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COMMUNICATION

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Synthesis of Enantiopure Benzo Fused Cyclic Sulfoximines Through Stereoselective [3 + 2] Cycloaddition between *N-tert*-Butanesulfinyl [(2-Pyridyl)sulfonyl]-difluoromethyl Ketimines and Arynes

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Dedicated to Prof. Dr. *Antonio Togni* on the occasion of his 65th birthday and retirement

The previously developed stereoselective [3 + 2] cycloaddition between *N-tert*-butanesulfinyl ketimines and arynes has been extended to the synthesis of enantiopure [(2-pyridyl)sulfonyl]difluoromethylated cyclic sulfoximines. The use of 2-PySO_2CF_2 as the facilitating group offers new opportunities for the elaboration of the [3 + 2] cycloaddition products by virtue of the diverse relativity of 2-pyridyl sulfones.

Keywords: arynes, cycloaddition, fluorine, *N-tert*-butanesulfinyl imine, sulfoximines.

Introduction

Sulfoximines, as monoaza analogues of sulfones, have played multiple roles in organic chemistry, agricultural chemistry and medicinal chemistry since their initial discovery in 1940s.[1–10] In agricultural chemistry and medicinal chemistry, biologically active sulfoximines have been developed as pesticides[10] and drugs.[5–9] In organic chemistry, sulfoximines have been used as chiral auxiliaries and ligands as well as new reagents.[2–4] Therefore, numerous methods have been developed for the construction of the sulfoximine functionality, including sulfur–nitrogen bond formation by direct nitrene transfer reaction to sulfoxides and sulfur–oxygen bond formation by direct oxidation of sulfimides.[1,11–13] The sulfur–carbon bond formation is also viable,[1,14] which mainly relies on the oxidation of sulfinamides to sulfonimidoyl halides or sulfonimidates followed by substitution with carbon nucleophiles.[15,16] However, little attention has been paid on direct *S*-functionalization of sulfinamides or sulfinimines with carbon electrophiles.[17–24] Moreover, cyclic sulfoximines, as a special class of heterocyclic compounds, have attracted attention from chemists due to their potential application as three-dimensional bioisosteres of relatively flat heterocycles.[25–28] However, methods for the synthesis of fluorine-containing cyclic sulfoximines are still rare.[29,30]

In 2014, we reported an unprecedented one-step method for the synthesis of enantiomerically pure benzo fused cyclic sulfoximines through stereoselective [3 + 2] cycloaddition between *N-tert*-butanesulfinyl imines and *in-situ* generated arynes by using (phenylsulfonyl)difluoromethyl group ($PhSO_2CF_2$) as a facilitating group (*Scheme 1,a*),[21] which not only represents the first efficient method for the construction of

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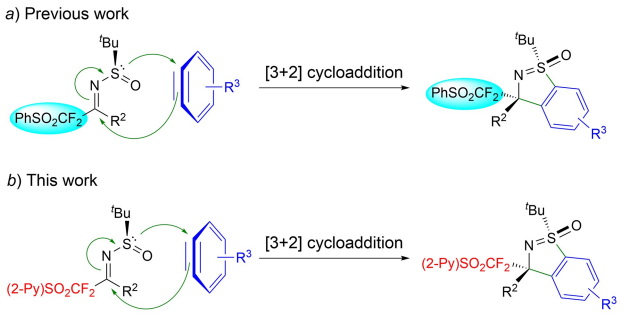


Scheme 1. [3 + 2] Cycloaddition between difluoro(sulfonyl) methylated *N-tert*-butanesulfinyl imines and arynes. 2-Py = 2-pyridyl.

sulfoximine moiety through direct sulfur–carbon bond formation between a sulfur-nucleophile and a carbon electrophile,[19–24] but also stands for an efficient protocol providing access to the optically active cyclic sulfoximines.[21–24] Moreover, the so-obtained $PhSO_2CF_2$-substituted cyclic sulfoximines can be easily transformed into the HCF_2-substituted cyclic sulfoximines through reductive desulfonylation or into the cyclic sulfinamides through stereoselective de-*tert*-butylation and formal nucleophilic substitution of the $PhSO_2CF_2$ group.[21] Considering that fluorinated heteroaryl sulfones, as represented by difluoromethyl 2-pyridyl sulfone, have been developed into more versatile fluoroalkylation reagents than the fluorinated phenyl sulfones and widely used for the incorporation of various fluorinated moieties into organic molecules,[31,32] we envisioned that the use of a (heteroarylsulfonyl)difluoromethyl group instead of $PhSO_2CF_2$ could provide new opportunities for the transformation of the fluorinated benzo fused cyclic sulfoximines, thus expanding the synthetic application of our previously developed [3 + 2] cycloaddition reaction between *N*-sulfinimines and arynes. Herein, we report our results using [(2-pyridyl)sulfonyl]difluoro methyl group (2-$PySO_2CF_2$) as a facilitating group (*Scheme 1,b*).[33]

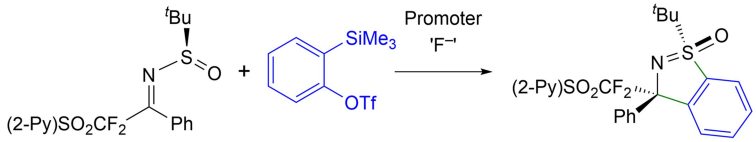
Results and Discussion

We began our investigation by choosing 2-$PySO_2CF_2$-subsituted *N-tert*-butanesulfinyl ketimine **1a** and *o*-trimethylsilyl phenyl triflate **2a** as the model substrates.[21,34] By using CsF as the promoter, the reaction between the 1,3-dipole **1a** and benzyne *in-situ* generated from **2a** proceeded smoothly in CH_3CN at room temperature. After 12 hours, cyclic sulfoximine **3a** was obtained in 44% yield with high diastereoselectivity (*Table 1*, *Entry 1*). Increasing the loadings of benzyne precursor **2a** and CsF could significantly improve the conversion of **1a** into the [3 + 2] cycloaddition product **3a** (*Table 1*, *Entries 2–4*), and a yield of 90% was obtained when 3.0 equiv. of **2a** and 5.0 equiv. of CsF were used. ^{19}F-NMR Monitoring of the progress of the reaction indicated completeness of the reaction within 12 hours (*Table 1*, *Entries 4–6*). Then we explored the influence of solvent and promoter on this [3 + 2] cycloaddition. It was found that the present [3 + 2] reaction was sensitive to reaction solvent and it was totally inhibited in THF, CH_2Cl_2 and toluene (*Table 1*, *Entries 7–9*); and promoters other than CsF, such as TMAF, TBAF and KF, were not effective in this reaction, even at an elevated temperature (*Table 1*, *Entries 10–13*). When the CsF-promoted reaction was conducted at elevated temperatures, although the consumption of **2a** was accelerated, the yield of **3a** was decreased to some extent due to the unmatched rate of benzyne generation to [3 + 2] cycloaddition (*Table 1*, *Entries 14* and *15*). Moreover, a lower temperature such as 0 °C significantly retarded the formation of **3a** due to the slower generation of benzyne (*Table 1*, *Entry 16*).

With the optimized reaction conditions in hand (*Table 1*, *Entry 4*), we further investigated the scope of the [3 + 2] cycloaddition between *N-tert*-butanesulfinyl difluoro[(2-pyridyl)sulfonyl]methyl ketimines and arynes. The ketimines **1** are air- and moisture-stable and could be easily prepared through condensation reaction of 2-$PySO_2CF_2$-subsituted ketones and the commercially available enantiopure *tert*-butylsulfinamide. Their structures including configuration of C=N bond were determined by the X-ray crystal structure analysis of **1h** (see *Supporting Information*).[1] As shown in *Table 2*, both electron-rich and electron-deficient aryl substituted ketimines could undergo the [3 + 2] cycloaddition reaction smoothly to provide the desired cyclic sulfoximines in good yields (**3a**–**3k**). The alkenyl- and alkyl-substituted ketimines are also viable substrates for this type of transformation, although yields tend to be lower. When non-symmetric aryne precursors, such as 4-methyl-2-(trimethylsilyl)phenyl triflate **2b** and 1-(trimethylsilyl)naphthalen-2-yl **2c**,

[1] CCDC 2056846 (**1h**) and 2056847 (**3h**) contain the supplementary crystallographic data for this article. These data can be obtained free of charge from *The Cambridge Crystallographic Data Centre* through https://www.ccdc.cam.ac.uk/structures/.

Table 1. Optimization of the reaction conditions.[a]



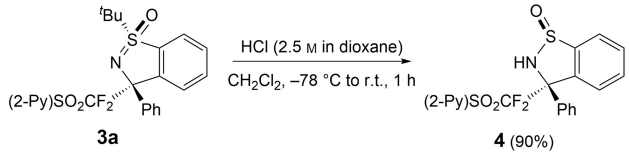
1a **2a** **3a**

Entry	**2a** (equiv.)	Promoter (equiv.)	Solvent	*T* [°C]	*t* [h]	Yield [%][b]	dr[b]
1	1.0	CsF (1.0)	CH_3CN	r.t.	12	44	>99:1
2	1.5	CsF (3.0)	CH_3CN	r.t.	12	69	>99:1
3	2.0	CsF (4.0)	CH_3CN	r.t.	12	89	>99:1
4	3.0	CsF (5.0)	CH_3CN	r.t.	12	90	>99:1
5	3.0	CsF (5.0)	CH_3CN	r.t.	4	86	>99:1
6	3.0	CsF (5.0)	CH_3CN	r.t.	8	89	>99:1
7	3.0	CsF (5.0)	THF	r.t.	12	0	>99:1
8	3.0	CsF (5.0)	CH_2Cl_2	r.t.	12	0	>99:1
9	3.0	CsF (5.0)	toluene	r.t.	12	0	>99:1
10	3.0	TMAF (5.0)	CH_3CN	r.t.	12	0	>99:1
11	3.0	TBAF (5.0)	CH_3CN	r.t.	12	0	>99:1
12	3.0	KF (5.0)	CH_3CN	r.t.	12	0	>99:1
13	3.0	KF (5.0)	CH_3CN	60	12	8	>99:1
14	3.0	CsF (5.0)	CH_3CN	60	4	84	>99:1
15	3.0	CsF (5.0)	CH_3CN	80	4	78	>99:1
16	3.0	CsF (5.0)	CH_3CN	0	12	64	>99:1

[a] Reaction conditions: **1a** (0.3 mmol), **2a** and promoter in solvent (5 mL) were stirred. [b] Yields and diastereomeric ratios were determined by ^{19}F-NMR spectroscopy using $PhCF_3$ as internal standard. TMAF = tetramethylammonium fluoride; TBAF = tetrabutylammonium fluoride.

were used in this [3+2] cycloaddition reaction, the benzo fused cyclic sulfoximines were obtained as a pair of regioisomers in high yields (**3n**/**3n**′ and **3o**/**3o**′). In all cases, the [3+2] cycloaddition reaction proceeded with excellent diastereoselectivity (dr >99:1). The high stereoselectivity of this cycloaddition reaction is further demonstrated by the excellent enantiomeric excess (ee) value of sulfoximine **3a** (>99% ee). The absolute configuration of cyclic sulfoximine **3h** was determined by its X-ray crystal structure and retention of the configuration at the sulfur atom was observed (see *Supporting Information*), and those of the others were assigned by analogy.

We next turned our attention to investigate the transformations of cyclic sulfoximines **3**. Initial attempt to prepare difluorinated sulfinate salt through direct removal of the 2-pyridyl group from **3a** with EtSNa/EtSH[35] gave the de-*tert*-butylated difluorinated sulfinate salt as the side product, which is difficult to separate from the desired product. Thereafter, we decided to remove the *tert*-butyl group first before conducting the depyridination reaction. Thus, treatment of cyclic sulfoximine **3a** with HCl-dioxane in CH_2Cl_2, as previously reported,[21] afforded cyclic

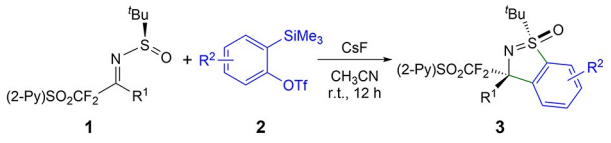


3a **4** (90%)

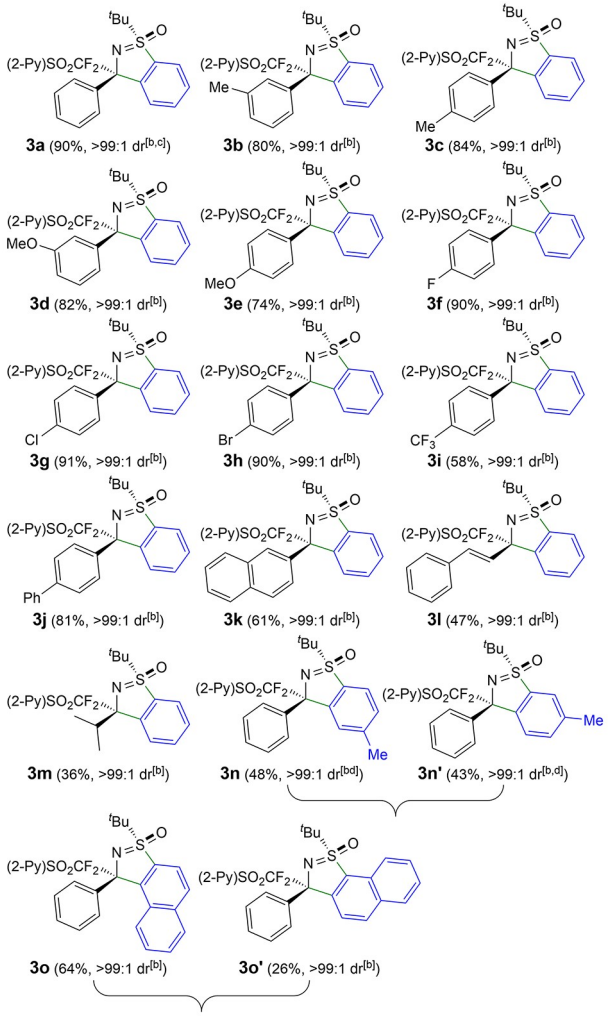
Scheme 2. Transformation from sulfoximine **3a** to sulfinamide **4**.

sulfinamide **4** in excellent yield with high diastereoselectivity (*Scheme 2*). The sulfinamide group in **4** can undergo either *S*- or *N*-functionalization. In the presence of *Selectfluor*,[36] sulfinamide **4** was converted to sulfonimidoyl fluoride **5** at room temperature as the sole diastereoisomer (*Scheme 3,a*). The absolute configuration at the stereogenic sulfur center is presumed to be retained as per previous report on electrophilic chlorination of chiral sulfinamides.[37–39] Sulfinamide **4** could also be further oxidized to cyclic sulfonamide **6** in 90% yield by 3-chloroperoxybenzoic acid (*m*-CPBA) (*Scheme 3,b*). Further modification of **4** could also be done on nitrogen atom of sulfinamide **4** through alkylation reaction with alkyl halides under basic conditions (*Scheme 3,c*). Notably, lower temperature

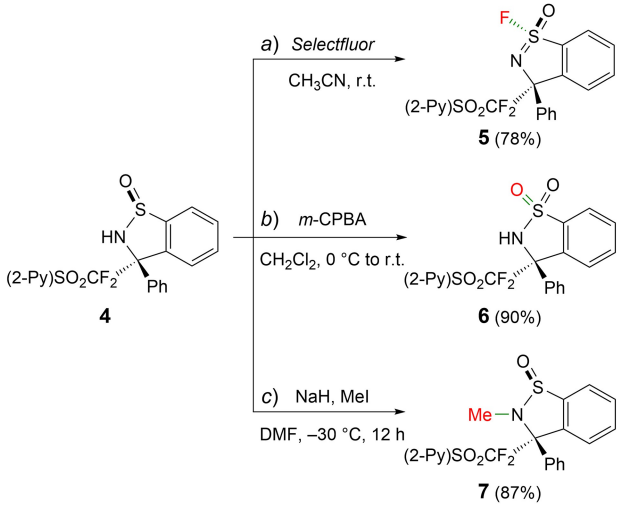
Table 2. [3 + 2] Cycloaddition between *N-tert*-butanesulfinyl imines **1** and aryne.[a]



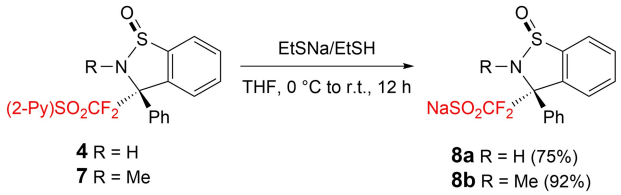
1 2 3



[a] Reaction conditions: **1** (0.3 mmol), **2** (0.9 mmol) and CsF (1.5 mmol) in CH_3CN (5 mL) were stirred at r.t. for 12 h, yield of isolated product. [b] Determined by ^{19}F-NMR spectroscopy. [c] Enantiomeric excess (ee) > 99%. [d] Isolated as a mixture of two regioisomers (**3n** + **3n**′).



Scheme 3. Transformations of sulfinamide **4**.

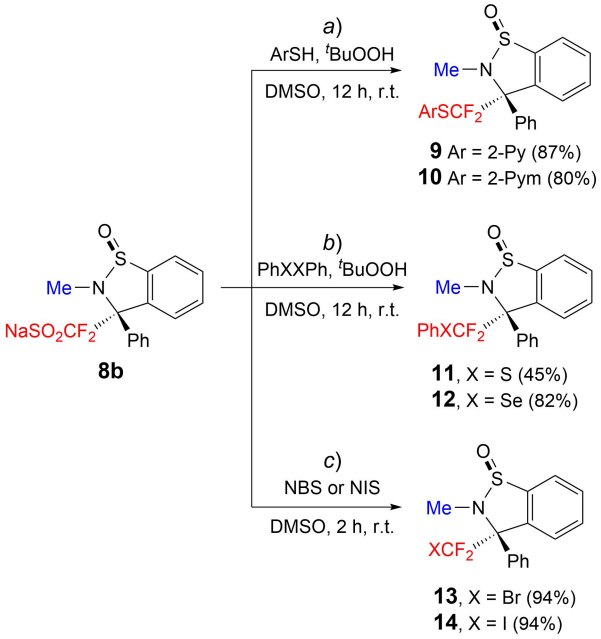


Scheme 4. Transformations from sulfinamides **4** and **7** to sulfinates **8**.

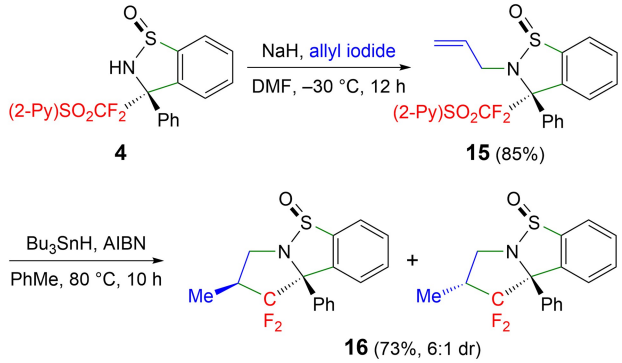
was required to stabilize the sulfinamide nitrogen anion and avoid the β-elimination of 2-PySO_2CF_2 anion. At −30 °C, the alkylation with methyl iodide occurred selectively on nitrogen atom of the sulfinamide group to afford *N*-methyl sulfinamide **7** in high yield.

By using the EtSNa/EtSH system, both the N–H unprotected cyclic sulfinamide **4** and *N*-alkylated cyclic sulfinamide **7** underwent the depyridination reaction smoothly, affording the corresponding difluoroalkyl sulfinate **8a** and **8b** in 75% and 90% yield, respectively (*Scheme 4*).

Difluoroalkyl sulfinate salts are excellent difluoroalkyl radical precursors under oxidative conditions.[40–43] However, radical fluoroalkylation with functionalized difluoroalkyl sulfinate salts has been paid little attention.[42,43] We showed that in the presence of ^{t}BuOOH, cyclic sulfinamide-containing difluoroalkyl sulfinate **8b** exhibited high reactivity towards thiols, giving difluoroalkyl sulfides **9** and **10** in good yields (*Scheme 5,a*). The reaction is also amenable to the use of a disulfide[44,45] and a diselenide instead of thiols and difluoroalkyl sulfide **11** and difluoroalkyl selenide **12** were isolated in 45% and 82% yield, respectively (*Scheme 5,b*). Furthermore, cyclic sulfinamide-containing difluoroalkyl sulfinate **8b** could be converted to difluoroalkyl halides **13** and **14**



Scheme 5. Transformations of sulfinate **8**. 2-Pym = 2-pyrimidyl.



Scheme 6. Radical ring-closing difluoroalkylation reaction.

by using NBS and NIS as the electrophilic halogenating reagent, respectively (*Scheme 5,c*).[46] Nevertheless, difluoroalkyl sulfinate **8b** failed to react with alkenes under oxidative conditions.

Finally, we examined the capability of using 2-$PySO_2CF_2$-subsituted bicyclic sulfinamide to directly generate difluoroalkyl radical for further cyclization to synthesize tricyclic compounds (*Scheme 6*). Thus, the bicyclic sulfinamide **3** was first transformed to the *N*-allylated product **15** in 85% yield by *N*-allylation with allyl iodide. Then the intramolecular radical cyclization reaction of **15** proceeded smoothly under thermal initiation in the presence of Bu_3SnH and a catalytic amount of AIBN,[47] affording the tricyclic sulfinamide **16** in 73% yield as a 6:1 mixture of two epimers. The so-obtained difluorinated tricyclic sulfinamide constitutes a new class of tricyclic scaffold, which is expected to find application in the design of novel bioactive small molecules.[48]

Conclusions

In summary, we have investigated the synthesis of enantiopure benzo fused cyclic sulfoximines through stereoselective [3 + 2] cycloaddition between a variety of *N-tert*-butanesulfinyl [(2-pyridyl)sulfonyl]-difluoromethyl ketimines as chiral *quasi*-1,3-dipoles and arynes *in situ*-generated from *o*-trimethylsilyl aryl triflates. Compared with our previous study, the use of 2-$PySO_2CF_2$ instead of $PhSO_2CF_2$ as the facilitating group offers more possibilities for further transformations of the [3 + 2] cycloaddition products.

Acknowledgements

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Author Contribution Statement

J. H. conceived this work. *J. R.*, *C. N.*, and *J. H.* designed the experiments and analyzed the data. *J. R.*, *C. N.*, *Y. G.* and *J. H.* discussed the results and wrote the manuscript. *J. R.* performed the experiments described in this manuscript.

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