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Copper-Catalyzed Highly Stereospecific Trifluoromethylation and Difluoroalkylation of Secondary Propargyl Sulfonates**

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

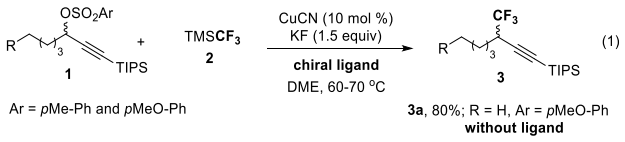
Abstract: It is challenging to stereoselectively introduce a trifluoromethyl group (CF_3) into organic molecules that can be readily transformed into versatile compounds. To date, only limited strategies through direct asymmetric trifluoromethylations have been reported. Here, we describe a new strategy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

Due to the unique characteristics of fluorine atom(s) and C-F bond(s), fluorine-containing organic compounds have been extensively applied in life and materials science,[1] and continue to receive increasingly demanding requirements in terms of precise molecule engineering, i.e., enabling to introduce fluorine atom(s) into organic molecules at desirable position with high stereoselectivity in a highly controllable manner. Over the past decade, despite of great achievements in the construction of Ar-F and Ar-R_f (R_f = fluoroalkyl) bonds,[2] the direct asymmetric fluoroalkylations are far less explored.[3]

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

As part of our ongoing study on transition-metal-catalyzed fluoroalkylation reactions,[11] herein, we demonstrate the feasibility of stereoselective copper catalyzed propargylic trifluoromethylation, in which the versatile synthetic utility of carbon-carbon triple bond 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) efficient catalytic system to stereoselectively construct C-CF_3 bond; (2) regiochemical selectivity, i.e., propargylic trifluoromethylation vs. allenic trifluoromethylation. Previously, the copper-catalyzed trifluoromethylation of secondary propargylic compounds always led to the trifluoromethylated allenes as the major products;[12] (3) broad substrate scope.

Initially, we began our studies by choosing secondary propargyl sulfonate **1** as a model substrate to construct the trifluoromethylated stereogenic center [eq 1]. The use of triisopropylsilyl (TIPS) as a protecting group for the alkyne **1** is because of its steric effect that can suppress the allenic side products.[13] After extensive efforts, we found that a range of enantiopure ligands, such as box, pybox, phox, taddol and binam only provided racemic products **3**; the use of nonchiral ligands, such as bpy and phen totally inhibited the reaction (for details, see the Supporting Information). It is worth noting that the absence of ligand benefited the propargylic trifluoromethylation, providing **3a** in a good yield (80**%**) along with small amount of allenic side product (2% yield). This finding suggested that employment of an enantioenriched substrate **1a** might provide an enantioenriched trifluoromethylated product **3a**.[14]



However, the previous copper-catalyzed trifluoromethylation of optically pure propargylic compounds afforded unfavorable racemic allenic products via cationic propargyl/allenyl-copper complexes involved pathway.[12b] To circumvent this challenge, we hypothesized that if a suitable leaving group at the propargylic position could enable the oxidative addition of copper to C-X (X, leaving group) bond without racemization, the asymmetric trifluoromethylation would be feasible. Accordingly, a series of leaving groups were examined by reaction of enantioenriched propargylic substrates *S*-**1** (99% ee) with $TMSCF_3$[15] in the presence of CuCN (10 mol %) in DME at 70 °C (Table 1, entries 1-5). The optically active *S*-**1** can be readily prepared by asymmetric synthesis of propargylic alcohol,[16] followed by protection.

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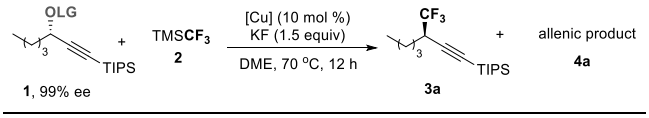
Table 1. Representative results for the optimization of stereospecific copper-catalyzed propargylic trifluoromethylation.[a]



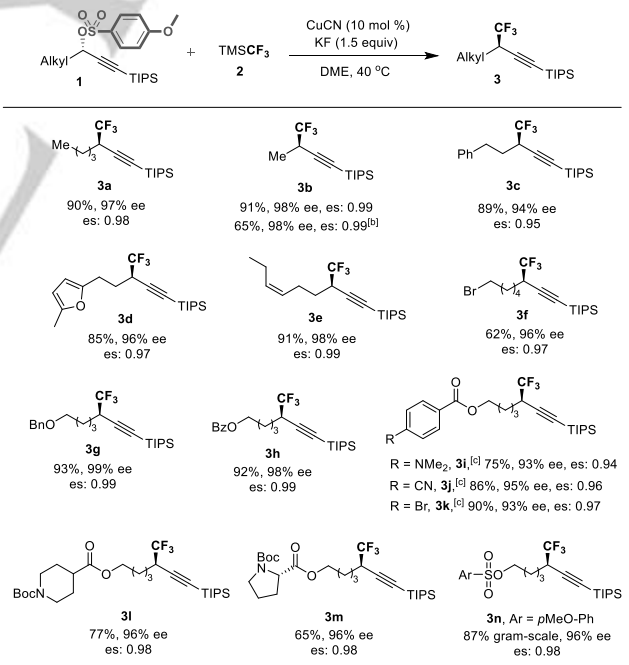
Entry	**1**, LG	[Cu]	yield [%],[b] **3a / 4a**
1	**1a**, *p*MeO-PhSO$_2$	CuCN	83[e] (97) / 2
2[c]	**1b**, *p*Me-PhSO$_2$	CuCN	----
3[c]	**1c**, *p*-*t*Bu-PhSO$_2$	CuCN	----
4[c]	**1d**, *p*NO$_2$-PhSO$_2$	CuCN	----
5	**1e**, MeSO$_2$	CuCN	71[e] (97) / 2
6[d]	**1a**, *p*MeO-PhSO$_2$	CuCN	90[e, f] (97) / trace
7	**1a**, *p*MeO-PhSO$_2$	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] Determined by ^{19}F NMR using fluorobenzene as an internal standard; numbers in parentheses are ee values. [c] Compounds **1b-d** are unstable and the yields of **3a** were not determined. [d] Reaction run at 40 °C for 24 h. [e] The es of **3a** is 0.98. es = ee$_{product}$/ee$_{starting\ material}$. [f] Isolated yield.

Among the tested leaving groups, *para*-methoxybenzenesulfonate **1a** showed beneficial effect and provided **3a** in an 83% yield with a high ee value (97% ee) and excellent enantiospecificity (es, 0.98) (entry 1), in striking contrast to previous results,[12b] in which a racemic allenic product was obtained. The use of tosylate and other aylsulfonates bearing *tert*-butyl or electron-deficient group resulted in unstable proparylic sulfonates **1c** and **1d** (entries 2-4), which were prone to formation of enyne upon purification with silica gel chromatography. We found that the mesylate was also a good leaving group, providing **3a** in a 71% yield with excellent enantiospecificity (es, 0.98) (entry 5). However, its corresponding proparylic sulfonate **1e** is less stable than **1a**. Other leaving groups, such as acetate, pivalate, trifluoroacetate and phosphonate led to no **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 benefited the reaction, while other solvents including DMF, CH_3CN and toluene resulted in low yields or no product (for details, see the Supporting Information). Finally, an optimal yield (90% yield upon isolation) of **3a** with 97% ee and 0.98 es was obtained by decreasing the reaction temperature to 40 °C with **1a** as a substrate, CuCN as a catalyst and DME as a solvent (entry 6). The absence of copper failed to afford **3a** (entry 7), thus demonstrating that copper is essential in promotion of the reaction.

With the viable reaction conditions in hand, a variety of optically active propargyl sulfonates *S*-**1** were examined (Table 2). Generally, the reaction showed excellent enantiospecificity (es, 0.94-0.99) and moderate to excellent yield (62-93%). Substrates bearing a furranyl, alkenyl, benzyloxyl, ester, cyano and dialkylamine group exhibited excellent tolerance to the current copper-catalyzed process (**3d**, **3e**, **3g**-**3j,** **3l**). Remarkably, the good chemoselectivity with an intact alkyl sulfonate moiety provided good opportunities for the downstream transformations (**3n**). Even the alkyl and aryl bromides were still compatible with the reaction conditions (**3f** and **3k**), thus highlighting the advantages of current reaction further. What is more, amino acid-containing substrate was also a competent coupling partner without influence of the enantiospecificity (**3m**). In light of the importance of fluorinated amino acids and their derivatives in modification of peptides based biologically active molecules and protein engineering,[18] this transformation offers potential 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 expanding 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)), phenyl group or hydrogen resulted in a mixture of propargylic and allenic products or no product **3** (for details, see the Scheme S2 in the Supporting Information). Thus, these results demonstrate that the presence of TIPS group on the secondary proparyl sulfonates is essential for the current stereospecific propargylic trifluoromethylation. We also examined other secondary sulfonates, such as benzyl and allyl sulfonates. But they all failed to provide corresponding trifluoromethylated products because of the instability of the substrates (for details, see the Scheme S3 in the Supporting Information).

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] Reaction was conducted at room temperature for 72 h. [c] **2** (2.0 equiv), CuCN (15 mol %), 70 °C, DME (2 mL), 12 h.

In addition to demonstrating the scope of this reaction, we investigated the stereospecific propargylic difluoroalkylation (Table 3) and chose trimethylsiyldifluoroamide **6** as a difluoroalkylating reagent for the current copper-catalyzed process, because difluoroamide moiety appears in several biological active molecules[19] and can serve as a versatile

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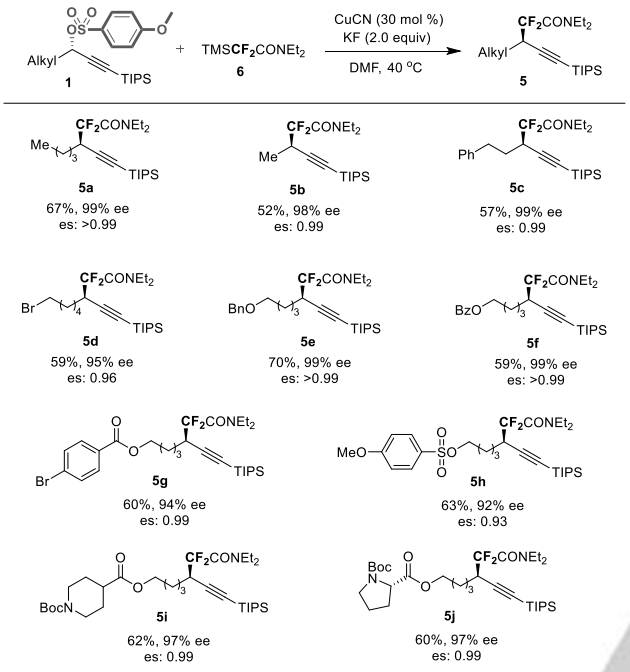
functional group (Table 3). However, no product **5a** was obtained when *S*-**1** was treated with **6** under standard reaction conditions. Switching DME to DMF benefited the reaction and a 67% yield of **5a** with 99% ee and >0.99 es was provided when 30 mol% of CuCN was used.

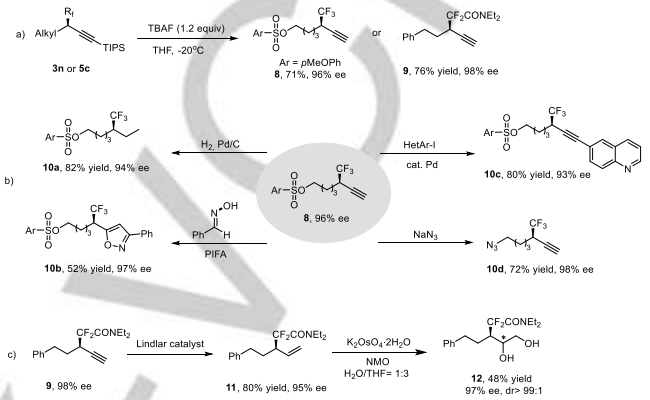
Table 3. Scope of the copper-catalyzed stereospecific propargylic difluoroalkylation.[a]



[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.

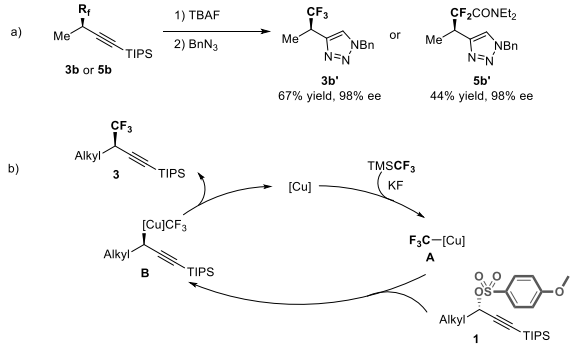
Under the optimal reaction conditions, a variety of propargylic sulfonates *S*-**1** underwent the difluoroalkylation reactions smoothly with high ee values and stereospecificities (es, 0.93 – >0.99). Again, excellent functional group compatibility (**5d**-**5j**) and high *chemo*-regioselectivity were observed (**5d**, **5g** and **5h**). It should be mentioned that it is hard to access these enantioenriched difluoroalkylated compounds through conventional methods, thus demonstrating the advantages of current approach further.

The importance and utility of this protocol can also be highlighted by the synthesis of diverse enantioenriched trifluoromethylated and difluoromethylenated molecules from compounds **3n** or **5c**. As shown in Scheme 1a, the TIPS group was readily deprotected by treatment of **3n** or **5c** with TBAF in THF at -20 °C, but higher reaction temperature would lead to some uncertain by-products. The resulting terminal alkynes **8** and **9** can serve as versatile building blocks for the synthesis of a variety of enantioenriched fluoroalkylated compounds that are difficult to access through conventional methods. For example, hydrogenation of **8** afforded enantioenriched trifluoromethylated alkane **10a** in a high yield without erosion of the ee value, thus offering an efficient route for 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 heterocycle through a [3+2] cyclization[20] to combine an *N*-heterocycle and chiral trifluoromethyl, two essential moieties for medicinal chemistry, into one molecule (**10b**). Additionally, the Sonogashira reaction of **8** with heteroaryl iodide proceeded smoothly, providing an alternative approach to access enantioenriched trifluoromethylated alkynes (**10c**). Furthermore, the transformation of **8** could be successfully conducted on the aliphatic chain as demonstrated by nucleophilic substitution of aliphatic sulfonate **8** with NaN_3 (**10d**). Transformations of **9** also furnished corresponding enantioenriched difluoroalkylated compounds efficiently. As shown in Scheme 1c, selective hydrogenation of **9** led to enantioenriched allylic difluoroalkylated compound **11** with high efficiency. Dihydroxylation of **11** afforded chiral diol **12** in a synthetically useful yield with excellent diastereoselectivity (dr > 99:1).



Scheme 1. Transformations of compounds **3n** and **5c**

The absolute configuration of final enantioenriched fluoroalkylated compounds was determined to be *R* by X-ray crystal structure analysis of compound **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, the transmetalation and reductive elimination are known to occur with retention of configuration,[22] we envisioned that an inversed configuration was occurred in the course of the oxidative addition of copper to the secondary propargyl sulfonates, which was consistent with previous reports for the palladium-catalyzed reactions.[23] On the basis of above results and previous reports on the copper-mediated trifluoromethylation,[2b, c] a plausible reaction mechanism was proposed (Scheme 2b). The reaction began with the formation of trifluoromethylcopper complex **A** between CuCN and $TMSCF_3$. The resulting **A** underwent oxidative addition with secondary propargyl sulfonate **1** to afford a configuration inversed propargyl Cu(III) species **B**. After a retentive reductive elimination of **B**, the final trifluoromethylated product **3** was produced with inverse of configuration.



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

In conclusion, we have developed the first example of 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 enantioenriched trifluoromethylated and difluoroalkylated alkynes are unknown and can serve as versatile building blocks for diversity-oriented organic synthesis, thus providing a useful protocol for applications in medicinal chemistry and materials science. An inversed configuration was observed for current copper-catalyzed stereospecific propargylic trifluoromethylation and difluoroalkylation, demonstrating that a S_N2 type oxidative addition of copper to secondary propargyl sulfonates may be involved in the reaction.[23, 24] We believe that the current copper-catalyzed process will prompt the research for transition-metal-catalyzed asymmetric fluoroalkylations.

Acknowledgements ((optional))

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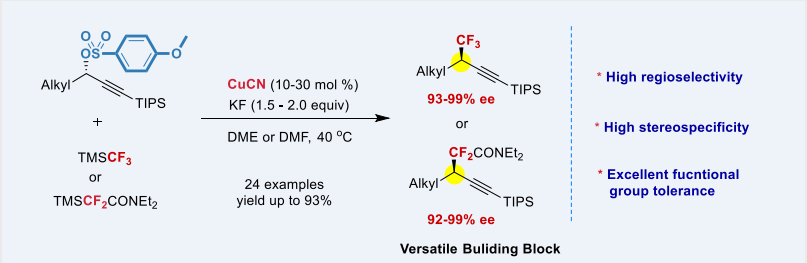

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Copper-Catalyzed Highly Stereospecific Trifluoromethylation and Difluoroalkylation of Secondary Propargyl Sulfonates

Chiral conversion: A title reaction has been developed (see Scheme). The reaction enables the propargylic trifluoromethylation and difluoroalkylation with high regioselectivity and stereospecificity. An inversed configuration was observed for current copper-catalyzed process, demonstrating that a S_N2 type oxidative addition of copper to secondary propargyl sulfonates may be involved in the reaction.