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Halogen Promoted Desulfurative Cleavage of Cyclopropylmethyl Thioethers and Amination of the Formed Cyclopropylcarbinyl Cations

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Dedicated to the memory of Prof. Gregorio Asensio

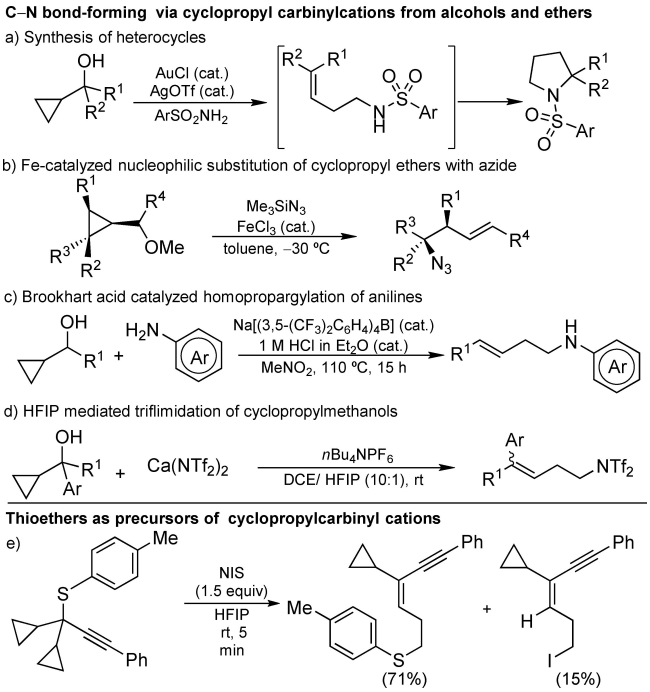
Cyclopropylmethyl sulfides react with *N*-fluorosulfonimide (NFSI) or molecular iodine, enabling C–S cleavage to generate cyclopropylcarbinyl cations, which evolve through cyclopropane ring-opening reactions into homoallyl cations suitable to react with nucleophiles present in the reaction media. This desulfurative cleavage of cyclopropylmethyl thioethers under non-acidic conditions facilitates homoallylation of *N*-based nucleophiles such as alkyl or aryl amines as well as sulfonimides through a one-pot protocol in one or two steps depending on the nucleophile. The reaction is initiated by a halogen-sulfur bond that causes C–S bond cleavage. Moreover, the reaction with iodine proceeds through homoallyl iodide intermediates.

Introduction

The development of C–N bond-forming reactions is a research field with the utmost impact on Organic synthesis due to the ubiquitous presence of nitrogenated compounds in drugs and material science building blocks.[1] For example, although classical approaches for the synthesis of homoallylic amines are commonly based on the addition of allyl organometallics to imines,[2] other alternative strategies involving C–N bond-forming[3] demonstrated to be highly versatile for the formation of these compounds like hydroamination reactions,[4] alkylation, reductive amination,[5] electrochemical processes,[6] or photoredox couplings.[7]

In this context, cyclopropane ring-opening reactions[8] were demonstrated to be valuable methods for accessing homoallyl amines. For example, cyclopropynyl carbinols activated by Ru-complexes reacted with anilines, affording the corresponding homoallyl amines through metal-allenydene intermediates.[9] In addition, non-classical cyclopropylcarbinyl cations behave as equivalents of homoallyl cations capable of reacting with suitable nucleophiles,[10] enabling, for example, *N*-alkylation reactions. Nevertheless, amination of cyclopropylcarbinyl cation has shown to be challenging due to the limited amine nucleophiles compatible with acidic conditions required to generate the cations from cyclopropyl carbinols and the related ethers or carbonyls.

To circumvent these issues regarding the rearrangements of cyclopropylcarbinyl cations, Chan and co-workers reported the use of *N*-sulfonyl nucleophiles in combination with Au/Ag catalysts to synthesize pyrrolidine[7] (Scheme 1a) or diazepines *N*-heterocycles[11] as well as ytterbium or iron catalysts to obtain *N*-homoallyl sulfonamides.[12] Also, trichloroacetimidates have been revealed as efficient intramolecular *N*-nucleophiles that give access to different heterocycles.[13] Less basic nucleophiles like azides[14] or TMSCN[15] were successfully employed in stereo-



Scheme 1. Cyclopropylcarbinyl cation in C–N bond-forming reactions

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selective ring-opening of highly substituted cyclopropyl ethers promoted by iron (Scheme 1b) and tin salts. More recently, Chazra reported an elegant protocol for the homoallylation of anilines by activating cyclopropylcarbinols with Brookhart acid as the catalyst (Scheme 1c).[16] Also, in 2022, Wang described cyclopropane ring-opening reactions to synthesize *E*-homoallyl triflimides using $Ca(NTf_2)_2$ in hexafluoroisopropanol (HFIP) (Scheme 1d).[17] Although most common sources for cyclopropylcarbinyl cations are based on the activation of alcohols or ethers,[10] other functional groups that remain underexplored could also be employed. Based on our experience on electrophilic activation of thioethers decorated with alkynes,[18] in a preliminary study, we found that cyclopropylcarbinyl cation could be easily generated after *S*-atom activation employing iodonium ions affording a homoallyl sulfide.[19] So, according to these precedents, we hypothesized that cyclopropylcarbinyl cations could be generated under non-acidic conditions by halonium-induced C–S bond cleavage,[20] facilitating subsequent *N*-alkylation reactions.

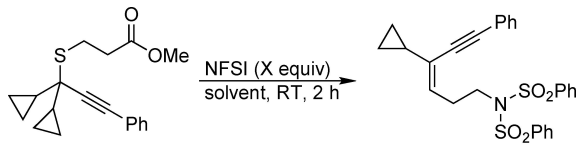
Results and Discussion

NFSI Promoted Desulfurative Cleavage of Thiothers

Various halonium ions and particularly electrophilic fluorinating reagents have been reported to achieve C–S cleavage after interaction with the S-atom of different organosulfur compounds like thioethers.[21,22] Moreover, *N*-fluorobenzenesulfonimides have shown the potential to act as nitrogen sources.[23] So, initially, we decided to study the reaction of NFSI with a model thioether **1aa** (Table 1), which is easily accessible by *p*-toluenesulfonic acid (PTSA) catalyzed thiolation reaction.[24]

Initially (entry 1), compound **1aa** was subjected to a reaction with NFSI in dichloromethane as solvent experiencing the C–S bond cleavage and C–N bond-forming reaction through the homoallylation of the benzenesulfonimidate anion affording compound **2a**. The reaction proceeds with high diastereoselectivity, obtaining almost exclusively the *Z* isomer. Inspired by this initial result, we evaluated THF, achieving higher yields. We also evaluated the use of an excess NFSI oxidant (entries 3 and 4). Stoichiometric amounts of NFSI gave rise to slightly lower yields caused by incomplete conversion of **2a**. However, higher amounts of NFSI (entry 4) were proven to be detrimental to the process, leading to more complex reaction crudes, probably due to side reactions derived from the degradation of desired product **2a** caused by the excess electrophilic fluorinating reagent. Then, other solvents were also tested (entries 5–8). When the green solvent ethyl acetate was employed (entry 5), a higher yield of **2a** was observed by minimizing the formation of degradation byproducts. An even better result was achieved when using butyl acetate. By contrast, acetonitrile provided lower yield and conversion (entry 7) and the use of methanol afforded the formation of an alternative byproduct derived from the nucleophilic attack of a methanol molecule to the propargylic position, giving rise to the corresponding methyl ether derivative as the major product.

Table 1. Reaction optimization for the synthesis of *N*-homoallyl benzenesulfonimides **2a**.[a]



1aa **2a**

Entry	NFSI equiv	Solvent	Conversion (%)[b]	Yield (%)[b] (*E*:*Z*)[c]
1	1.1	CH_2Cl_2	>95	56 (1:15)
2	1.1	THF	>95	70 (1:15)
3	1.0	THF	89	63 (1:15)
4	1.5	THF	>95	58 (1:15)
5	1.1	EtOAc	>95	78 (1:15)
6	1.1	*n*BuOAc	>95	85 (82)[d] (1:15)
7	1.1	MeCN	82	61 (1:12)
8	1.1	MeOH	80	–[e]

[a] Reaction conditions: **1aa** (0.2 mmol), NFSI (0.22 mmol) solvent (2 ml, 0.1 M) at rt for 2 h. [b] Conversion and yield were determined by ^{1}H NMR analysis of the reaction crude using CH_2Br_2 as an internal standard and referred to the starting product **1aa**. [c] Determined by ^{1}H NMR and NOE 1D experiments from the reaction crude. [d] In parentheses, isolated yield after purification by column chromatography referred to starting product **1aa**. [e] No formation of **2a** was observed, a nucleophilic attack of MeOH at the propargylic position occurs, affording (3,3-dicyclopropyl-3-methoxyprop-1-yn-1-yl)benzene as major product (60% yield determined by ^{1}H NMR analysis of the reaction crude using CH_2Br_2 as internal standard and referred to starting material **1aa**).

With these results in hand, we proceeded to evaluate the scope of the reaction regarding the different substituents of the starting cyclopropylmethyl sulfide (Table 2). Initially, we decided to maintain the alkyne moiety, varying the propargylic position. Replacing one of the cyclopropane rings of **1aa** by a phenyl group afforded the desired homopropargylic sulfonimide **2b** (entry 2) in high yields and excellent diastereoselectivity. The introduction of a methyl group at position R^3 of the cyclopropane ring was well-tolerated, allowing the reaction to obtain **2c** (entry 3), although in lower yield and diastereoselectivity. An alkyne (**1da**) bearing a TMS substituent was demonstrated to be compatible with the reaction conditions (entry 4). Next, we decided to test if the alkyne was decisive in allowing the reaction (entries 5–10). Replacing the alkyne with a phenyl group afforded the desired product (**2e**), although almost as an equimolecular mixture of diastereoisomers. Trying to achieve higher diastereoselectivities, we decide to replace the cyclopropyl group of **1aa** with methyl or butyl alkyl chains. Although almost one diastereoisomer was obtained, the yield decreased considerably in all these cases (entries 6–9). The presence of strong electron-withdrawing (**1ha**) or electron-donating (**1ia**) groups at the arene provided desired products in similar yields. Nevertheless, secondary thioether **1ja** (entry 10) performed readily well under optimized conditions, affording the *E*-isomer

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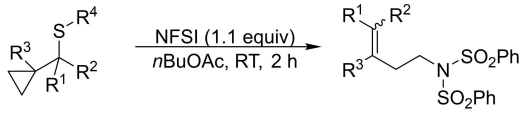
Table 2. Reaction scope for the synthesis of *N*-homoallyl benzenesulfonimides **2** by desulfurative cleavage.[a]



1 **2**

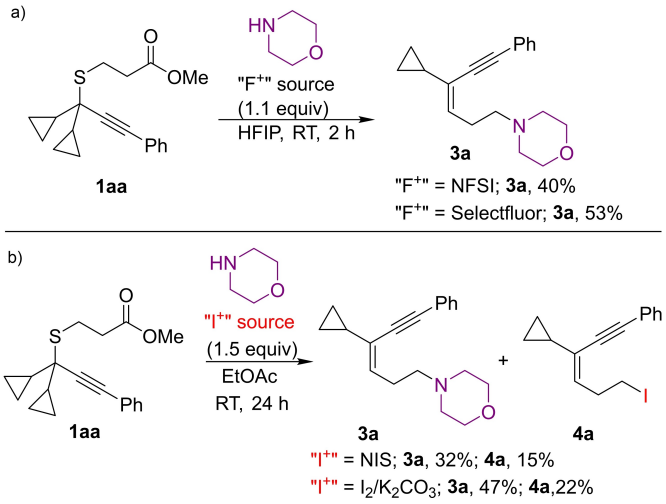
entry	1	R^1	R^2	R^3	R^4	2	Yield (%)[b] (*E*:*Z*)
1	**1aa**	*c*-C_3H_5	C≡C–Ph	H	$(CH_2)_2CO_2Me$	**2a**	82 (1:15
2	**1ba**	Ph	C≡C–Ph	H	$(CH_2)_2CO_2Me$	**2b**	77 (1:>50)
3	**1ca**	Me	C≡C–Ph	Me	$(CH_2)_2CO_2Me$	**2c**	50 (1:2)
4	**1da**	Ph	C≡C–TMS	H	$(CH_2)_2CO_2Me$	**2d**	68 (1:50)
5	**1ea**	*c*-C_3H_5	Ph	H	$(CH_2)_2CO_2Me$	**2e**	60 (1.5:1)
6	**1fa**	Me	Ph	H	$(CH_2)_2CO_2Me$	**2f**	40 (>50:1)
7	**1ga**	*n*Bu	Ph	H	$(CH_2)_2CO_2Me$	**2g**	35 (>50:1)
8	**1ha**	Me	4-$(CF_3)C_6H_4$	H	$(CH_2)_2CO_2Me$	**2h**	41 (>50:1)
9	**1ia**	Me	4-$(MeO)C_6H_4$	H	$(CH_2)_2CO_2Me$	**2i**	39 (>50:1)
10	**1ja**	Ph	H	H	$(CH_2)_2CO_2Me$	**2j**	77 (>50:1)
11	**1ka**	*n*Bu	2-thienyl	H	$(CH_2)_2CO_2Me$	**2k**	–[c]
12	**1ab**	*c*-C_3H_5	C≡C–Ph	H	$(CH_2)_{11}Me$	**2a**	78 (1:20)
13	**1ac**	*c*-C_3H_5	C≡C–Ph	H	4-$(MeO)C_6H_4$	**2a**	63 (1:15)
14	**1ad**	*c*-C_3H_5	C≡C–Ph	H	4-$(Me)C_6H_4$	**2a**	58 (1:15)
15	**1lb**	Me	4-ClC_6H_4	H	$(CH_2)_{11}Me$	**2l**	44 (>50:1)
16	**1mb**	Ph	Ph	H	$(CH_2)_{11}Me$	**2m**	79

[a] Reaction conditions: **1aa** (0.2 mmol), NFSI (0.22 mmol) *n*BuOAc (2 ml, 0.1 M) at RT for 2 h. [b] Isolated yield after purification by column chromatography referred to starting material **1**. [c] A complex mixture of products was obtained.

of homoallyl sulfonimide **2j** in excellent yield. Unfortunately, heterocyclic substituents at the propargylic position (**1ka**) were not tolerated, delivering complex reaction mixtures (entry 11).

Finally, we evaluated the influence of the substituent on the thioorganyl moiety, which is cleaved (entries 12–16), observing that unfunctionalized alkyl chains showed similar behavior to the model compound **1aa** (entry 12). By contrast, aromatic sulfides **1ac–ad** afforded slightly lower yields (entries 13 and 14), although the presence of electron-donating groups attached to the arene (**1ac**) achieved better results than **1ad**. Interestingly, parent alcohols were demonstrated to be unreactive under these reaction conditions (See Supporting Information).

Next, we decided to study if other *N*-based nucleophiles, such as alkyl amines, could be engaged in the reactions. So, the reaction of model compound **1a** with NFSI in the presence of an excess of morpholine (3.0 equiv) as an external nucleophile was evaluated. Whereas the use of conventional solvents did not provide positive results, when HFIP was tested, the formation of the sulfonimide **2a** was avoided, enabling *N*-alkylation of the morpholine to afford homoallyl amine **3a** in moderate yields (Scheme 2a). Interestingly, the reaction proceeded in higher yields when Selectfluor was used as the promoter. Nevertheless, various undetermined byproducts were also formed in both cases, probably due to alternative degradation pathways, so we decided to test milder oxidant



Scheme 2. Cyclopropyl carbinyl cation in C–N bond forming reactions.

halonium sources. In this sense, NIS and I_2/K_2CO_3 as monopositive iodonium sources were shown to be successful in favoring the C–S cleavage, allowing the subsequent amination, particularly when employing EtOAc as solvent (Scheme 2b). Interestingly, the formation of homoallyl iodide **4a** byproduct was observed under these reaction conditions. Considering that iodide **4a** could be an intermediate for the formation of homoallyl amine **3a**, we evaluated the formation of iodide in

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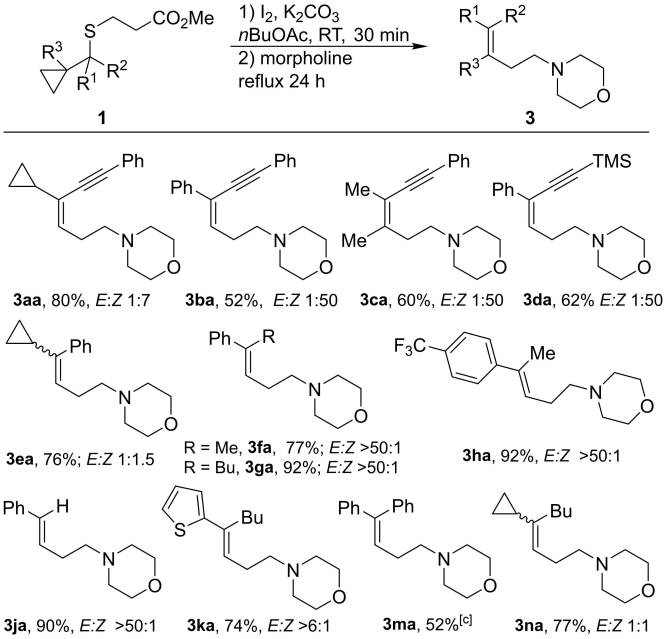
the absence of the external nucleophile, observing full conversion of the thioether **1 aa** after 30 minutes. Then, the addition of morpholine followed by further evolution achieved the formation of products **3 a** and **4 a** with similar yields.

Iodine Promoted Desulfurative Cleavage

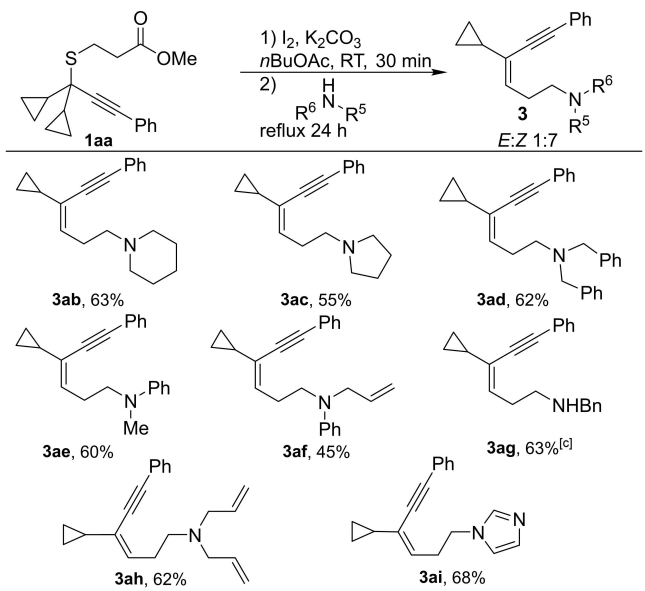
Inspired by these results and after some optimization,[20] we determined that ideal reaction conditions implied a two-step one-pot reaction, in which initially, the homoallyl iodide **4 a** is formed at room temperature in butyl acetate as the solvent and in the absence of the external nucleophile. Then, morpholine is added, followed by heating the mixture to reflux to achieve substitution of the iodine, leading to the formation of homoallyl amine **3 a**.

Interestingly, the use of *n*BuOAc instead of EtOAc allows higher reaction temperatures in the second step, which renders in the use of lower amounts of the external nucleophile (from 3.0 equiv. to 1.5 equiv.). Then, different thioethers were evaluated under these reaction conditions to synthesize a variety of *N*-homoallyl morpholines (Scheme 3). The reaction demonstrated a wide scope with all the propargylic thioethers affording almost exclusively the *Z* isomer of homoallyl morpholines (**3 aa**–**da**) due to the lower steric hindrance of the alkyne substituent. Even the tetrasubstituted alkene **3 ca** was obtained with elevated diastereoselectivity by contrast with the reaction with NFSI (see Table 2). In general terms, benzylic thioethers showed to be excellent substrates, allowing the synthesis of *N*-homoallyl morpholines (**3 fa**–**ja**) in very high yields and elevated diastereoselectivities, even those derived from secondary thioethers like **3 ja**. Under these reaction conditions, even an electron-rich heteroarene **1 ka**, which was demonstrated to be more challenging in the C–S bond cleavage reactions promoted by NFSI, like a thiophene substituent, was well-tolerated to obtain desired amine **3 ka** in high yield. By contrast, substrate **1 mb** was found to be less efficiently activated by the I_2/K_2CO_3, achieving the corresponding *N*-alkyl morpholine **3 ma** in slightly lower yields. Finally, a trialkyl substituted thioether **1 na** was also tested, achieving the formation of compound **3 na** as an equimolecular mixture of diastereoisomers in elevated yields.

Next, we proceed to study the influence of the *N*-based nucleophile over the one-pot sequence using thioether **1 aa** as the alkylating agent (Scheme 4). Interestingly, in all cases, homoallylic amines were obtained with almost identical diastereoselectivities, which indicates that the nature of the initial thioether **1** is crucial to determine the configuration of the alkene unit. These results go in accordance with the fact that in this protocol, an iodide acts as the nucleophile that induces the opening of the cyclopropane to afford an intermediate homoallyl iodide that then reacts with the different amines. Cyclic secondary amines were successfully employed to generate the corresponding reaction products (**3 ab** and **3 ac**). Then, a wide variety of non-cyclic amines were also tested, achieving similar results (**3 ad**–**3 ai**). In this sense, dibenzylamine successfully reacted, affording the *N*-homoallyl *N*,*N*-dibenzylamine **3 ad** in good yields. Next, we evaluated less nucleophilic aromatic amines. When *N*-methylaniline was subjected to the optimized reaction conditions, homoallylation was successfully achieved, affording **3 ae**. Nevertheless, when unsubstituted anilines were tested, complex mixtures of multiple byproducts were obtained.



Scheme 3. Synthesis of *N*-homoallyl morpholines from. [a] Reaction conditions: **1** (0.2 mmol), I_2 (0.22 mmol), K_2CO_3 (0.22 mmol), *n*BuOAc (2 ml, 0.1 M) 30 min at RT then morpholine (0.3 mmol) at *n*BuOAc reflux for 24 h. [b] Isolated yield after purification by column chromatography referred to the starting material **1**. [c] Thioether **1 mb** derived 1-dodecanethiol was used as starting material.



Scheme 4. Synthesis of homoallyl of amines using thioether **1 aa** as alkylating agent. [a] Reaction conditions: **1 aa** (0.2 mmol), I_2 (0.22 mmol), K_2CO_3 (0.22 mmol), *n*BuOAc (2 ml, 0.1 M) 30 min at RT then morpholine (0.3 mmol) at *n*BuOAc reflux for 24 h. [b] Isolated yield after purification by column chromatography referred to starting product **1 aa**. [c] Reaction performed in THF.

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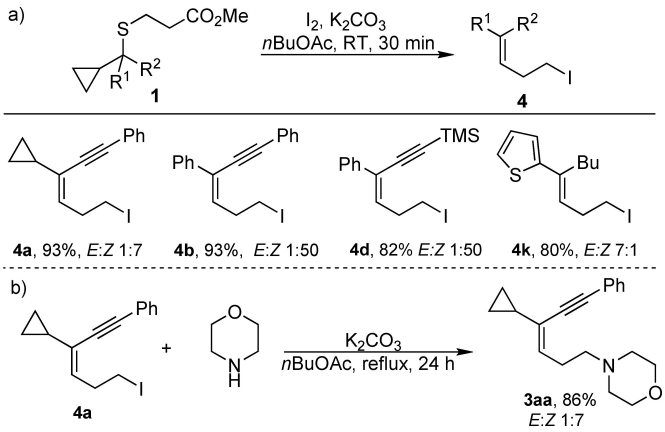
Only trace amounts of desired homoallylation products were observed from the reaction crude. Similarly, when primary benzylamine was employed, a lower yield of desired amine **3 ag** was afforded due to the competitive acetylation reaction of the *N*-nucleophile with the solvent. The reaction was performed in THF under reflux to avoid these side byproducts, employing higher amounts of the nucleophile (3.0 equiv) to achieve comparable yields. Unfortunately, this alternative procedure was demonstrated to be inefficient for the primary anilines. We have also found that diallyl amine could also be employed without observing appreciable degradation byproducts. Interestingly, during the course of these reactions, a disulfide byproduct derived from the cleavage of the thioorganyl moiety was observed.

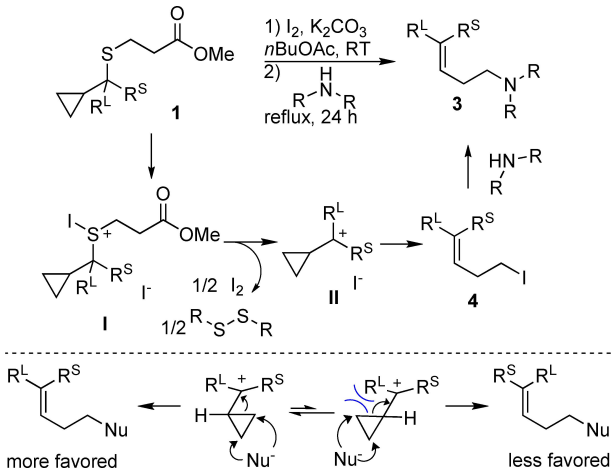
Finally, other substrates different from primary or secondary amines capable of acting as *N*-based nucleophiles were subjected to the reaction conditions. Interestingly, imidazole was demonstrated to be a suitable reaction partner, generating compound **3 ai** in good yields and with similar diastereoselectivity to the *N*-homoallyl amines

Interestingly, iodides **4** could be isolated in high yields after quenching the reaction after the first step (Scheme 5a). In addition, a selection of iodides (**4 aa**, **4 ba**, **4 da** and **4 ka**) could be easily synthesized in high yields by applying this approach. When the isolated iodide **4 aa** was subjected to the reaction with morpholine under previous conditions, similarly to the second step of the one-pot procedure, the desired amine **3 aa** was obtained with similar yield and selectivity (Scheme 5b). To gain further insights into a plausible reaction mechanism, we proceeded to evaluate the reaction performance in the presence of persistent radical TEMPO. When model thioether **1 aa** was subjected to the reaction with the molecular iodine potassium carbonate system in the presence of an excess of TEMPO, the formation of intermediate homoallyl iodide was detected by GC-MS. The mixture was subjected to the second step after the addition of morpholine, and evolution into the final product **3 aa** was observed in a similar extension. Moreover, no byproducts derived from the reaction of TEMPO with cyclopropyl methyl radicals were detected. A similar experiment was also performed employing NFSI, achieving comparable results. So, these experiments may suggest that a carbocationic mechanism mainly operates in the reaction.

A tentative mechanism is depicted in Scheme 6. Initially, the halonium ion interacts with the sulfur atom of the thioether, forming a halogen-chalcogen bond to generate the sulfonium intermediate. The cyclopropane substituent facilitates a subsequent C–S bond cleavage due to the formation of a non-classical cyclopropylcarbinyl cation **II**. This reactive intermediate could then evolve through a nucleophilic attack on the cyclopropane ring, inducing its opening to act as a homoallyl cation equivalent. The nucleophile attack takes place preferentially on the same side, which is located in the less sterically demanding substituent (R^S). In this context, the iodide generated in the reaction is a suitable nucleophile to react with carbocation **II**, generating a homoallylic iodide intermediate **4**. Then, nucleophilic substitution takes place after adding the amine, enabling the *N*-alkylation of the amine to form products **3**.



Scheme 5. Synthesis of selected iodides **4** and control experiments.

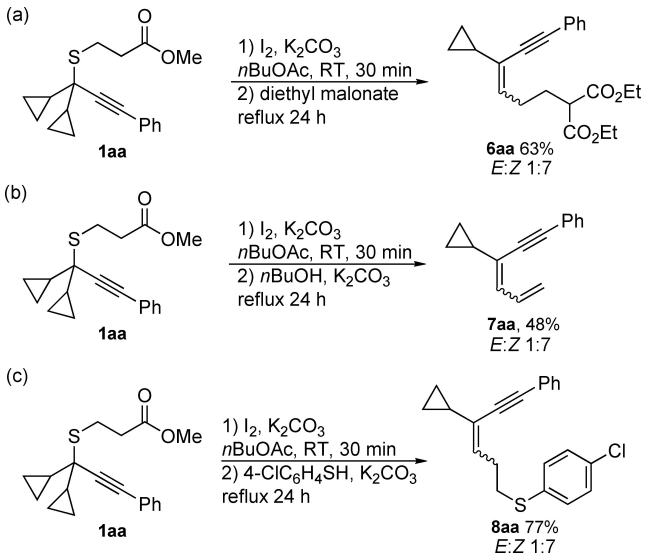


Scheme 6. Mechanistic proposal.

In addition, this protocol has the potential to be extended to other nucleophiles capable of reacting under basic conditions (Scheme 7). To illustrate this, we decided to replace the amines with diethyl malonate (Scheme 7a). In this case, the amount of base was increased to deprotonate the 1,3-dicarbonyl compound. Under these modified reaction conditions, the malonate was efficiently introduced at the homoallylic position, affording the derivative **6 aa**. When employing aliphatic alcohols under standard reaction conditions (Scheme 7b), alternative reaction pathways were detected. In this case, an elimination reaction was conducted to the formation of 1,3-dien-5-yne **7 aa** in moderate yields as a mixture of diastereoisomers. Thiol nucleophiles were demonstrated to be more reactive, affording the desired sulfide **8 aa** derived from the related nucleophilic substitution of the iodide intermediate **4 aa** with the 4-chlorophenyl thiolate (Scheme 7c).

Conclusions

In summary, herein, we have investigated the reactivity of the scarcely studied cyclopropylmethyl thioethers towards *S*-atom



Scheme 7. Reaction with other nucleophiles.

activation by sources of monopositive halonium ions. Our preliminary studies have shown that the interaction of the NFSI or molecular iodine with the sulfide causes enabling C–S bond cleavage in conventional solvents, generating a non-classical cyclopropylcarbinyl cation. Taking advantage of the rearrangements of these types of carbocations, we have designed complementary C–N bond-forming protocols for the synthesis of homoallylic amines and *N*-benzenesulfonimides under non-acidic conditions. The use of NFSI reagent as both sources of electrophilic fluorine and *N*-based nucleophile was demonstrated useful for the synthesis of *N*-homoallyl benzenesulfonimides in a one-pot one-step sequence after desulfurative cleavage, cyclopropylcarbinyl cation rearrangement and C–N bond forming reaction. The homoallylation of more basic nucleophiles was best achieved through a one-pot, two-step sequence in which initially, the thioether is transformed into a homoallyl iodide after the desulfurative cleavage and the cyclopropylcarbinyl cation rearrangement. Then, the homoallyl iodide intermediate reacts with the amine in the second step. Both protocols were shown to occur with a high control over the regio- and diastereoselectivity of the process.

Supporting Information

Full experimental procedures, characterization data, and copies of NMR spectra are included. The authors have cited additional references within the Supporting Information.[25–29]

Acknowledgements

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Organosulfur compounds · C–S bond cleavage · amines · halogen · carbocations

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