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Catalytic asymmetric trifluoromethylthiolation via enantioselective [2,3]-sigmatropic rearrangement of sulfonium ylides

Zhikun Zhang, Zhe Sheng, Weizhi Yu, Guojiao Wu, Rui Zhang, Wen-Dao Chu, Yan Zhang and Jianbo Wang*

The trifluoromethylthio (SCF_3) functional group has been of increasing importance in drug design and development as a consequence of its unique electronic properties and high stability coupled with its high lipophilicity. As a result, methods to introduce this highly electronegative functional group have attracted considerable attention in recent years. Although significant progress has been made in the introduction of SCF_3 functionality into a variety of molecules, there remain significant challenges regarding the enantioselective synthesis of SCF_3-containing compounds. Here, an asymmetric trifluoromethylthiolation that proceeds through the enantioselective [2,3]-sigmatropic rearrangement of a sulfonium ylide generated from a metal carbene and sulfide (Doyle–Kirmse reaction) has been developed using chiral Rh(II) and Cu(I) catalysts. This transformation features mild reaction conditions and excellent enantioselectivities (up to 98% yield and 98% e.e.), thus providing a unique, highly efficient and enantioselective method for the construction of C(sp^3)–SCF_3 bonds bearing chiral centres.

The introduction of SCF_3 into small organic molecules has recently attracted considerable attention in the fields of pharmaceuticals, agrochemicals and materials science[1–5]. This is attributed to the fact that the incorporation of an SCF_3 group into organic molecules can significantly affect their physicochemical and pharmacokinetic properties due to its electron-withdrawing nature, high lipophilicity and metabolic stability. As a result, the development of efficient approaches to construct C–SCF_3 bonds has been studied intensively, and new methods based on both nucleophilic and electrophilic trifluoromethylthiolation reagents have been reported[6–13]. In contrast, the catalytic asymmetric trifluoromethylthiolation has remained a challenging task, and there are few examples in the literature (Fig. 1a)[14–19]. In 2013, a highly enantioselective quinidine-catalysed trifluoromethylthiolation of β-ketoesters derived from indanones using *N*-trifluoromethylthiophthalimide as the electrophilic "SCF_3" source was reported[14]. A similar reaction system has also been applied to enantioselective trifluoromethylthiolation of oxindoles[15]. In the same year, the quinine-catalysed enantioselective trifluoromethylthiolation of β-ketoesters by employing electrophilic trifluoromethylthiolation reagent was disclosed[16]. Later, the same reagent was used in the trifluoromethylthiolation of β-ketoesters with copper–boxmi complex catalysts[17]. Cinchona alkaloid-catalysed enantioselective trifluoromethylthiolation of oxindoles has been developed by also employing *in situ* generated electrophilic trifluoromethylthiolation reagent[18]. More recently, an enantioselective trifluoromethylthiolating lactonization using an indane-based chiral sulfide as the catalyst was reported[19]. Regardless of this remarkable progress during the past few years, the field is still in its infancy, as the reported reactions are limited in scope, mainly focused on β-ketoester type substrates. Thus, further development of novel approaches to achieve enantioselective trifluoromethylthiolation is still highly desirable.

In our efforts to develop new methods of this sort, we recognized that the [2,3]-sigmatropic rearrangement of a sulfonium ylide is a unique method to construct C(sp^3)–S bond[20–27], and thus we sought to exploit this type of transformation to introduce SCF_3 groups into organic compounds. Moreover, based on previous studies[28–37], we hypothesized that such a reaction should proceed stereoselectively and possibly permit the enantioselective construction of these molecules. In the catalytic reaction, the sulfonium ylides for the [2,3]-sigmatropic rearrangement are formed through the reaction of allyl or propargyl sulfides and metal carbene species generated by Rh(II)- or Cu(I)-catalysed reaction with diazo substrates (Doyle–Kirmse reaction). The catalytic enantioselective variant of this reaction is attractive; however, until now the enantioselectivities that have been achieved remain mediocre[23–40]. The challenge lies in discriminating between the heterotopic lone pairs of sulfur by a chiral metal carbene (Fig. 1b). In 2002, we achieved moderate enantioselectivity (78% e.e.) with a chiral copper catalyst, which still represents the highest e.e. value for a [2,3]-sigmatropic rearrangement of a sulfonium ylide under catalytic conditions[34]. With our double asymmetric induction approach by exploring diazo substrate bearing chiral auxiliary, high stereoselectivities have been achieved later[37]. Herein we report the highly enantioselective $Rh_2L^*_4$- and Cu(I)/L*-catalysed [2,3]-sigmatropic rearrangement of sulfonium ylides, which are generated from allyl or propargyl trifluoromethyl sulfides (Fig. 1b). The reactions represent a unique approach for the enantioselective construction of C(sp^3)–SCF_3 bonds, alongside the highest enantioselectivities ever achieved for the Doyle-Kirmse reaction.

Results and discussion

Our previous studies have demonstrated that both chiral Cu(I) and Rh(II) catalysts are effective in enantioselective Doyle–Kirmse reaction[34–39], so we first focused on employing commercially available

Beijing National Laboratory of Molecular Sciences (BNLMS), Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry, Peking University, Beijing 100871, China. *e-mail: wangjb@pku.edu.cn

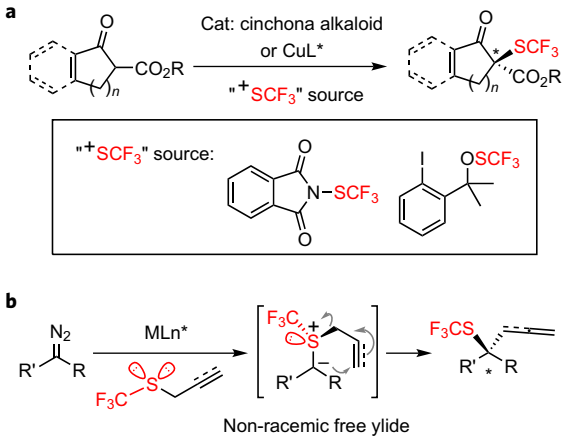
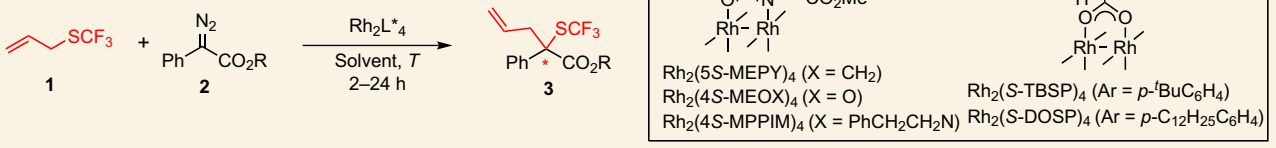


Figure 1 | Catalytic asymmetric trifluoromethylthiolation. a, Asymmetric trifluoromethylthiolation with electrophilic trifluoromethylthiolating reagents. **b**, Asymmetric trifluoromethylthiolation through enantioselective Doyle–Kirmse reaction.

chiral Rh(II) catalysts, which have been successfully applied in a series of catalytic asymmetric carbene transfer reactions[41,42]. The [2,3]-sigmatropic rearrangement of sulfonium ylide generated from a metal carbene and allyl trifluoromethyl sulfide has not been previously documented, so to verify if such a reaction works with CF_3-bearing allyl sulfide an initial experiment was carried out with allyl trifluoromethyl sulfide **1** and phenyldiazoacetate **2** (R = Me) as the substrates, and the commonly used non-chiral $Rh_2(OAc)_4$ as the catalyst (Table 1, entry 1). Gratifyingly, the expected product **3** was formed as detected by GC–MS and ^{19}F NMR, and further confirmed by ^1H NMR and ^{13}C NMR. Subsequently, we proceeded to screen a series of previously developed[41,42] chiral Rh(II) catalysts in order to realize the enantioselective version of the reaction (Table 1, entries 2–6). It was apparent that Rh_2(*S*-TBSP)$_4$ and Rh_2(*S*-DOSP)$_4$ afforded moderate yields and enantioselectivities (Table 1, entries 2–3). With Rh_2(*S*-DOSP)$_4$ as the catalyst, we further studied the effect of reaction temperature (Table 1, entries 7–12). Significantly improved results in terms of both yield and e.e. could be obtained by carrying out the reaction at low temperature. The reaction afforded optimal results at −30 °C, whereas the reaction became sluggish and the yields were diminished when carried out below −40 °C. Subsequently, we examined the effects of the ester moiety of the diazoacetate. We concluded that the enantioselectivities were considerably diminished as the steric bulk of the ester moiety increased (Table 1, entries 13–16).

Finally, the effect of solvent was investigated (Table 1, entries 17–21). Notably, previous studies have indicated that Rh_2(*S*-DOSP)$_4$-catalysed asymmetric reactions of donor–acceptor diazo compounds are favoured in nonpolar solvents[43]. We found that in the current reaction the nonpolar solvents cyclopentane and *n*-pentane also afforded improved enantioselectivities. With *n*-pentane as the solvent, the reaction at −30 °C with 1 mol% Rh_2(*S*-DOSP)$_4$ gave 95% isolated yield and 91% e.e. (Table 1, entry 21). As anticipated, a similar yield and selectivity, but reversed chirality, could be obtained by using Rh_2(*R*-DOSP)$_4$ (Table 1, entry 22).

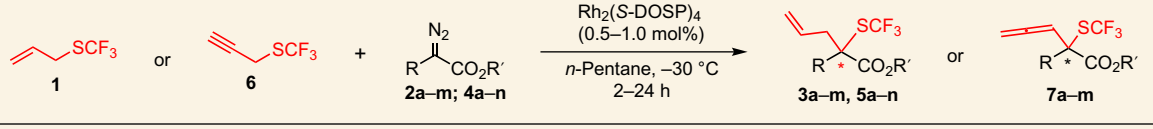
Table 1 | Optimization of the reaction conditions.

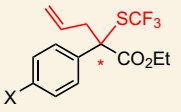


Entry*	2, R	Rh_2L_4	*T* (°C)	*t* (h)	Solvent	Yield (%)†	e.e. (%)‡
1	Me	$Rh_2(OAc)_4$	40	5	CH_2Cl_2	72	0
2	Me	Rh_2(*S*-TBSP)$_4$	40	2	CH_2Cl_2	38	48
3	Me	Rh_2(*S*-DOSP)$_4$	40	2	CH_2Cl_2	44	56
4	Me	Rh_2(5*S*-MEPY)$_4$	40	3	CH_2Cl_2	44	2
5	Me	Rh_2(4*S*-MEOX)$_4$	40	3	CH_2Cl_2	<5	13
6	Me	Rh_2(4*S*-MPPIM)$_4$	40	5	CH_2Cl_2	15	20
7	Me	Rh_2(*S*-DOSP)$_4$	20	2	CH_2Cl_2	85	58
8	Me	Rh_2(*S*-DOSP)$_4$	0	3	CH_2Cl_2	93	65
9	Me	Rh_2(*S*-DOSP)$_4$	−10	4	CH_2Cl_2	89	68
10	Me	Rh_2(*S*-DOSP)$_4$	−30	9	CH_2Cl_2	90	72
11	Me	Rh_2(*S*-DOSP)$_4$	−40	12	CH_2Cl_2	78	72
12	Me	Rh_2(*S*-DOSP)$_4$	−60	24	CH_2Cl_2	<5	70
13	Et	Rh_2(*S*-DOSP)$_4$	−30	12	CH_2Cl_2	72	74
14	^{i}Pr	Rh_2(*S*-DOSP)$_4$	−30	12	CH_2Cl_2	53	56
15	^{t}Bu	Rh_2(*S*-DOSP)$_4$	−30	12	CH_2Cl_2	61	11
16	Ph	Rh_2(*S*-DOSP)$_4$	−30	12	CH_2Cl_2	81	7
17	Et	Rh_2(*S*-DOSP)$_4$	20	12	$PhCH_3$	63	74
18	Et	Rh_2(*S*-DOSP)$_4$	20	12	*n*-Pentane	58	79
19	Et	Rh_2(*S*-DOSP)$_4$	20	12	Cyclopentane	69	79
20	Et	Rh_2(*S*-DOSP)$_4$	20	12	$CHCl_3$	86	52
21	Et	Rh_2(*S*-DOSP)$_4$	−30	24	*n*-Pentane	95§	91
22	Et	Rh_2(*R*-DOSP)$_4$	−30	24	*n*-Pentane	85§	−89

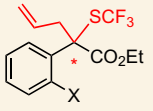
*Entry 1 was carried with **1** (0.2 mmol), **2** (0.24 mmol) and $Rh_2(OAc)_4$ (1.1 mol%); entries 2–20 were carried with **1** (0.2 mmol), **2** (0.2 mmol) and $Rh_2L^*_4$ (0.13 mol%); entries 21–22 were carried with **1** (0.22 mmol), **2** (0.2 mmol) and $Rh_2L^*_4$ (1.0 mol%). †Unless otherwise noted, the yields refer to ^{19}F NMR (400 MHz) yield with trifluorotoluene as the internal standard. ‡Determined by HPLC on a chiral stationary phase (for details, see Supplementary Section 9). §Isolated yield with preparative thin-layer chromatography. Rh_2(*S*-TBSP)$_4$: dirhodium(II) tetrakis[(*S*)-*N*-(*p*-butylphenylsulfonyl)prolinate]; Rh_2(5*S*-MEPY)$_4$: dirhodium(II) tetrakis[methyl 2-pyrrolidone-5(*S*)-carboxylate]; Rh_2(4*S*-MEOX)$_4$: dirhodium(II) tetrakis[methyl 2-oxazolidone-4(*S*)-carboxylate]; Rh_2(4*S*-MPPIM): dirhodium(II) tetrakis[methyl 1-(3-phenylpropanoyl)-2-oxoimidazolidine-4(*S*)-carboxylate]; Rh_2(*S*-DOSP)$_4$: dirhodium(II) tetrakis[(*S*)-*N*-(*p*-dodecylphenylsulfonyl)prolinate].

Table 2 | Substrate scope for the [2,3]-sigmatropic rearrangement.

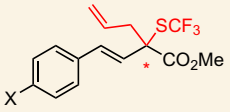




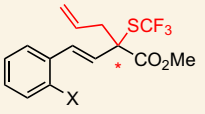
3a, X = H, 95%, 91% e.e.
3b, X = Me, 88%, 89% e.e.
3c, X = F, 98%, 91% e.e.
3d, X = Br, 76%, 86% e.e.
3e, X = OMe, 73%, 79% e.e.
3f, X= Ph, 64%, 88% e.e.



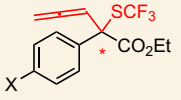
3g, X = F, 99%, 75% e.e.
3h, X = Cl, 98%, 91% e.e.
3i, X = I, 98%, 85% e.e.
3j, X = Me, 99%, 90% e.e.



5a, X = H, 99%, 98% e.e.
5b, X = Me, 99%, 95% e.e.
5c, X = OMe, 74%, 76% e.e.
5d, X = F, 98%, 98% e.e.
5e, X = Cl, 99%, 98% e.e.
5f, X= Br, 98%, 98% e.e.
5g, X= I, 84%, 96% e.e.
5h, X= CF_3, 94%, 96% e.e.
5i, X= CO_2Me, 87%, 93% e.e.

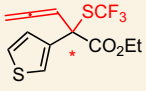


5j, X = F, 94%, 93% e.e.
5k, X = Me, 76%, 86% e.e.

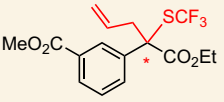


7a, X = H, 65%, 90% e.e.
7b, X = Me, 55%, 87% e.e.
7c, X = F, 74%, 92% e.e.
7d, X = OMe, 61%, 67% e.e.

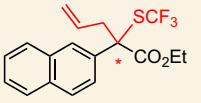
7e, 33%, 81% e.e.



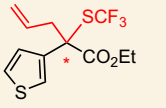
7f, 65%, 84% e.e.



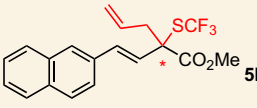
3k, 44%, 86% e.e.



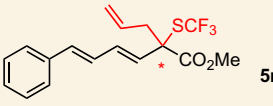
3l, 88%, 84% e.e.



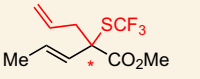
3m, 84%, 92% e.e.



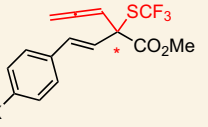
5l, 76%, 93% e.e.



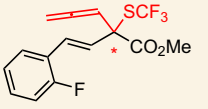
5m, 89%, 94% e.e.



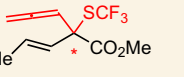
5n, 82%, 93% e.e.



7g, X = H, 74%, 90% e.e.
7h, X = F, 68%, 86% e.e.
7i, X= Br, 54%, 85% e.e.
7j, X = CF_3, 85%, 91% e.e.
7k, X = CO_2Me, 60%, 85% e.e.



7l, 50%, 70% e.e.



7m, 51%, 90% e.e.

Reaction conditions: detailed procedures can be found in the Supplementary Section 3. Generally, with 0.2 mmol scale, the solution of **2** or **4**, **1** or **6** and Rh_2(*S*-DOSP)$_4$ (1.0 or 0.5 mol%) in pentane was stirred at –30 °C for 2–24 h. All of the yields refer to the isolated products with preparative thin-layer chromatography. The e.e. value was determined by HPLC on a chiral stationary phase (for details, see Supplementary Section 9). For 3j, the reaction was carried out at –5 °C.

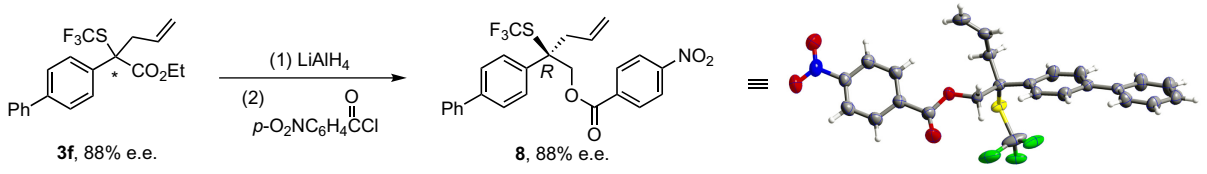
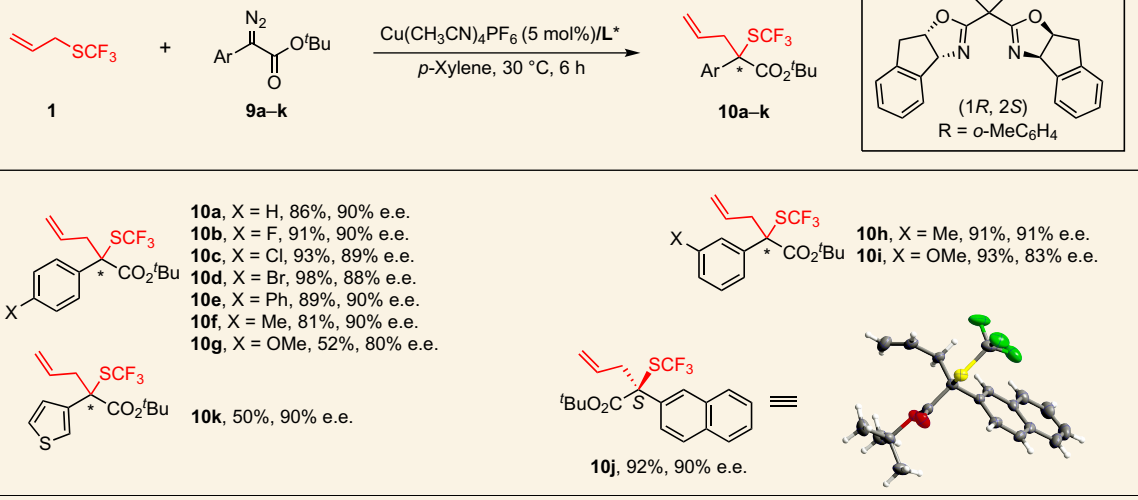


Figure 2 | Assignment of the absolute configuration of the product 3f. Absolute configuration confirmation through two-step derivatization. Crystals of **8** were grown by diffusion of hexane into a diethyl ether solution of **8**. Supplementary Section 7 gives the detailed crystal data.

With the optimized reaction conditions in hand, the substrate scope of this reaction was then investigated with a series of aryl diazoesters. As shown in Table 2, various aryl diazoesters **2a**–**m** reacted smoothly with allyl trifluoromethyl sulfide **1** to afford the corresponding chiral trifluoromethyl sulfides **3a**–**m** in good-to-excellent yields and good enantioselectivities. The reaction with aryldiazoester bearing an electron-donating methoxy group on the aromatic ring gave diminished yield and enantioselectivity (**3e**, 73%, 79% e.e.). The low yield is due to side reactions, mainly dimerization of the diazoester. This is perhaps due to the relatively weak interaction between less electron-deficient carbenic carbon and the sulfur of **1**. The low yield in the case of **3k** is mainly attributed to the

Table 3 | Substrate scope for the Cu(I)-catalysed [2,3]-sigmatropic rearrangement.



Reaction conditions: 1 (0.2 mmol), **9a–k** (0.4 mmol), $Cu(CH_3CN)_4PF_6$ (5 mol%), **L*** (6 mol%), *p*-xylene (2 ml), 30 °C, 6 h. All of the yields refer to isolated yield by preparative thin-layer chromatography. The e. e. values were determined by HPLC on a chiral stationary phase (for details, see Supplementary Section 9). For 10f, the reaction time was 10 h.

poor solubility of the diazo substrates in *n*-pentane. The steric bulk also affected the reaction as shown by the case of **3j**, for which the reaction temperature needed to be raised to −5 °C. For comparison, it is noteworthy that the steric bulk of the ester moiety significantly affects the reaction outcome as shown in Table 1 (entries 14–16)

Next, we investigated the reaction scope with respect to vinyldiazoacetates **4a–n**. For the reaction with vinyldiazoacetates the catalyst loading could be reduced to 0.5 mol%. As summarized in Table 2, excellent yields and enantioselectivities could be obtained with most substrates. We found that the steric of the ester moiety had a noticeable effect on enantioselectivity, similar to previous observations: the reaction with ethyl ester gave only 87% e.e., whereas methyl ester afforded 98% e.e. Electronic effects were also observed: the reaction with vinyldiazoacetate bearing an electron-rich methoxy substituent gave diminished yield and e.e. (**5c**). Gratifyingly, the reaction with styryldiazoester and propenyldiazoester also worked smoothly (**5m** and **5n**).

We further expanded the [2,3]-sigmatropic rearrangement to propargyl sulfide **6** in which the allenyl sulfides were the corresponding products[35]. As shown in Table 2, the reaction of trifluoromethyl propargyl sulfide **6** with aryldiazoacetates **2** or vinyldiazoacetates **4** afforded the corresponding sulfide products in moderate to good yields and enantioselectivities.

To assign the absolute configuration of the newly generated stereogenic carbon centre of the product, the optically active product **3f** was converted into ester **8** through reduction and acylation (Fig. 2). The X-ray crystallographic analysis of single crystal of **8** determined the absolute configuration of the stereogenic carbon centre to be *R* (Supplementary Section 7.1).

Encouraged by the high enantioselectivities achieved by chiral Rh (II) catalysts in Doyle–Kirmse reaction, we investigated the same reaction with Cu(I) catalysts bearing chiral ligands. Cu(I) catalysts are low cost and tunable with chiral ligands, and our previous studies have suggested they are effective catalysts in achieving high stereoselectivity in Doyle–Kirmse reaction[34–37]. As shown in Table 3, after extensive screening of the ligands, we found that ligand **L*** afforded the optimal results in terms of both yield and enantioselectivity (for the details of the reaction optimization, see Supplementary Section 5.2). With the optimized reaction conditions in hand, we investigated the scope of the substrates with a series of aryldiazoesters. It was observed that good yields and enantioselectivities could be obtained for aryl diazoesters in general. The reaction with aryldiazoesters bearing electron-poor or electron-neutral aromatic rings afforded good yields and enantioselectivities. In the case of **10g**, in which the diazo substrates bear an electron-rich aromatic ring, the reaction did not give good yield of the product and the enantioselectivity was only moderately high. This is attributed to the fact that such diazo compounds are less stable, thus resulting in significant amounts of side products. The diazoester bearing a heteroaromatic ring also gave a good e.e., although only a moderate yield (**10k**). The absolute configuration of the product **10j** was determined as *S* by X-ray crystallography (Supplementary Section 7.2). Unfortunately, the reaction with vinyldiazoacetates under the same conditions gave poor enantioselectivities, and the reaction with propargyl sulfide **6** was sluggish.

The reaction mechanism of the [2,3]-sigmatropic rearrangement of sulfur ylide generated from metal carbene under catalytic reaction has been investigated previously. An outstanding question is whether the [2,3]-sigmatropic rearrangement proceeds through a free ylide or a metal-bound ylide[28–33,44]. In the case of the [2,3]-sigmatropic rearrangement involving an oxonium ylide, the reaction is proposed to proceed with a metal-bound ylide through a formal backside displacement of the metal catalyst[45–47]. However, the asymmetric induction model established for oxonium ylide failed to correctly predict the absolute configuration of the rearrangement products in the current study. Moreover, our previous study on Cu(I)-catalysed reactions suggested that the [2,3]-sigmatropic rearrangement most likely proceeds through a free ylide[34,37]. For the Rh(II)-catalysed reaction, we propose that the enantioselection is due to the formation of a chiral free sulfur ylide through the differentiation of the heterotopic lone pairs of the sulfur atom by a chiral metal carbene. The high enantioselectivity observed in this reaction system may be attributed to the following factors: (1) the Rh_2(*S*-DOSP)$_4$ has great face selectivity with aryldiazoacetates and vinyldiazoacetates to generate the sulfur ylide in high enantioselectivity; (2) the free sulfur ylide has sufficient configurational stability; (3) the subsequent concerted [2,3]-sigmatropic rearrangement is facile with complete transfer of the chirality from sulfur to carbon[48,49].

Control experiments were carried out to gain insights into the mechanism of the trifluoromethylthiolation reaction. First, the dependence of diastereoselectivity and the Rh(II) catalysts was investigated. If the diastereoselectivity varied with the Rh(II) catalysts

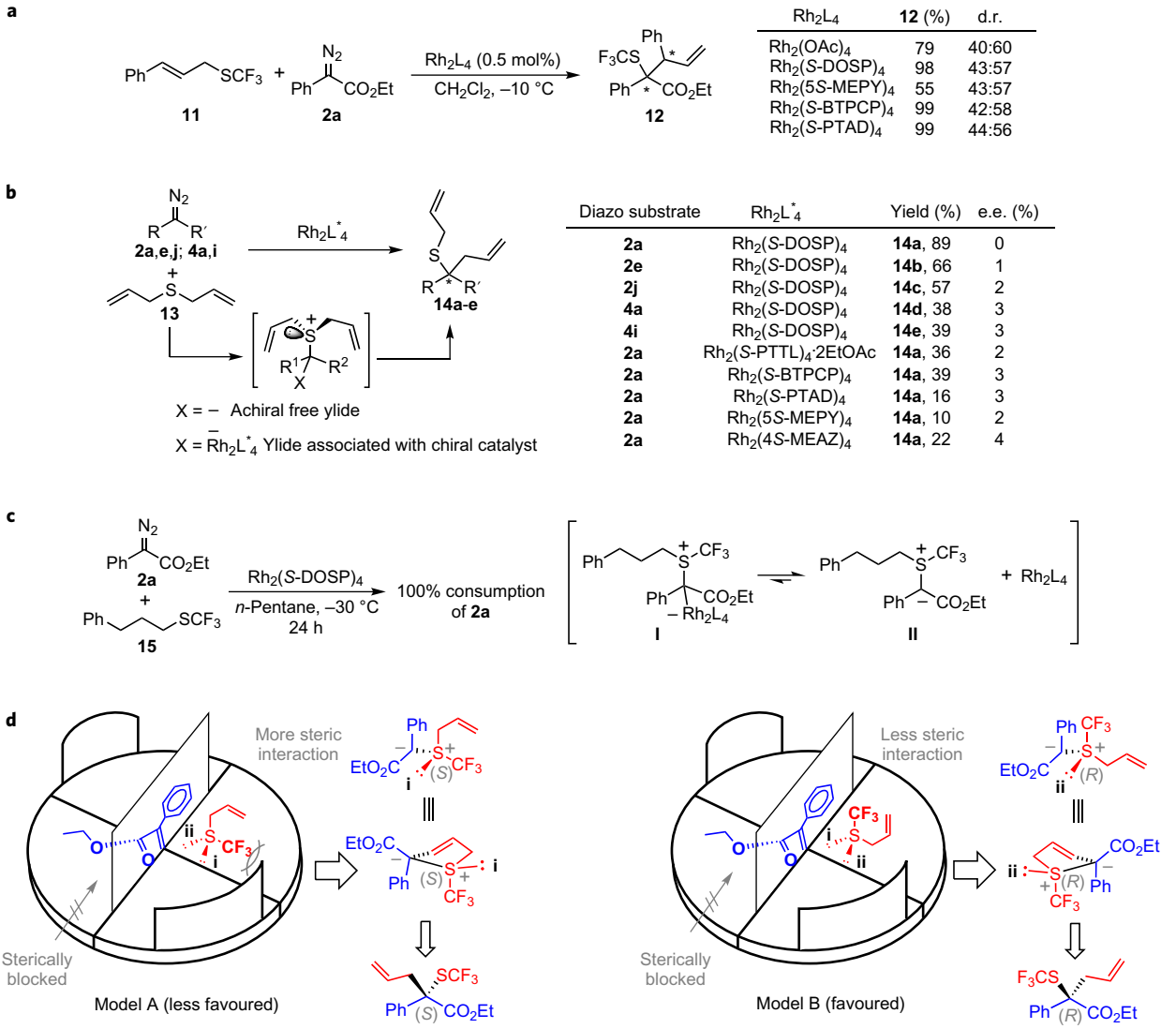


Figure 3 | Mechanistic experiments. a, Study on the dependence of diastereoselectivities on the Rh(II) catalysts. **b**,**c**, control experiments with sulfides **13** (**b**) and **15** (**c**) for proving the free ylide process of [2,3]-sigmatropic rearrangement. **d**, Proposed model of asymmetric induction. Rh_2(*S*-BTPCP)$_4$: dirhodium(II) tetrakis[(*S*)-(+)-[(1*S*)-1-(4-bromophenyl)-2,2-diphenylcyclopropanecarboxylate]; Rh_2(*S*-PTAD)$_4$: dirhodium(II) tetrakis[(*S*)-(+)-(1-adamantyl)-(*N*-phthalimido) acetate]; Rh_2(*S*-PTTL)$_4$: dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-*t*-leucinate]; Rh_2(4*S*-MEAZ)$_4$: dirhodium(II) tetrakis[methyl-2-oxaazetidine-4(*S*)-carboxylate]. The labels i and ii refer to the enantiotopic lone pairs of the trifluoromethylallylthioether that furnish the *R* and *S* products, respectively.

used in the reaction, the [2,3]-sigmatropic rearrangement is likely to proceed through Rh(II)-associated ylide and vice versa. This is due to the fact that the diastereoselectivity-determining step (or the C–C bond forming step) is the [2,3]-sigmatropic rearrangement of the ylide. Consequently, if the rearrangement proceeds through the ylide without the Rh(II)-catalyst attached, the outcome of the diastereoselectivity of this C–C bond forming step should be irrelevant to the Rh(II) catalyst. As shown in Fig. 3a, the reaction of sulfide **11** and diazoacetate **2a** with different Rh(II) catalysts afforded the product **12** with essentially identical diastereoselectivities, thus supporting a free ylide mechanism. Furthermore, we tested the reaction of diazoester with symmetric diallyl sulfide **13** in the presence of a chiral Rh(II) catalyst (Fig. 3b). If the [2,3]-sigmatropic rearrangement occurs with the chiral Rh(II) catalyst associated with the ylide, the reaction is expected to give the product **14** with some enantioselectivity; conversely, if the reaction proceeds through free sulfur ylide, there should be no enantioselectivity since the ylide intermediate is achiral. The experiments were carried out with a combination of various diazoesters and a series of chiral Rh(II) catalysts and the e.e. values of the products in all the reactions are close to zero (0–4% e.e.) (Fig. 3b), further supporting a free ylide mechanism. In another control experiment, the sulfur ylide **15** generated an ylide which cannot undergo the [2,3]-sigmatropic rearrangement because of the lack of a double bond. It was observed that under the same reaction conditions the diazo substrate **2a** was consumed completely to give unidentified products, indicating that the Rh(II) catalyst is easily dissociated from the ylide (from I to II), which further catalyses the dinitrogen extrusion of the diazo substrates (Fig. 3c).

According to the guiding principles proposed by Davies on donor/acceptor Rh(II) carbene reactions[50], an asymmetric induction model is proposed (Fig. 3d). Owing to the steric effect of the chiral ligand, the lone pair of the electrons of sulfur (i) and (ii) attacks the carbenic carbon from right. When the lone pair electrons (ii) attack the carbenic carbon (model A) the steric hindrance and electronic repulsion between the trifluoromethyl group and the ligand makes this process less favourable than mode B, in which the lone pair electrons (i) attack the carbenic carbon and thus the relatively flexible

allyl substituent points to the ligand. As a result, the sulfonium ylide with chiral sulfur centre of (*R*) configuration is formed, followed by a concerted [2,3]-sigmatropic rearrangement to transfer the chirality from sulfur to carbon[48].

For the Cu(I)-catalysed reaction, similar mechanistic experiments were carried out (for details, see Supplementary Section 5.4). The reaction of sulfide **11** and diazo substrate **9a** catalysed by Cu(I) catalysts with a series of chiral ligands afforded the products with essentially identical diastereoselectivities. Moreover, the reaction with symmetric sulfide **13** gave no enantioselectivity. These results suggest that for the Cu(I)-catalysed Doyle–Kirmse reaction, the [2,3] sigmatropic rearrangement also proceeds through free ylide, which is consistent with our previous studies[34–37].

Conclusion

In summary, we have developed a new approach toward the enantioselective construction of the chiral C(sp^3)–SCF_3 bond through Rh(II)- and Cu(I)-catalysed [2,3]-sigmatropic rearrangements of sulfonium ylides generated from metal carbenes and sulfides. These reactions occur under mild conditions and exhibit wide substrate compatibility. It is worth mentioning that this is the only successful catalytic asymmetric Doyle–Kirmse reaction, with high yields and enantioselectivities demonstrated over a wide range of aryldiazoacetates and vinyldiazoacetates. Exploring the mechanism of this classic reaction in detail supports a pathway that involves the transfer of chirality from sulfur of the chiral free ylide intermediate to the carbon of the product in both Rh(II)- and Cu(I)-catalysed systems, which will have further implications in the development of new reactions that exploit this process. From the viewpoint of organic synthesis, the reaction is a practical method toward accessing a series of chiral building blocks containing quaternary stereocentres bearing an SCF_3 group, which are potentially useful drug development candidates.

Methods

General procedure for Rh_2(*S*-DOSP)$_4$-catalysed [2,3]-sigmatropic rearrangement. *Aryldiazoacetates.* Under a nitrogen atmosphere, pentane (2–4 ml), allyl trifluoromethyl sulfide **1** (31 mg, 0.22 mmol, 1.1 equiv.) or propargyl trifluoromethyl sulfide **6** (34 mg, 0.24 mmol, 1.2 equiv.) were successively added to a dry 10 ml Schlenk reaction tube. To the solution was then added the aryldiazoacetate **2** (0.2 mmol, 1.0 equiv.), and the reaction tube was immersed in a −30 °C bath. After 5 min, a solution of Rh_2(*S*-DOSP)$_4$ (0.5 mol%) in 0.25 ml pentane was added dropwise to the reaction tube. The reaction solution was stirred for 12 h. If the typical colour of diazo compounds did not disappear, an additional solution of Rh_2(*S*-DOSP)$_4$ (0.5 mol%) in 0.25 ml pentane was added. The reaction was terminated when the colour of diazo compounds completely disappeared. The solvent was removed with rotary evaporation under reduced pressure to leave a crude mixture, which was purified by preparative thin layer chromatography to afford pure product.

Vinyldiazoacetates. Under a nitrogen atmosphere, pentane (2–6 ml), allyl trifluoromethyl sulfide **1** (28 mg, 0.20 mmol, 1.0 equiv.) or propargyl trifluoromethyl sulfide **6** (28 mg, 0.20 mmol, 1.0 equiv.) were successively added to a dry 10 ml Schlenk reaction tube. The vinyldiazoacetate **4** (0.24 mmol, 1.2 equiv.) for **1** and vinyldiazoacetate **4** (0.26 mmol, 1.3 equiv.) for **6** was added to the solution. Then the reaction tube was immersed in a−30 °C bath. After 5 min, a solution of Rh_2(*S*-DOSP)$_4$ (0.5 mol%) in 0.25 ml pentane was added dropwise to the reaction tube. The reaction was stopped when the colour of diazo compound disappeared. The solvent was removed with rotary evaporation under reduced pressure to leave a crude mixture, which was purified by preparative thin layer chromatography to afford pure product.

Data availability. Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre (CCDC) as CCDC 1502511 (**8**) and 1528864 (**10j**) and can be obtained free of charge from the CCDC via http://www.ccdc.cam.ac.uk/getstructures.

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Author contributions

Z.Z., Z.S., W.Y., G.W. and R.Z. performed the experiments. W.-D.C. and Y.Z. participated in the discussion and helped the measurement of optical purities. J.W. conceived and supervised the project. Z.Z. and J.W. wrote the manuscript.

Additional information

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Competing financial interests

The authors declare no competing financial interests.