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# Preparation of trifluoromethylated ynamines and their reactions with some electrophilic reagents

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**Abstract**—*N*,*N*-Dialkyl(3,3,3-trifluoro-1-propynyl)amines were prepared by a three-step procedure starting from commercially available 2,2,3,3,3-pentafluoropropanol. The reactions of these trifluoromethylated ynamines with some electrophiles, such as aldehydes, halogens or *N*-halosuccinimides (NXS), were investigated. The fluorinated ynamines reacted with aldehydes in the presence of a catalytic amount of Lewis acid to provide the corresponding α-(trifluoromethyl)-α,β-unsaturated amides in good to excellent yields with high *Z*-stereoselectivity. These ynamines reacted with molecular bomine to give, after treatment with sodium hydrogen carbonate, *N*,*N*-dialkyl-2-bromo-3,3,3-trifluoropropanamides in good yields. The reaction with an equimolecular amount of NXS in aqueous acetonitrile also gave the corresponding 2-halo-3,3,3-trifluoropropanamides in good to excellent yields. On the other hand, the reaction of the ynamine with NXS in anhydrous acetonitrile led to the formation of the addition products in high yields. Upon treating the addition products with an equimolecular amount of NX′S in aqueous acetonitrile, the corresponding 2,2-dihalo(X,X′)-3,3,3-trifluoropropanamides were produced in nearly quantitative yields.


## 1. Introduction

*N*,*N*-Disubstituted-1-alkynylamines, the common name 'ynamines,' are regarded as the alkynes activated through the interaction of the amino group linked directly to a triple bond, and thereby liable to undergoing the reactions with a variety of electrophiles. Many kinds of ynamines have hitherto been prepared and utilized in organic synthesis.[1–5] Although fluorine-containing counterparts are expected to be useful building blocks for preparing various organofluorine compounds, there are found few or no reports on their preparations and synthetic applications[6,7] in the literature. On the other hand, the theoretical data obtained from the MO calculations for *N*,*N*-dimethyl-3,3,3-trifluoro-1-propynylamine as well as *N*,*N*-dimethyl-1-propynylamine inform us with the differences in electronic states between these ynamines, as shown in Figure 1. These situations prompted us to develop the method for the preparation of trifluoromethylated ynamines, *N*,*N*-dialkyl(3,3,3-trifluoro-1-propynyl)amines (**2**), by use of commercially available 2,2,3,3,3-pentafluoropropanol, and to examine their reactivities toward several electrophilic reagents.[8–12]

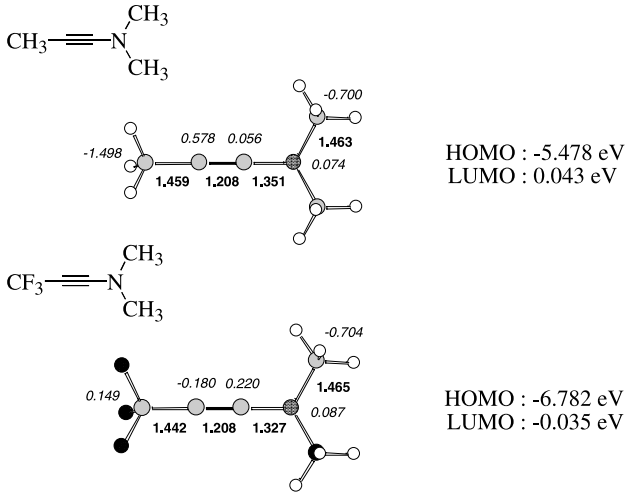


**Fig. 1.** MO calculations for nonfluorinated and fluorinated ynamines.

In this paper, we wish to describe the practical methods for the preparation of the trifluoromethylated ynamines **2** and the results of their reactions with several electrophiles, such as aldehydes, halogens, and *N*-halosuccinimides (NXS), leading to α-(trifluoromethyl)-α,β-unsaturated amides, 2-halo- and 2,2-dihalo-3,3,3-trifluoropropanamides, which are

*Keywords*: Ynamine; Carbonyl compound; Halogen; *N*-Halosuccinimide; α-Trifluoromethyl-α,β-unsaturated amide; 2-Halo-3,3,3-trifluoropropanamide; 2,2-Dihalo-3,3,3-trifluoropropanamide; Trifluoromethylated cyclobutene cyanine.
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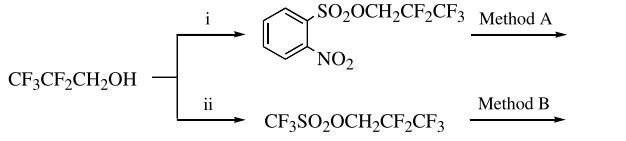
exceedingly valuable and fundamental synthons for the construction of trifluoromethylated carbon frameworks.[13–17]

## 2. Results and discussion

### 2.1. Preparation of the trifluoromethylated ynamines 2

*N*,*N*-Dialkyl(2,2,3,3,3-pentafluoropropyl)amines (**1**) were chosen as the precursors of the trifluoromethylated ynamines **2**. The amines **1** were prepared by the two different procedures starting from commercially available 2,2,3,3,3-pentafluoropropanol, as shown in Scheme 1. The polyfluoro alcohol was converted into the sulfonate esters by the reaction with *o*-nitrobenzenesulfonyl chloride and NaOH in $H_2O$ at 60 °C for 2 h (98%)[18] or by the reaction with trifluoromethanesulfonic anhydride at reflux temperature for 3 h (84%).[19] *o*-Nitrobenzenesulfonate and trifluoromethanesulfonate were subjected to the Hofmann-like degradation reaction with *N*,*N*-dimethylbenzylamine[20] (Method A) or polyfluoroalkylation of a secondary amine (Method B).




$CF_3CF_2CH_2NR_2$

**1a-d**

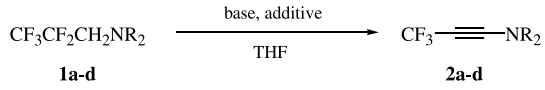
R = Bu (**a**), Me (**b**), -$(CH_2)_5$- (**c**), *i*-Pr (**d**)

i: *o*-nitrobenzenesulfonyl chloride, NaOH/$H_2O$, 60 °C, 2 h.
ii: $(CF_3SO_2)_2O$, neat, reflux, 3 h.
Method A: $R_2NH$ or $BnNMe_2$, neat, 140-160 °C.
Method B: $R_2NH$, neat.

**Scheme 1.**

The degradation between *o*-nitrobenzenesulfonate and dibutylamine (Method A) provided *N*,*N*-dibutyl(2,2,3,3,3-pentafluoropropyl)amine (**1a**) in a lower yield (48%), compared with the reaction using trifluoromethanesulfonate (Method B, 93%). This trend was observed for preparing *N*-(2,2,3,3,3-pentafluoropropyl)piperidine (**1c**) by the reactions of *o*-nitrobenzenesulfonate and trifluoromethanesulfonate. Such trends in the yields of **1** are attributable to the difference in reactivity between the two sulfonate esters. Worth remarking is that the degradation reaction between *o*-nitrobenzenesulfonate and excess *N*,*N*-dimethylbenzylamine (3 equiv) (Method A) is recommended for obtaining *N*,*N*-dimethyl-(2,2,3,3,3-pentafluoropropyl)amine (**1b**) in good yield.[20] *N*,*N*-Diisopropyl-(2,2,3,3,3-pentafluoropropyl)amine (**1d**) was obtained in 45% yield according to Method B.

These fluorinated amines **1** could be converted into the desired ynamines **2** by dehydrofluorination with a base (Scheme 2). The results are summarized in Table 1. The reaction of **1a** with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at 0 °C for 2 h gave the ynamine **2a** in 14% yield, together with 75% of the starting amine **1a** recovered (entry 1). The reaction conducted at room




**1a-d** **2a-d**

**Scheme 2.**

**Table 1**. Preparation of **2** from the tertiary amines **1**

| Entry | **1** | Base (2.2 equiv) | Additive (2.2 equiv) | Temperature (°C) | Time (h) | Yield of **2** (%)[a] |
|---|---|---|---|---|---|---|
| 1 | **1a** | LDA | None | 0 | 2 | 14 |
| 2 | **1a** | LDA | None | Room temperature | 2 | 47 |
| 3 | **1a** | LDA | None | Room temperature | 24 | 66 |
| 4 | **1a** | LDA | DMPU | 0 | 2 | 84 |
| 5 | **1a** | LDA | DMPU | Room temperature | 2 | 94 (75) |
| 6 | **1a** | BuLi | None | Room temperature | 2 | 5 |
| 7 | **1a** | *t*-BuOK | None | Room temperature | 24 | 23[b] |
| 8 | **1b** | LDA | DMPU | 0 | 2 | 92 |
| 9 | **1c** | LDA | DMPU | Room temperature | 2 | 97 |
| 10 | **1d** | LDA | DMPU | Room temperature | 24 | 66 |

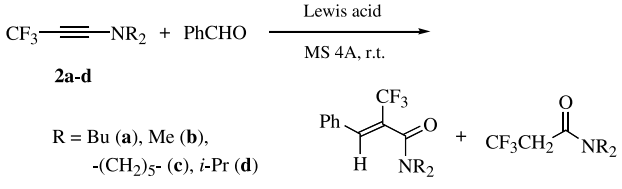
[a] Measured by $^{19}F$ NMR. Value in parentheses is of isolated yield.
[b] *N*,*N*-Dibuty(2,3,3,3-tetrafluoro-1-propenyl)amine was given in 33% yield.

temperature and/or for a long reaction period resulted in increasing the yields of **2a** (entries 2 and 3). The use of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) as an additive permitted the reaction to proceed very efficiently (entries 4 and 5). Other bases, such as butyllithium and potassium *t*-butoxide, were not so useful for the reaction (entries 6 and 7). *N*,*N*-Dialkyl(3,3,3-trifluoropropynyl)amines **2b–d** were also prepared by the reactions of **1b–d** with LDA in THF–DMPU at 0 °C or room temperature, as shown in entries 8–10.

It should be mentioned that all of these ynamines **2** are highly susceptible to hydrolysis under acidic conditions.[12] Thus, on simple treatment of **2** with a 5% HCl aqueous solution at ambient temperature for 15 min, the corresponding *N*,*N*-dialkyl-3,3,3-trifluoropropanamides **4** were produced in 65–90% yields.

### 2.2. Reaction of the ynamines 2 with carbonyl compounds

The reaction of **2a** with benzaldehyde was initially investigated under various conditions, as shown in Scheme 3, and the results are summarized in Table 2.




**2a-d**

R = Bu (**a**), Me (**b**), -$(CH_2)_5$- (**c**), *i*-Pr (**d**)

**3aa-3da** **4a-d**

**Scheme 3.**

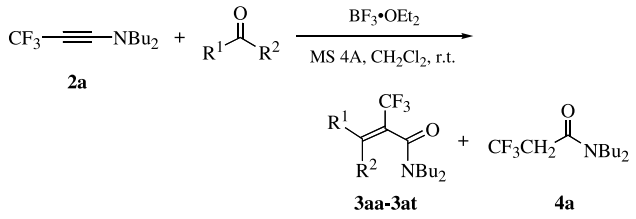
**Table 2**. Reaction of the ynamines **2** with benzaldehyde

| Entry | 2 | Lewis acid[a] | Solvent | Time (h) | Yield of **3a** (%)[b] |
|---|---|---|---|---|---|
| 1 | **2a** | None | $CH_2CL_2$ | 24 | 3 |
| 2 | **2a** | $BF_3\cdot OEt_2$ | $CH_2CL_2$ | 1 | 92 |
| 3[c] | **2a** | $BF_3\cdot OEt_2$ | $CH_2CL_2$ | 1 | 28 |
| 4 | **2a** | $ZnBr_2$ | $CH_2CL_2$ | 1 | 90 |
| 5 | **2a** | $TiCl_4$ | $CH_2CL_2$ | 1 | 80 |
| 6 | **2a** | $SnCl_4$ | $CH_2CL_2$ | 1 | 81 |
| 7 | **2a** | $BF_3\cdot OEt_2$ | Toluene | 1 | 84 |
| 8 | **2a** | $BF_3\cdot OEt_2$ | $Et_2O$ | 1 | 82 |
| 9 | **2a** | $BF_3\cdot OEt_2$ | THF | 1 | 82 |
| 10[c] | **2a** | $La(OTf)_3$[d] | $CH_2CL_2$ | 24 | 71 |
| 11[c] | **2b** | $La(OTf)_3$[d] | $CH_2CL_2$ | 24 | 65 |
| 12[c] | **2c** | $La(OTf)_3$[d] | $CH_2CL_2$ | 24 | 73 |
| 13 | **2d** | $BF_3\cdot OEt_2$ | $CH_2CL_2$ | 1 | 40 |

[a] Lewis acid (0.1 equiv) used, unless otherwise noted.
[b] Isolated yields.
[c] Without MS 4 Å.
[d] $La(OTf)_3$ (0.3 equiv) used.

The treatment of **2a** with benzaldehyde in dichloromethane ($CH_2Cl_2$) in the presence of molecular sieves 4 Å (MS 4 Å) revealed little or no evidence of reaction. Workup of this reaction mixture with a 5% HCl aqueous solution afforded *N*,*N*-dibutyl-3,3,3-trifluoropropanamide (**4a**) and the corresponding α-(trifluoromethyl)-α,β-unsaturated amide **3aa** in 79 and 3% yield, respectively (entry 1). The addition of boron trifluoride etherate ($BF_3\cdot OEt_2$) (0.1 equiv) as a Lewis acid promoted the reaction effectively, leading to a high yield of the amide **3aa** as an isomeric mixture of *Z*/*E*=>97:<3 (entry 2). MS 4 Å was requisite to suppress the formation of **4a**, which may be based upon the acidic hydration with a small quantity of water contaminating **2a**. $^{19}F$ NMR analysis of the reaction in the absence of MS 4 Å revealed the in situ formation of **4a** (66%) as well as **3aa** (28%) (entry 3). Zinc bromide, titanium(IV) chloride, and tin(IV) chloride were applicable to the reaction, giving good yields of **3aa** (entries 4–6). Toluene, diethyl ether, and THF could be used as the solvents (entries 7–9). In addition, lanthanum(III) triflate, known to be hard to hydrolysis,[21] was effective for the reaction of **2a** without MS 4 Å, affording an acceptable result (entry 10). The similar reaction of **2b** or **2c** with benzaldehyde in the presence of $La(OTf)_3$ offered the corresponding α,β-unsaturated amides **3ba** and **3ca** in fairly good yields with high *Z*-stereoselectivity (entries 11 and 12). The ynamine **2d** reacted reluctantly in the presence of $BF_3\cdot OEt_2$ to give the amide **3da** in 40% yield (entry 13). It is likely that the bulky isopropyl groups on the nitrogen of **2d** are responsible for low efficiency of the reaction.

Next, the reactions of **2a** with other aldehydes or ketones were carried out by using $BF_3\cdot OEt_2$ as a Lewis acid and $CH_2Cl_2$ as a solvent (Scheme 4). Various sorts of aldehydes, such as aromatic, heteroaromatic, α,β-unsaturated, and aliphatic aldehydes, were made to react with **2a** in the presence of 0.1 equiv of $BF_3\cdot OEt_2$ and MS 4 Å in $CH_2Cl_2$ at room temperature for 1 h, and the usual workup provided the corresponding α-(trifluoromethyl)-α,β-unsaturated amides **3ab–at** in 75–97% yields. Of synthetic value is that the reactions of **2a** with aldehydes, except 2,2-dimethylpropanal, occurred in a highly stereoselective fashion to give the (*Z*)-isomers of **3a** predominantly

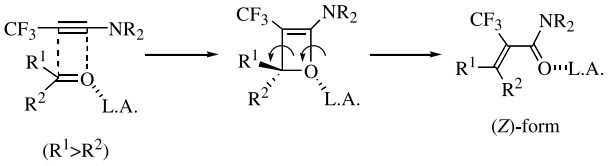



$R^1$, $R^2$ = Ph, H (**a**), *p*-$MeC_6H_4$, H (**b**), *p*-$MeOC_6H_4$, H (**c**), *p*-$ClC_6H_4$, H (**d**), 1-naphthyl, H (**e**), 2-thienyl, H (**f**), 2-furyl, H (**g**), (*E*)-PhCH=CH, H (**h**), (*Z*)-PhCH=CF, H (**i**), (*E*)-MeCH=CH, H (**j**), $CH_2$=C(Me), H (**k**), Pr, H (**l**), Hex, H (**m**), *i*-Pr, H (**n**), *c*-Hex, H (**o**), *t*-Bu, H (**p**), Me, Me (**q**), Et, Et (**r**), -$(CH_2)_5$- (**s**), Ph, Me (**t**)

**Scheme 4.**

(>96% *Z*). Although the reaction with 2,2-dimethylpropanal required 0.2 equiv of $BF_3\cdot OEt_2$ and a longer reaction time (2 h), the corresponding amide **3ap** was given in 68% yield as a mixture of *Z*/*E*=56:44. A variety of ketones, such as acetone, 3-pentanone, cyclohexanone, and acetophenone, were also found to participate in the reaction with **2a** to give the corresponding α,β-unsaturated amides **3aq–at** in 72–85% yields. All the reactions with ketones necessitated a prolonged reaction time (2 h) for obtaining satisfactory results. The reaction with acetophenone took place with an appreciably low stereoselectivity to form **3at** as a mixture of *Z*/*E*=71:29.

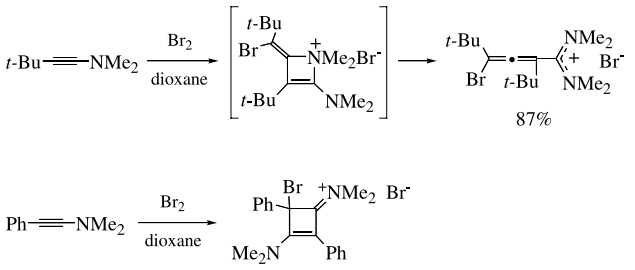
The above-cited reactions of **2** with carbonyl compounds are presumed to occur via the mechanism shown in Scheme 5, which is essentially analogous to that proposed recently for the reaction between alkynolates and carbonyl compounds.[22] Thus, the ynamine **2** may attack a carbonyl compound activated by a Lewis acid[23] to form an intermediary oxetene. This intermediate would be subject to a metathesis process in such a way that both the Lewis acid part and the substituent $R^1$ or $R^2$ ($R^1>R^2$) exert their repulsive interaction minimally, leading to the preferential formation of the (*Z*)-isomers of **3**.




**Scheme 5.**

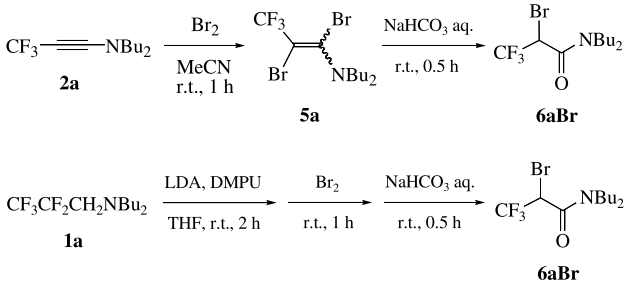
## 2.3. Reaction of the ynamines 2 with bromine or iodine

The nonfluorinated ynamines are known to undergo the unique reactions with bromine to give a different type of product depending on an alkynyl substituent, as depicted in Scheme 6. Thus, *t*-butylethynyl(dimethyl)amine reacts with bromine in dioxane to afford the corresponding allene amidinium salt,[24] and the reaction of phenylethynyl(dimethyl)amine gives rise to the cyclobutene cyanine salt.[25] Such unique behaviors of the ynamines strongly stimulated us to examine the reaction of the fluorinated ynamines **2** with bromine.



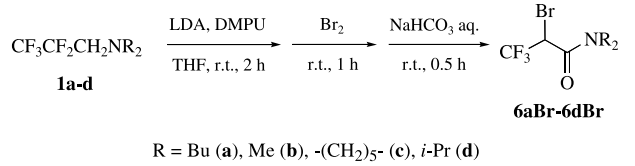
Scheme 6.

As shown in Scheme 7, when the ynamine **2a** was allowed to react with bromine (1.1 equiv) in acetonitrile (MeCN) in the presence of MS 4 Å at ambient temperature for 1 h, *N*,*N*-dibutyl(1,2-dibromo-3,3,3-trifluoro-1-propenyl)amine (**5a**) was formed quantitatively. Although the enamine **5a** was not so stable for isolation, its structural determination was made by IR and $^{13}C$ NMR analyses of the crude product after filtration and concentration of the reaction mixture. $^{19}F$ NMR analysis indicated that **5a** consisted of two geometrical isomers in a ratio of 78:22. Other solvents, such as $CH_2Cl_2$, THF, diethyl ether, and dioxane, could also be employed similarly. The resultant enamine **5a** was readily hydrolyzed to *N*,*N*-dibutyl-2-bromo-3,3,3-trifluoropropanamide (**6aBr**) by simple treatment with a saturated $NaHCO_3$ aqueous solution at room temperature for 0.5 h. In order to simplify the access to 2-bromo propanamide **6aBr**, we examined the one-pot reaction starting from **1a**, the precursor of **2a**. Thus, the amine **1a** was treated with LDA (2.2 equiv) and DMPU (2.2 equiv) in THF at room temperature for 2 h, and bromine (2.0 equiv) was successively added to the reaction mixture at 0 °C. After stirring at room temperature for 1 h, addition of a saturated $NaHCO_3$ aqueous solution, followed by a usual workup, led to the amide **6aBr** in 75% overall yield.



Scheme 7.

This one-pot reaction procedure was applicable for other amines **1b–d**, as shown in Scheme 8. The results are summarized in Table 3. The alkyl substituents at the nitrogen atom of **1** were observed to influence the yields of the amides **6Br**. The amines **1a–c** carrying a butyl, methyl and pentamethylene group provided the corresponding



Scheme 8.

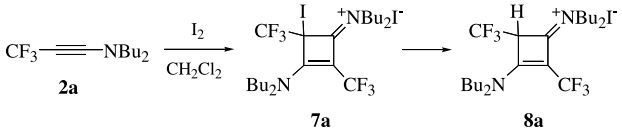
**Table 3**. The one-pot preparation of **6Br** from **1**

| Entry | R | Temperature (°C) | Yield of **6Br** (%)[a] | |
|---|---|---|---|---|
| 1 | Bu | Room temperature | **6aBr** | 75 |
| 2 | Me | 0 | **6bBr** | 64 |
| 3 | $-(CH_2)_5-$ | Room temperature | **6cBr** | 78 |
| 4 | *i*-Pr | Room temperature | **6dBr** | 37 (41) |

[a] Isolated yields. Value in parentheses stands for the recovery of **1** determined by $^{19}F$ NMR.

bromo amides **6aBr–cBr** in satisfactory yields, as shown in entries 1–3, but the amine **1d** having a bulky group, such as isopropyl, gave **6dBr** in a lower yield, along with the recovery of unchanged **1d** (entry 4).

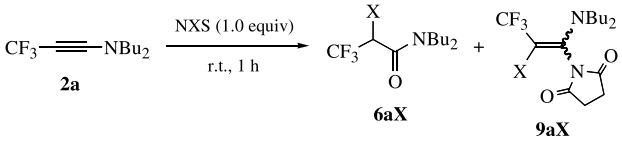
The reaction of the ynamine **2a** with iodine was also performed under the similar conditions to that with bromine. As depicted in Scheme 9, the corresponding cyclobutene cyanine **7a** was obtained in 51% yield, no addition product like **5a** being detected in the reaction mixture. The product **7a** could be isolated as a white solid and be kept for several days at ambient temperature under argon without any detectable changes. Interestingly, on standing for several days in contact with air, **7a** was deiodinated gradually to form **8a**. The mechanistic details of this transformation remain obscure at the present time. Successive treatment of the in situ formed **7a** with water gave rise to **8a** in 49% overall yield.



Scheme 9.

## 2.4. Reaction of the ynamine 2a with NXS in a water-containing solvent

We next examined the reaction of the ynamine **2a** with *N*-bromosuccinimide (NBS), which is one of the easy-handling brominating agents,[26] as shown in Scheme 10 and Table 4. When the ynamine **2a** was allowed an exposure to NBS (1.0 equiv) in water at room temperature for 1 h, the amide **6aBr** was given in 57% yield, together with 27% yield of the addition product **9aBr**, which was a mixture of two geometrical isomers in a ratio of 76:24 (entry 1). A THF–$H_2O$ (3/2 v/v) mixed solvent afforded a comparable yield of **6aBr** and an increased yield of **9aBr** (entry 2). With the reaction in acetone–$H_2O$ (3/2 v/v), the yields were appreciably decreased (entry 3). Interestingly, the use of a carbon tetrachloride–$H_2O$ (3/2 v/v) mixed solvent, a two phase solvent system, resulted in the formation of **9aBr** in preference to **6aBr** (entry 4). Eventually, the most satisfactory result was obtained for the reaction using a



Scheme 10.

**Table 4**. Reactions of **2a** with NXS in mixed solvents

| Entry | NXS | Solvent | Yield of **6aX** (%)[a] | Yield of **9aX** (%)[a] |
|---|---|---|---|---|
| 1 | NBS | $H_2O$ | 57 | 27 |
| 2 | NBS | THF–$H_2O$ | 54 | 44 |
| 3 | NBS | Acetone–$H_2O$ | 31 | 20 |
| 4 | NBS | $CCl_4$–$H_2O$ | 42 | 51 |
| 5 | NBS | MeCN–$H_2O$ | 85 | 12 |
| 6 | NBS[b] | MeCN–$H_2O$ | 27, 46[c] | 10 |
| 7 | NCS | MeCN–$H_2O$ | 85 | 3 |
| 8 | NIS | MeCN–$H_2O$ | 80 | tr |

[a] Isolated yields.
[b] NBS (2.0 equiv) used.
[c] Isolated yields of 2,2-dibromo-3,3,3-trifluoropropanamide (**10aBrBr**).

MeCN–$H_2O$ mixed solvent, where **6aBr** was provided in 85% yield and **9aBr** in 12% yield (entry 5).

With optimum conditions (entry 5) in hand, we conducted the halogenation reaction of **2a** with other *N*-halosuccinimides (NXS), such as NCS and NIS. As shown in entries 7 and 8, the reaction of **2a** with NCS or NIS proceeded efficiently to give the corresponding 2-halo amides **6aCl** and **6aI** in 85 and 80% yield, respectively. In both cases, the addition product **9aCl** or **9aI** was formed in less than 3% yield. The 2-chloro amide **6aCl** could also be obtained in 75% yield through the reaction of **2a** with aqueous sodium hypochloride (5 equiv) in MeCN at ambient temperature for 1 h. It is very interesting that the use of 2.0 equiv of NBS brought about the formation of *N*,*N*-dibutyl-2,2-dibromo-3,3,3-trifluoropropanamide (**10aBrBr**) as a major product, along with the products **6aBr** and **9aBr** (entry 6).

### 2.5. Reaction of the ynamine 2a with NXS in anhydrous MeCN

Next, the reaction between **2a** and NXS was investigated under anhydrous reaction conditions. The results of the reactions are summarized in Table 5.

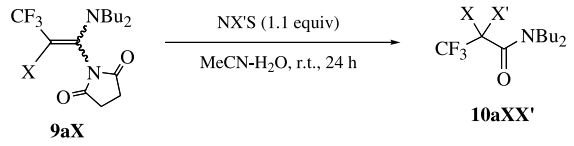
**Table 5**. Reaction of **2a** with NXS in anhydrous MeCN

| Entry | NXS | Yield of **6aX** (%)[a] | Yield of **9aX** (%)[a] | Isomer ratio **9aX** (%)[b] |
|---|---|---|---|---|
| 1 | NBS | tr | 99 | 74:26 |
| 2 | NCS | tr | 83 | 53:47 |
| 3 | NIS | 0 | 66 (87) | 73:27 |

[a] Isolated yields. Value in parentheses is of yield measured by $^{19}$F NMR.
[b] Determined by $^{19}$F NMR.

When **2a** was allowed to react with NXS (1.0 equiv) in anhydrous MeCN in the presence of MS 4 Å at room temperature for 1 h, the corresponding addition product **9aX** was exclusively obtained in good yield as a mixture of the geometrical isomers. Little or no 2-halo propanamide **6aX** was produced in the reaction. The addition product **9aI** was susceptible to decomposition during isolation by silica gel column chromatography, resulting in a remarkable decrease in an isolated yield (entry 3). To be noted is that neither **9aBr** nor **9aCl** was changed even when treated with a HCl aqueous solution in MeCN–$H_2O$ (3/2 v/v) at room temperature for 24 h, the corresponding 2-halo propanamides **6aBr** and **6aCl** being not obtained at all. These findings strongly suggest that the 2-halo propanamides **6aX**, formed in the reaction of **2a** under aqueous conditions (Scheme 10), are not derived from the hydrolysis of in situ formed **9aX** but from the addition of a halonium ion to the acetylenic β-carbon of **2a** followed by attack with water.

It was further found that these addition products **9aX** reacted readily with *N*-halosuccinimides (NX′S) in a MeCN–$H_2O$ mixed solvent at room temperature, leading to high yields of the corresponding 2,2-dihalo propanamides **10aXX′**, which are extremely difficult to prepare, as shown in Scheme 11 and Table 6.




**Scheme 11.**

**Table 6**. Reaction of the addition products **9aX** with NX′S

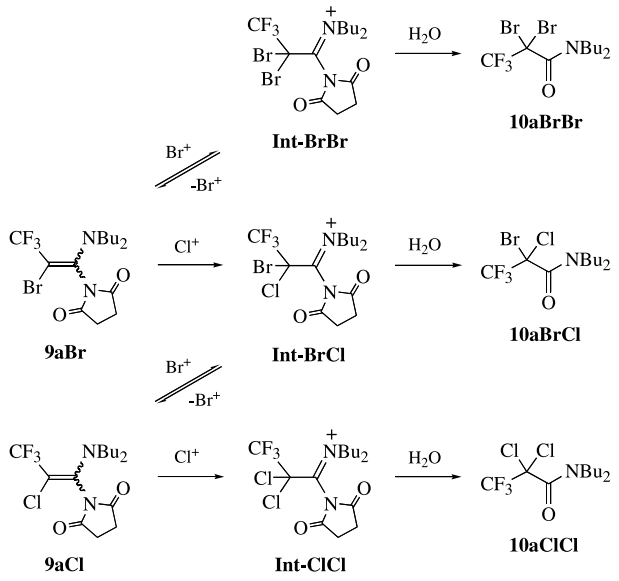
| Entry | **9aX** | X′ | Yield of **10aXX′** (%)[a] | | | |
|---|---|---|---|---|---|---|
| | | | **ClCl** | **ClBr** | **BrBr** | **ClI** |
| 1 | **9aCl** | Cl | 99 | 0 | 0 | 0 |
| 2 | **9aBr** | Br | 0 | 0 | 99 | 0 |
| 3 | **9aCl** | Br | 0 | 99 | 0 | 0 |
| 4 | **9aBr** | Cl | 35 | 42 | 21 | 0 |
| 5[b] | **9aI** | Cl | 27 | 0 | 0 | 0 |

[a] Isolated yields.
[b] The addition product **9aCl** was obtained in 5% yield.

Thus, on treating **9aCl** or **9aBr** with NCS or NBS (1.1 equiv) in MeCN–$H_2O$ (3/2 v/v) at room temperature for 24 h, the corresponding 2,2-dihalo propanamides **10aClCl** and **10aBrBr** were obtained, respectively, in quantitative yields (entries 1 and 2). The treatment of **9aCl** with NBS likewise gave high yield of the amide **10aClBr** carrying two different halogens at the α carbon (entry 3). However, the reaction of **9aBr** with NCS under the same conditions led to **10aClCl**, **10aClBr**, and **10aBrBr** in 35, 42, and 21% yields, respectively (entry 4). The reaction of **9aI** with NCS gave rise to **10aClCl** and **9aCl** in 27 and 55% yields, respectively, no expected product **10aClI** being formed at all (entry 5).

### 2.6. Mechanistic aspects for the reaction of 9aX with NX′S

A possible mechanism for the reaction of **9aX** with NX′S is as follows. As shown in Scheme 12, the addition product **9aBr** reacts with chloronium ion, generated from NCS, to form the intermediate **Int-BrCl**, which undergoes hydrolysis with water to give the product 2-bromo-2-chloro propanamide **10aBrCl**. This intermediate **Int-BrCl** may also be subject to the elimination of bromonium ion to generate **9aCl**. No elimination of chloronium ion occurs on **Int-BrCl** in any extent, in view of the fact that the reaction of **9aCl** with NBS led to the exclusive formation of **10aClBr** (corresponding to **10aBrCl** in Scheme 12), as shown in entry 3 of Table 6. The in situ generated **9aCl** may react with chloronium ion to give the intermediate **Int-ClCl**, which is hydrolyzed with water to afford the product




**Scheme 12.**

**10aClCl**. On the other hand, **9aBr** may also react with bromonium ion, generated in situ via elimination from **Int-BrCl**, to form **Int-BrBr**, which is hydrolyzed to give the product **10aBrBr**.

It is also possible to explain the formation of **10aClCl** and **9aCl** in the reaction of **9aI** with NCS according to this mechanism.

## 3. Experimental

### 3.1. Measurements and materials

Infrared spectra (IR) were measured in a liquid film or KBr disk method with a Shimadzu FTIR-8200PC spectrophotometer. $^{1}H$ and $^{13}C$ NMR spectra were obtained with GE QE-300 (300 MHz for $^{1}H$ and 75 MHz for $^{13}C$) and Bruker DRX-500 (500 MHz for $^{1}H$ and 125 MHz for $^{13}C$) spectrometers in a chloroform-*d* ($CDCl_3$) solution with tetramethylsilane as an internal reference. A JEOL JNM EX90A (84.1 MHz) spectrometer was used to measure $^{19}F$ NMR spectra in $CDCl_3$ using trichlorofluoromethane as an internal standard. Mass (MS) and high resolution mass spectra (HRMS) were taken on a Hitachi M-80B and JEOL JMS-700 mass spectrometer by electron impact (EI) or chemical ionization (CI) method. Melting points were obtained on a Shimadzu MM-2 micro melting point determination apparatus and are uncorrected. The elemental analyses of products were carried out with a Yanaco CHN CORDER MT-5 instrument.

THF and diethyl ether were freshly distilled from sodium benzophenone ketyl under argon. MeCN was distilled from calcium hydride and stored under argon. Other solvents were dried according to the conventional methods prior to use. Butyllithium (a 1.6 M hexane solution) was commercially available from Aldrich or Kanto Chemical Co. Aldehydes and ketones were distilled (or vacuum distilled) over calcium hydride or recrystallized from appropriate solvents, and were stored under argon. All chemicals were of reagent grade and, if necessary, were purified in the usual manner prior to use. 2,2,3,3,3-Pentafluoropropyl *o*-nitrobenzenesulfonate and trifluoromethanesulfonate were prepared according to the literature method[18] or slightly modified procedure.[19] All reactions were carried out under an atmosphere of argon.

### 3.2. Typical procedure for the preparation of the tertiary amines 1

*Method A*. A mixture of *o*-nitrobenzenesulfonate (50.27 g, 150 mmol) and *N*,*N*-dimethylbenzylamine (60.84 g, 450 mmol) was heated with stirring at such temperatures (140–160 °C) that in situ formed tertiary amine **1b** was constantly distilled. The collected distillate was subjected to fractional distillation giving the amine **1b** (86% yield).

*Method B*. A mixture of trifluoromethanesulfonate (42.32 g, 150 mmol) and dibutylamine (58.16 g, 450 mmol) was stirred without solvent at 60 °C for 1 h. After cooling to room temperature, the mixture was filtered to remove dibutylammonium salt, which was washed with diethyl ether (ca. 50 mL). The filtrate was washed successively with 5% HCl (100 mL×2) and with water (50 mL), followed by drying over anhydrous $Na_2SO_4$, filtration, and concentration. The residual oil was distilled to afford **1a** (93% yield).

**3.2.1. *N*,*N*-Dibutyl(2,2,3,3,3-pentafluoropropyl)amine (1a).** Bp 75.0–76.0 °C/20 mmHg; IR (neat) 2960, 1190, 1110 ($cm^{-1}$); $^{1}H$ NMR $\delta$ 0.91 (t, $J$=7.1 Hz, 6H), 1.22–1.49 (m, 8H), 2.57 (t, $J$=7.1 Hz, 4H), 3.03 (tq, $J$=15.8, 1.1 Hz, 2H); $^{13}C$ NMR $\delta$ 13.9, 20.2, 29.4, 53.6 (t, $J$=21.8 Hz), 55.2, 115.0 (tq, $J$=253.9, 35.6 Hz), 119.2 (tq, $J$=35.6, 286.7 Hz); $^{19}F$ NMR $\delta$ −117.8 (t, $J$=15.8 Hz, 2F), −82.2 (t, $J$=1.1 Hz, 3F); MS (EI) *m*/*z* (rel intensity) 261 ($M^+$, 6), 218 (100); HRMS (EI) calcd for $C_{11}H_{20}F_5N$ ($M^+$): 261.1516, found 261.1515. Anal. Calcd for $C_{11}H_{20}F_5N$: C 50.57, H 7.72, N 5.36. Found: C 49.94, H 7.62, N 5.41.

**3.2.2. *N*,*N*-Dimethyl(2,2,3,3,3-pentafluoropropyl)amine (1b).** Bp 58.0 °C; IR (neat) 2960, 1200, 1105 ($cm^{-1}$); $^{1}H$ NMR $\delta$ 2.41 (s, 6H), 2.93 (tq, $J$=15.6, 1.1 Hz, 2H); $^{13}C$ NMR $\delta$ 46.5, 57.8 (t, $J$=22.3 Hz), 115.0 (tq, $J$=254.1, 35.8 Hz), 119.1 (tq, $J$=35.8, 285.6 Hz); $^{19}F$ NMR $\delta$ −117.3 (t, $J$=15.6 Hz, 2F), −82.2 (t, $J$=1.1 Hz, 3F); MS (EI) *m*/*z* (rel intensity) 177 ($M^+$, 100); HRMS (EI) calcd for $C_5H_8F_5N$ ($M^+$): 177.0577, found 177.0573.

**3.2.3. *N*-(2,2,3,3,3-Pentafluoropropyl)piperidine (1c).** Bp 122.0–123.0 °C; IR (neat) 2941, 1198, 1134 ($cm^{-1}$); $^{1}H$ NMR $\delta$ 1.38–1.46 (m, 2H), 1.55–1.463 (m, 4H), 2.58 (t, $J$=5.3 Hz, 4H), 2.91 (tq, $J$=15.6, 1.2 Hz, 2H); $^{13}C$ NMR $\delta$ 23.7, 26.0, 55.7, 57.4 (t, $J$=22.0 Hz), 114.9 (tq, $J$=290.1, 35.6 Hz), 119.1 (tq, $J$=35.6, 286.2 Hz); $^{19}F$ NMR $\delta$ −119.5 (t, $J$=15.6 Hz, 2F), −84.5 (t, $J$=1.2 Hz, 3F); MS (EI) *m*/*z* (rel intensity) 217 ($M^+$, 19), 98 (100); HRMS (EI) calcd for $C_8H_{12}F_5N$ ($M^+$): 217.0870, found 217.0894.

**3.2.4. *N*,*N*-Diisopropyl(2,2,3,3,3-pentafluoropropyl)-amine (1d).** Bp 136.0–136.5 °C; IR (neat) 2972, 1194, 1153 ($cm^{-1}$); $^{1}H$ NMR $\delta$ 1.02 (d, $J$=6.5 Hz, 12H), 2.99–3.11 (m, 4H); $^{13}C$ NMR $\delta$ 20.8, 45.4 (t, $J$=22.3 Hz), 49.5, 114.7 (tq, $J$=252.1, 35.5 Hz), 119.6 (tq, $J$=35.5,

286.5 Hz); $^{19}$F NMR $\delta$ −120.4 (t, $J$=15.6 Hz, 2F), −84.4 (s, 3F); MS (EI) *m/z* (rel intensity) 233 ($M^+$, 2), 176 (100); HRMS (EI) calcd for $C_9H_{16}F_5N$ ($M^+$): 233.2102, found 233.1207.

### 3.3. Typical procedure for the preparation of the ynamines 2

To a solution of LDA (2.2 mmol) in THF (3.0 mL) was gradually added a solution of **1a** (0.262 g, 1.0 mmol) in THF (1.0 mL) and DMPU (0.282 g, 2.2 mmol) at 0 °C under argon. The mixture was stirred at room temperature for 2 h. After being quenched with water, the resulting mixture was extracted with diethyl ether (20 mL×3) and the combined ethereal extracts were dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure to leave crude **2a**, of which the yield was determined by $^{19}$F NMR using α,α,α-trifluorotoluene as the reference. The ynamine **2a** was subjected to the following reactions without any purifications.

**3.3.1. *N*,*N*-Dibutyl(3,3,3-trifluoro-1-propynyl)amine (2a).** Bp 36 °C/15 mmHg; IR (neat) 2361 ($cm^{-1}$); $^1$H NMR $\delta$ 0.94 (t, $J$=7.2 Hz, 6H), 1.31–1.43 (m, 4H), 1.55–1.65 (m, 4H), 2.98 (t, $J$=7.2 Hz, 4H); $^{13}$C NMR $\delta$ 13.5, 19.7, 29.7, 52.6, 55.8 (q, $J$=52.08 Hz), 100.5 (q, $J$=7.12 Hz), 118.3 (q, $J$=255.01 Hz); $^{19}$F NMR $\delta$ −46.2 (s, 3F); MS (EI) *m/z* (rel intensity) 221 ($M^+$, 19), 128 (100); HRMS (EI) calcd for $C_{11}H_{18}F_3N$ ($M^+$): 221.1391, found 221.1378.

**3.3.2. *N*,*N*-Dimethyl(3,3,3-trifluoro-1-propynyl)amine (2b).** IR (THF soln) 2218 ($cm^{-1}$); $^{19}$F NMR (THF) $\delta$ −46.2 (s, 3F). Other spectral data could not be obtained due to contamination with the solvent.

**3.3.3. *N*-(3,3,3-Trifluoro-1-propynyl)piperidine (2c).** IR (neat) 2203 ($cm^{-1}$); $^1$H NMR $\delta$ 1.22 (d, $J$=6.5 Hz, 12H), 3.19 (sept, $J$=6.5 Hz, 4H); $^{13}$C NMR $\delta$ 21.2, 52.3, 60.7 (q, $J$=51.7 Hz), 98.7 (q, $J$=5.5 Hz), 118.7 (q, $J$=255.1 Hz); $^{19}$F NMR $\delta$ −44.8 (s, 3F).

**3.3.4. *N*,*N*-Diisopropyl(3,3,3-trifluoro-1-propynyl)amine (2d).** IR (neat) 2203 ($cm^{-1}$); $^1$H NMR $\delta$ 1.22 (d, $J$=6.5 Hz, 12H), 3.19 (sept, $J$=6.5 Hz, 4H); $^{13}$C NMR $\delta$ 21.2, 52.3, 60.7 (q, $J$=51.7 Hz), 98.7 (q, $J$=5.5 Hz), 118.7 (q, $J$=255.1 Hz); $^{19}$F NMR $\delta$ −44.8 (s, 3F).

### 3.4. Typical procedure for the reaction of the ynamines 2 with carbonyl compounds

To a solution of **2a** (1.0 mmol) in $CH_2Cl_2$ (3.0 mL) containing MS 4 Å (1.0 g) were dropwise added successively benzaldehyde (1.1 mmol) and $BF_3\cdot OEt_2$ (0.1 mmol) at 0 °C under an argon atmosphere. After stirring at room temperature for 1 h, the mixture was filtered to remove MS 4 Å. The filtrate was poured into 3% HCl (10 mL) and the resulting mixture was extracted with $CH_2Cl_2$ (10 mL×3). The combined organic layers were washed with brine (20 mL), dried over anhydrous $Na_2SO_4$, and concentrated in vacuo to leave a residual oil, which was submitted to $^{19}$F NMR analysis. The residual oil was chromatographed on a silica gel column with benzene to provide analytically pure product **3aa** (92% yield), together with a small amount of **4a**.

**3.4.1. *N*,*N*-Dibutyl-(*Z*)-3-phenyl-2-(trifluoromethyl)-2-propenamide (3aa).** IR (neat) 1640 ($cm^{-1}$); $^1$H NMR $\delta$ 0.94 (t, $J$=7.1 Hz, 3H), 0.96 (t, $J$=7.1 Hz, 3H), 1.23–1.46 (m, 4H), 1.53–1.68 (m, 4H), 3.39 (t, $J$=7.9 Hz, 2H), 3.44 (t, $J$=7.6 Hz, 2H), 6.94 (s, 1H), 7.35–7.44 (m, 5H); $^{13}$C NMR $\delta$ 13.7, 13.8, 19.9, 20.1, 29.2, 30.5, 44.4, 48.5, 121.8 (q, $J$=274.7 Hz), 127.5 (q, $J$=32.6 Hz), 128.4, 128.9 (q, $J$=2.0 Hz), 129.4, 132.5, 137.9 (q, $J$=4.1 Hz), 165.5 (q, $J$=2.1 Hz); $^{19}$F NMR $\delta$ −54.7 (s, 3F); MS (EI) *m/z* (rel intensity) 327 ($M^+$, 7), 199 (100); HRMS (EI) calcd for $C_{18}H_{24}F_3NO$ ($M^+$): 327.1810, found 327.1807. Anal. Calcd for $C_{18}H_{24}F_3NO$: C 66.04, H 7.39, N 4.28. Found: C 66.48, H 7.45, N 4.07.

**3.4.2. *N*,*N*-Dimethyl-(*Z*)-3-phenyl-2-(trifluoromethyl)-2-propenamide (3ba).** Mp 71–72 °C; IR (KBr) 1628 ($cm^{-1}$); $^1$H NMR $\delta$ 3.05 (s, 3H), 3.12 (s, 3H), 6.98 (s, 1H), 7.36–7.45 (m, 5H); $^{13}$C NMR $\delta$ 34.9, 38.6, 121.7 (q, $J$=274.7 Hz), 126.8 (q, $J$=32.7 Hz), 128.4, 129.0, 129.6, 132.3, 138.8 (q, $J$=4.0 Hz), 165.6 (q, $J$=2.3 Hz); $^{19}$F NMR $\delta$ −57.7 (s, 3F); MS (EI) *m/z* (rel intensity) 243 ($M^+$, 31), 199 (100); HRMS (EI) calcd for $C_{12}H_{12}F_3NO$ ($M^+$): 243.0871, found 243.0871. Anal. Calcd for $C_{12}H_{12}F_3NO$: C 59.26, H 4.97, N 5.76. Found: C 59.54, H 5.03, N 5.34.

**3.4.3. *N*,*N*-Pentamethylene-(*Z*)-3-phenyl-2-(trifluoromethyl)-2-propenamide (3ca).** IR (neat) 1639 ($cm^{-1}$); $^1$H NMR $\delta$ 1.57–1.66 (m, 6H), 3.53–3.63 (m, 4H), 6.94 (s, 1H), 7.31–7.44 (m, 5H); $^{13}$C NMR $\delta$ 24.2, 25.2, 26.0, 42.8, 48.2, 121.7 (q, $J$=274.9 Hz), 126.7 (q, $J$=32.6 Hz), 128.3, 128.9, 128.9, 129.4, 132.3, 138.0 (q, $J$=3.2 Hz), 163.8 (q, $J$=2.4 Hz); $^{19}$F NMR $\delta$ −57.7 (s, 3F); MS (EI) *m/z* (rel intensity) 283 ($M^+$, 24), 199 (100); HRMS (EI) calcd for $C_{15}H_{16}F_3NO$ ($M^+$): 283.1184, found 283.1176.

**3.4.4. *N*,*N*-Diisopropyl-(*Z*)-3-phenyl-2-(trifluoromethyl)-2-propenamide (3da).** IR (neat) 1639 ($cm^{-1}$); $^1$H NMR $\delta$ 1.24 (d, $J$=6.4 Hz, 6H), 1.50 (d, $J$=6.2 Hz, 6H), 3.41–3.60 (m, 1H), 4.11–4.30 (m, 1H), 6.86 (s, 1H), 7.35–7.46 (m, 5H); $^{13}$C NMR $\delta$ 20.0, 20.2, 45.9, 51.1, 121.9 (q, $J$=274.8 Hz), 128.3, 128.6 (q, $J$=31.8 Hz), 128.9 (q, $J$=1.9 Hz), 129.2, 132.5, 136.2 (q, $J$=3.4 Hz), 164.4 (q, $J$=2.2 Hz); $^{19}$F NMR $\delta$ −57.7 (s, 3F); MS (EI) *m/z* (rel intensity) 299 ($M^+$, 11), 199 (100); HRMS (EI) calcd for $C_{16}H_{20}F_3NO$ ($M^+$): 299.1498, found 299.1500.

### 3.5. Reaction of the ynamine 2a with bromine

To a mixture of the ynamine **2a** (1.0 mmol) and MS 4 Å (1.0 g) in anhydrous MeCN was gradually added bromine (0.320 g, 2.0 mmol) at 0 °C. After stirring at room temperature for 1 h, a saturated $NaHCO_3$ aqueous solution (20 mL) was added to the mixture at room temperature and then the resultant mixture was stirred for 0.5 h. Water (10 mL) and diethyl ether (30 mL) were added to the mixture. The organic layer was separated and the aqueous layer was extracted with diethyl ether (20 mL×4). The combined ethereal layers were washed with brine (20 mL) and dried over anhydrous $Na_2SO_4$. After evaporating the solvents, the residue was chromatographed on silica gel

with hexane–benzene (1/1) to give *N*,*N*-dibutyl-2-bromo-3,3,3-trifluoropropanamide (**6aBr**) (87% yield).

On the other hand, after treating **2a** with bromine at 0 °C for 1 h as described above, the reaction mixture was concentrated under reduced pressure. Hexane was added to the resulting residue to precipitate a crude solid, which was too labile to be purified. However, spectral analyses of this crude solid made it possible to determine successfully the structure of the product **5a**.

**3.5.1. *N*,*N*-Dibutyl-2-bromo-3,3,3-trifluoropropanamide (6aBr).** Yield 87%; IR (neat) 2963, 2936, 2874, 1663, 1458, 1346, 1277, 1161, 1119, 876, 698, 671 ($cm^{-1}$); $^1H$ NMR $\delta$ 0.93 (t, $J$=7.5 Hz, 3H), 0.98 (t, $J$=7.5 Hz, 3H) 1.26–1.73 (m, 8H), 3.19–3.54 (m, 4H), 4.77 (q, $J$=6.0 Hz, 1H); $^{13}C$ NMR $\delta$ 13.4, 13.5, 19.7, 19.7, 28.9, 31.1, 37.1 (q, $J$=33.1 Hz), 46.3, 48.2, 122.2 (q, $J$=278.1 Hz), 161.6; $^{19}F$ NMR $\delta$ −69.0 (d, $J$=6.0 Hz, 3F); MS (CI) *m*/*z* (rel intensity) 320 (M+H+2, 100), 318 (M+H, 100), 274 (38), 238 (100), 231 (52), 196 (50), 156 (55); HRMS (CI) calcd for $C_{11}H_{20}BrF_3NO$: 318.0680, found 318.0643. Anal. Calcd for $C_{11}H_{19}BrF_3NO$: C 41.52, H 6.02, N 4.40. Found: C 41.72, H 5.82, N 4.21.

**3.5.2. *N*,*N*-Dibutyl(1,2-dibromo-3,3,3-trifluoropropenyl)-amine (5a).** Yield 99%; IR (neat) 3506, 2963, 2936, 2874, 1651, 1601, 1578, 1466, 1346, 1250, 1192, 1119, 876 ($cm^{-1}$); $^1H$ NMR $\delta$ 0.90 (t, $J$=7.0 Hz, 6H), 1.25–1.35 (m, 4H), 1.41–1.51 (m, 4H), 2.68 (t, $J$=7.8 Hz, 4H) for the major isomer, 2.91 (t, $J$=7.3 Hz, 4H) for the minor isomer; $^{13}C$ NMR $\delta$ 13.6, 20.2, 29.0, 55.4, 111.1 (q, $J$=35.0 Hz), 120.6 (q, $J$=273.9 Hz), 151.1 for the major isomer; 13.6, 20.2, 29.4, 53.7, 97.0 (q, $J$=37.6 Hz), 121.0 (q, $J$=272.1 Hz), 139.3 (q, $J$=3.8 Hz) for the minor isomer; $^{19}F$ NMR $\delta$ −57.5 (s, 3F) for the major isomer, −55.3 (s, 3F) for the minor isomer.

### 3.6. Typical procedure for the one-pot synthesis of *N*,*N*-dialkyl-2-bromo-3,3,3-trifluoropropanamides (6aBr–dBr) from the tertiary amines 1

To a solution of LDA (2.2 mmol) in anhydrous THF (2.0 mL) was dropwise added a solution of **1a** (0.261 g, 1.0 mmol) in THF (1.0 mL) and DMPU (0.282 g, 2.2 mmol) at 0 °C and the mixture was stirred at room temperature for 2 h. After addition of bromine (0.320 g, 2.0 mmol) at 0 °C, the mixture was stirred at room temperature for 1 h. A saturated $NaHCO_3$ aqueous solution (30 mL) was then added to the reaction mixture at room temperature and the mixture was stirred for 0.5 h. This mixture was treated in the same manner as described above to give **6aBr** (75% yield).

The similar reactions of other amines **1b–d** provided the corresponding 2-bromo propanamides **6bBr–dBr**.

**3.6.1. *N*,*N*-Dimethyl-2-bromo-3,3,3-trifluoropropanamide (6bBr).** Yield 64%; IR (neat) 2993, 1659, 1501, 1458, 1420, 1358, 1281, 1258, 1204, 1165, 1115, 1065, 876, 841, 691, 656 ($cm^{-1}$); $^1H$ NMR $\delta$ 2.97 (s, 3H), 3.08 (s, 3H), 4.82 (q, $J$=6.0 Hz, 1H); $^{13}C$ NMR $\delta$ 36.2, 37.2 (q, $J$=32.9 Hz), 37.7, 122.2 (q, $J$=277.7 Hz), 162.1; $^{19}F$ NMR $\delta$ −69.0 (d, $J$=6.0 Hz, 3F).

**3.6.2. *N*,*N*-Pentamethylene-2-bromo-3,3,3-trifluoropropanamide (6cBr).** Yield 78%; IR (neat) 3001, 2986, 2947, 2858, 1643, 1462, 1369, 1323, 1373, 1157, 1123, 1015, 964, 872, 853, 806, 783, 691, 656 ($cm^{-1}$); $^1H$ NMR $\delta$ 1.53–1.68 (m, 6H), 3.34–3.67 (m, 4H), 4.84 (q, $J$=6.2 Hz, 1H); $^{13}C$ NMR $\delta$ 24.0, 25.1, 25.9, 37.2 (q, $J$=32.6 Hz), 43.4, 47.6, 122.3 (q, $J$=277.7 Hz), 160.3; $^{19}F$ NMR $\delta$ −70.7 (d, $J$=6.2 Hz, 3F).

**3.6.3. *N*,*N*-Diisopropyl-2-bromo-3,3,3-trifluoropropanamide (6dBr).** Yield 37%; IR (neat) 2974, 2939, 2882, 1655, 1477, 1450, 1377, 1362, 1335, 1273, 1200, 1150, 1126, 1045, 876, 799, 691, 640 ($cm^{-1}$); $^1H$ NMR $\delta$ 1.29 (d, $J$=6.5 Hz, 3H), 1.27 (d, $J$=7.0 Hz, 3H), 1.38 (d, $J$=6.5 Hz, 3H), 1.39 (d, $J$=6.5 Hz, 3H), 3.54 (br s, 1H), 3.86 (sept, $J$=6.5 Hz, 1H), 4.68 (q, $J$=6.0 Hz, 1H); $^{13}C$ NMR $\delta$ 19.6, 20.2, 20.4, 21.1, 38.8 (q, $J$=31.8 Hz), 46.9, 49.9, 122.4 (q, $J$=277.8 Hz), 160.7; $^{19}F$ NMR $\delta$ −68.6 (d, $J$=6.0 Hz, 3F).

### 3.7. Reaction of the ynamine 2a with iodine

To a mixture of the ynamine **2a** (1.0 mmol) and MS 4 Å (1.0 g) in anhydrous MeCN (3.0 mL) was gradually added iodine (0.254 g, 1.0 mmol) at room temperature under argon and the mixture was stirred for 1 h. A saturated $NaHCO_3$ aqueous solution (20 mL) was added to the mixture at room temperature, and the whole mixture was stirred for 0.5 h. The solvent was removed in vacuo to leave the crude product, which was recrystallized from diethyl ether to give pure *N*,*N*,*N*′,*N*′-tetrabutyl-4-iodo-2,4-bis(trifluoromethyl)-1-cyclobutene cyanine iodide (**7a**) (51% yield). On standing in contact with the atmosphere or treating with water, this salt was readily converted into *N*,*N*,*N*′*N*′-tetrabutyl-2,4-bis(trifluoromethyl)-2-cyclobutene cyanine iodide (**8a**).

**3.7.1. *N*,*N*,*N*′,*N*′-Tetrabutyl-4-iodo-2,4-bis(trifluoromethyl)-2-cyclobutene cyanine iodide (7a).** Yield 51%; mp 133–1350 °C; IR (KBr) 2963, 2905, 2878, 1589, 1462, 1315, 1250, 1153, 1126, 1080, 1061, 941, 737 ($cm^{-1}$); $^1H$ NMR $\delta$ 0.96 (t, $J$=7.5 Hz, 6H), 0.99 (t, $J$=7.5 Hz, 6H), 1.33–1.45 (m, 8H), 1.49–1.89 (m, 8H), 3.43–3.58 (m, 4H), 3.63–3.69 (m, 2H), 3.77–3.83 (m, 2H); $^{13}C$ NMR $\delta$ 13.3, 13.6, 19.4, 19.5, 28.6, 29.5, 43.1 (q, $J$=31.2 Hz), 52.0 (q, $J$=4.1 Hz), 53.3 (q, $J$=2.0 Hz), 95.7 (q, $J$=41.8 Hz), 117.9 (q, $J$=268.6 Hz), 121.8 (q, $J$=279.2 Hz), 160.4; $^{19}F$ NMR $\delta$ −52.2 (s, 3F), −63.5 (s, 3F); MS (FAB) *m*/*z* (rel intensity) 1265 (2M−I, 100); HRMS (FAB) calcd for $C_{44}H_{72}F_{12}I_3N_4$ (2M−I): 1265.2699, found 1265.2708.

**3.7.2. *N*,*N*,*N*′,*N*′-Tetrabutyl-2,4-bis(trifluoromethyl)-2-cyclobutene cyanine iodide (8a).** Yield 49%; mp 136.5–137.0 °C; IR (KBr) 2963, 2936, 2874, 1728, 1620, 1466, 1373, 1331, 1258, 1234, 1215, 1173, 1119, 1080, 1053, 983, 937, 864, 733, 652 ($cm^{-1}$); $^1H$ NMR $\delta$ 0.93 (t, $J$=7.0 Hz, 6H), 0.94 (t, $J$=6.5 Hz, 6H), 1.31–1.43 (m, 8H), 1.49–1.58 (m, 2H), 1.68–1.84 (m, 4H), 1.88–1.97 (m, 2H), 3.44–3.66 (m, 8H), 6.72–6.74 (m, 1H); $^{13}C$ NMR $\delta$ 13.3, 13.5, 19.7, 19.7, 28.9, 29.7, 51.5 (q, $J$=3.9 Hz), 54.7, 58.0 (q, $J$=30.2 Hz), 100.3 (q, $J$=42.0 Hz), 117.8 (q, $J$=267.7 Hz), 122.4 (q, $J$=282.0 Hz), 155.8; $^{19}F$ NMR $\delta$ −54.5 (s, 3F), −65.4 (d, $J$=4.4 Hz, 3F); MS (FAB) *m*/*z* (rel intensity) 1013 (2M−I, 100); HRMS (FAB) calcd for $C_{44}H_{74}F_{12}IN_4$

(2M−I): 1013.4766, found 1013.4760. Anal. Calcd for $C_{22}H_{37}F_6IN_2$: C 46.32, H 6.54, N 4.91. Found: C 45.97, H 6.23, N 4.55.

### 3.8. Typical procedure for the reaction of the ynamine 2a with NXS in a water-containing solvent

To a solution of **2a** (1.0 mmol) in MeCN–water (3/2 v/v, 5 mL) was added NBS (0.180 g, 1.0 mmol) at room temperature. After stirring at room temperature for 1 h, the mixture was extracted with diethyl ether (20 mL×4). The combined extracts were washed with brine (20 mL), followed by drying over anhydrous $Na_2SO_4$, filtration and concentration in vacuo. The crude residue was purified by column chromatography on silica gel with hexane–benzene (1/2) to afford *N*,*N*-dibutyl-2-bromo-3,3,3-trifluoropropanamide (**6aBr**) (85% yield) and *N*-[2-bromo-1-(*N*,*N*-dibutylamino)-3,3,3-trifluoro-1-propenyl]succinimide (**9aBr**) (12% yield).

Other 2-bromo propanamides **6aX** were synthesized in a similar manner.

**3.8.1. *N*,*N*-Dibutyl-2-chloro-3,3,3-trifluoropropanamide (6aCl).** Yield 85%; IR (neat) 2963, 2936, 2874, 1670, 1458, 1350, 1281, 1165, 1119, 934, 887, 733, 687, 644 ($cm^{-1}$); $^1H$ NMR $\delta$ 0.93 (t, $J$=7.2 Hz, 3H), 0.97 (t, $J$=7.2 Hz, 3H), 1.26–1.43 (m, 4H), 1.50–1.61 (m, 4H), 3.25–3.47 (m, 4H), 4.85 (q, $J$=6.6 Hz, 1H); $^{13}C$ NMR $\delta$ 13.6, 13.6, 19.8, 19.9, 29.2, 31.3, 46.5, 48.1, 49.9 (q, $J$=33.4 Hz), 122.2 (q, $J$=279.6 Hz), 161.3; $^{19}F$ NMR $\delta$ −71.4 (d, $J$=6.6 Hz, 3F); MS (EI) *m*/*z* (rel intensity) 275 (M+2, 1), 273 ($M^+$, 3), 238 (47), 232 (9), 230 (26), 190 (33), 188 (100), 174 (14), 156 (14); HRMS (EI) calcd for $C_{11}H_{19}ClF_3NO$: 273.1107, found 273.1082. Anal. Calcd for $C_{11}H_{19}ClF_3NO$: C 48.27, H 7.00, N 5.12. Found: C 48.12, H 6.67, N, 5.12.

**3.8.2. *N*,*N*-Dibutyl-2-iodo-3,3,3-trifluoropropanamide (6aI).** Yield 80%; IR (neat) 2963, 2936, 2874, 1659, 1458, 1342, 1265, 1157, 1145, 1092, 664, 617 ($cm^{-1}$); $^1H$ NMR $\delta$ 0.93 (t, $J$=7.2 Hz, 3H), 0.98 (t, $J$=7.2 Hz, 3H), 1.26–1.43 (m, 4H), 1.48–1.77 (m, 4H), 3.10–3.59 (m, 4H), 4.84 (q, $J$=6.6 Hz, 1H); $^{19}F$ NMR $\delta$ −66.0 (d, $J$=6.6 Hz, 3F); MS (EI) *m*/*z* (rel intensity) 365 ($M^+$, 1), 322 (51), 280 (66), 238 (100), 209 (12), 196 (47), 156 (16), 86 (84); HRMS (EI) calcd for $C_{11}H_{19}F_3INO$: 365.0465, found 365.0463.

### 3.9. Typical procedure for the reaction of the ynamine 2a with NXS in anhydrous MeCN

To a mixture of **2a** (1.0 mmol) and MS 4 Å (1.0 g) in MeCN (3.0 mL) was gradually added NBS (0.180 g, 1.0 mmol) at ambient temperature under an argon atmosphere. After stirring for 1 h, the mixture was filtered to remove the resulting solids and the filtrate was concentrated in vacuo. The residue was chromatographed on silica gel using benzene as an eluent to provide a mixture of the *E* and *Z* isomers of *N*-[2-bromo-1-(*N*,*N*-dibutylamino)-3,3,3-trifluoro-1-propenyl]succinimide (**9aBr**) (99% yield).

Other addition products **9aX** were prepared in a similar manner.

**3.9.1. *N*-[2-Bromo-1-(*N*′,*N*′-dibutylamino)-3,3,3-trifluoro-1-propenyl]succinimide (9aBr).** Yield 99%; mp 55–57 °C; IR (KBr) 2962, 2936, 2874, 1732, 1605, 1462, 1381, 1346, 1273, 1169, 1115, 1053, 1003, 941, 679 ($cm^{-1}$); $^1H$ NMR $\delta$ 0.91 (t, $J$=7.2 Hz, 3H), 0.92 (t, $J$=7.2 Hz, 3H), 1.23–1.58 (m, 8H), 2.81 (s, 4H) for the major isomer, 2.82 (s, 4H) for the minor isomer, 3.03 (t, $J$=7.5 Hz, 2H), 3.07 (t, $J$=7.5 Hz, 2H); $^{19}F$ NMR $\delta$ −59.4 (s, 3F) for the major isomer, −59.9 (s, 3F) for the minor isomer; MS (EI) *m*/*z* (rel intensity) 400 (M+2, 11), 398 ($M^+$, 11), 319 (100), 299 (9), 221 (12), 220 (11), 164 (61); HRMS (EI) calcd for $C_{15}H_{22}BrF_3N_2O_2$: 398.0817, found 398.0822. Anal. Calcd for $C_{15}H_{22}BrF_3N_2O_2$: C 45.13, H 5.55, N 7.02. Found: C 44.66, H 5.38, N, 6.74.

**3.9.2. *N*-[2-Chloro-1-(*N*′,*N*′-dibutylamino)-3,3,3-trifluoro-1-propenyl]succinimide (9aCl).** Yield 83%; mp 44.0–45.5 °C; IR (KBr) 2963, 2936 (s), 2878, 1732, 1670, 1620, 1462, 1427, 1350, 1281, 1234, 1119, 1057, 968, 945, 683 ($cm^{-1}$); $^1H$ NMR $\delta$ 0.92 (t, $J$=7.5 Hz, 6H) for the major isomer, 1.25–1.34 (m, 4H), 1.49–1.56 (m, 4H), 2.81 (br s, 4H), 3.06 (t, $J$=7.5 Hz, 4H), 0.90 (t, $J$=7.5 Hz, 6H) for the minor isomer, 1.25–1.34 (m, 4H), 1.49–1.56 (m, 4H), 2.83 (br s, 4H), 3.02 (t, $J$=7.5 Hz, 4H); $^{13}C$ NMR $\delta$ 13.8, 19.9, 28.2, 30.2, 50.1, 97.3 (q, $J$=36.7 Hz), 121.9 (q, $J$=269.9 Hz), 137.2, 174.7 for the major isomer, 13.7, 19.9, 28.3, 29.9, 51.1, 97.4 (q, $J$=36.7 Hz), 121.9 (q, $J$=269.9 Hz), 140.0 (q, $J$=2.4 Hz), 174.2 for the minor isomer; $^{19}F$ NMR $\delta$ −62.7 (s, 3F) for the major isomer, −63.3 (s, 3F) for the minor isomer; MS (EI) *m*/*z* (rel intensity) 356 (M+2, 7), 354 ($M^+$, 22), 319 (100), 313 (19), 311 (55), 277 (46), 263 (22), 229 (12), 164 (34), 162 (12), 151 (11), 57 (13); HRMS (EI) calcd for $C_{15}H_{22}ClF_3N_2O_2$: 354.1321, found 354.1316. Anal. Calcd for $C_{15}H_{22}ClF_3N_2O_2$: C 50.78, H 6.25, N 7.90. Found: C 51.00, H 6.12, N 7.71.

**3.9.3. *N*-[2-Iodo-1-(*N*′,*N*′-dibutylamino)-3,3,3-trifluoro-1-propenyl]succinimide (9aI).** Yield 66%; mp 66–69 °C; IR (KBr) 2963, 2939, 2874, 1728, 1639, 1585, 1462, 1339, 1250, 1165, 1096, 930, 706 ($cm^{-1}$); $^1H$ NMR $\delta$ 0.90 (t, $J$=7.3 Hz, 6H), 1.21–1.34 (m, 4H), 1.47–1.55 (m, 4H), 2.76–2.86 (m, 4H), 3.07 (t, $J$=7.8 Hz, 4H); $^{13}C$ NMR $\delta$ 13.7, 19.9, 28.5, 29.9, 51.3, 59.9 (q, $J$=37.3 Hz), 122.3 (q, $J$=268.9 Hz), 144.7 (q, $J$=2.8 Hz), 174.2 for the major isomer, 13.8, 20.0, 28.2, 30.0, 51.1, 59.9 (q, $J$=37.3 Hz), 122.3 (q, $J$=268.9 Hz), 144.7 (q, $J$=2.8 Hz), 174.2 for the minor isomer; $^{19}F$ NMR $\delta$ −54.0 (s, 3F) for the major isomer, −56.0 (s, 3F) for the minor isomer; MS (EI) *m*/*z* (rel intensity) 446 ($M^+$, 28), 403 (37), 347 (11), 319 (100), 278 (16), 277 (99), 238 (42), 236 (20), 235 (22), 221 (22), 196 (25), 165 (40), 164 (81), 86 (60), 84 (13), 57 (38); HRMS (EI) calcd for $C_{15}H_{22}F_3IN_2O_2$: 446.0678, found 446.0687.

### 3.10. Typical procedure for the reaction of 9aX with NXS or NX′S in a MeCN–water mixed solvent

To a solution of **9aBr** (0.399 g, 1.0 mmol) in MeCN–water (3/2 v/v, 5 mL) was gradually added NBS (0.196 g, 1.1 mmol) and then the mixture was stirred at ambient temperature for 24 h. After addition of water (20 mL), the mixture was extracted with diethyl ether (10 mL×5). The combined ethereal extracts were washed with brine (20 mL) and dried over anhydrous $Na_2SO_4$. After evaporating the solvents, the resulting residue was chromatographed on silica gel with hexane–benzene

(1/1) to give *N*,*N*-dibutyl-2,2-dibromo-3,3,3-trifluoropropanamide (**10aBrBr**) (99% yield).

The reactions between **9aX** and various NXS or NX′S were carried out in the same manner.

**3.10.1. *N*,*N*-Dibutyl-2,2-dibromo-3,3,3-trifluoropropanamide (10aBrBr).** Yield 99%; IR (neat) 2963, 2936, 2874, 1663, 1466, 1427, 1292, 1238, 1200, 1173, 895, 814, 710, 664 ($cm^{-1}$); $^1H$ NMR $\delta$ 0.87 (t, $J=7.2$ Hz, 3H), 0.92 (t, $J=7.2$ Hz, 3H), 1.19–1.71 (m, 8H), 3.28 (t, $J=7.5$ Hz, 2H), 3.63 (t, $J=8.0$ Hz, 2H); $^{13}C$ NMR $\delta$ 13.6, 13.7, 19.9, 20.0, 28.5, 29.4, 46.5, 49.7, 50.9 (q, $J=29.2$ Hz), 121.2 (q, $J=279.9$ Hz), 159.7; $^{19}F$ NMR $\delta$ −70.5 (s, 3F); MS (EI) *m*/*z* (rel intensity) 399 (M+4, 1), 397 (M+2, 2), 395 ($M^+$, 1), 356 (52), 354 (100), 352 (55), 310 (81), 300 (17), 298 (35), 296 (17), 276 (13), 274 (14), 256 (11), 214 (15), 212 (16); HRMS (EI) calcd for $C_{11}H_{18}Br_2F_3N$: 394.9707, found 394.9718. Anal. Calcd for $C_{11}H_{18}Br_2F_3N$: C 33.27, H 4.57, N 3.53. Found: C 33.01, H 4.40, N 3.30.

**3.10.2. *N*,*N*-Dibutyl-2-bromo-2-chloro-3,3,3-trifluoropropanamide (10aClBr).** Yield 99%; IR (neat) 2963, 2936, 2874, 1670, 1466, 1377, 1292, 1242, 1207, 1177, 910, 833, 679 ($cm^{-1}$); $^1H$ NMR $\delta$ 0.94 (t, $J=7.5$ Hz, 3H), 0.99 (t, $J=7.5$ Hz, 3H), 1.31–1.43 (m, 2H), 1.54–1.60 (m, 2H), 1.68–1.76 (m, 2H), 3.26–3.42 (m, 4H), 3.54–3.60 (m, 2H), 3.75–3.81 (m, 2H); $^{13}C$ NMR $\delta$ 13.8, 19.0, 20.0, 28.6, 29.7, 46.7, 49.2, 64.6 (q, $J=30.1$ Hz), 121.3 (q, $J=281.2$ Hz), 159.7; $^{19}F$ NMR $\delta$ −72.6 (s, 3F); MS (CI) *m*/*z* (rel intensity) 356 (M+H+4, 79), 355 (M+4, 22), 354 (M+H+2, 35), 353 (M+2, 19), 352 (M+H, 55), 310 (20), 308 (15), 274 (20), 272 (49), 238 (16), 156 (39); HRMS (CI) calcd for $C_{11}H_{19}BrClF_3NO$ (M+H): 352.0291, found 352.0254. Anal. Calcd for $C_{11}H_{18}BrClF_3NO$: C 37.47, H 5.15, N 3.97. Found: C 37.51, H 5.10, N 3.91.

**3.10.3. *N*,*N*-Dibutyl-2,2-dichloro-3,3,3-trifluoropropanamide (10aClCl).** Yield 99%; IR (neat) 2963, 2878, 1674, 1466, 1431, 1381, 1250, 1215, 1180, 922, 860, 718, 691 ($cm^{-1}$); $^1H$ NMR $\delta$ 0.93 (t, $J=7.5$ Hz, 3H), 0.97 (t, $J=7.5$ Hz, 3H), 1.32 (tq, $J=7.5$, 7.5 Hz, 2H), 1.37 (tq, $J=7.5$, 7.5 Hz, 2H), 1.56 (tt, $J=7.5$, 7.5 Hz, 2H), 1.68 (tt, $J=7.5$, 7.5 Hz, 2H), 3.32 (t, $J=7.5$ Hz, 2H), 3.62 (t, $J=7.5$ Hz, 2H); $^{13}C$ NMR $\delta$ 13.7, 19.9, 20.1, 28.7, 29.9, 46.8, 48.8, 76.9 (q, $J=30.7$ Hz), 121.3 (q, $J=282.2$ Hz), 159.5; $^{19}F$ NMR $\delta$ −75.5 (s, 3F); MS (EI) *m*/*z* (rel intensity) 311 (M+4, 1), 309 (M+2, 2), 307 ($M^+$, 2), 274 (31), 272 (77), 268 (18), 266 (80), 264 (90), 230 (21), 226 (45), 224 (94), 222 (100), 210 (55), 208 (70), 156 (68), 84 (18), 57 (81); HRMS (EI) calcd for $C_{11}H_{18}Cl_2F_3NO$: 307.0717, found 307.0719. Anal. Calcd for $C_{11}H_{18}Cl_2F_3NO$: C 42.87, H, 5.89, N 4.55. Found: C 42.00, H 5.65, N 4.01.

### 3.11. Reaction of the ynamine 2a with sodium hypochloride

To a solution of the ynamine **2a** (1.0 mmol) in MeCN (2.0 mL) was gradually added aqueous sodium hypochloride (5.0 mmol) at 0 °C. After stirring at room temperature for 1 h, water (10 mL) and diethyl ether (30 mL) were added. The organic layer was separated and the aqueous layer was extracted with diethyl ether (20 mL × 4). The combined extracts were washed with brine (20 mL) and dried over anhydrous $Na_2SO_4$. After evaporating the solvents, the resultant residue was chromatographed on silica gel with hexane–benzene (1/1) to give **6aCl** (75% yield).

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