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Copper-catalyzed carbene insertion into the sulfur–sulfur bond of benzenesulfonothioate†

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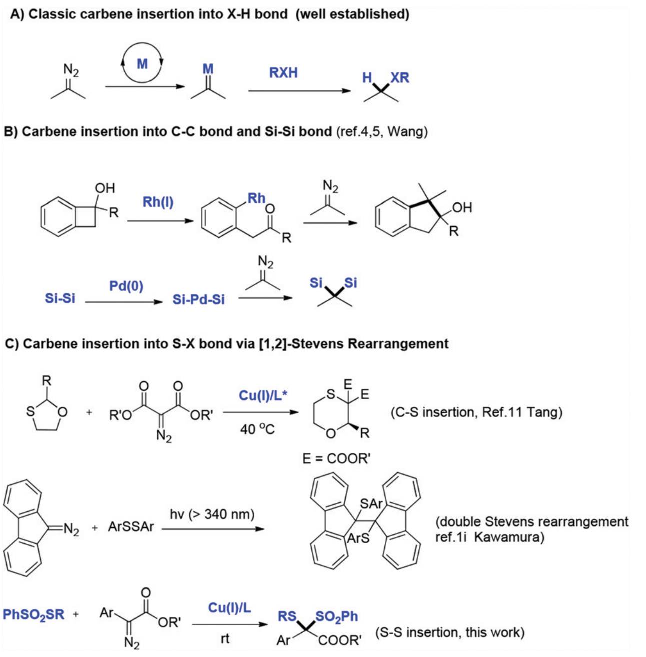
An unprecedented copper-catalyzed intermolecular sulfur–sulfur bond insertion between aryldiazoacetates and benzenesulfonothioate has been successfully developed. Diverse α-disulfur functionalized esters were synthesized in good to excellent yields. The sulfur ylide formation and subsequent Stevens rearrangement are considered as the key steps for the discovered reaction.

Carbene insertion into σ bonds has the advantage of forming two new bonds on one carbon in a single operation and has attracted tremendous attention from synthetic chemists.[1] Of the many catalytic processes that have been developed, X–H (X = C, O, N, Si, *etc.*) bond insertion is the most popular and has found wide applications in organic synthesis (Scheme 1A).[2] Many of them have been successfully developed in the asymmetric catalysis version.[3] However, carbene insertion into other types of σ bond is still underdeveloped. Recently, the Wang group reported a rhodium catalyzed carbene insertion into the strained C–C bond of benzocyclobutenols and the reaction initiated with a Rh(I)-induced four-membered ring-opening reaction generating a key arylrhodium species (Scheme 1B).[4] Later, the same group reported palladium-catalyzed carbene insertion reactions into Si–Si and Sn–Sn bonds, which started with the oxidative addition of Si–Si and Sn–Sn bonds to a Pd(0) catalyst (Scheme 1B).[5] All these insertion reactions begin with generating a key organometallic intermediate.

Reacting with hetero atom generating ylide intermediates is another very important reaction of metal carbenoids.[6] The transition-metal catalyzed decomposition of diazo compounds could generate metal carbenes *in situ*,[7] which when further reacted with sulfides, is an alternative approach to generate sulfur ylides[8] under neutral conditions without the use of strong base. This sulfonium intermediate could undergo various types of important rearrangement including [2,3]-sigmatropic rearrangement[9] and [1,2]-Stevens rearrangement generating structurally diverse sulfides. This [1,2]-Stevens rearrangement could be regarded as a formal insertion reaction to S–X bonds.[10] In 2009, the Tang group reported an enantioselective [1,2]-Stevens rearrangement of sulfur ylides *via* the decomposition of diazomalonates catalyzed by a copper/sidearm-bisoxazoline complex.[11] This formal C–S bond insertion expands a five-membered 1,3-oxathiolanes ring into a six-membered ring (Scheme 1C). Very recently, the Xu group reported a formal N–S bond insertion of *N*-phenyl-sulfenyl phthalimide *via* a rhodium-catalyzed Stevens rearrangement.[12] The Kawamura group reported a formal di-insertion reaction of fluorenylidene into the S–S bond of diaryl disulfides *via* a double Stevens rearrangement upon irradiation (>340 nm).[1i]



Scheme 1 Catalytic carbene insertion into σ bonds.

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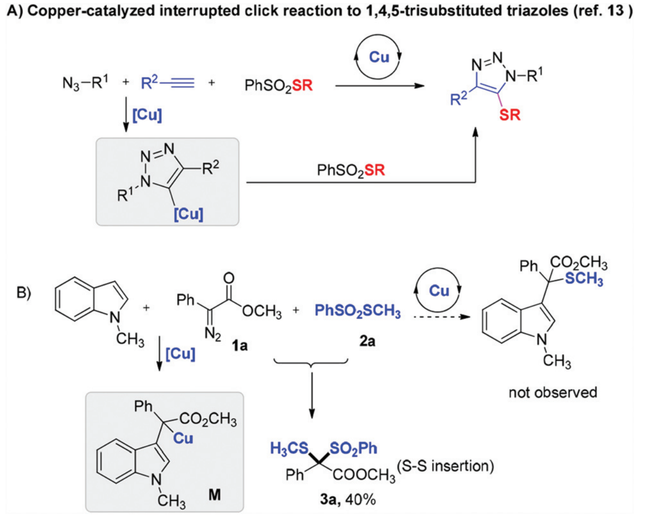
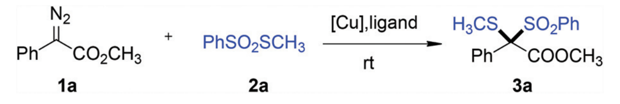


Scheme 2 Unexpected formation of the S–S bond insertion product.

Table 1 Optimization of reaction conditions[a]



Entry	Catalyst	L	Solvent	Yield[b]/%
1[c]	CuI	bpy	DCM	50
2[c]	Cu_2O	bpy	DCM	0
3[c]	CuSCN	bpy	DCM	50
4[c]	CuTc	bpy	DCM	82
5	**CuTc**	**bpy**	**DCM**	**82**
6	CuTc	bpy	DCE	Trace
7	CuTc	bpy	Dioxane	Trace
8	CuTc	bpy	CH_3CN	64
9	CuTc	bpy	THF	0
10	CuTc	dtbpy	DCM	Trace
11	CuTc	terpy	DCM	77
12[d]	CuTc	bpy	DCM	58
13[e]	CuTc	bpy	DCM	Trace
14[f]	CuTc	bpy	DCM	82
15[g]	CuTc	bpy	DCM	65

[a] Reaction conditions: **1a** (0.4 mmol), **2a** (0.2 mmol), CuTc (10% mol), and 4 Å molecular sieve (100 mg) in dry DCM (2 mL) at room temperature under a N_2 atmosphere for 10 h. [b] Isolated yield. [c] Copper catalyst (20% mol). [d] No molecular sieves. [e] The reaction is carried out under an air atmosphere. [f] DCM (1 mL). [g] DCM (3 mL).

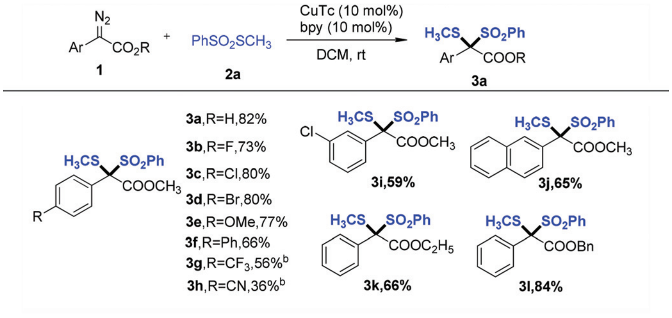
Herein, we wish to report the copper-catalyzed S–S bond insertion reaction of benzenesulfonothioate *via* Stevens rearrangement, which leads to the formation of two C–S bonds at one carbon simultaneously (Scheme 1C).

Recently, we discovered that benzenesulfonothioates are an excellent type of electrophilic sulfenylating reagent, and have been successfully employed in the interrupted click reaction to generate diverse 5-thiotrizoles by intercepting the *in situ* formed cuprate–triazole intermediate (Scheme 2A).[13] Following this concept, when we tried to use benzenesulfonothioate to intercept the *in situ* formed carbene insertion copper(I) intermediate **M**, the desired three-component sulfuration product was not observed, but an unexpected S–S bond insertion product **3a** was isolated in 40% yield (Scheme 2B). This is a two-component reaction and the indole moiety didn't participate in this reaction. This type of carbene insertion reaction into a S–S bond has not been described yet. We reported herein our preliminary results on this S–S bond insertion reaction.

Inspired by the above results, phenyldiazoacetate **1a** and benzenesulfonothioate **2a** were chosen as model substrates to optimize the reaction conditions (Table 1). Various copper(I) catalysts were screened (entries 1–4) and CuTc was the optimal catalyst, generating the desired product **3a** in 82% yield with only 10 mol% catalyst loading in DCM at room temperature (entry 5). The effect of solvents was further examined (entries 5–9) and DCM proved to be the most favourable. Then various ligands were tested and 4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbpy) did not yield any product. A slightly lower yield of 77% was obtained when terpyridine (terpy) was used as the ligand. No product was observed in the absence of the nitrogen ligand. A 4 Å molecular sieve is quite important to this reaction and a decreased yield was observed when it was removed from the reaction system (entry 12). When the reaction was open to an air atmosphere, almost no product was observed (entry 13). Increasing the concentration of the reaction system didn't affect the yield (entry 14), but diluted reaction conditions led to a large decrease in yield (entry 15).

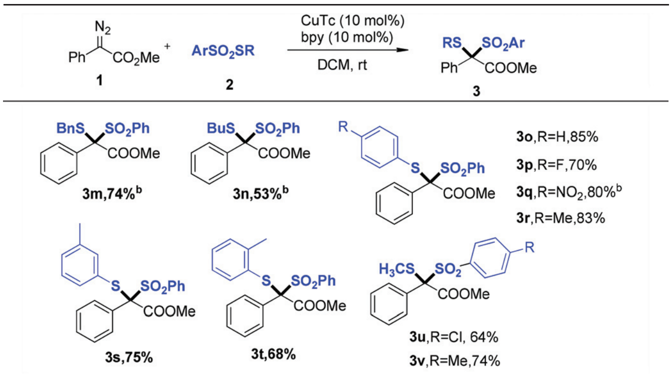
With the optimized conditions established (Table 1, entry 5), the substrate scope of this copper-catalyzed carbene insertion reaction was examined. As summarized in Table 2, a large variety of disulfur functionalized esters were synthesized in good to excellent yields with a very wide scope. Methyl aryldiazoacetates bearing both electron-withdrawing groups, including CF_3, CN, and a F atom, and electron-donating groups, such as a methoxy group at the *para* position of the phenyl ring, were compatible with the standard conditions and the corresponding products could be obtained in good to excellent yields (**3a**–**3h**). Strong electron-withdrawing CF_3 and cyano group substituted diazo compounds were less reactive, and the

Table 2 Substrate scope of aryldiazoacetates[a]



[a] Reaction conditions: **1a** (0.4 mmol), **2a** (0.2 mmol), CuTc (10 mol%), ligand (10 mol%) and 4 Å molecular sieve (100 mg) in dry DCM (2 mL) under a N_2 atmosphere for 10 h. Isolated yield of the product. [b] At 40 °C.

Table 3 Substrate scope of benzenesulfonothioate[a]



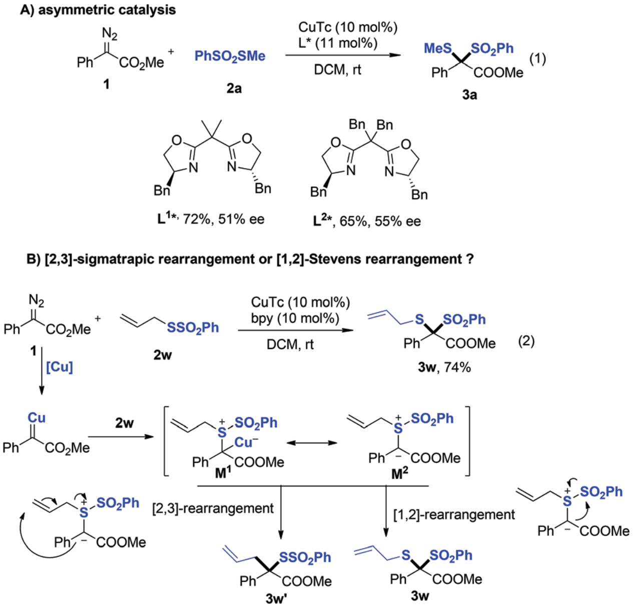
[a] Reaction conditions: **1a** (0.4 mmol), **2** (0.2 mmol), CuTc (10 mol%), ligand (10 mol%) and 4 Å molecular sieve (100 mg) in dry DCM (2 mL) under a N_2 atmosphere for 10 h. Isolated yields were reported. [b] At 40 °C.

products **3g** and **3h** were isolated in 56% and 36% yields at 40 °C respectively. A substituent at the *meta* position is compatible (**3i**), however *ortho*-substituted aryldiazoacetates only gave trace products because of steric hindrance. Other esters such as ethyl and benzyl ester derived aryldiazoacetates reacted smoothly, affording the desired products in 66% and 84% yields (**3k** and **3l**). However other diazocompounds such as ethyl diazoacetate and diazomalonates are not applicable under these conditions.

Then the scope of the benzenesulfonothioate **2** was explored (Table 3). Substrates bearing various alkyl groups on the sulfur atom are all able to react (**3a** and **3m–v**). For the aromatic benzenesulfonothioates, various functional groups such as F, NO_2, and Me at various positions on the aromatic ring are tolerated, giving the corresponding products in good to excellent yields under standard conditions (**3o–t**). Then various sulfonates were explored and both *para*-Cl and Me-substituted substrates were viable in the transformation (**3u–v**).

The above reactions were performed under mild conditions at room temperature with the assistance of dinitrogen ligands, which prompted us to further explore the possibility of developing an asymmetric reaction by using chiral oxazoline ligands (for details, see ESI†). After the detailed screening of various chiral oxazoline ligands, the highest ee of 55% could be obtained by using a bibenzyl substituted bisoxazoline ligand **L^{2*}** (Scheme 3A) which demonstrated that an asymmetric S–S insertion reaction is possible.

To further probe the reaction mechanism of this reaction, another allyl benzenesulfonothioate **2w** was prepared and subjected to the standard reaction. As illustrated in Scheme 3, the reaction of copper carbene with **2w** could generate a copper associated sulfur ylide **M^1** or a free sulfur ylide **M^2**. This ylide could undergo a [1,2]-rearrangement and would generate the normal S–S bond insertion product **3w**. However, for this allyl thioester, another [2,3]-rearrangement is also possible which would generate the product **3w′**. We performed this reaction and it was observed that only the [1,2]-rearrangement product **3w** was formed under standard conditions. These results indicated that the [1,2]-rearrangement reaction of this reaction requires a lower energy barrier in comparison to the [2,3]-Stevens rearrangement.



Scheme 3 Asymmetric reactions and proposed mechanism.

In summary, we have developed a highly efficient copper(I)-catalyzed carbene insertion reaction of the S–S bonds of benzenesulfonothioates. Two new C–S bonds were formed simultaneously at one carbon. The sulfur ylide formation and subsequent Stevens rearrangement are considered as the key steps for the discovered reaction. When a chiral oxazoline ligand was applied in this reaction, a moderate enantioselectivity could be obtained. The reaction provides a valuable reference for the further development of other carbene insertion reactions.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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