyldifluorosilicate) could give better yield and excellent diastereoselectivity (Table 1, Entries 4–7). It is worthy to note that 1.0 equiv. of TBAT is used to ensure complete conversion of reagent **2a**. Also, temperature is important and a lower temperature is helpful for higher yield (Table 1, Entries 5 and 6). The best yield and diastereoselectivity were reached with 1.5 equiv. of $TMSCCl_3$ and 1.0 equiv. of TBAT in THF solution at –60 °C (Table 1, Entry 7).

Table 1. Survey of the reaction conditions.



Entry	Fluoride source (equiv.)	Solvent	*T* [°C]	*dr*[a]	Yield [%][b]
1	CsF (1.1)	DMF	–20	82:18	30
2	CsF (1.1)	THF	–20	80:20	67
3	CsF (1.1)	diglyme	–20	85:15	50
4	TBAT (0.5)	THF	–20	99:1	52
5	TBAT (1.0)	THF	–20	99:1	71
6	TBAT (1.0)	THF	–60	99:1	83
7[c]	TBAT (1.0)	THF	–60	99:1	94

[a] Determined by ^1H NMR spectroscopy and HPLC analysis of the crude product. [b] Isolated yield (**3a** + **3a′**). [c] 1.5 equiv. of $TMSCCl_3$ was used.

Eventually, the above conditions were applied to a wide array of structurally diverse imines as summarized in Table 2. A remarkable feature of this reaction is that it can be applied to non-enolizable, enolizable, aromatic, and heterocyclic imines alike. High diastereoselectivity was observed in each case, and good to excellent yields were obtained with non-enolizable imines (Table 2, Entries 1–10) and with imines that bear only one α-hydrogen atom (Table 2, Entry 11). Note that the electronic withdrawing/donating nature of the substituent on the aromatic ring had an undetectable effect on both the yield and diastereoselectivity. However, relatively lower yields (35%) were obtained in the case of imine **2l**, which bears two α-hydrogen atoms (Table 2, entry 12). Careful TLC analysis revealed that imine **2l** disappeared shortly after the reaction was performed and indicates a labile enolization of **2l** under such basic conditions. On the other hand, relatively lower diastereoselectivities were obtained for all entries when CsF was used as the fluoride source (Table 2, values in parentheses). The fluoride difference upon diastereoselectivities appears to be due to the steric bulk of tetrabutylammonium counterion, which played an important role in the trichloromethyl transfer process.[19]

The absolute configuration of sulfinamide **3a** was determined by single-crystal X-ray analysis (Figure 1a), and was consistent with our prediction based on a commonly used nonchelation-controlled transition-state mode to give the Cram products (Figure 1b), in which the *tert*-butyl group adopts the antiperiplanar arrangement with respect to the C=N bond.[15,20] However, recent studies indicated that, mainly due to the contribution of intramolecular hydrogen bonding of the oxygen with the imine hydrogen, the sulfinyl oxygen in a s-*cis* arrangement with respect to the C=N bond is the most stable conformation for the *N*-(phenylsulfinyl)imine.[21] The approach of the nucleophile (CCl_3^-) to this conformation would also lead to the observed stereoselectivity as shown in Figure 1c. We tentatively assume that one or both transition-state modes are involved in this trichloromethylation reaction. The configurations of **3b**–**l** were assigned by analogy.

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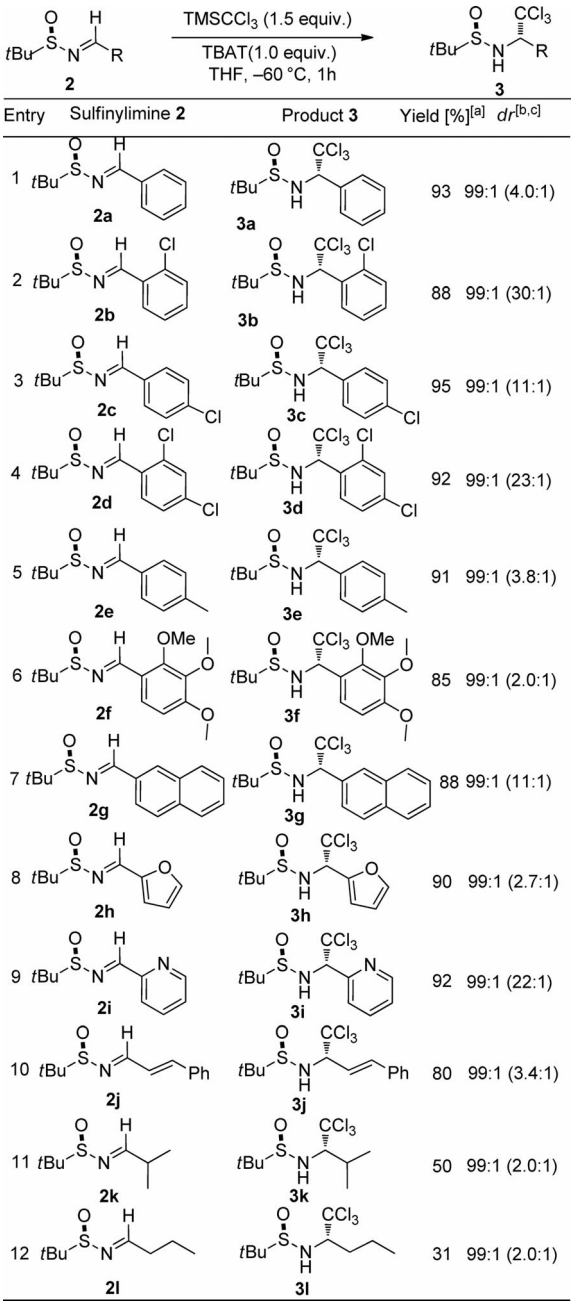
Table 2. Trichloromethylation of *N*-(*tert*-butylsulfinyl)aldimines **2** by using $TMSCCl_3$ (**1**).



Entry	Sulfinylimine **2**	Product **3**	Yield [%][a]	*dr*[b,c]
1	**2a**	**3a**	93	99:1 (4.0:1)
2	**2b**	**3b**	88	99:1 (30:1)
3	**2c**	**3c**	95	99:1 (11:1)
4	**2d**	**3d**	92	99:1 (23:1)
5	**2e**	**3e**	91	99:1 (3.8:1)
6	**2f**	**3f**	85	99:1 (2.0:1)
7	**2g**	**3g**	88	99:1 (11:1)
8	**2h**	**3h**	90	99:1 (2.7:1)
9	**2i**	**3i**	92	99:1 (22:1)
10	**2j**	**3j**	80	99:1 (3.4:1)
11	**2k**	**3k**	50	99:1 (2.0:1)
12	**2l**	**3l**	31	99:1 (2.0:1)

[a] Yield of isolated pure material. [b] The *dr* values in parentheses are those obtained with CsF as the fluoride source. [c] Determined by ^{1}H NMR spectroscopy and HPLC analysis of the crude reaction mixture. For more details, see the Supporting Information.

In 2001 Prakash, Olah, and co-workers reported an elegant diastereoselective nucleophilic trifluoromethylation of *N*-(*tert*-butylsulfinyl)imines using the Ruppert–Prakash reagent ($TMSCF_3$).[19a] Compared to the trifluoromethyl anion (CF_3^-) (generated from $TMSCF_3$ in the presence of a fluoride activator), the trichloromethyl anion (CCl_3^-) showed similar reactivity: both of which worked better for non-enolizable imines than enolizable ones.

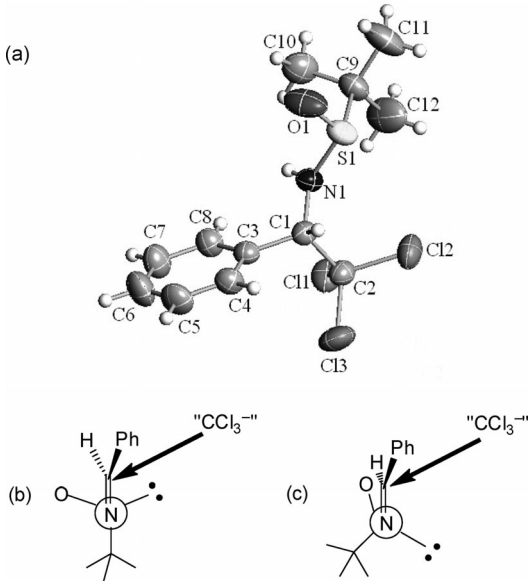
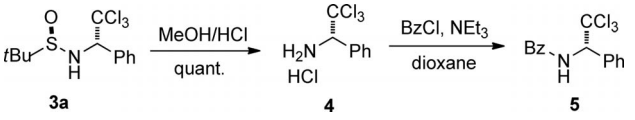


Figure 1. The X-ray crystal structure of **3a** (a) and depiction of its stereoselective formation (b, c).

The *t*BuS(O) group can be easily removed following reported procedures without affecting the trichloromethyl group.[20] For instance, compound **3a** was subject to acid-catalyzed alcoholysis with HCl/MeOH to afford α-trichloromethyl 2-benzenemethanamine **4** in near-quantitative yield (Scheme 2). To ensure that there was no racemization during the deprotection process, we converted amine salt **4** into benzamide derivative **5**. The optical purity of **5** (99%*ee*), determined by chiral HPLC, indicated that the above deprotection procedure was reliable for the preparation of enantiomerically pure α-trichloromethylamines.



Scheme 2. Conversion of **3a** into amine salt **4** and benzamide derivative **5**.

Conclusions

In summary, we have successfully developed the first highly stereoselective and facile synthesis of α-trichloromethylamines by using a straightforward trichloromethylation strategy. Trichloromethylation of (*R*)-(*N*-*tert*-butylsulfinyl)-aldimines with trimethyl(trichloromethyl)silane ($TMSCCl_3$) affords the corresponding products in excellent yields and with high diastereoselectivity (≥99%*dr*). Facile and convenient deprotection of the *tert*-butylsulfinyl group gives the target trichloromethylamines in quantitative yield without affecting the trichloromethyl group. The synthetic applications of α-trichloromethylamines are still under investigation in our lab.

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Experimental Section

General Procedure for the Trichloromethylation of Imines by using $TMSCCl_3$ (1): $TMSCCl_3$ (**1**; 1.5 equiv., 1.5 mmol) in THF (3 mL) was added to a mixture of imine **2** (1 mmol) and TBAT (1 equiv., 1 mmol) in THF (8 mL) at –60 °C. The reaction mixture was stirred for 1 h. Then, a half-saturated NH_4Cl/H_2O solution (2 mL) was added at low temperature, and the quenched reaction mixture was extracted with ethyl acetate (3×). The combined organic layers were dried with anhydrous $MgSO_4$. Evaporation of the solvent afforded the crude product, which was subjected to flash chromatography to give the corresponding sulfonamide **3**.

CCDC-784869 (for **3a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Experimental details, characterization data, and copies of the ^1H and ^{13}C NMR spectra of the new compounds.

Acknowledgments

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