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Enantioselective Construction of Axially Chiral Amino Sulfide Vinyl Arenes via Chiral Sulfide-Catalyzed Electrophilic Carbothiolation of Alkynes

Yaoyu Liang, Jieying Ji, Xiaoyan Zhang, Quanbin Jiang, Jie Luo, and Xiaodan Zhao*

Abstract: *Enantioselective construction of axially chiral compounds via electrophilic carbothiolation of alkynes is disclosed for the first time. This enantioselective transformation is enabled by the use of Ts-protected bifunctional sulfide catalyst and Ms-protected ortho-alkynylaryl amines. Both electrophilic arylthiolating and electrophilic trifluoromethylthiolating reagents are suitable for this reaction. The obtained products of axially chiral vinyl-aryl amino sulfides can be easily converted into biaryl amino sulfides, biaryl amino sulfoxides, biaryl amines, vinyl-aryl amines, and other valuable difunctionalized compounds.*

Axially chiral compounds contain an axial chirality that originates from restricted rotation about a single bond. They are prevalent in many natural products and bioactive molecules,[1] and are useful chiral ligands and catalysts in enantioselective catalysis.[2] For example, TMC-95A is a biologically active natural product;[3] (SO,SO)-, (P,S)- or (N,P)-difunctionalized compounds **A**-**C** can serve as ligands for a variety of metal-catalyzed enantioselective reactions;[4-5] trialkylsulfonium salt **D** is an efficient bifunctional organocatalyst for the enantioselective conjugate additions of 3-substituted oxindoles to maleimides;[6a] biaryl amino alcohol **E** is a photocatalyst efficiently promoting the enantioselective [2+2] photocycloaddition of 4-alkenyl-substituted coumarins (Fig. 1).[6b]

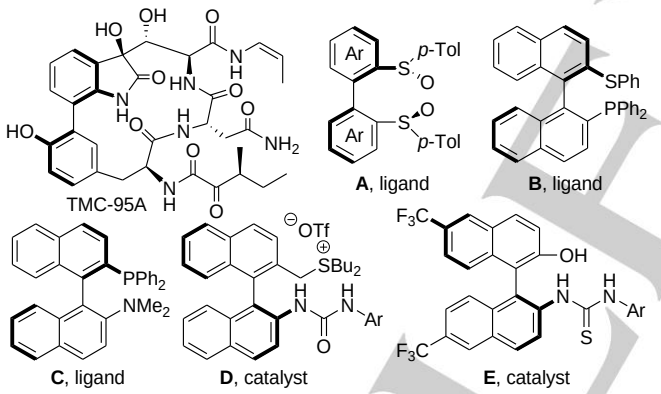
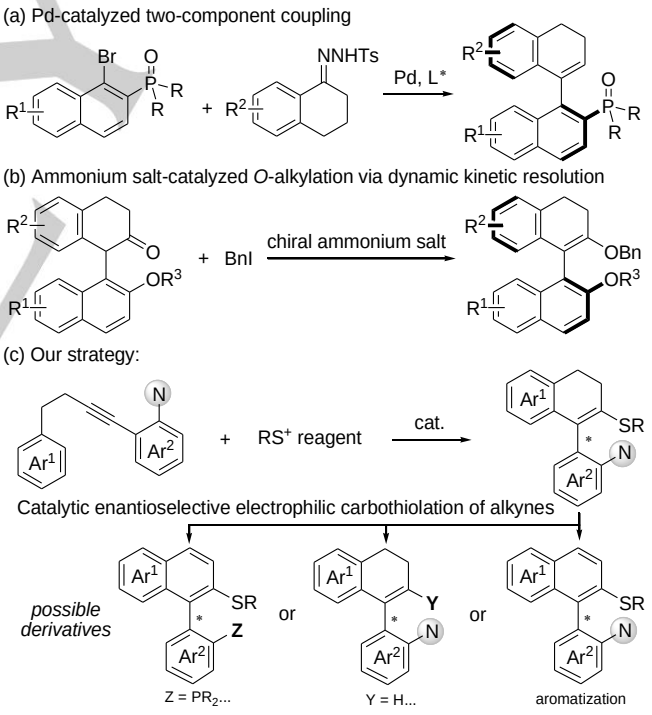


Figure 1. Representative examples of axially chiral bioactive natural product, ligands, and catalysts.

Due to the importance of axially chiral compounds, a large number of catalytic enantioselective synthetic methods have been developed for their synthesis.[7-16] Most of them focused on the synthesis of axially chiral biaryls including transition metal-catalyzed aryl-aryl cross-coupling,[7b,8] oxidative couplings,[9] kinetic resolution,[10] desymmetrization,[11] point-to-axial chirality transfer,[12] *de novo* construction of an aromatic ring,[13] Cu-catalyzed ring-opening reaction of diaryliodonium salts,[14] and others.[15] To meet the requirements of broader substitution patterns and structural diversity, attention has been paid to the development of catalytic enantioselective methods for the synthesis of axially chiral compounds based on dihydronaphthyl-naphthyl skeleton with different starting materials in recent years.[17] In this content, Gu developed palladium-catalyzed enantioselective coupling of aryl bromides with hydrazones (Scheme 1a),[17a] and Smith reported ammonium salt-catalyzed atropselective *O*-alkylation of racemic 1-aryl-2-tetralones via dynamic kinetic resolution (Scheme 1b).[17c] In these transforamtions, the formed vinyl-aryl axially chiral compounds not only could act as an olefin-containing axially chiral ligand or a precursor for the synthesis of point chiral compounds, but also could be aromatized to axially chiral binaphthyls under mild conditions. Despite these advances, structural diversity and the substituents on the aromatic ring of the prepared axially chiral compounds still remain limited. These limitations hamper the wider applications of axially chiral compounds. Thus, development of new methods for their synthesis is highly desirable.



Scheme 1. Catalytic enantioselective construction of axially chiral vinyl-aryl compounds and our strategy.

Catalytic electrophilic thiolation reaction provides a facile and straightforward route for the transformation of alkenes and alkynes to sulfur-containing molecules.[18-23] In the past few years, considerable efforts have been devoted to the development of catalytic enantioselective versions. Particularly, by chiral chalcogenophosphoramide[19,21] and chiral bifunctional chalcogenide catalysis,[22] a range of chiral sulfur-containing compounds could be prepared efficiently. However, these

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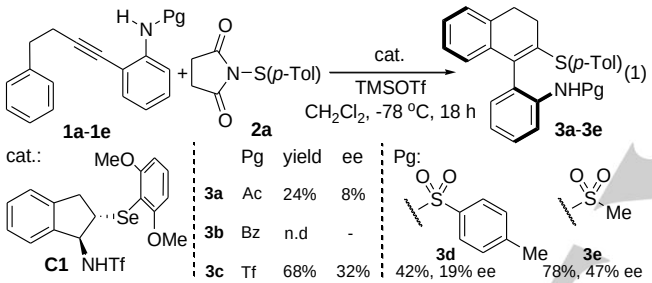
electrophilic reactions only furnished point chiral compounds and have never been applied to enantioselective construction of axially chiral molecules. As a continuation of our interest in electrophilic reactions,[22,24] we hypothesized that enantioselective electrophilic thiolation might be suitable for enantioselective synthesis of axially chiral compounds. We reasoned that using sterically hindered alkynylarenes as substrates, electrohphilic carbothiolation might generate an enantiopure axially chiral vinyl-aryl compound in the presence of chiral catalyst. Because of the good transformability and appropriate metal coordination property of the amino group, *ortho*-alkynylaryl amines were preferred to be used and an axially chiral amino sulfide based on vinyl-aryl skeleton was expected as products (Scheme 1c). Herein, we report our discovery that *ortho*-alkynylaryl amines could efficiently afford enantiopure axially chiral vinyl-aryl amino sulfides via chiral Ts-protected bifunctional sulfide catalysis.

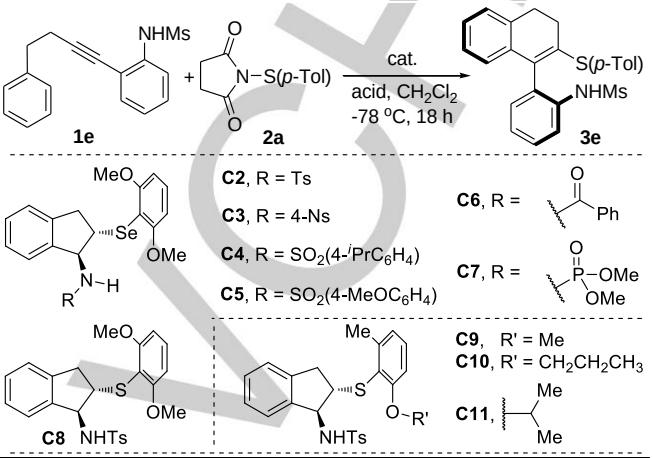
To the best of our knowledge, this is the first successful example of catalytic enantioselective synthesis of 2-amino-2′-thio axially chiral compounds.[10a] Importantly, this amino sulfide is a previliged scaffold and can serve as a platform molecule (Scheme 1c): (i) It is a precursor of potential (S,N)-ligand and -catalyst. (ii) It might be easily aromatized to axially chiral biaryl amino sulfide. (iii) It might be transformed to other axially chiral difunctionalized compounds because of the transformability of the thio group and the amino group.



Keeping the hypothesis in mind, we first tested catalytic electrophilic arylthiolation of Ac-protected alkynylaniline **1a** in the presence of electrophilic sulfur reagent **2a** and TMSOTf (eq 1). Easily prepared, chiral Tf-protected bifunctional selenide **C1** was utilized as catalyst. Gratifyingly, the desired product of axially chiral amino sulfide **3a** was formed, albeit in low yield with only 8% ee. Using Bz-protected alkynylaniline **1b** as substrate, the reaction did not occur at all. Considering the effect of hydrogen bonding from the substrate, the alkynylaniline was protected by the Tf group leading to evidently higher enantioselectivity of the reaction. The protecting groups were further adjusted. Ms-protected alkynylaniline **1e** was found to give the desired product in higher ee.

After the proper protecting group on alkynylaniline was determined, more reaction conditions were screened (Table 1). Owing to the effect of hydrogen bonding from the catalyst that might play a critical role in the reaction,[22a] different protecting groups were attempted to install on the catalyst. To our delight, when the selenide catalyst was protected by the Ts group, the reaction gave the desired product in excellent yield with 69% ee (entry 1). Other protecting groups, i.e. Ns and 4-isopropyl- and 4-methoxy-substituted benzenesulfonyl groups were slightly less efficient than the Ts group (entries 2-4). When Bz and phosphonate groups were used, the products were formed in almost racemic formation (entries 5 and 6). To our surprise, sulfide catalyst **C8** delivered better enantioselectivity than selenide catalyst **C2** (entry 7). Then, other sulfide catalysts with different groups at the *ortho*-position of the phenyl group were examined. Catalyst with one methyl group led to slightly higher ee (entry 8). Replacing the methoxy group with propoxy group, the enantioselectivity increased to 87% (entry 9). Catalyst with bulky isopropoxy group led to slighly higher ee (entry 10). Furthermore, Lewis acid and Brønsted acids such as Tf_2NH, TfOH, TESOTf, TBSOTf, and BF_3•Et_2O were less effective than TMSOTf (entries 11-15). Using the mixed solvents of dichloromethane and chloroform, the best enantioselectivity of the reaction was achieved (entry 16). Electrophilic sulfur reagents based on phthalimide, pyrrolidinone, imidazolidinedione, and saccharin scaffolds were less effective than **2a** (see the supplementary information).

Table 1: Condition optimization.[a]



Entry	Cat.	Acid	Yield [%][b]	Ee [%][c]
1	**C2**	TMSOTf	96	69
2	**C3**	TMSOTf	91	63
3	**C4**	TMSOTf	96	68
4	**C5**	TMSOTf	89	66
5	**C6**	TMSOTf	66	5
6	**C7**	TMSOTf	46	2
7	**C8**	TMSOTf	88	73
8	**C9**	TMSOTf	98	75
9	**C10**	TMSOTf	99	87
10	**C11**	TMSOTf	95	89
11	**C11**	Tf_2NH	97	80
12	**C11**	TfOH	61	87
13	**C11**	TESOTf	85	88
14	**C11**	TBSOTf	82	86
15	**C11**	BF_3·Et_2O	13	88
16[d]	**C11**	TMSOTf	96	93
17[e]	**C11**	TMSOTf	94	91
18[f]	**C11**	TMSOTf	82	92

[a] Reaction conditions: **1e** (0.05 mmol), **2a** (1.5 equiv), cat. (10 mol%), acid (3.0 equiv), CH_2Cl_2 (2.0 mL), -78 °C, 18 h. [b] NMR yield using quinoline as the internal standard. [c] Determined by HPLC analysis. [d] CH_2Cl_2 (1.0 mL) + $CHCl_3$ (1.0 mL) as solvents. [e] CH_2Cl_2 (1.0 mL) + $ClCH_2CH_2Cl$ (1.0 mL) as solvents. [f] CH_2Cl_2 (1.0 mL) + toluene (1.0 mL) as solvents.

With the optimal conditions in hand, the scope of alkynes was evaluated (Scheme 2). First, various tethered aryl groups as nucleophiles were investigated. Different substituent groups at the *para* position of the phenyl ring did not have a dramatic impact on the chemical yields and enantioselectivities of the reactions (**3e**-**3j**). When the substituent group was placed at the *ortho* position of the phenyl ring or the phenyl group was replaced by the naphthyl group, the reactions still proceeded very well to give the desired products in excellent yields with excellent ees (**3k** and **3l**). Next, different substituent groups on the phenyl ring of the aniline group were examined (**3m** and **3n**). Methyl-substituted substrate gave product **3m** in only 79% ee under the standard conditions. However, when *N*-(*p*-TolS)-imidazolidinedione was used as electrophilic sulfur reagent instead of **2a**, the enantioselectivity of reaction increased to 91%. The phenyl-substituted substrate gave the corresponding product **3n** in high ee under the standard conditions. Furthermore, a series of substituted naphthylamines were utilized as substrates, all the reactions underwent electrophilic

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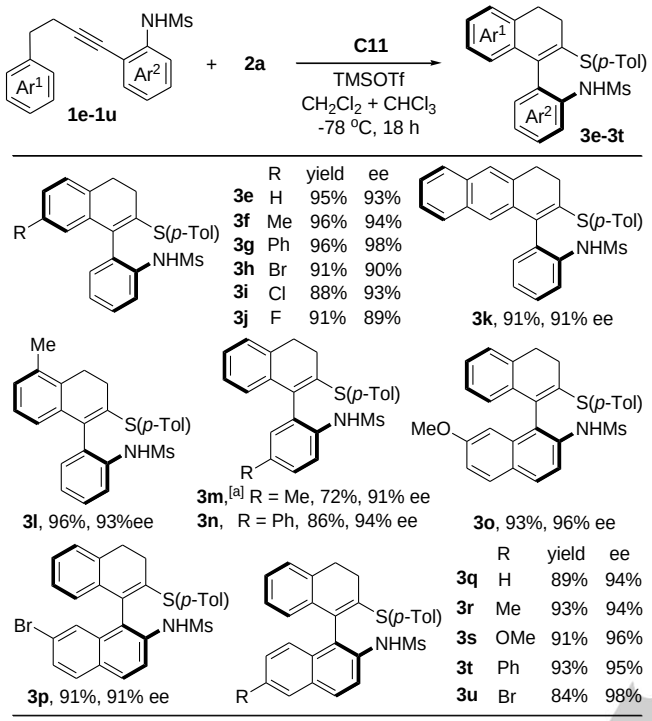
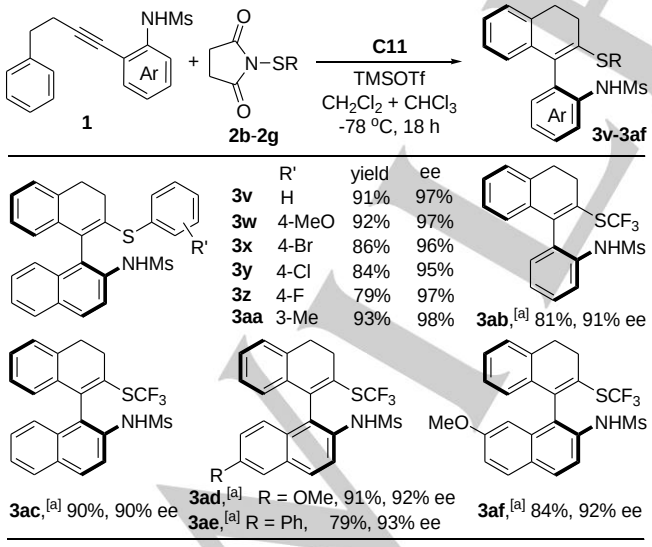
thiolation to produce axially chiral products in high yields with excellent ees (**3o**-**3u**). It is worthy to mention that the methoxy substituent did not influence the reaction at all although the electron-rich aryl ring had a possibility to suffer from direct thiolation (**3o** and **3s**).

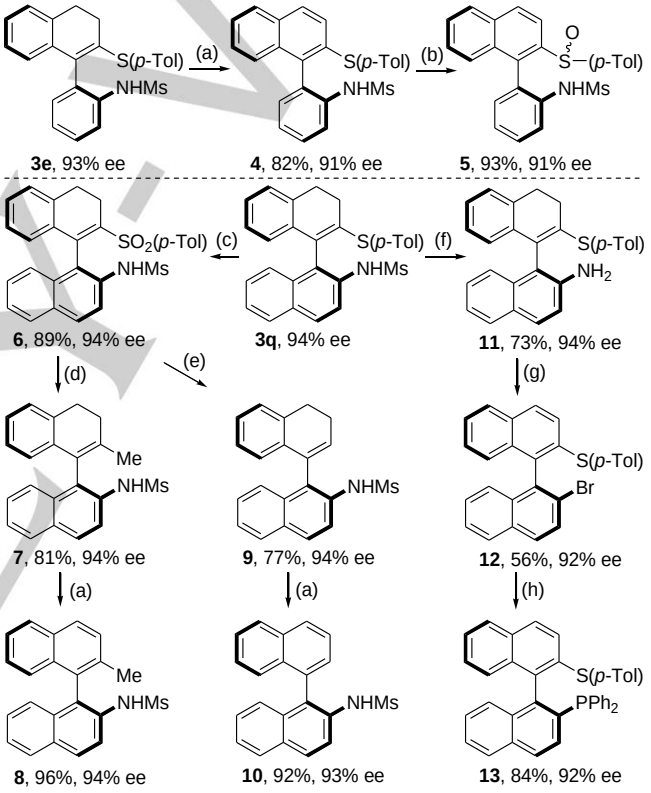


Scheme 2. Enantioselective construction of axially chiral compounds with different alkynes. Reaction conditions: **1e**-**1u** (0.1 mmol), **2a** (1.5 equiv), TMSOTf (3.0 equiv), **C11** (10 mol%), CH_2Cl_2 (2.0 mL) + $CHCl_3$ (2.0 mL), -78 °C, 18 h. The yields refer to isolated yields. The ee value was determined by HPLC analysis. [a] *N*-(*p*-TolS)-imidazolidinedione instead of **2a**.



Scheme 3. Enantioselective construction of axially chiral compounds with different electrophilic sulfur reagents. Reaction conditions: **1** (0.1 mmol), **2b**-**2g** (1.5 equiv), TMSOTf (3.0 equiv), **C11** (10 mol%), CH_2Cl_2 (2.0 mL) + $CHCl_3$ (2.0 mL), -78 °C, 18 h. The yields refer to isolated yields. The ee value was determined by HPLC analysis. [a] *N*-CF_3S-saccharin was used.

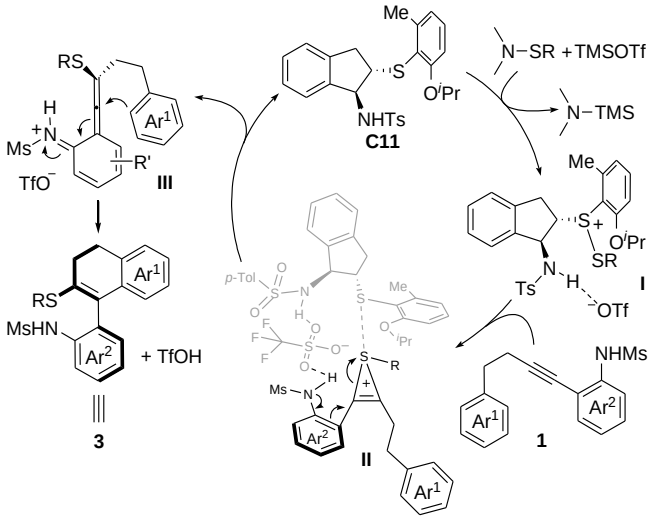
The scope of electrophilic sulfur reagents was explored (Scheme 3). A range of *para*-substituted aryl sulfur reagents gave the desired axially chiral products in excellent yields with excellent enantioselectivities (**3v**-**3z**, 95-97% ees). It was noted that these sulfur reagents included *para*-methoxy-substituted one (**3w**, 97% ee). Similarly, the reaction of *meta*-methyl-substituted sulfur reagent proceeded smoothly to afford the desired product (**3aa**, 98% ee). Next, we turned our attention to the reaction with electrophilic trifluoromethylthiolating reagent (CF_3S^+) because the CF_3S group is an important class of fluorine-containing group and has unique properties.[25] Until now, no report has been demonstrated for enantioselective synthesis of CF_3S-containing axially chiral molecules.[22] Pleasedly, enantioselective electrophilic trifluoromethylthiolation occurred efficiently to form the desired axially chiral products using electrophilic *N*-CF_3S-saccharin after the screening of conditions. Both *o*-alkynylanilines and -naphthylamines underwent thiolation to give the products in high yields with excellent enantioselectivities (**3ab**-**3af**, 90-93% ees). These results indicated the generality of this method.



Scheme 4. Further transformations of products. Conditions: (a) DDQ, DCM, rt, 12 h. (b) saccharin-Cl, THF, -78 °C, 12 h. (c) *m*-CPBA, DCM, rt, overnight. (d) MeMgBr, $Fe(acac)_3$, THF, rt, overnight. (e) Mg, MeOH, rt, 12 h. (f) $(Boc)_2O$, DMAP, DCM, rt, 8 h; then *n*-BuLi, O_2, THF, 0 °C to rt, 2 h; then TFA, DCM, rt, 8 h. (g) $NaNO_2$, H_2SO_4, AcOH, KBr, $ZnBr_2$, rt, 3 h; then, KBr, hexane, 50 °C, 24 h. (h) *n*-BuLi, Ph_2PCl, THF, -78 °C to rt, 4 h.

To elucidate the practical applications of this method, the further transformations of the obtained products were carried out (Scheme 4). For instance, **3e** was easily transformed to 2-amino-2′-thiobiaryl compound **4** under mild conditions, and then further oxidized to the corresponding chiral sulfoxide **5** in high yield and excellent stereoselectivity (*dr* > 20:1). Product **3q** was treated with *m*-CPBA to afford sulfone **6** efficiently. Sulfone **6** could react with Grignard reagent to generate methylated compound **7** under the catalysis of $Fe(acac)_3$. The sulfone also could be transformed to compound **9**, a potential axially chiral (N,olefin)-ligand,[26] via the reduction of the sulfone group. Compounds **7** and **9** were aromatized to form chiral

monofunctional biarylamines under mild conditions. Furthermore, the deprotection of the amino group was easy, which led to the formation of amine **11** in good yield. The amine **11** could be transformed to phosphine **13**, a known ligand,[5c] via a bromination-cross coupling process. In these transformations, the enantiosectivities of the reactions changed slightly. These transformations indicated that the products are a good platform molecule, which provides a convenient route for the synthesis of a variety of valuable axially chiral compounds bearing an amino group, a thio group or both amino and thio groups.



Scheme 5. Possible mechanism.

On the basis of the previous studies,[16b-f,22h] a plausible reaction pathway is depicted (Scheme 5). First, the electrophilic sulfur reagent is activated by catalyst **C11** to form intermediate **I** under the assistance of Lewis acid. Intermediate **I** reacts with substrate **1** to give thiirenium ion intermediate **II** with an acid-derived anion bridge. Then, intermediate **II** may be further converted to a chiral aza-vinylidene-quinone methide (aza-VQM) intermediate **III** and regenerate the catalyst.[16b-f] The following intramolecular hydroarylation on the intermediate **III** results in axially chiral product **3.** Both the amino groups on catalyst and substrate are crucial in the enantiocontrol. When they are protected by appropriate groups, proper hydrogen bonding can lead to the best enantioselectivity of reaction. Not surprisingly, when the amino group on substrate was replaced by methoxy or methyl group, the reaction gave racemic products (see the supplementary information). Furthermore, the reaction gave messy products when changing the triple bond on substrate **1** to a double bond. This result may be attributed to the absence of the aza-VQM intermediate in the reaction.

In summary, we have developed a new strategy to construct enantiopure axially chiral amino sulfides with various substituents by chiral sulfide catalyzed enantioselective electrophilic carbothiolation of alkynes. The yields were high and the enantioselectivities of reactions were excellent. The obtained products could be further converted into valuable axially chiral compounds under mild conditions in simple steps. The further applications of the formed axially chiral compounds are ongoing in our laboratory.

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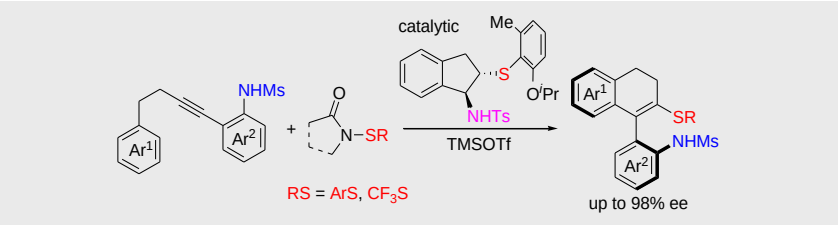

Enantioselective construction of axially chiral compounds via electrophilic carbothiolation of alkynes is disclosed for the first time. This enantioselective transformation is enabled by the use of Ts-protected bifunctional sulfide catalyst and Ms-protected *ortho*-alkynylaryl amines. Both electrophilic arylthiolating and electrophilic trifluoromethylthiolating reagents are suitable for this reaction. The obtained products of axially chiral vinyl-aryl amino sulfides can be easily converted into biaryl amino sulfides, biaryl amino sulfoxides, biaryl amines, vinyl-aryl amines, and other valuable difunctionalized compounds.

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Enantioselective Construction of Axially Chiral Amino Sulfide Vinyl Arenes via Chiral Sulfide-Catalyzed Electrophilic Carbothiolation of Alkynes