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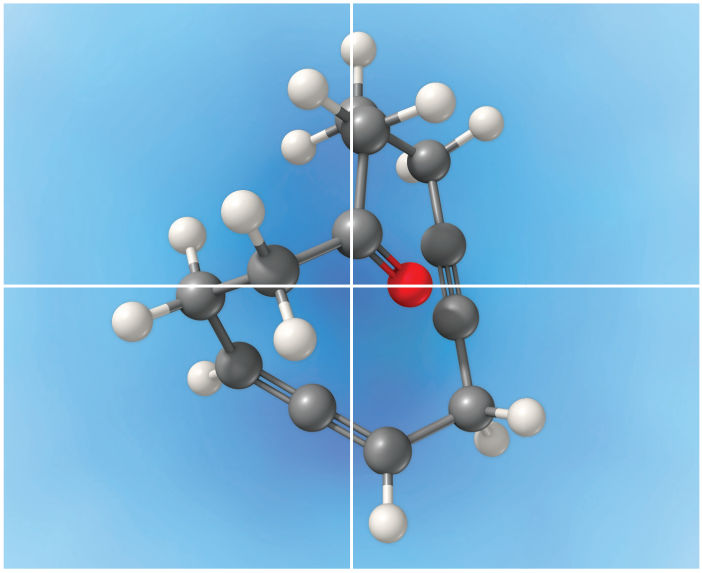

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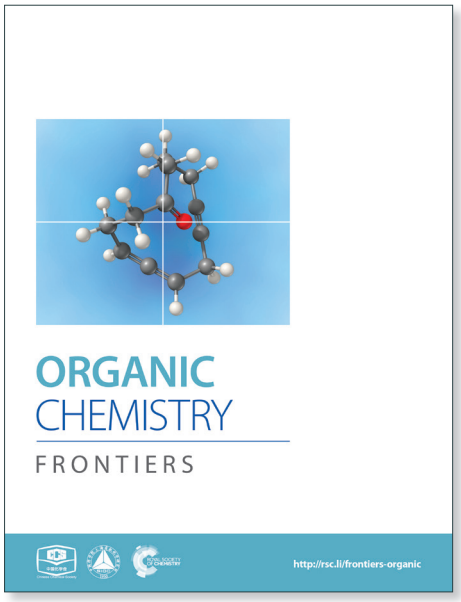

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ARTICLE TYPE

Solvent-controlled Nucleophilic Trifloromethylthiolation of Morita-Baylis-Hillman Carbonates: Dual Roles of DABCO in Activating the Zard's Trifluoromethylthiolation Reagent and the MBH Carbonates

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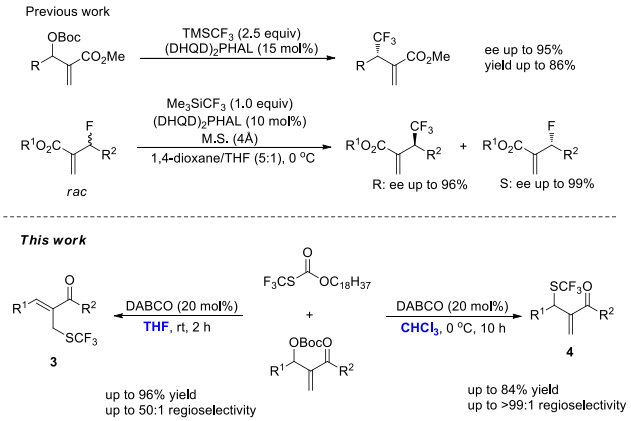
A novel amine-catalyzed nucleophilic trifloromethylthiolation between Morita-Baylis-Hillman carbonates and O-octadecyl-S-trifluorothiolcarbonate has been developed. The regioselectivity of this reaction can be controlled by choosing different solvent, affording primary allylic SCF_3 products in THF and secondary allylic SCF_3 products in $CHCl_3$ as major products. The mechanistic investigation indicated that DABCO plays dual roles in activating the Zard's trifluoromethylthiolation reagent and the MBH carbonates.

Fluorinated functional groups are key structural motifs found in various agrochemicals and pharmaceuticals.[1] Approximately 30% of all agrochemicals and 20% of all pharmaceuticals on the market contain fluorine. Hence, the development of efficient methods for the selective introduction of fluorine into organic molecules has already become one of the hottest fields in modern chemistry.[2] Among these substituents, the trifluoromethylthio group (CF_3S-) plays an important part because of its high lipophilicity and strong electron-withdrawing effect. These characteristics have the similarity with those of trifluoromethyl (CF_3-) and trifluoromethoxy (CF_3O-) groups.[3] Although impressive progress has been made in the formation of C(sp^2)-SCF_3 bond in the past several years, the methods for the direct formation of C(sp^3)-SCF_3 bonds has been less developed. Thus far, the successful examples included: 1) the trifluoromethylthiolations of β-ketoesters with electrophilic trifluoromethylthiolation reagents;[4] 2) Lewis acid mediated difunctionalization of alkene with electrophilic trifluoromethylthiolation reagents;[5] 3) the substitution reactions of aliphatic halides with nucleophilic trifluoromethylthiolation reagents;[6] and 4) copper-mediated trifluoromethylthiolations of α-diazo compounds with $AgSCF_3$, etc.[7]

Lewis bases are widely used to catalyze asymmetric allylic alkylation using Morita-Baylis-Hillman (MBH) adducts as electrophiles, through a S_N2'/S_N2' cascade and this synthetic method has emerged as a powerful strategy for the construction of multifunctional compounds.[8] Recently, this synthetic method has been used to synthesize organofluorine compounds. For example, Shibata and Jiang have independently reported $(DHQD)_2PHAL$-catalyzed asymmetric allylic trifluoromethylation of Morita-Baylis-Hillman carbonates using Rupert-Prakash reagent (Scheme 1).[9] Moreover, Shibata has also reported a $(DHQD)_2PHAL$-catalyzed kinetic resolution of allyl fluorides to synthesize chiral allyl fluorides and trifluoromethylated compounds (Scheme 1).[10] To the best of our knowledge, only one case of forming the C(sp^3)–SCF_3 bond using Lewis bases catalyzed S_N2'/S_N2' substitution has been reported during the preparation of this manuscript.[11] With these precedents in mind and in connection with our ongoing efforts on developing novel reactions using nitrogen-containing Lewis bases as nucleophilic catalysts, we envisaged that an appropriate nucleophilic SCF_3 reagent could be utilized in the direct introduction of a SCF_3 unit in a catalytic manner. Herein, we report the solvent-controlled allylic trifluoromethylthiolation reaction of MBH adducts catalyzed by DABCO.



Scheme 1. Amine catalyzed allylic alkylation of MBH adducts for synthesizing fluorine-bearing compounds

We began our studies on the direct allylic trifluoromethylthiolation of MBH carbonates by utilizing *O*-octadecyl-*S*-trifluorothiolcarbonate ($CF_3SCO_2C_{18}H_{37}$) as the nucleophilic trifluoromethylthiolation reagent in the presence of DABCO.[12] We chose *O*-octadecyl-*S*-trifluorothiolcarbonate as the SCF_3 source based on two factors described as following: 1) *O*-octadecyl-*S*-trifluorothiolcarbonate is an efficient, cheap, air-stable, and easily available reagent; 2) *O*-octadecyl-*S*-trifluorothiolcarbonate can be activated by amine to generate trifluoromethylthiolate anion *in situ*. The results are summarized in Table 1. We found that primary allylic SCF_3 product **3a** was obtained in 40% yield as a major product along with concomitant formation of secondary allylic SCF_3 product **4a** in 14% yield when the reaction was carried out in CH_3CN under the catalysis of DABCO (20 mol %) at room temperature for 2 h (Table 1, entry 1). Instead of DABCO, other commonly used Lewis bases such as DMAP, DBU, Et_3N and PPh_3 were also tested; however, no reaction occurred under the same reaction conditions. Further solvent screening indicated that 1) primary allylic SCF_3 product **3a** was obtained favourably in THF; 2) the reaction afforded secondary allylic SCF_3 product **4a** as major product in halohydrocarbon solvent. For example, using $CHCl_3$ as the solvent afforded the corresponding secondary allylic SCF_3 product **4a** in 47% yield along with a ratio of **4a**:**3a** = 23.0:1 (Table 1, entries 2-8). In THF, **3a** was formed exclusively (Table 1, entries 9-11). When the reaction was carried out in THF, lowering the temperature to 0 °C did not improve the yield of product **3a** (Table 1, entry 10). However, increasing the amount of *O*-octadecyl-*S*-trifluorothiolcarbonate to 2.0 equiv, the corresponding primary allylic

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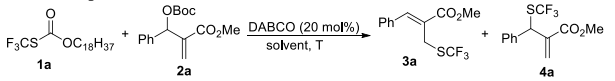
SCF_3 product **3a** was obtained in 90% yield in THF (Table 1, entry 11). When $CHCl_3$ was chose as solvent, lowering the temperature to 0 °C and increasing the amount of *O*-octadecyl-*S*-trifluorothiolcarbonate to 2.0 equiv, the corresponding secondary allylic SCF_3 product **4a** was obtained in 71% yield along with a ratio of **4a**:**3a** = 26.0:1 (Table 1, entry 13).

Table 1. Optimization of the Reaction Conditions



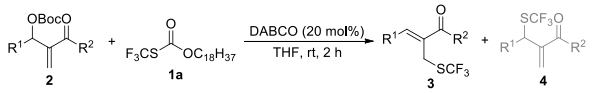
1a 2a 3a 4a

entry[a]	solvent	T (°C)	yield of **3a** (%)[c]	yield of **4a** (%)[b]	**3a**:**4a**
1	CH_3CN	rt	40	14	2.9:1
2	toluene	rt	40	31	1.3:1
3	DMF	rt	5	-	-
4	EtOAc	rt	54	-	-
5	n-hexane	rt	13	18	1:1.4
6	CH_2ClCH_2Cl	rt	13	39	1:3.0
7	CH_2Cl_2	rt	2	40	1:20
8	$CHCl_3$	rt	2	47	1:23.0
9	THF	rt	74	-	-
10[d]	THF	0	50	-	-
11[e]	THF	rt	90	-	-
12[d]	$CHCl_3$	0	2	50	1:25.0
13[d, e]	$CHCl_3$	0	3	71	1:26.0

[a]**2a** (0.05 mmol) and **1a** (0.05 mmol) were mixed in 0.5 mL of solvent. DABCO (20 mol%) was added and the mixture was stirred further for two hours. [b,c]The yields were determined using ^{1}H NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard. [d] The reaction time was prolonged to 10 hours. [e]2.0 eq **1a** was used.

With the optimized reaction conditions in hand, we next investigated the generality of this allylic trifluoromethylthiolation for synthesizing primary allylic SCF_3 products (Table 2). As for MBH carbonates **2b** and **2c**, the reaction afforded the desired products **3b** and **3c** with excellent yields and regioselectivities (Table 2, entries 1-2). However, when R^1 was 4-BrC_6H_4 or 4-$NO_2C_6H_4$ and methyl ester group was changed to *t*-butyl ester group, the corresponding products **3d** and **3f** were obtained in lower yields along with lower regioselectivities, presumably due to the steric hindrance (Table 2, entries 3 and 5). For MBH carbonates **2g** and **2h** having an electron-rich aromatic group, the reaction could not acquire good regioselectivities, perhaps due to the electronic effects (Table 2, entries 6-7). Using MBH carbonate **2i** containing a 2-bromophenyl group, the corresponding product **3i** was obtained in 90% yield and 25:1 regioselectivity (Table 2, entry 8). We were also pleased to find that MBH carbonates bearing naphthalenyl group and heteroaromatic group were also suitable for this reaction, affording the corresponding products **3j**-**3n** in good yields and good regioselectivities (Table 2, entries 9-13). The structure of product **3l** was confirmed by X-ray diffraction and its ORTEP drawing is shown in Figure 1 (see Supporting Information for the CIF data). Notably, the reaction afforded product **3o** in 96% yield and 50.0:1 regioselectivity as for vinyl methyl ketone derived MBH carbonate **2o** (Table 2, entry14).

Table 2. Substrate Scope for DABCO-catalyzed Primary Allylic Trifluoromethylthiolation Reaction of MBH Adducts.



2 1a 3 4

entry[a]	R^1, R^2	yield of **3** (%)[b]	**3**:**4**[c]
1	**2b**, 4-ClC_6H_4, OMe	**3b**, 93	40.0:1
2	**2c**, 4-CNC_6H_4, OMe	**3c**, 91	42.0:1
3	**2d**, 4-BrC_6H_4, O^{t}Bu	**3d**, 50	1.1:1
4	**2e**, 4-BrC_6H_4, OMe	**3e**, 94	60.0:1
5[d]	**2f**, 4-$NO_2C_6H_4$, O^{t}Bu	**3f**, 61	10.0:1
6	**2g**, 4-$MeOC_6H_4$, OEt	**3g**, 47	1.4:1
7	**2h**, 3-MeC_6H_4, OMe	**3h**, 80	5.0:1
8	**2i**, 2-BrC_6H_4, OMe	**3i**, 90	25.0:1
9	**2j**, 1-naphthalenyl, OMe	**3j**, 91	18.0:1
10	**2k**, 2-naphthalenyl, OMe	**3k**, 89	15.0:1
11	**2l**, 2-thienyl, OMe	**3l**, 94	32.0:1
12	**2m**, 2-furyl, OMe	**3m**, 75	38.0:1
13	**2n**, 2-pyridyl, OMe	**3n**, 87	49.0:1
14	**2o**, Ph, Me	**3o**, 96	50.0:1

[a]**2** (0.2 mmol) and **1** (0.4 mmol) were mixed in 2.0 mL of THF. DABCO (20 mol%) was added and the mixture was stirred further for two hours at rt. [b]Isolated yields. [c]The ratios of **3**:**4** were determined by ^{1}H NMR spectroscopic data of the crude products. [d]Z:E = 16.3:1.

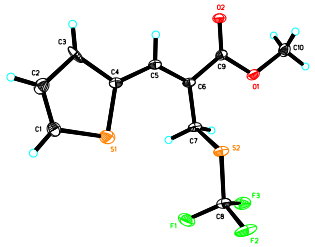
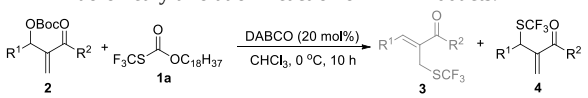


Figure 1. ORTEP drawing of **3l**

Under the optimized reaction conditions, we next investigated the generality of this allylic trifluoromethylthiolation for synthesizing secondary allylic SCF_3 products and the results are summarized in Table 3. When R^1 was 4-ClC_6H_4 or 4-NCC_6H_4 for MBH carbonate **2b** or **2c**, the reaction proceeded smoothly to give the corresponding trifluoromethylthiolated products **4b** or **4c** in 84% yield and 46% yield, respectively, but the regioselectivity for MBH carbonate **2c** was not ideal, suggesting that the substituent on the phenyl ring plays a significant role in the reaction outcomes (Table 3, entries 1-2). The cyano substituent on the phenyl ring might have different electronic property from chlorine atom, causing the lower regioselectivity in the case of **2c**. As for MBH carbonates **2d** and **2f** having sterically hindered *t*-butyl ester group, the reaction had to be carried out at room temperature, affording the corresponding trifluoromethylthiolated products **3d** and **3f** in good yields and good regioselectivities (Table 3, entries 3 and 5). Comparing with MBH carbonates bearing electron-deficient aromatic group, the reaction of **2g** and **2h** bearing electron-rich aromatic ring with **1a** could acquire better regioselectivities (Table 3, entries 6-7). In the case of MBH carbonate **2i**, the trifluoromethylthiolated product **4i** was obtained in 79% yield and 13.0:1 regioselectivity (Table 3, entry 8). With regard to MBH carbonates **2j** and **2k** bearing naphthalenyl group, the reaction could afford the desired products **4j** and **4k** in good yields and regioselectivities (Table 3, entries 9-10). Using MBH carbonate **2l** bearing a 2-thienyl aromatic ring as substrate, the catalyst loading had to be increased to 40 mol % in order to consume the starting material completely, affording the corresponding product **4l** in 60% yield and 5:1 regioselectivity (Table 3, entry 11). When R^1 was a 2-furyl group for MBH carbonate, the reaction rate was sluggish at 0 °C, thus the reaction had to be conducted at room temperature, furnishing the corresponding product **4m** in 26% yield along with 2.1:1 regioselectivity (Table 3, entry 12). As for MBH carbonate **2n**, the corresponding product **4n** was obtained in medium yield and excellent regioselectivity, presumably due to the electronic effect (Table 3, entry 13). In the case of vinyl methyl ketone derived MBH carbonate **2o**, the reaction yielded **3o** as major product although chloroform was employed as solvent, only affording the secondary allylic SCF_3 product **4o** in 37% yield (Table 3, entry 14).

Table 3. Substrate Scope for DABCO-catalyzed Secondary Allylic Trifluoromethylthiolation Reaction of MBH Adducts.[a,b,c,d]



2 1a 3 4

entry[a]	R^1, R^2	yield of **4** (%)[b]	**4**:**3**[c]
1	**2b**, 4-ClC_6H_4, OMe	**4b**, 84	12.0:1
2	**2c**, 4-CNC_6H_4, OMe	**4c**, 46	1.6:1
3[d]	**2d**, 4-BrC_6H_4, O^{t}Bu	**4d**, 76	13.0:1
4	**2e**, 4-BrC_6H_4, OMe	**4e**, 50	20.0:1
5[d]	**2f**, 4-$NO_2C_6H_4$, O^{t}Bu	**4f**, 83	31.0:1
6[e]	**2g**, 4-$MeOC_6H_4$, OEt	**4g**, 63	50:.0:1
7	**2h**, 3-MeC_6H_4, OMe	**4h**, 84	34.0:1
8	**2i**, 2-BrC_6H_4, OMe	**4i**, 79	13.0:1
9	**2j**, 1-naphthalenyl, OMe	**4j**, 81	39.0:1
10	**2k**, 2-naphthalenyl, OMe	**4k**, 77	15.0:1
11[e]	**2l**, 2-thienyl, OMe	**4l**, 60	5.0:1
12[d]	**2m**, 2-furyl, OMe	**4m**, 26	2.1:1
13	**2n**, 2-pyridyl, OMe	**4n**, 51	>99:1
14	**2o**, Ph, Me	**4o**, 37	0.6:1

[a]**2** (0.2 mmol) and **1** (0.2 mmol) were mixed in 2.0 mL of $CHCl_3$. DABCO (20 mol%) was added and the reaction mixture was stirred further for ten hours at 0 °C. [b]Isolated yields. [c] The ratios of **3**:**4** were determined by ^{1}H NMR spectroscopic data of the crude products. [d]Carried out at rt. [e]40 mol% of DABCO was added.

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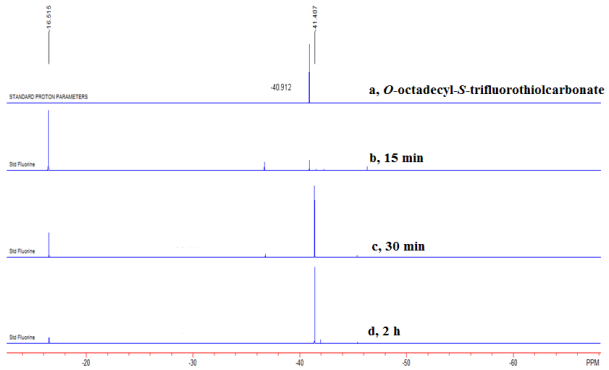
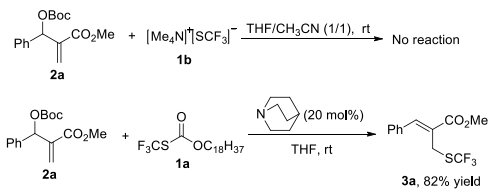


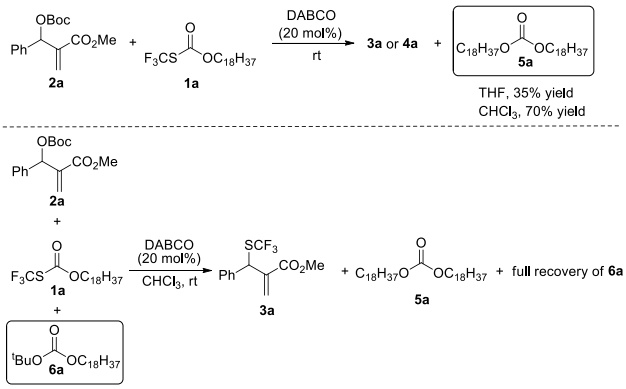
Figure 2. ^{19}F NMR spectroscopic tracing experiment (376 MHz, $CDCl_3$, $CFCl_3$): a) ^{19}F NMR spectrum of *O*-octadecyl-*S*-trifluorothiolcarbonate (δ = -40.912); b) the reaction was carried out for 15 min; c) the reaction was carried out for 30 min; d) the reaction was carried out for 2 h.

After investigating the substrate scope, we next focused on the exploration of the reaction mechanism. As reported by Deng and co-workers, tertiary amine catalyzed cyanation of ketones underwent a quaternary ammonium salt intermediate generated in situ from cyanoformate and the tertiary amine.[13] Due to the similar electronic property between *O*-octadecyl-*S*-trifluorothiolcarbonate and cyanoformate, we supposed that this allylic trifluoromethylthiolation underwent a quaternary ammonium salt intermediate as well. To verify the existence of ammonium salt intermediate, we treated **1a** (1.0 equiv), **2a** (1.0 equiv) with DABCO (1.0 equiv) in $CDCl_3$ and monitored the reaction proceeding by ^{19}F NMR spectroscopy. As shown in Figure 2, after a reaction time of 15 min, a signal at δ = -16.515 was observed. We hypothesized that this signal corresponded to the ammonium salt species generated in situ from **1a** and DABCO because it was close to the signal of $[Me_4N][SCF_3]$ in ^{19}F NMR spectrum (δ = -6.49, CD_3CN).[14] Treating **2a** with **1b** in THF/CH_3CN in the absence of DABCO, no reaction occurred, suggesting that the newly generated SCF_3 anion could not nucleophilically attack **2a** without the assistance of DABCO (Scheme 2). These experiments indicated that DABCO played dual roles in activating the Zard's trifluoromethylthiolation reagent and the MBH carbonates. When THF was chosen as solvent, the trifluoromethylthiolated product **3a** was obtained in 82% yield under the catalysis of quinuclidine, which might suggest that the mechanism of activating the Zard's trifluoromethylthiolation reagent and the MBH carbonate by the two nitrogen atoms of one DABCO molecule was unlikely (Scheme 2).

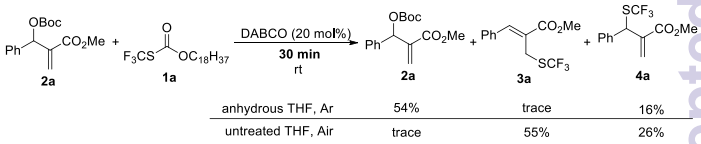


Scheme 2. Control Experiments to Probe the Reaction Mechanisms

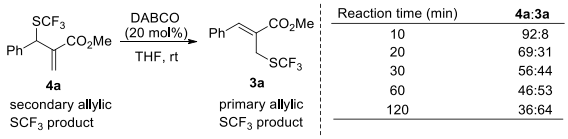
When the reaction was conducted in THF and $CHCl_3$, carbonate **5a** was isolated in 35% and 70% yields, respectively. Treating **1a**, **2a** and **6a** in $CHCl_3$ under the catalysis of DABCO, we could recover **6a** completely by silica gel column chromatography, suggesting that **6a** could not be transformed into **5a** (Scheme 3). During further exploration of the reaction mechanism, we found that water played a crucial role in the reaction. When the reaction was carried out in anhydrous THF under Ar atmosphere for 30 min, **4a** was obtained in 16% yield along with 54% of **2a** recovered after the reaction was quenched by hydrochloric acid. However, treating **1a** with **2a** in untreated THF under ambient atmosphere afforded **3a** in 55% yield along with **4a** in 26% yield (Scheme 4). Moreover, the control experiment shown in Scheme 5 indicated that **4a** can be transformed into **3a** under the catalysis of DABCO in THF, suggesting that the formation of **4a** was a kinetic-controlled process and the formation of **3a** was a thermodynamic-controlled process (Scheme 5).[15] The similar phenomenon has been also observed by Cahard and his co-workers.[11]



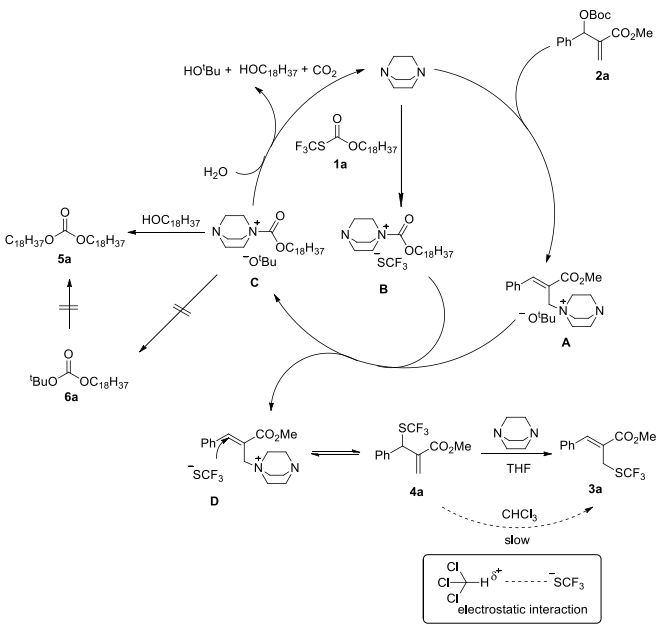
Scheme 3. The Isolation of Carbonate **5a**.



Scheme 4. The Water Effect in the Allylic Trifloromethylthiolation Reaction.



Scheme 5. The Transformations of **4a** into **3a** in THF



Scheme 6. A Proposed Mechanism

A plausible mechanism has been proposed in Scheme 6 on the basis of above investigations. The solvent-controlled allylic trifluoromethylthiolation reactions are initiated by the formation of ammonium salt intermediates **A** and **B** derived from the nucleophilic addition of DABCO to **2a** and **1a**, respectively. The exchange between SCF_3 anion and *t*-butoxyl anion delivers ammonium salt intermediates **C**

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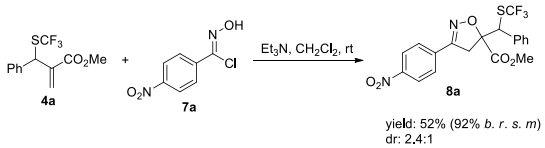
and **D**. An intermolecular S_N2' reaction converts allylammonium ion **D** to the kinetic product **4a**. Under the catalysis of DABCO, the transformation of **4a** to **3a** can take place readily in THF. However, when the reaction was conducted in $CHCl_3$, the transformation of **4a** to **3a** can hardly take place because the electrostatic interaction between SCF_3 anion and $CHCl_3$ weakens the nucleophilicity of SCF_3 anion. The nucleophilic attack of H_2O to ammonium salt intermediate **C** yields *tert*-butanol, *N*-octadecanol, carbon dioxide and regenerates DABCO for the catalytic cycle. Carbonate **5a** is generated via the nucleophilic addition of *N*-octadecanol to ammonium salt intermediate **C**, but carbonate **6a** can not be formed because of the weak nucleophilicity of *t*-butoxyl anion.

Furthermore, the product **4a** could be smoothly transformed into isoxazole **8a** incorporating a SCF_3 group as a diastereoisomeric mixtures via a 1,3-dipolar cycloaddition (Scheme 7).



Scheme 7. The Transformations of **4a** into **8a**

In summary, we have developed a novel amine-catalyzed nucleophilic trifloromethylthiolation between Morita-Baylis-Hillman carbonates and *O*-octadecyl-*S*-trifluorothiolcarbonate under mild conditions. The regioselectivity of this reaction can be controlled by choosing different solvent, affording primary allylic SCF_3 products in THF and secondary allylic SCF_3 products in $CHCl_3$ as major products. The mechanistic investigation showed that DABCO plays dual roles in activating the Zard's trifluoromethylthiolation reagent and the MBH carbonates. Various cinchona alkaloids derived catalysts did not catalyze this reaction. Therefore, at the present stage, we did not get any success in the asymmetric version of this reaction. Nevertheless, the asymmetric variant of this reaction will be further explored in our laboratory.

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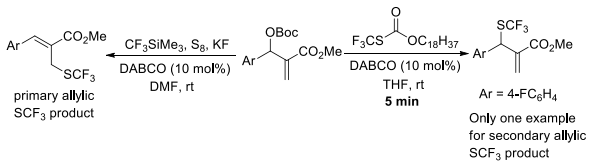

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