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Diastereoselective Trifluoromethylation of Chiral α,β-Unsaturated *N-tert*-Butanesulfinyl Ketimines with Ruppert-Prakash Reagent: Asymmetric Synthesis of α-Tertiary Trifluoromethyl Allylic Amines

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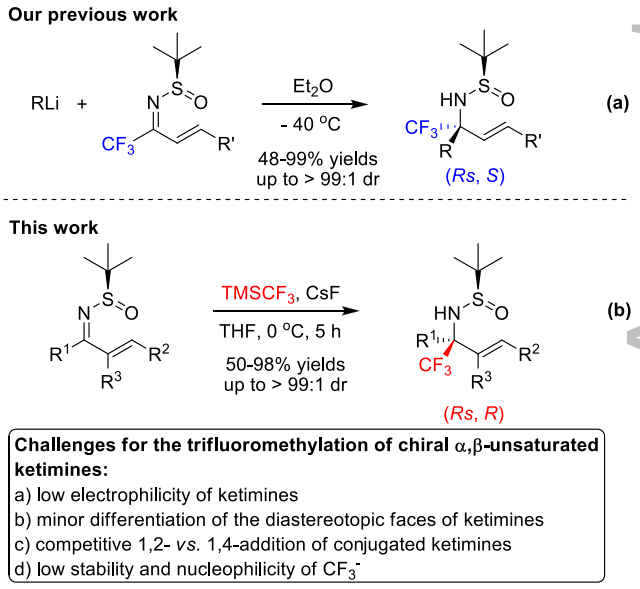
Abstract. The diastereoselective trifluoromethylation of chiral α,β-unsaturated *N-tert*-butanesulfinyl ketimines with Ruppert-Prakash reagent ($TMSCF_3$) has been attained, which provided a convenient and straightforward method for the asymmetric synthesis of structurally diverse α-tertiary trifluoromethyl allylic amines in high yields and with excellent diastereoselectivities (dr up to > 99:1). The stereochemical outcome of the present diastereoselective trifluoromethylation of the α,β-unsaturated *N-tert*-butanesulfinyl ketimines suggested that a cyclic six-membered transition state is involved in the reaction, which is remarkably different from that of the trifluoromethylation of *N-tert*-butanesulfinyl aldimines.

Keywords: Allylic compounds; Trifluoromethylation; Fluorine; Ketimines; Ruppert-Prakash reagent

Chiral trifluoromethylated allylic amines are an important structural motif because of their versatile synthetic utility as chiral building blocks in the synthesis of pharmaceuticals and agrochemicals.[1] Their versatility can be attributed to the presence of the strongly electron withdrawing trifluoromethyl group which can tune the basicity of amines and thus enhance the lipophilicity, metabolic stability and bioactivity of a target drug molecule.[2] Therefore, great efforts have been devoted to their asymmetric synthesis.[3-6] However, most of the reported methods focus on the preparation of chiral α-secondary trifluoromethyl allylic amines.[3] Due to the lack of efficient methods for the highly stereoselective construction of tetrasubstituted carbon stereogenic centers with a trifluoromethyl group, strategies for the asymmetric synthesis of α-tertiary trifluoromethyl allylic amines are very rare. Recently, Ohshima and Huang independently reported a single case of the synthesis of a chiral α-tertiary trifluoromethyl allylic amine from different CF_3-substituted ketimines, which involved multiple steps and resulted in low yields.[4] More recently, our group developed a general and efficient method for the asymmetric synthesis of structurally diverse α-tertiary trifluoromethyl allylic amines by the regioselective addition of organolithium reagents to chiral trifluoromethyl α,β-unsaturated *N-tert*-butanesulfinyl ketimines (Scheme 1, eq. a).[5] However, the use of organolithium reagents is known to make the reaction



Scheme 1. Methods for the asymmetric synthesis of α-tertiary trifluoromethyl allylic amines.

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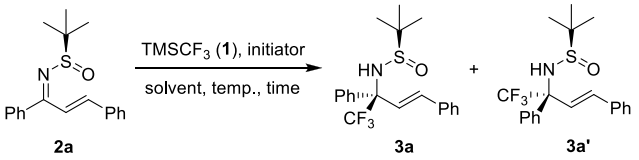
process considerably tedious and this severely restricts their application in such processes. In addition, our group also developed several efficient methods for the stereoselective synthesis of functionalized α-tertiary trifluoromethyl allylic amines.[6] Nevertheless, the direct asymmetric synthesis of α-trifluoromethyl allylic amines bearing a tetrasubstituted carbon stereogenic center is highly sought after, but remains a significant challenge in organic synthesis.

The stereoselective nucleophilic trifluoromethylation of imines provides one of the most convenient and straightforward approach for the synthesis of chiral α-trifluoromethyl amines.[7] Although the stereoselective trifluoromethylation of aldimines has been extensively investigated,[8] the corresponding asymmetric trifluoromethylation of ketimines still remains a formidable challenge.[9] The difficulties in the nucleophilic trifluoromethylation of ketimines are ascribed to the relatively lower reactivity of ketimines as compared to aldimines, and the low thermal stability and nucleophilicity of trifluoromethylated carbanion CF_3^- (referred to as the "negative fluorine effect" proposed by Hu and co-workers[10]). In addition, a minor steric discrimination of the substituents on a ketimine and the existence of its *E* and *Z* isomers render the differentiation of the stereotopic faces of the ketimine more difficult. Recently, Chen and Xu reported the first asymmetric trifluoromethylation of "double" activated ketimines derived from isatins and *N-tert*-butanesulfinamide.[9a] However, the reactions gave very low diastereoselectivities (generally 2:1 dr or lower). To the best of our knowledge, there are no reports on the asymmetric trifluoromethylation of α,β-unsaturated *N-tert*-butanesulfinyl ketimines[11] which is more challenging compared to the corresponding reaction with nonconjugated ketimines. This is primarily due to their ambident electrophilic character which results into a competition between the 1,2- and 1,4-addition reactions.[12] As a continuation of our interest in the chemistry of chiral α,β-unsaturated *N-tert*-butanesulfinyl ketimines,[5-6] we report herein the first highly regio- and diastereoselective trifluoromethylation of chiral α,β-unsaturated *N-tert*-butanesulfinyl ketimines with the Ruppert-Prakash reagent ($TMSCF_3$) (Scheme 1, eq. b). The reaction proceeds solely via a 1,2-addition mechanism, affording the corresponding α-tertiary trifluoromethyl allylic amines in good to high yields and with excellent diastereoselectivities.

We began our investigations by examining the feasibility of the asymmetric trifluoromethylation of α,β-unsaturated *N-tert*-butanesulfinyl ketimine **2a** with the Ruppert-Prakash reagent ($TMSCF_3$, **1**). TMAF, which was previously reported to be an efficient initiator in the asymmetric trifluoromethylation of aldimines,[8b-c] was initially selected to activate the $TMSCF_3$ for the trifluoromethylation of ketimine **2a**. The reaction was found to proceed smoothly, giving only the 1,2-adduct and a good diastereoselectivity (**3a:3a′** = 90:10), but low yield (43%) (Table 1, entry 1). Increasing the amount of TMAF and $TMSCF_3$, meanwhile elevating the reaction temperature had no effect on the reaction yield or the diastereoselectivity (Table 1, entry 2). It is well-known that the choice of an appropriate initiator is critical in the trifluoromethylation reactions with $TMSCF_3$.[7a,d] Remarkably, the use of CsF instead of TMAF as the

Table 1. Optimization of the Reaction Conditions.[a)]



Entry	Initiator	**1** (equiv.)	Solvent	T / °C	Yield (%)[b)]	**3a**:**3a′** (dr)[c)]
1[d)]	TMAF	1.5	THF	-25	43	90:10
2[d)]	TMAF[f)]	3.0	THF	-10	28	86:14
3[d)]	CsF[f)]	3.0	THF	-25	61	92:8
4[d)]	CsF[f)]	3.0	THF	0	77	92:8
5[d)]	CsF[f)]	4.0	THF	0	83	93:7
6[d)]	CsF[f)]	5.0	THF	0	100	93:7
7	CsF	5.0	THF	0	100[h)]	93:7
8[d)]	CsF	5.0	THF	-10	100	94:6
9[e)]	CsF	5.0	THF	-20	74	95:5
10	CsF[g)]	5.0	THF	0	60	93:7
11	CsF	5.0	DMF	0	NR[i)]	-
12	CsF	5.0	Toluene	0	29	96:4
13	CsF	5.0	DCM	0	5	88:12
14	CsF	5.0	Et_2O	0	18	93:7
15	TMAF	5.0	THF	0	42	88:12
16	TBAF	5.0	THF	0	8	60:40
17	KF	5.0	THF	0	NR[i)]	-
18	CuF_2	5.0	THF	0	NR[i)]	-
19	*t*BuOK	5.0	THF	0	75	93:7
20	NaOAc	5.0	THF	0	NR[i)]	-
21	Cs_2CO_3	5.0	THF	0	12	88:12
22	K_2CO_3	5.0	THF	0	NR[i)]	-

[a)] 1.1 equiv. of initiator relative to that of **2a** was used and the reaction time was 5 h unless stated otherwise. [b)] Yields were determined by ^{19}F NMR spectroscopy using $C_6H_5CF_3$ as internal standard. [c)] Diastereomeric ratio was determined by ^{19}F NMR spectroscopic analysis of the crude reaction mixture. [d)] The reaction time was 12 h. [e)] The reaction time was 24 h. [f)] 2.0 equiv. of initiator was used. [g)] 0.5 equiv. of CsF was used. [h)] 98% of isolated yield was obtained after flash chromatography. [i)] NR = No reaction. TMAF = tetramethylammonium fluoride, TBAF = tetrabutylammonium fluoride.

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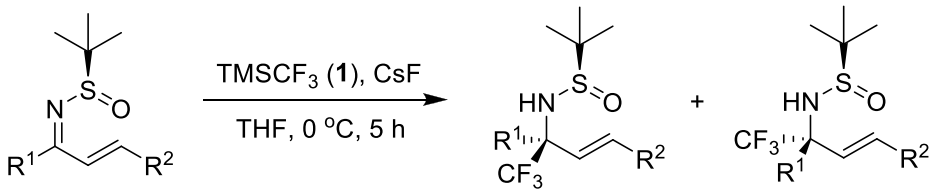
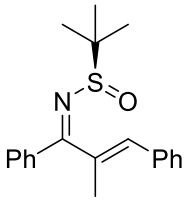
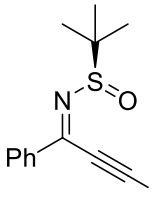
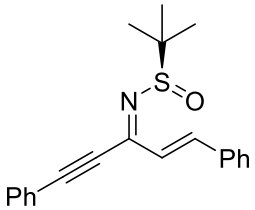
Table 2. The Direct Asymmetric Trifluoromethylation of α,β-Unsaturated *N*-*tert*-Butanesulfinyl Ketimines **2** with $TMSCF_3$ **1**.[a)]



2 **3** **3'**

Entry	**2**	R^1	R^2	Product	Yield (%)[b)]	**3**:**3′** (dr)[c)]
1	**2a**	Ph	Ph	**3a+3a′**	100 (98)	93:7
2	**2b**	4-$NO_2C_6H_4$	Ph	**3b+3b′**	100 (97)	> 99:1
3	**2c**	4-ClC_6H_4	Ph	**3c+3c′**	86 (80)	90:10
4	**2d**	4-PhC_6H_4	Ph	**3d+3d′**	100 (95)	95:5
5	**2e**	4-$MeOC_6H_4$	Ph	**3e+3e′**	57 (50)	95:5
6	**2f**	2-Furyl	Ph	**3f+3f′**	91 (86)	73:27
7	**2g**	*t*-Bu	Ph	**3g+3g′**	100 (94)	98:2
8	**2h**	Ph	4-$MeOC_6H_4$	**3h+3h′**	80 (78)	95:5
9	**2i**	Ph	4-ClC_6H_4	**3i+3i′**	100 (94)	93:7
10	**2j**	Ph	4-MeC_6H_4	**3j+3j′**	82 (78)	94:6
11	**2k**	Ph	2-Furyl	**3k+3k′**	78 (70)	94:6
12	**2l**			**3l+3l′**	70 (65)	93:7
13	**2m**			**3m+3m′**	96 (90)	98:2
14	**2n**			**3n+3n′**	87 (84)	98:2

[a)] In all cases, 5.0 equiv. of $TMSCF_3$ (**1**) and 1.1 equiv. of CsF were used. [b)] Yield was determined by ^{19}F NMR spectroscopy using $C_6H_5CF_3$ as internal standard. Isolated yield in the brackets. [c)] Diastereomeric ratio was determined by ^{19}F NMR spectroscopic analysis of the crude reaction mixture.

initiator dramatically improved the yield, while imparting high diastereoselectivities (Table 1, entries 3-10). Gratifyingly, when 1.1 equiv. of CsF and 5.0 equiv. of $TMSCF_3$ were used for the reaction at 0 °C for 5 h, a quantitative yield determined by ^{19}F NMR spectroscopy (98% isolated yield after flash chromatography) and high diastereoselectivity (**3a:3a′** = 93:7) were obtained (Table 1, entry 7). Decreasing the amount of CsF to 0.5 equiv. or performing the reaction at -20 °C resulted in a significant reduction of the yield (Table 1, entries 9-10). Among the solvents tested, THF was proven to be the best solvent for this reaction (Table 1, entries 7 and 11-14). A further evaluation of the various Lewis

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base initiators indicated that CsF proved be the optimal one for this trifluoromethylation, although *t*BuOk was also found to promote the reaction efficiently (Table 1, entries 7 and 15-22). It is worth noting that the use of 5.0 equiv. of $TMSCF_3$ is essential for obtaining high yields of the addition product (Table 1, entries 4-8).

Having identified the optimal reaction conditions (Table 1, entry 7), the substrate scope and generality of the direct asymmetric trifluoromethylation reaction was then investigated with a wide range of electronically and sterically diverse α,β-unsaturated *N*-*tert*-butanesulfinyl ketimines **2**.[13] As shown in Table 2, the regio- and diastereoselective trifluoromethylation reaction of α,β-unsaturated ketimines **2** proved to be surprisingly general. All the reactions took place readily in a 1,2-addition manner and afforded the corresponding α-tertiary trifluoromethyl allylic amines in good to high yields and with excellent diastereoselectivities. The electronic properties of the substituents on the phenyl ring of **2** did not have any significant effect on the stereochemical outcome of the reaction (Table 2, entries 1-5 and 8-10). However, the trifluoromethylation of ketimine **2e** gave only a moderate yield, which is believed to be a consequence of the decreased reactivity of the ketimine **2e** due to the presence of the strong electron-donating effect of *para*-methoxy substituent (Table 2, entry 5). The heteroaryl substituted ketimines are also tolerated in the trifluoromethylation reaction; however, the trifluoromethylation of ketimine **2f**, where R^1 is a furyl substituent, resulted in a moderate diastereoselectivity (Table 2, entries 6 and 11). The alkyl substituted ketimine **2g** was also suitable for this trifluoromethylation reaction, affording the corresponding product **3g** in high yield and with excellent diastereoselectivity (96% *de*) (Table 2, entry 7). However, the trifluoromethylation of β-alkyl substituted ketimines (R^2 = alkyl) was very complex and no product formation could be observed. This is mainly because of the basicity of the CF_3 anion.[14] It is evident that the substitution at the α-position of ketimine **2l** by a methyl group has no influence on the diastereoselectivity of the reaction (Table 2, entry 12). It is worth mentioning that the synthetically versatile propargylic amines[15] and homoallylic propargylic amines[5] which bear a tetrasubstituted carbon stereogenic center with a trifluoromethyl group can also be obtained by the trifluoromethylation of the α,β-acetylenic ketimines **2m** and **2n** in high yields and with excellent diastereoselectivities (Table 2, entries 13-14).

The absolute configuration of the product **3a** was assigned as (*Rs*, *R*) upon the removal of the *N*-sulfinyl group under acidic conditions, followed by the comparison of the optical rotation with that of a known compound.[5,16] The absolute configurations of the products **3b–n** were assigned by analogy. It should be noted that comparing to the addition of organolithium reagents to trifluoromethyl α,β-unsaturated *N*-*tert*-butanesulfinyl ketimines (Scheme 1, eq. a),[5] the direct trifluoromethylation of nonfluorinated α,β-unsaturated *N*-*tert*-butanesulfinyl ketimines produced the opposite *R* configuration products predominantly for the newly created stereogenic center by using the same configured *N*-*tert*-butanesulfinyl amide (Scheme 1, eq. b), thus providing an alternative and complementary method for the asymmetric synthesis of either stereoisomer of α-tertiary trifluoromethyl allylic amines. Based on the observed diastereofacial selectivity, it is proposed that a cyclic six-membered transition state is formed, wherein the bulky *tert*-butyl group preferentially adopts an equatorial position and the trifluoromethide ion preferably attacks the less hindered *Si* face of the α,β-unsaturated ketimines **2** (Figure 1). The stereocontrol mode of the current diastereoselective trifluoromethylation of the α,β-unsaturated ketimines is completely opposite to the previously reported nucleophilic fluoroalkylation of *N*-*tert*-butanesulfinyl aldimines (nonchelation controlled mode),[8a-d,11,17] but similar to that of the previous precedents for the indirect mono- and difluoromethylation of *N*-*tert*-butanesulfinyl ketimines.[18] However, the exactly underlying reaction pathway of the diastereoselective trifluoromethylation of α,β-unsaturated ketimines **2** depicted in this study is still elusive.

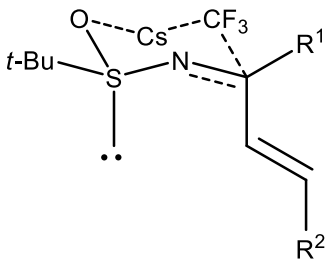

Figure 1. Proposed transition state for the CsF-mediated direct trifluoromethylation of α,β-unsaturated *N*-*tert*-butanesulfinyl ketimines with $TMSCF_3$..

In summary, we have successfully developed the first direct asymmetric trifluoromethylation of α,β-unsaturated *N*-*tert*-butanesulfinyl ketimines with the Ruppert-Prakash reagent. The reaction is highly regio- and diastereoselective. A variety of structurally diverse chiral α-tertiary trifluoromethyl allylic amines can be obtained in good to high yields and with excellent diastereoselectivities using this reaction scheme, thus providing an alternative and complementary method to our previously developed protocol.[5] These α-tertiary trifluoromethyl allylic amines represent potentially useful structural motifs for the synthesis of a variety of bioactive compounds.[5] The stereocontrol mode of the present diastereoselective trifluoromethylation of the α,β-unsaturated ketimines suggested the involvement of a cyclic six-membered transition state in the reaction. This is in sharp contrast to the previously reported nucleophilic trifluoromethylation of *N*-*tert*-butanesulfinyl aldimines. Further studies to clarify the reaction mechanism and expand the substrate

scope of this methodology are currently in progress in our laboratory.

Experimental Section

General procedure for the asymmetric trifluoromethylation of α,β-unsaturated *N-tert*-butanesulfinyl ketimines 2 with $TMSCF_3$ 1

In a glove box, α,β-unsaturated *N-tert*-butanesulfinyl ketimines (***R***)-**2** (0.1 mmol) and CsF (0.11 mmol) were added to a reaction tube that is equipped with a stirring bar. The tube was capped with a septum and taken out. Under an atmosphere of N_2, THF (2.0 mL) was added and the mixture was stirring for 10 minutes at 0ºC. Next, $TMSCF_3$ **1** (0.5 mmol) was added by syringe and the reaction solution was stirred at 0ºC for 5 h then quenched with saturated aqueous NH_4Cl solution (2 mL). The resulting mixture was extracted with EtOAc (10 mL x 3). The combined organic solution was dried over Na_2SO_4. After the removal of volatile solvents under vacuum, the crude product was further purified by silica gel column chromatography (petroleum ether / EtOAc = 5:1 as eluent) to give product **3**.

Acknowledgements

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Diastereoselective Trifluoromethylation of Chiral α,β-Unsaturated *N*-*tert*-Butanesulfinyl Ketimines with Ruppert-Prakash Reagent: Asymmetric Synthesis of α-Tertiary Trifluoromethyl Allylic Amines

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