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Superacid mediated reactions applied to 4-aminobenzofused sultams and fluorinated 4-aminobenzene sulfonamides synthesis

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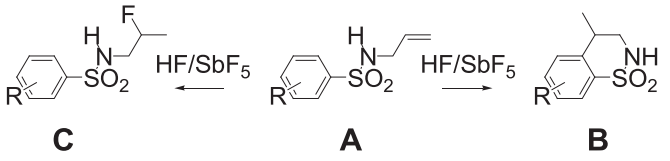
ABSTRACT

A novel series of 4-aminobenzofused sultams was prepared using an efficient synthetic procedure based on superacid mediated reactions followed either by copper-catalyzed coupling or S_NAr reactions. The synthetic potential of the method toward the divergent synthesis of novel potent bioactive (fluorinated) aminobenzofused sultams and fluorinated 4-aminobenzene sulfonamides was shown, making it a new valuable process to synthesize a large diversity of compounds in bioactive 4-aminobenzene sulfonamide family.

1. Introduction

Since the discovery of antibiotic and antibacterial properties of sulfa drugs,[1] sulfanilamide core became very popular in SAR studies in medicinal chemistry research. The role of 4-aminobenzene sulfonamide substrates in matrix metalloprotease inhibition,[2] carbonic anhydrases inhibition,[3] HIV protease inhibition[4] or pyruvate kinase isozyme activation[5] has been largely proved. Sulfanilamides are classically prepared from aniline derivatives, by chlorosulfonylation method after N-acetylation.[6] Even if this method has been largely used, it requires four synthetic steps, due to the inevitable nitrogen protection and deprotection,[7] and harshness conditions (sulfonylation with concentrated sulfuric acid or oleum and chlorination with phosphorus pentachloride). Surprisingly, in spite of the recently reported very specific palladium-catalyzed transfer hydrogenation of nitrobenzene sulfonamide,[8] palladium-catalyzed intramolecular cyclization,[9] or Grignard-based sulfonamide synthesis from 4-bromoaniline,[10] no general route to 4-aminobenzene sulfonamides has been reported. As a consequence, the diversity of aminobenzene sulfonamide functionality in pharmaceutical research is limited. Based on superelectrophilic activation[11] in superacid,[12] we recently reported an extension of our work on unsaturated nitrogen containing compounds behavior in HF/SbF_5,[13] toward the synthesis of benzofused sultams and fluorinated benzenesulfonamides (Scheme 1).[14]



Scheme 1. Benzofused sultams and fluorinated benzenesulfonamides synthesis in superacid HF/SbF_5.

However, the synthesis of 4-aminobenzofused sultams from corresponding 4-aminosulfonamides ($R{=}NR_1R_2$) could not be achieved by using our methodology. To circumvent this problem, starting from 4-fluorosulfonamide (R=F), we envisaged to use a sequential superacid/S_NAr strategy. Herein we report, the extension of this work and the development of alternative routes to novel 4-aminobenzofused sultams and fluorinated 4-aminobenzene sulfonamides.

2. Results and discussion

Starting from *N*-allylic benzenesulfonamides **A**, substituted in *para* position with an halogen atom, after either intramolecular Friedel–Crafts type cyclization or hydrofluorination reaction in superacid HF/SbF_5, benzofused sultams **B** or fluorinated benzenesulfonamides **C** should be formed selectively. Then N-alkylation followed by nucleophilic aromatic substitution should allow the formation of a high diversity of 4-aminobenzofused sultams **D** and fluorinated 4-aminobenzene sulfonamides **E** (Scheme 2).

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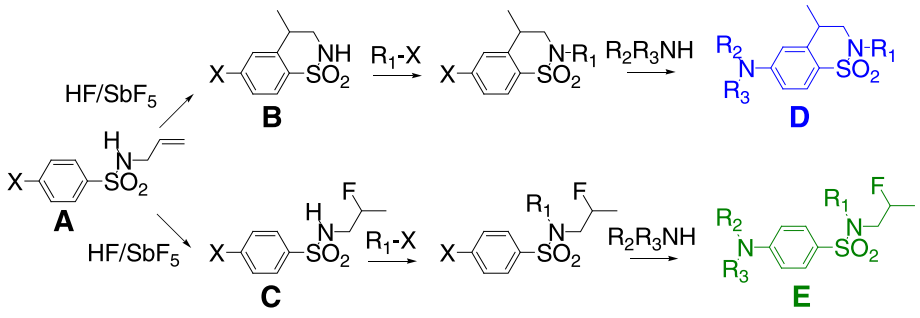
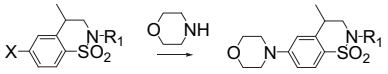


Scheme 2. Synthesis of 4-aminobenzofused sultams and fluorinated 4-aminobenzene sulfonamides.

Whereas nucleophilic aromatic substitution on 4-nitro-fluoroaromatics is a reaction of broad applicability, activation by electron withdrawing groups other than nitro is less used. This is mainly due to the decreased ability to stabilize the negative charge in the intermediate anion during the S_NAr process. By comparing the σ_p-values of nitro group (1.27) versus SO_2NMe_2 (0.99),[15] it is not surprising that reports on replacement of fluorine (or halogen atom) with nitrogen on 4-halogenobenzene sulfonamides are rare despite the enormous biological potential of the sulfanilamide derivatives.[16] Thus, we examined carefully the S_NAr reaction of the proposed strategy (Table 1).

Table 1
Nucleophilic aromatic substitution of 4-halogenated benzofused sultams with morpholine[a]

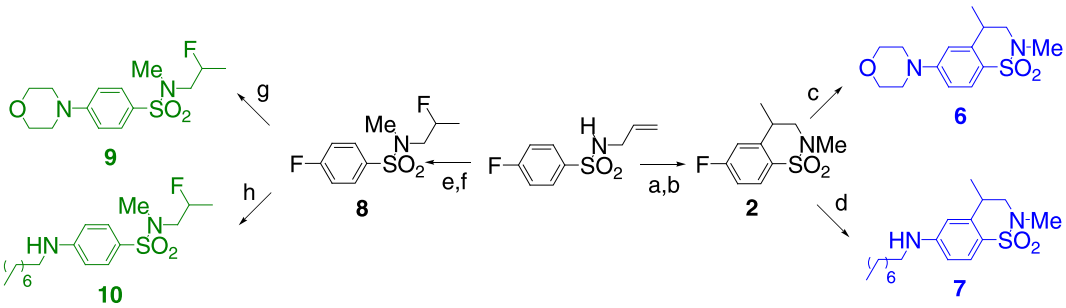


Entry	X	R_1	Substrate	Time	Product	Yield[b]
1	F	H	**1**	12 h	—[c]	—[c]
2	F	H	**1**	72 h	—[c]	—[c]
3	F	H	**1**	120 h	**5**	5%
4	F	Me	**2**	120 h	**6**	16%
5[d]	F	H	**1**	48 h	**5**	54%
6[d]	Cl	H	**3**	48 h	—[c]	—[c]
7[d]	Cl	H	**3**	120 h	**5**	7%
8[d]	Cl	H	**3**	30 days	**5**	15%
9[d]	Br	H	**4**	124 h	—[c]	—[c]
10[d]	F	H	**1**	120 h	**5**	91%
11[d]	F	Me	**2**	48 h	**6**	88%

[a] Reaction conditions: morpholine (1 equiv), K_2CO_3, DMSO, reflux.
[b] Yields obtained after purification by flash-chromatography.
[c] No reaction.
[d] Morpholine (5 equiv), neat, 100 °C.

Using morpholine as nucleophilic partner, and various sultams as substrates, we evaluated the ability to perform the S_NAr reaction. First attempts, with fluorinated sultam **1** were unsuccessful (Table 1, entries 1 and 2). By increasing reaction time, the reaction led to a large mixture of compounds, and only a small amount of desired product could be obtained (Table 1, entry 3). As the acidity of the sulfonamide proton could probably allow the formation of the corresponding anion in the basic conditions, preventing substrate from the nucleophilic aromatic substitution, corresponding *N*-methyl sultam **2** was subjected to reaction in similar conditions (Table 1, entry 4). Even if the reaction became selective, its rate was found to be very slow. After 5 days of reaction, the desired product **6** could only be obtained in 16% yield. However, using neat conditions, with an excess of morpholine (5 equiv), allowed the formation of product **5** in 54% yield (Table 1, entry 5). By increasing reaction time, product **5** could be formed in 91% yield, and only 2 days of reaction were necessary to fully convert *N*-methyl analog **2** to product **6** (88% yield) in the same reaction conditions (Table 1, entries 10–11). Similar conditions were also applied to bromo and chloro derivatives. Not surprisingly, product **5** was formed in very low yield starting from chloroderivative, and thus after prolonged reaction time (30 days). The reaction did not occur with bromo substituted substrate **4**. This study confirmed the necessity to perform N-alkylation of the sulfonamide function before performing the S_NAr reaction and allowed us to find optimized conditions.

Then, starting from *N*-allyl-4-flurobenzene sulfonamide, by using the proposed strategy, compounds of type **D** and **E** were synthesized (Scheme 3). Selective superelectrophilic activated intramolecular Friedel–Crafts type reaction gave the corresponding sultam in 54% yield, which was subsequently *N*-methylated with methyliodide to afford compound **2** in 95% yield. *N*-Alkylated sultam **2** was subjected to the S_NAr reaction with morpholine to give the 4-aminobenzofused sultam **6** in 88% yield. The compatibility of the S_NAr reaction with primary amines was also tested. The reaction of sultam **2**, in the presence of octylamine, gave product **7** in 74% yield. Starting from the same substrate, by modifying superacid reaction conditions, the hydrofluorination reaction yielded corresponding fluorinated sulfonamide in 88% yield. A subsequent N-methylation led to the formation of product **8**. Then, fluorinated compound **8** was treated with either

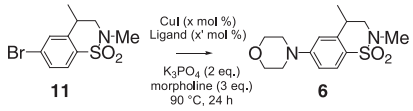


Scheme 3. Reagents and conditions: (a) HF/SbF_5 (mol %SbF_5=13.6), −20 °C, 10 min, 54%; (b) CH_3I (1 equiv), K_2CO_3, DMF, rt, 12 h, 95%; (c) morpholine (5 equiv), reflux, 48 h, 88%; (d) octylamine (5 equiv), reflux, 72 h, 74%; (e) HF/SbF_5 (mol %SbF_5=3.8), −20 °C, 10 min, 88%; (f) CH_3I (1 equiv), K_2CO_3, DMF, rt, 12 h, 95%; (g) morpholine (5 equiv), reflux, 48 h, 76%; (h) octylamine (5 equiv), reflux, 48 h, 76%.

morpholine or octylamine, and gave, respectively, products **9** and **10** in good yields. However, despite the efficiency of this superacid-based multistep divergent synthesis of 4-aminobenzene sulfonamides, the S_NAr reaction is the critical step of this synthetic method. The nucleophilic aromatic substitution with sensitive amines could not be achieved by using these conditions, and using a large excess of amine could be a limitation with more elaborated amines. As a consequence, we explored the ability to find an alternative to the S_NAr step. Despite the high efficiency of the Pd-catalyzed Buchwald–Hartwig reaction,[17] the use of expensive palladium and elaborate phosphine ligands would limit its application to large scale production. Recently, the attractiveness of cheap copper catalysts and the availability of copper ligands led to the resurgence of interests in copper-catalyzed Ullman-type reactions.[18] However, to the best of our knowledge the examples of aminobenzene sulfonamides synthesis via a copper-catalyzed N-arylation approach are relatively rare.[19] In these cases, microwave or high temperature conditions were needed to perform the reaction and *ortho* sulfonamide substituent seemed to favor the reaction.[20] We therefore sought to investigate whether superacid chemistry combined to copper-catalyzed Ullman-type N-arylation could become an alternative to the previously described strategy.

The investigation was initiated by evaluating the coupling reaction of 4-brominated sultam **11**, product of Friedel–Crafts intramolecular superacid reaction (Scheme 1, structure of type **B** with R=Br), with morpholine as a model reaction, to screen several reaction parameters, such as temperature, ligand, solvent, and catalyst amount (Table 2). First, a test reaction without copper-ligand system confirmed that classical S_NAr reaction did not occur.

Table 2
Optimization of the Ullmann-type coupling[a]



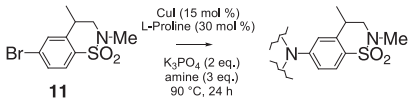
Entry	CuI (mol %)	Ligand (mol %)	Yield[b] (%)
1	—	—	—[c]
2	5	1,10-Phenantroline (20)	—[c]
3	5	2-Acetylcyclohexanone (20)	—[c]
4	5	Dipivaloylmethane (20)	12
5	5	2-Phenylphenol (20)	22
6	5	*N*,*N*-Diethylsalicylamide (20)	—[c]
7[d]	5	L-Proline (10)	35
8[d]	10	L-Proline (20)	51
9[d]	10	L-Proline (20)	56[e]
10[d]	10	L-Proline (20)	70[e,f]
11[d]	15	L-Proline (30)	70[f]

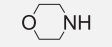
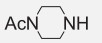
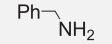
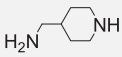
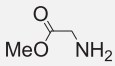
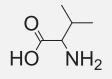
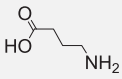
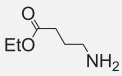
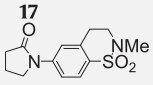
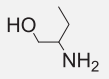
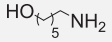
[a] Reaction conditions: substrate (0.34 mmol), CuI (*x* mol %), ligand (*x'* mol %), morpholine (3 equiv), K_3PO_4 (2 equiv), DMF (3 mL), 90 °C, 24 h.
[b] Yield obtained after purification.
[c] No reaction.
[d] DMSO was substituted to DMF.
[e] Reaction time (72 h).
[f] Solvent (0.2 mL).

Then, a series of ligands was screened. By using 5 mol % of CuI and 20 mol % of ligand, it appeared that neither diamine ligands nor diketone ones were efficient (Table 2, entries 2–4). The use of 2-phenylphenol allowed to convert substrate to sultam **6** in low yield (Table 2, entry 5). However, increasing CuI and ligand amounts did not improve the conversion, and thus even with higher temperature and longer reaction time. Based on the recent reports of Ma, showing the ability to use aminoacids as ideal promoters in the CuI-catalyzed coupling reaction of aryl halides with amines,[21] we evaluated the catalytic activity of CuI/L-proline system. The first attempt confirmed that this catalytic system could be efficient to perform the reaction (Table 2, entry 7). By increasing the amount of the catalytic system, compound **6** was formed in 56% yield (Table 2, entries 8 and 9). After decreasing the dilution and using 15 mol % of CuI and 30 mol % of L-proline, optimized conditions were found (Table 2, entries 10 and 11). It is noteworthy that the base modification (K_2CO_3, Cs_2CO_3) had no positive effect on the reaction.

We next extended the scope of the reaction to various amine derivatives (Table 3). We found that the reaction was applicable to a broad range of derivatives. The coupling reactions were performed well for the secondary amines (Table 3, entries 1–3). In addition, primary amines were found to be compatible with the reaction (Table 3, entries 4–6).

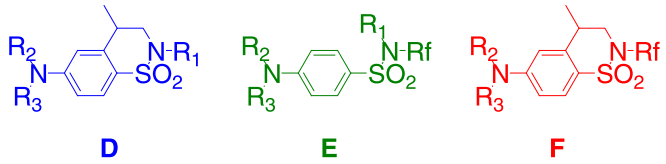
Table 3
CuI-Catalyzed coupling reaction of sultam with amines[a]



Entry	Amine	Product	Yield[b] (%)
1		**6**	70
2		**12**	87
3		**13**	63
4		**7**	62[c]
5		**14**	71[c]
6		**15**	32[c,d]
7		—	—[e]
8		—	—[e]
9		—	—[e]
10		**16**	75
11		**17**  **18**	0 64[f]
12		**19**	72[c,f]
13		**20**	65[c]
14	NH_3 (aq)	**21**	81[f]

[a] Reaction conditions: substrate (0.34 mmol), CuI (15 mol %), L-proline (30 mol %), amine (3 equiv), K_3PO_4 (2 equiv), DMSO (0.3 mL), 90 °C, 24 h.
[b] Yield obtained after purification.
[c] Cs_2CO_3 was substituted to K_3PO_4.
[d] Side products formation.
[e] No reaction.
[f] Reaction time: 72 h.

It is noteworthy that for primary amines, the use of Cs_2CO_3 was preferred to K_3PO_4. As previously observed in Ullman-type

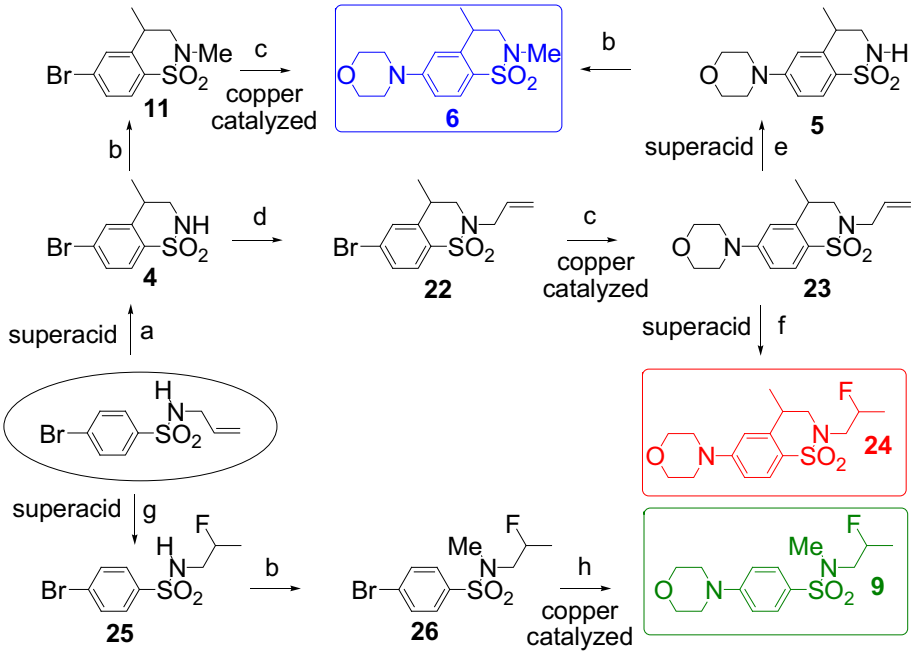


Scheme 4. Targeted original 4-aminobenzene sulfonamides.

reactions, the choice of the base is dramatically important, but its effect remains unclear and its choice remained empirical in our case.[22] Interestingly, in a synthetic point of view, allylamine was found to be an excellent partner for the coupling reaction (Table 3, entry 5). Despite strong efforts to catalyze the coupling of diamine and α-aminoacids derivatives (screening of different ligands, bases, temperature conditions), the reaction of these substrates remained unsuccessful (Table 3, entries 7–9). Intrigued by these results, we explored the reaction efficiency with γ-aminoacids derivatives. In these cases, the catalytic system was found to be suitable for the formation of corresponding coupling products **16** and **18** (Table 3, entries 10 and 11). In basic conditions, **17** led probably to the corresponding pyrrolidin-2-one **18** after intramolecular cyclization. The observed difference of reactivity, depending on the distance between amino and carboxyl groups, might be due to the ability of aminoacids derivatives to play the role of competitive ligands.[21] A similar behavior of aminopiperidine could also be postulated. By using Cs_2CO_3 as a base, the reaction also displayed a great tolerance to aminoalcohol substrates (Table 3, entries 12 and 13). With aminoalcohol substrates, a full chemoselectivity (N-arylation vs O-arylation) was observed, probably due to the choice of the ligand.[18b] Based on the recently reported elegant CuI-catalyzed amination reactions using aqueous ammonia,[23] we turned our attention to the formation of amino-product **21**. We were pleased to observe the full conversion of substrate **11** after 3 days reaction, with the formation of desired product **21** in 81% yield (Table 3, entry 14). With this novel route to 4-aminobenzofused sultam in hand, we tested this strategy in a multistep superacid-based synthesis of novel functionalized sultams. To the best of our knowledge, multistep synthesis involving HF/SbF_5 superacid chemistry at several stages has not been previously done. This method should allow accessing rapidly a large variety of diversely substituted cyclic or acyclic 4-aminobenzene sulfonamides **D**, **E** or **F** where R_{1-3} could be functionalized alkyl groups and Rf fluorinated alkyl groups. (Scheme 4).

As a model study, *N*-allyl-4-bromobenzene sulfonamide was used as a starting material for the synthesis of 4-aminobenzofused sultams **D**, fluorinated 4-aminobenzofused sultams **E** or fluorinated 4-aminobenzene sulfonamides **F** (Scheme 5). A Friedel–Crafts superacid-promoted intramolecular reaction afforded sultam **4** in 62% yield. Aware of the necessity to protect nitrogen atom to perform the copper-catalyzed amination,[24] two strategies could be employed at this stage. The first strategy combined a preliminary N-alkylation (formation of product **11**), followed by a copper-catalyzed Ullman-type reaction and afforded 4-aminobenzofused sultam **6** in good yield.

Then, based on the recently reported deallylation process of *N*-allylic sulfonamides in superacid HF/SbF_5,[14] we examined a second strategy, with allylic protective group. Starting from the same substrate, a Friedel–Crafts superacid-promoted intramolecular reaction afforded sultam **4**, which was N-protected with an allylic group (formation of product **22**). Then Ullman-type reaction gave in optimized conditions 4-aminobenzofused sultam **23** in 70% yield. At this stage an original deallylation reaction in HF/SbF_5 afforded product **5** (92% yield). A final N-alkylation gave product **6** in good overall yield. The ability to introduce the *N*-alkyl group at the last stage of the synthesis shows the high synthetic potential of this strategy. Moreover, the excellent yield obtained for the coupling reaction of morpholine with *N*-allylic substrate should allow delivering efficiently a large variety of 4-aminobenzofused sultams of type **D**. Interestingly, by a simple modification of superacid conditions, we also proved that fluorinated 4-aminobenzofused sultams of type **F** could easily be obtained with this methodology. Starting from *N*-allylic compound **23**, superacid mediated hydrofluorination led to fluorinated product **24** in 69% yield. The potent modifications of fluorinated alkyl group, by using superacid reactions (hydrofluorination,[13a,e] bromofluorination,[13f] hydroxylation,[13a] difluorination,[13c]…), strengthen the high



Scheme 5. Superacid/copper mediated multistep divergent synthesis of 4-aminobenzene sulfonamides. Reagents and conditions: (a) HF/SbF_5 (mol % SbF_5=13.6), −20 °C, 10 min, 62%. (b) CH_3I, K_2CO_3, DMF, rt, 12 h, >95% (c) CuI, L-proline, morpholine, K_3PO_4, DMSO, 90 °C, 24 h, 70%. (d) allylbromide, K_2CO_3, DMF, rt, 12 h, 83%. (e) HF/SbF_5 (mol % SbF_5=27), 0 °C, 10 min, 92%. (f) HF/SbF_5 (mol % SbF_5=3.8), −20 °C, 10 min, 69%. (g) HF/SbF_5 (mol % SbF_5=3.8), −20 °C, 10 min, 42%. (h) CuI, L-proline, morpholine, K_3PO_4, DMSO, 90 °C, 24 h, 61%.

divergent character of this method and its potential toward original fluorinated 4-aminobenzofused sultams synthesis. Encouraged by the recently reported Ullman-type reaction of fluoroalcohols,[25] which confirmed the compatibility of fluorinated substrates with copper-catalyzed reaction, we tested the ability to synthesize fluorinated 4-aminobenzene sulfonamide of type **E** by using a similar strategy. Starting from the same substrate, superacid mediated hydrofluorination followed by N-alkylation yielded fluorinated product **26** in good yield. As previously observed, the coupling of fluorinated substrate was compatible with the CuI catalytic system, yielded desired product **9** in 61% yield. Again, a simple modification of superacid conditions should allow the formation of a large variety of type **E** fluorinated novel products.

3. Conclusion

In conclusion, a rapid and versatile novel method, based on sequential superacid/copper mediated reactions, for the synthesis of diversified 4-aminobenzofused sultams is reported. This method has been extended to a multistep strategy, offering a very attractive alternative for the synthesis of a large variety of potent novel bioactive (fluorinated) molecules in aminobenzene sulfonamide family. Starting from the same substrate, a strong divergent character of this method was confirmed with the formation of diversely substituted cyclic or acyclic fluorinated (or not) 4-aminobenzene sulfonamides. Moreover, this is the first reported multistep sequence involving superacid chemistry at different stages. This work emphasizes the high potential of this original chemistry in organic synthesis.

4. Experimental section

4.1. General procedure for the superacid-promoted synthesis of benzofused sultams

To a mixture of HF/SbF_5 (6 mL, 4/2 M ratio) maintained at −20 °C, was added nitrogen derivative (1 mmol). The mixture was magnetically stirred at the same temperature for reaction time. The reaction mixture was then neutralized with water-ice/Na_2CO_3, extracted with dichloromethane (×3). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Products were isolated by column chromatography over silica gel.

*4.1.1. Compound **1**: 6-fluoro-4-methyl-3,4-dihydro-2H benzo[1,2] thiazine 1,1-dioxide.* Optimized procedure (10 min reaction time) was followed, starting from 215 mg of *N*-allyl-4-fluorobenzenesulfonamide (1 mmol). Purification by flash column chromatography (70/29.5/0.5: dichloromethane/petroleum ether/NH_3 aq) afforded 117 mg of the title compound as a solid (54%). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 1.28 (d, J=7.1 Hz, 3H, CH_3), 2.98 (m, 1H, H-4), 3.37 (m, 1H, H-3), 3.72 (m, 1H, H-3), 5.38 (t, J=7.0 Hz, 1H, NH), 6.94 (m, 2H, H-5, and H-7), 7.64 (m, 1H, H-8). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 19.4 (s, CH_3), 32.2 (s, CH, C-4), 48.4 (s, CH_2, C-3), 115.4 (d, $^2J_{C-F}$=22 Hz, CH, C-7), 115.8 (d, $^2J_{C-F}$=22 Hz, CH, C-5), 128.1 (d, $^3J_{C-F}$=9 Hz, CH, C-8), 133.5 (d, $^4J_{C-F}$=3 Hz, C-9), 144.1 (d, $^3J_{C-F}$=8 Hz, C-10), 164.7 (d, $^1J_{C-F}$=252 Hz, C-6). ^{19}F {^{1}H} NMR (282 MHz, $CDCl_3$, ppm): −105.5. MS (GCT, CI^+): m/z (relative intensity %) 215 $[M]^+$ (65). HRMS (ESI): calcd for: ($C_9H_{10}NO_2FS$) 215.04163, found 215.0417. Melting point (°C): 93.5.

4.2. General procedure for the S_NAr reactions of sultams with amines

A mixture of sultam (1 mmol), amine (5 mmol), K_2CO_3 (2 mmol) was heated at 100 °C for the appropriate reaction time. The cooled mixture was partitioned between water and ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with H_2O, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel.

*4.2.1. Compound **6**: 2,4-dimethyl-6-morpholin-4-yl-3,4-dihydro-2H-benzo[1,2] thiazine 1,1-dioxide.* Optimized procedure (48 h reaction time) was followed; purification by flash column chromatography (1/99,methanol/dichloromethane) gave 260 mg of the title compound as a solid (88%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 1.33 (d, J=6.8 Hz, 3H, CH_3), 2.83 (s, 3H, NCH_3), 3.20 (m, 5H, H-3′, and H-4), 3.59 (m, 2H, H-3), 3.83 (m, 4H, H-2′), 6.70 (s, 1H, H-5), 6.83 (d, J=8.8 Hz, 1H, H-7), 7.22 (d, J=8.8 Hz, 1H, H-8). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 19.3 (CH_3), 28.2 (CH, C-4), 35.5 (NCH_3), 48.1 ($2CH_2$, C-3′), 55.5 (CH_2, C-3), 66.6 ($2CH_2$, C-2′), 112.8 (CH, C-5), 113.5 (CH, C-7), 125.2 (C-9), 126.2 (CH, C-8), 141.3 (C-6), 153.6 (C-10). MS (GCT, CI^+): m/z (relative intensity %) 296 $[M]^+$ (100). HRMS (ESI): calcd for: ($C_{14}H_{20}N_2O_3NaS$) 319.10923, found 319.1090. Melting point (°C): 120–121.

4.3. General procedure for the CuI-catalyzed reactions of sultams with amines

A mixture of sultam (0.34 mmol), amine (1 mmol), K_3PO_4 (0.68 mmol), CuI (0.05 mmol), and the appropriate ligand (0.1 mmol) in 0.2 mL of DMSO was heated at 90 °C. The cooled mixture was partitioned between water and ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with H_2O, dried over Mg_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel.

*4.3.1. Compound **12**: 2,4-dimethyl-6-piperidin-1-yl-3,4-dihydro-2H-benzo[1,2] thiazine 1,1-dioxide.* Optimized procedure (24 h reaction time) was followed; purification by flash column chromatography (100%, dichloromethane) gave 87 mg of the title compound as a solid (87%). ^{1}H NMR(400 MHz, $CDCl_3$, ppm): 1.31 (d, J=6.8 Hz, 3H, CH_3), 1.64 (m, 6H, H-3′ et H-4′), 2.82 (s, 3H, NCH_3), 3.17 (m, 1H, H-4), 3.25 (m, 4H, H-2′), 3.50 (dd, J=14.4, 5.6 Hz, 1H, H-3), 3.63 (dd, J=14.4, 5.6 Hz, 1H, H-3), 6.68 (s, 1H, H-5), 6.81 (dd, J=8.8, 2.4 Hz, 1H, H-7), 7.22 (d, J=9.2 Hz, 1H, H-8). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 19.2 (CH_3), 24.2 (CH_2, C-4′), 25.3 ($2CH_2$, C-3′), 28.1 (CH, C-4), 35.4 (NCH_3), 49.0 ($2CH_2$, C-2′), 55.5 (CH_2, C-3), 112.9 (CH, C-5), 113.7 (CH, C-7), 123.5 (C-9), 126.1 (CH, C-8), 141.1 (C-10), 153.9 (C-6). MS (GCT, CI^+): m/z (relative intensity %) 294 $[M]^+$ (100). HRMS (ESI): calcd for: ($C_{15}H_{22}N_2O_2NaS$) 317.1300, found 317.1297. Melting point (°C): 109–110.

4.4. Synthesis of product 24

To a mixture of HF/SbF_5 (6 mL, 4/2 M ratio) maintained at −20 °C, was added *N*-allyl-4-bromobenzene sulfonamide (1 mmol). The mixture was magnetically stirred at the same temperature for reaction time. The reaction mixture was then neutralized with water-ice/Na_2CO_3, extracted with dichloromethane (×3). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography over silica gel (70/30: dichloromethane/petroleum ether) afforded 171 mg of product **4** as a colorless oil (55%).

*4.4.1. Compound **4**: 6-bromo-4-methyl-3,4-dihydro-2H-benzo[1,2] thiazine 1,1-dioxide.* ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 1.27 (d, J=7.1 Hz, 3H, CH_3), 2.95 (m, 1H, H-4), 3.36 (m, 1H, H-3), 3.72 (m, 1H, H-3), 5.24 (t, J=7.6 Hz, 1H, NH), 7.35 (m, 2H, H-5, and H-7), 7.46 (d, J=8.9 Hz, 1H, H-8). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 19.5 (CH_3), 31.8 (CH, C-4), 48.3 (CH_2, C-3), 125.9 (CH, C-7), 127.1 (C-6), 131.0 (CH, C-8), 132.0 (CH, C-5), 136.3 (C-9), 142.8 (C-10). MS (GCT, CI^+): m/z

(relative intensity %) 275 $[M]^+$ (10), 277 $[M]^+$ (10). HRMS (ESI): calcd for: ($C_9H_{10}NO_2SNaBr$) 297.95133, found 297.9510.

To a suspension of K_2CO_3 (276 mg, 2 mmol) in DMF (5 mL) was added dropwise substrate **4** (276 mg, 1 mmol). The mixture was stirred for 15 min and allylbromide (0.094 ml, 1.1 mmol) was added. The resulting mixture was stirred for 12 h under an N_2 atmosphere at room temperature and then partitioned between EtOAc (50 mL) and water (30 mL). The organic phase was separated and dried, and then the solvent was removed in vacuo. 262 mg (83%) of product **22** was isolated by column chromatography purification (dichloromethane). Then, a mixture of substrate **22** (0.34 mmol), morpholine (1 mmol), K_3PO_4 (0.68 mmol), CuI (0.05 mmol), and L-proline (0.1 mmol) in 0.2 mL of DMSO was heated at 90 °C for 24 h. The cooled mixture was partitioned between water and ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with H_2O, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residual oil by flash column chromatography (100%, dichloromethane) gave 77 mg of compound **23** as a colorless oil (70%).

*4.4.2. Compound **23**: 2-allyl-4-methyl-6-morpholin-4-yl-3,4-dihydro-2H-benzo[1,2] thiazine 1,1-dioxide.* ^1H NMR (400 MHz, $CDCl_3$, ppm): 1.29 (d, J=7.2 Hz, 3H, CH_3), 3.10 (m, 1H, H-4), 3.20 (t, J=4.8 Hz, 4H, H-3′), 3.53 (m, 3H, H-3, and H-2″), 3.80 (t, J=4.8 Hz, 4H, H-2′), 3.99 (dd, J=14.4, 5.2 Hz, 1H, H-2″), 5.25 (m, 2H, H-4″), 5.80 (s, 1H, H-3″), 6.68 (d, J=2.0 Hz, 1H, H-5), 6.81 (dd, J=8.8, 2.4 Hz, 1H, H-7), 7.63 (d, J=8.8 Hz, 1H, H-8). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 19.4 (CH_3), 29.1 (CH, C-4), 47.9 ($2CH_2$, C-3′), 49.9 (CH_2, C-3′), 51.2 (CH_2, C-3), 66.6 ($2CH_2$, C-2′), 112.9 (CH, C-5), 113.4 (CH, C-7), 119.5 (CH, C-4″), 125.8 (CH, C-8), 126.4 (C-9), 132.9 (CH, C-3″), 141.6 (C-6), 153.6 (C-10). MS (GCT, CI^+): m/z (relative intensity %) 345 $[M+Na]^+$ (100). HRMS (ESI): calcd for: ($C_{16}H_{22}N_2O_3NaS$) 345.1248, found 345.1248.

To a mixture of HF/SbF_5 (3 mL, 7/1 M ratio) maintained at −20 °C for 10 min, was added substrate **23** (1 mmol). The mixture was magnetically stirred at the same temperature for reaction time. The reaction mixture was then neutralized with water-ice/Na_2CO_3, extracted with dichloromethane (×3). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Products were isolated by column chromatography purification (40/60, ethyl acetate/petroleum ether) and 236 mg of the compound **24** was obtained as a colorless oil (69%).

*4.4.3. Compound **24**: 2-(2-fluoro-propyl)-4-methyl-6-morpholin-4-yl-3,4-dihydro-2H-benzo[1,2] thiazine 1,1-dioxide.* ^1H NMR (400 MHz, $CDCl_3$, ppm): 1.37 (m, 6H, CH_3, and H-3″), 3.12 (m, 1H, H-4), 3.23 (t, J=5.2 Hz, 4H, H-3′), 3.57 (m, 4H, H-1″, and H-3), 3.84 (t, J=4.8 Hz, 4H, H-2′), 4.90 (dm, J=48.4 Hz, 1H, H-2″), 6.70 (s, 1H, H-5), 6.82 (dd, J=8.8, 2.0 Hz, 1H, H-7), 7.67 (d, J=8.8 Hz, 1H, H-8). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 18.0 and 18.6 (2d, J=22 Hz, C-3″), 19.1 and 19.3 (CH_3), 29.1 and 29.6 (CH, C-4), 47.9 (s, $2CH_2$, C-3′), 51.9 and 52.0 (2d, J=21 Hz, CH_2, C-1″), 54.1 and 54.3 (CH_2, C-3), 66.5 (s, $2CH_2$, C-2′), 90.3 and 91.4 (2d, J=168 Hz, CH, C-2″), 112.9 (s, CH, C-5), 113.3 (CH, C-7), 125.7 and 125.8 (CH, C-8), 126.3 and 126.6 (C-9), 141.6 and 141.7 (C-6), 153.6 (s, C-10). ^{19}F $\{^1H\}$ NMR (282 MHz, $CDCl_3$, ppm): −179.4. MS (GCT, CI^+): m/z (relative intensity %) 365 $[M+Na]^+$ (100). HRMS (ESI): calcd for: ($C_{16}H_{23}N_2O_3FNaS$) 365.1311, found 365.1311.

4.5. Synthesis of product 9

To a mixture of HF/SbF_5 (3 mL, 7/1 M ratio) maintained at −20 °C for 10 min, was added *N*-allyl-4-bromobenzene sulfonamide (2 mmol). The mixture was magnetically stirred at the same temperature for reaction time. The reaction mixture was then neutralized with water-ice/Na_2CO_3, extracted with dichloromethane (×3). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Products were isolated by column chromatography purification (50/50: dichloromethane/petroleum ether) to give 250 mg of compound **25** as a solid (42%).

*4.5.1. Compound **25**: 4-bromo-N-(2-fluoropropyl)-benzenesulfonamide.* ^1H NMR (300 MHz, $CDCl_3$, ppm): 1.30 (dd, J=23.8, 6.3 Hz, 3H, H-3′), 3.12 (m, 2H, H-1′), 4.70 (dm, J=48.9 Hz, 1H, H-2′), 5.07 (m, 1H, NH), 7.66 (d, J=8.7 Hz, 2H, H-3), 7.73 (d, J=8.7 Hz, 2H, H-2). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 18.5 (d, J=22 Hz, CH_3, C-3′), 48.5 (d, J=21 Hz, CH_2, C-1′), 89.5 (d, J=167 Hz, CH, C-2′), 128.2 (C-4), 128.9 (2CH, C-2), 132.9 (2CH, C-3), 139.3 (C-1). ^{19}F $\{^1H\}$ NMR (282 MHz, $CDCl_3$, ppm): −180.4. MS (GCT, CI^+): m/z (relative intensity %) 222 $[M-CH_3CHF]^+$ (12), 220 $[M-CH_3CHF]^+$ (18). HRMS (ESI): calcd for: ($C_9H_{11}NO_2FSBrNa$) 317.9576, found 317.9579. Melting point (°C): 101–102.

To a suspension of K_2CO_3 (138 mg, 1 mmol) in DMF (2 mL) was added dropwise **25** (148 mg, 0.5 mmol). The mixture was stirred for 15 min and CH_3I (0.035 ml, 0.55 mmol) was added. The resulting mixture was stirred for 8 h under an N_2 atmosphere and then partitioned between EtOAc (50 mL) and water (30 mL). The organic phase was separated and dried, then the solvent was removed in vacuo, and 154 mg of the desired compound **26** was obtained as a solid (>95%). Then, a mixture of substrate **26** (0.34 mmol), morpholine (1 mmol), K_3PO_4 (0.68 mmol), CuI (0.05 mmol), and L-proline (0.1 mmol) in 0.2 mL of DMSO was heated at 90 °C for 24 h. The cooled mixture was partitioned between water and ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with H_2O, dried over $MgSO_4$, and concentrated in vacuo. The residual oil was loaded on a silica gel column. Purification by flash column chromatography (100%, dichloromethane) gave 66 mg of compound **9** as a solid (61%).

*4.5.2. Compound **9**: N-(2-fluoro-propyl)-N-methyl-4-morpholin-4-yl-benzenesulfonamide.* ^1H NMR (400 MHz, $CDCl_3$, ppm): 1.35 (dd, J=23.6, 6.4 Hz, 3H, H-3′), 2.79 (s, 3H, NCH_3), 3.14 (m, 6H, H-1′, and H-2″), 3.84 (t, J=4.8 Hz, 4H, H-3″), 4.83 (dm, J=48.8 Hz, 1H, H-2′), 6.89 (d, J=9.2 Hz, 2H, H-3), 7.72 (d, J=9.2 Hz, 2H, H-2). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 18.4 (d, J=22 Hz, CH_3, C-3′), 36.7 (d, J=3 Hz, NCH_3), 47.5 (s, $2CH_2$, C-2″), 54.9 (d, J=22 Hz, CH_2, C-1′), 66.5 (s, $2CH_2$, C-3″), 90.3 (d, J=168 Hz, CH, C-2′), 113.8 (s, 2CH, C-3), 126.5 (s, C-1), 129.1 (s, 2CH, C-2), 153.8 (s, C-4). ^{19}F $\{^1H\}$ NMR (282 MHz, $CDCl_3$, ppm): −179.7. MS (GCT, CI^+): m/z (relative intensity %) 339 $[M+Na]^+$ (100), 317 $[M]^+$ (65). HRMS (ESI): calcd for: ($C_{14}H_{21}N_2O_3FNaS$) 339.1154, found 339.1156. Melting point (°C): 103–104.

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Supplementary data

Experimental procedures, products characterization and copies of NMR spectra. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.06.095.

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