Fluorination

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Copper-Catalyzed Highly Stereoselective Trifluoromethylation and Difluoroalkylation of Secondary Propargyl Sulfonates

*Xing Gao, Yu-Lan Xiao, Xiaolong Wan, and Xingang Zhang**

Abstract: *It is challenging to stereoselectively introduce a trifluoromethyl group (CF_3) into organic molecules. To date, only limited strategies involving direct asymmetric trifluoromethylation have been reported. Herein, we describe a new strategy for direct asymmetric trifluoromethylation through the copper-catalyzed stereospecific trifluoromethylation of optically active secondary propargyl sulfonates. The reaction enables propargylic trifluoromethylation with high regioselectivity and stereoselectivity. The reaction could also be extended to stereospecific propargylic difluoroalkylation. Transformations of the resulting enantiomerically enriched fluoroalkylated alkynes led to a variety of chiral fluoroalkylated compounds, thus providing a useful protocol for applications in the synthesis of fluorinated complexes.*

Owing to the unique characteristics of the fluorine atom and C–F bonds, fluorine-containing organic compounds have been extensively applied in life and materials science.[1] The requirements in terms of precise molecular engineering, that is, the ability to introduce fluorine atoms into organic molecules at a desirable position with high stereoselectivity in a highly controllable manner, are becoming increasingly demanding. Despite great achievements over the past decade in the construction of Ar–F and Ar–R_f (R_f = fluoroalkyl) bonds,[2] the asymmetric construction of C–R_f bonds has been far less explored.[3]

As a distinct fluoroalkyl moiety, the trifluoromethyl group (CF_3) appears in numerous pharmaceuticals, agrochemicals, and advanced functional materials; in particular, many therapeutic drugs contain a trifluoromethylated stereogenic center that is usually formed from a prochiral CF_3-containing substrate.[4] To date, however, only limited strategies based on direct asymmetric trifluoromethylation have been reported, many of which have focused on the organocatalyzed enantioselective nucleophilic trifluoromethylation of ketones (aldehydes),[3,5] imines,[6] and active Morita–Baylis–Hillman (MBH) carbonates.[7] Catalytic enantioselective electrophilic[8] and radical[9] α-trifluoromethylation of carbonyl compounds have also proved to be useful strategies to prepare enantiomerically enriched trifluoromethylated compounds. Despite the importance of these methods, they are all restricted to the fuctionalization of carbonyl compounds. To extend the diversity of synthetic structures, asymmetric transition-metal-catalyzed trifluoromethylation would be a promising alternative to the above methods. Although transition-metal-catalyzed cross-coupling reactions have proved to be powerful, practical, and efficient for the construction of C–C bonds at stereogenic centers,[10] it remains a formidable challenge to directly adapt these strategies and access chiral trifluoromethylated compounds, mostly owing to the lack of efficient catalytic systems. To the best of our knowledge, asymmetric transition-metal-catalyzed trifluoromethylation has not been reported thus far.

As part of our ongoing study on transition-metal-catalyzed fluoroalkylation reactions,[11] we demonstrate herein the feasibility of stereoselective copper-catalyzed propargylic trifluoromethylation, in which the versatile synthetic utility of carbon–carbon triple bonds can be applied in the synthesis of biologically active molecules and advanced functional materials. In this study, we focused our research on addressing three crucial issues of this reaction: 1) the development of an efficient catalytic system to stereoselectively construct a C–CF_3 bond at a stereogenic center; 2) regiochemical selectivity, that is, propargylic trifluoromethylation versus allenic trifluoromethylation (previously, the copper-catalyzed trifluoromethylation of secondary propargylic compounds always led to the trifluoromethylated allenes as the major products[12]); and 3) the generality of the transformation.

We began our studies by choosing the secondary propargyl sulfonates **1** as model substrates for the construction of the trifluoromethylated stereogenic center [Eq. (1)]. Triisopropylsilyl (TIPS) was used as a protecting group for the alkyne because its steric bulk can suppress the formation of allene side products.[13] After extensive investigation, we found that a range of enantiomerically pure ligands, such as box, pybox, phox, taddol, and binam, only provided the racemic product **3**; the use of nonchiral ligands, such as bpy and phen, totally inhibited the reaction (for details, see the Supporting Information). Notably, the absence of a ligand improved the propargylic trifluoromethylation to provide **3a** in good yield (80%) along with a small amount of an allenic side product (2% yield). This finding suggested that the use of enantiomerically enriched substrate **1a** might lead to the enantiomerically enriched trifluoromethylated product **3a**.[14]

However, a previous copper-catalyzed trifluoromethylation of optically pure propargylic compounds afforded racemic allene products through a pathway involving cationic propargyl/allenyl copper complexes.[12b] To circumvent this challenge, we hypothesized that if a suitable leaving group at the propargylic position could enable the oxidative addition

[*] X. Gao, Y.-L. Xiao, X. Wan, Prof. Dr. X. Zhang
Key Laboratory of Organofluorine Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry
University of Chinese Academy of Sciences
Chinese Academy of Sciences
345 Lingling Lu, Shanghai 200032 (China)
E-mail: xgzhang@mail.sioc.ac.cn

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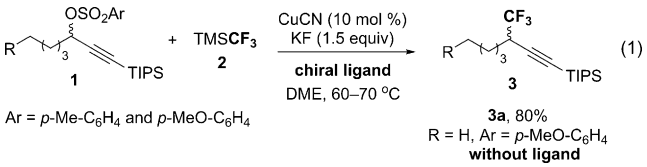
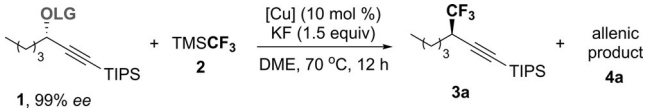


of copper to the C–X (X, leaving group) bond without racemization, the asymmetric trifluoromethylation would be feasible. Accordingly, a series of enantiomerically enriched propargylic substrates (*S*)-**1** (99% *ee*) with different leaving groups were examined by treatment with $TMSCF_3$[15] in the presence of CuCN (10 mol%) in DME at 70°C (Table 1, entries 1–5). The optically active substrates (*S*)-**1** can be readily prepared by asymmetric synthesis of the propargylic alcohol,[16] followed by protection.

Table 1: Representative results for the optimization of the stereospecific copper-catalyzed propargylic trifluoromethylation.[a]



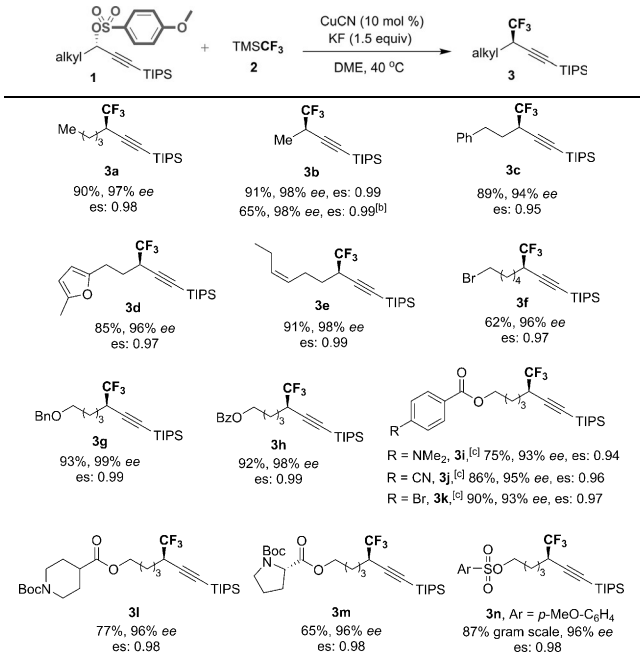
Entry	**1**, LG	[Cu]	Yield [%],[b] **3a**/**4a**
1	**1a**, *p*-MeO-$C_6H_4SO_2$	CuCN	83[c] (97)/ 2
2[d]	**1b**, *p*-Me-$C_6H_4SO_2$	CuCN	–
3[d]	**1c**, *p*-*t*Bu-$C_6H_4SO_2$	CuCN	–
4[d]	**1d**, *p*-NO_2-$C_6H_4SO_2$	CuCN	–
5	**1e**, $MeSO_2$	CuCN	71[c] (97)/ 2
6[e]	**1a**, *p*-MeO-$C_6H_4SO_2$	CuCN	90[c,f] (97)/ trace
7	**1a**, *p*-MeO-$C_6H_4SO_2$	none	n.d.

[a] Reaction conditions (unless otherwise specified): **1** (0.3 mmol, 1.0 equiv), **2** (0.45 mmol, 1.5 equiv), DME (2 mL), 12 h. [b] The yield was determined by ^{19}F NMR spectroscopy with fluorobenzene as an internal standard; values in parentheses are *ee* values. [c] The es value of **3a** was 0.98 ($es = ee_{product}/ee_{starting\ material}$). [d] Compounds **1b–d** are unstable, and the yield of **3a** was not determined. [e] The reaction was carried out at 40°C for 24 h. [f] Yield of the isolated product. DME = dimethoxyethane.

Among the tested leaving groups, the *para*-methoxybenzenesulfonate group in **1a** showed a beneficial effect and provided **3a** in 83% yield with a high *ee* value (97% *ee*) and excellent enantiospecificity (es, 0.98; Table 1, entry 1), in striking contrast to previous results (formation of a racemic allene product).[12b] The use of tosylate and other aryl sulfonates bearing a *tert*-butyl or electron-deficient group resulted in unstable propargylic sulfonates **1b–d** (entries 2–4), which were prone to the formation of an enyne upon purification by silica-gel chromatography. We found that mesylate was also a good leaving group, providing **3a** in 71% yield with excellent enantiospecificity (es, 0.98; entry 5). However, the corresponding proparylic sulfonate **1e** is less stable than **1a**. Other leaving groups, such as acetate, pivalate, trifluoroacetate, and phosphonate led to no formation of **3a** (see the Supporting Information).[17] The reaction was not sensitive to the copper source, and a series of copper(I) salts provided **3a** in comparable yields (for details, see the Supporting Information). Further optimization of the reaction conditions showed that ethereal solvents were beneficial to the reaction, whereas other solvents, including DMF, CH_3CN, and toluene, resulted in low yields or no product (for details, see the Supporting Information). Finally, **3a** was obtained in optimal yield (90% yield upon isolation) with 97% *ee* and 0.98 es by decreasing the reaction temperature to 40°C with **1a** as the substrate, CuCN as the catalyst, and DME as the solvent (entry 6). A reaction in the absence of copper failed to afford **3a** (entry 7), thus demonstrating that copper is essential in promoting the reaction.

Having developed viable reaction conditions, we examined a variety of optically active propargyl sulfonates (*S*)-**1** (Table 2). Generally, the reaction showed excellent enantiospecificity (es, 0.94–0.99) and moderate to excellent yield (62–93%). Substrates bearing a furanyl, alkenyl, benzyloxy, ester, cyano, or dialkylamine group exhibited excellent tolerance toward the current copper-catalyzed process (products **3d**, **3e**, **3g–j**, **3l**). Remarkably, good chemoselectivity in the presence of an additional alkyl sulfonate moiety, which remained intact, provided good opportunities for downstream transformations (product **3n**). Even alkyl and aryl bromides were compatible with the reaction conditions (products **3f** and **3k**), thus highlighting the advantages of current reaction further. What is more, an amino acid containing substrate was also a competent coupling partner without influence on the enantiospecificity (product **3m**). In light of the importance of fluorinated amino acids and their derivatives in the modification of peptide-based biologically active molecules and protein engineering,[18] this transformation offers potential

Table 2: Scope of the copper-catalyzed stereospecific propargylic trifluoromethylation.[a]



[a] Reaction conditions (unless otherwise specified): **1** (0.3 mmol, 1.0 equiv), **2** (0.45 mmol, 1.5 equiv), DME (2 mL), 24 h. [b] The reaction was conducted at room temperature for 72 h. [c] Reaction conditions: **2** (2.0 equiv), CuCN (15 mol%), 70°C, DME (2 mL), 12 h. Bn = benzyl, Boc = *tert*-butoxycarbonyl, Bz = benzoyl.

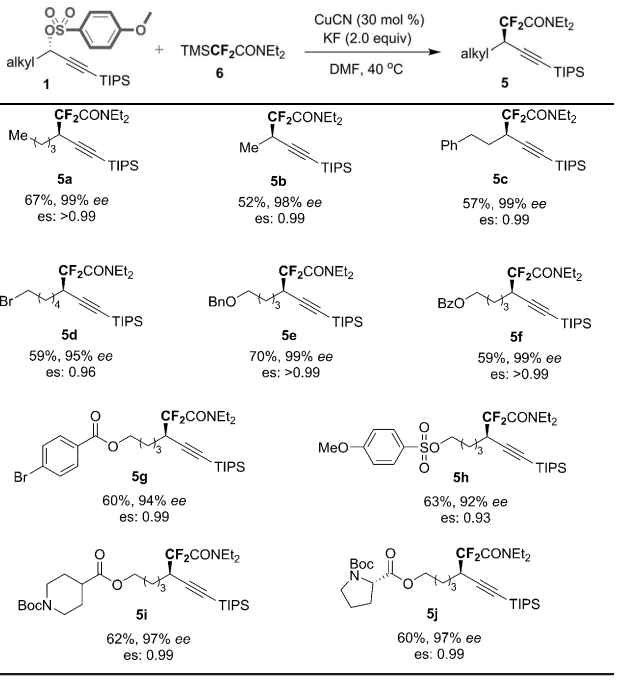
applications in medicinal chemistry and chemical biology. The reaction conditions are readily scalable, as demonstrated by the gram-scale synthesis of **3n** with high efficiency and excellent enantiospecificity (es, 0.98; 96% *ee*). Notably, the reaction can also be conducted at room temperature by extending the reaction time to 72 h, as demonstrated by the synthesis of compound **3b**. However, the replacement of TIPS with less hindered silyl groups (e.g. trimethylsilyl (TMS), triethylsilyl (TES), or *tert*-butyldimethylsilyl (TBDMS)), a phenyl group, or a hydrogen atom resulted in a mixture of propargylic and allenic products or no product **3** (see Scheme S2 in the Supporting Information). Thus, the presence of a TIPS group on the secondary proparyl sulfonate is essential for the current stereospecific propargylic trifluoromethylation. We also examined other secondary sulfonates, such as benzyl and allyl sulfonates. However, they all failed to provide the corresponding trifluoromethylated products because of the instability of the substrates (see Scheme S3).

We investigated the extension of this reaction to stereospecific propargylic difluoroalkylation (Table 3) and chose trimethylsilyldifluoroamide **6** as the difluoroalkylating reagent, because a difluoroamide moiety appears in several biologically active molecules[19] and can serve as a versatile functional group (Table 3). However, no product **5a** was obtained when **1a** was treated with **6** under the standard reaction conditions. Changing the solvent from DME to DMF was beneficial, and **5a** was obtained in 67% yield with 99% *ee* and > 0.99 es when 30 mol% of CuCN was used.

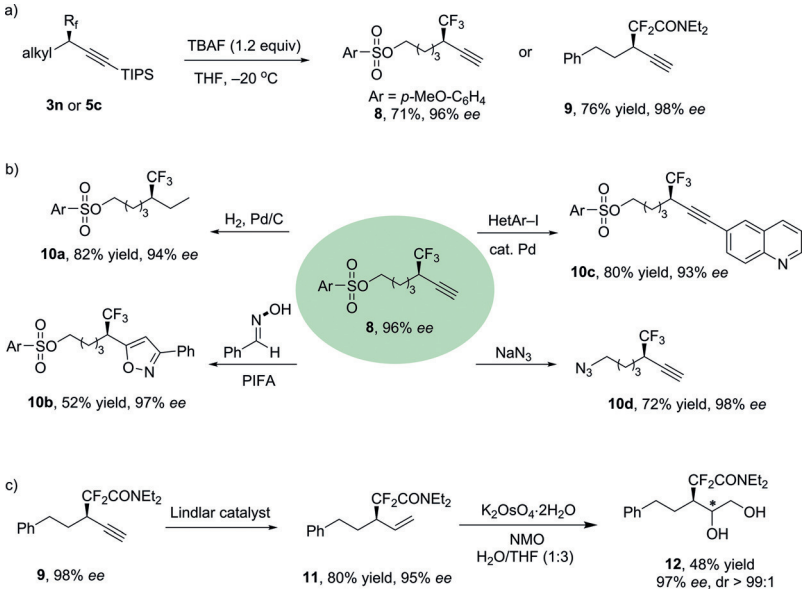
Under the optimal reaction conditions, a variety of propargyl sulfonates (*S*)-**1** underwent difluoroalkylation smoothly to give the products with high *ee* values and stereospecificity (es, 0.93–0.99). Again, excellent functional-group compatibility (products **5d–j**) and high chemo- and regioselectivity were observed (products **5d**, **5g** and **5h**). It is hard to access these enantiomerically enriched difluoroalkylated compounds by conventional methods, thus demonstrating the advantages of the current approach further.

The utility of this protocol is also highlighted by the synthesis of diverse enantiomerically enriched trifluoromethylated and difluoroalkylated molecules from compounds **3n** or **5c**. The TIPS group was readily removed by the treatment of **3n** or **5c** with TBAF in THF at −20 °C (Scheme 1a), but a higher reaction temperature led to the formation of by-products. The resulting terminal alkynes **8** and **9** can serve as versatile building blocks for the synthesis of a variety of enantiomerically enriched fluoroalkylated compounds that are difficult to access by conventional methods. For example, the hydrogenation of **8** afforded the enantiomerically enriched trifluoromethylated alkane **10a** in high yield without erosion of the *ee* value, thus offering an efficient route for the site-selective introduction of a trifluoromethylated stereogenic center into an aliphatic chain (Scheme 1b). The alkynyl moiety could also be employed for the construction of a heterocycle through a [3+2] cyclization reaction[20] to combine a N-heterocycle and chiral trifluoromethyl group, two essential moieties for medicinal chemistry, in one molecule (product **10b**). Additionally, the Sonogashira reaction of **8** with a heteroaryl iodide proceeded smoothly, thus providing an alternative approach to access enantiomerically enriched trifluoromethylated alkynes (product **10c**). Further-

Table 3: Scope of the copper-catalyzed stereospecific propargylic difluoroalkylation.[a]



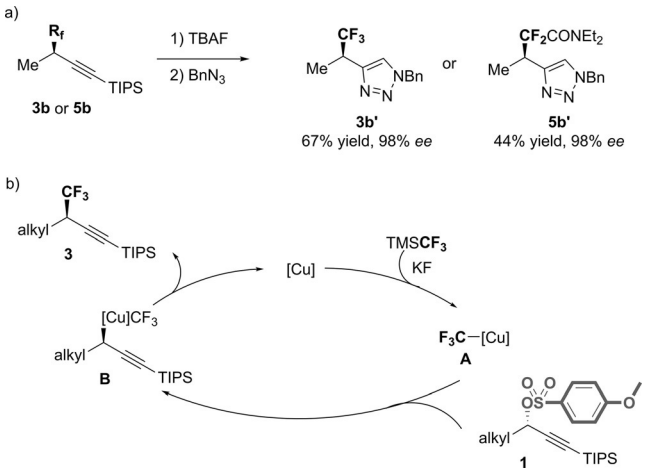
[a] Reaction conditions (unless otherwise specified): **1** (0.3 mmol, 1.0 equiv), **6** (0.6 mmol, 2.0 equiv), DMF (2 mL), 12 h.



Scheme 1. Transformations of compounds **3n** and **5c**. NMO = *N*-methylmorpholine *N*-oxide, PIFA = (bis(trifluoroacetoxy)iodo)benzene, TBAF = tetrabutylammonium fluoride.

more, the transformation of **8** could be successfully conducted on the aliphatic chain, as demonstrated by nucleophilic substitution with NaN_3 (product **10d**). Transformations of **9** also furnished the corresponding enantiomerically enriched difluoroalkylated compounds efficiently. The selective hydrogenation of **9** led to the chiral allylic difluoroalkylated compound **11** with high efficiency (Scheme 1c). Dihydroxylation of **11** afforded chiral diol **12** in synthetically useful yield with excellent diastereoselectivity (dr > 99:1).

The absolute configuration of the final enantiomerically enriched fluoroalkylated compounds was determined to be *R* by X-ray crystal-structure analysis of compounds **3b′**, **3e′**, and **5b′**,[21] which were derived from compound **3b**, **3e**, and **5b**, respectively, through a [3+2] cyclization with benzyl azide (Scheme 2a). In view of the fact that usually transmetalation



Scheme 2. Determination of the absolute configuration of compounds **3** and **5** and proposed reaction mechanism.

and reductive elimination are known to occur with retention of configuration,[22] we envisioned that inversion of configuration occurred in the course of the oxidative addition of copper to the secondary propargyl sulfonate, which is consistent with previous reports on the palladium-catalyzed reactions.[23] On the basis of above results and previous reports on copper-mediated trifluoromethylation,[2b] we propose the following reaction mechanism (Scheme 2b): The reaction begins with the formation of trifluoromethylcopper complex **A** between CuCN and $TMSCF_3$. The resulting complex **A** undergoes oxidative addition with a secondary propargyl sulfonate **1** to afford a configuration-inversed propargyl Cu^{III} species **B**. After the stereoretentive reductive elimination of **B**, the final trifluoromethylated product **3** was produced with overall inversion of configuration.

In conclusion, we have developed the first example of the copper-catalyzed stereospecific trifluoromethylation and difluoroalkylation of secondary propargyl sulfonates. The reaction proceeded under mild reaction conditions with high regioselectivity and stereospecificity (es up to > 0.99), broad substrate scope, as well as excellent functional-group compatibility. All of the resulting chiral trifluoromethylated and difluoroalkylated alkynes are unknown and could serve as versatile building blocks for diversity-oriented organic synthesis, thus providing a useful protocol for applications in medicinal chemistry and materials science. Inversion of configuration was observed in the current copper-catalyzed stereospecific propargylic trifluoromethylation and difluoroalkylation, thus demonstrating that S_N2-type oxidative addition of copper to the secondary propargyl sulfonate may be involved in the reaction.[23,24] We believe that this copper-catalyzed process will prompt research on transition-metal-catalyzed asymmetric fluoroalkylation reactions.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric catalysis · copper · difluoroalkylation · propargyl sulfonates · trifluoromethylation

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