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View Article Online DOI: 10.1039/C6CC02641A

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of

# **Chemical Communications**

# COMMUNICATION



Received 00th January 20xx, Accepted 00th January 20xx

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DOI: 10.1039/x0xx00000x

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Rh(II)-catalyzed sulfur ylide [1,2]-rearrangement of carbenoids generated from aryldiazoacetates has been realized via N-S bond insertion, generating tertiary sulfides in moderate to excellent yields. This demonstrates the first use of the sulfur ylide [1,2]-rearrangement undergoing through N-S bond insertion. This protocol could proceed smoothly with high regioselectivity, low catalyst loading (0.1 mol% Rh<sub>2</sub>(OAc)<sub>4</sub>), gram-scale reaction and broad substrate scope. And the product could be converted into glycine derivatives through simple procedures.

The metal carbenoids are important and useful intermediates that play a critical role in diverse transformations due to their high reactivity. The catalytic insertion of metal carbenoids into X-H (X = C, N, O, Si, S, *etc.*) bonds is a powerful method for constructing versatile chemical frameworks and has received considerable attention in the past decades.<sup>[11]</sup> On the other hand, the reaction of sulfide with metal carbenes, which can be easily generated in situ by the transition-metal catalyzed decomposition of diazo compounds, is an available approach to form sulfonium ylide.<sup>[21]</sup> This protocol has been demonstrated as an efficient and operationally simple method in contrast to the classic approaches with using stoichiometric base.



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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x00xx00000x These authors contributed equally to this work. **Scheme 1**. Two main types of reactions of the ylide generated from metal carbene.

The key intermediate, sulfur ylide, can mainly fall into two types of reactions as shown in Scheme 1: (1) [2,3]-sigmatropic rearrangement. (2) [1,2]-sigmatropic rearrangement. With regards to simple allylic or propargyl sulfides, [2,3]-sigmatropic rearrangement is the major reaction pathway, providing access to structurally diverse allylic sulfides or allene sulfides.<sup>[3,4]</sup> Amongst the reported [1,2]-sigmatropic rearrangement based on sulfur ylide, previous studies mainly got through the [1,2]-C-C-shift to form new C-C bond, always by means of the expansion of the heterocycles.<sup>[5-7]</sup> To the best of our knowledge, the reports on other types of the [1,2]-sigmatropic rearrangements are rather limited. Herein, we describe a catalytic [1,2]-C-N-shift reaction of sulfonium ylides, leading to the formation of new C-N and C-S bonds.



**Scheme 2.** Different reaction pathway of N-S bonds *via* sulfur ylide.

According to Wang's work, Rh(II)-catalyzed thia-Sommelet-Hauser rearrangement of sulfonium ylides afforded a series of 3-arylthio-1,3-disubstituted-oxindoles (Scheme 2a).<sup>[8]</sup> We proposed that N-phenyl-sulfenyl phthalimide, a good sulfur(II) electrophile, could form sulfoium ylide intermediate by the reaction of the metal carbene, which could be easily generated

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from the metal-catalyzed reaction of  $\alpha$ -diazocarbonyl compounds (Scheme 2b). The initially formed sulfur ylide may subsequently undergoes [2,3]-sigmatropic rearrangement, leading to compound **A**. Meanwhile, compounds **B** and **C** would be formed *via* N-S bond and C-S bond insertion, respectively.<sup>[9]</sup>

Initially, when a 2:1 mixture of methyl phenyldiazoacetate 2a and N-phenyl-sulfenyl phthalimide 1a in toluene was catalyzed by 5 mol% of Rh2(OAc)4, N-S bond insertion product 3aa was isolated as the sole product in 72% yield (entry 1, Table 1), the structure of 3aa was further confirmed by X-ray crystallography (Figure 1).<sup>[10]</sup> It is worth noting that no products A and C were detected in this reaction. This indicates that [1,2]-C-N-shift (N-S bond insertion, B) is a favored reaction pathway. We surmised that the N-S bond insertion was obtained as the major product, probably, because N-S bond was weaker than C-S bond. Then we found when 1.5 equiv. of 2a was used in the reaction, the yield of the product was decreased to 64% (entry 2, Table 1). Further investigation by altering the catalyst and solvents revealed some interesting aspects about this reaction (Table 1). First, the reaction catalyzed by Rh<sub>2</sub>(OAc)<sub>4</sub> gave the insertion product in good yield. By contrast, other transition metals, including Fe, Pd, Cu, Co, Ni were evaluated under the standard reaction conditions and all produced the desired product in lower yields than the corresponding Rh catalyst (entries 3-7, Table 1), because the reactions were not converted completely for other metals as the catalysts. Meanwhile, other Rh(II) catalysts (e.g. Rh<sub>2</sub>(O<sub>2</sub>n- $Oct)_4$ ,  $(Rh_2(R-DOSP)_4))$  were evaluated, giving the products in lower yield, probably because of the steric hindrance of the catalysts. Second, solvents play a significant effect on the yield of the product. Through the solvents screening, n-hexane was determined as the best solvent, affording the product in 85% yield (entry 12, Table 1). We surmised that both the poor solubility of the substrate 1a in hexane and the stability of Rhcarbenoid in hexane are important to this transformation. The reaction was permitted with reducing the catalyst loading to 1 mol% without compromising yield (entry 14, Table 1). However, in the absence of Rh catalyst, no reaction took place (entry 15, Table 1). Furthermore, the temperature was found as an important parameter for this transformation. When the reaction was conducted under lower temperature (50 °C and room temperature), the desired product was obtained in 49% and 38% yield, respectively (entries 16, 17, Table 1). Finally, we determined the optimal reaction conditions as follows: 2.0 equiv. of 2a, 1 mol%  $Rh_2(OAc)_4$  as a catalyst, hexane as a solvent, 80 °C.

 
 Table 1. Rh-Catalyzed formal N-S bond insertion reaction of methyl phenyldiazoacetate into N-phenyl-sulfenyl phthalimide.



DOI: 10.1039/C6CC02641A Journal Name

entry	cat. (5 mol%)	solvent	yield (%) <sup>b</sup>
1	Rh <sub>2</sub> (OAc) <sub>4</sub>	toluene	72
2 <sup>c</sup>	Rh₂(OAc)₄	toluene	64
3	FeCl <sub>2</sub>	toluene	14
4	Pd(PPh <sub>3</sub> ) <sub>4</sub>	toluene	24
5	Cul	toluene	27
6	CoCl <sub>2</sub>	toluene	28
7	NiCl₂·6H₂O	toluene	21
8	Rh <sub>2</sub> (OAc) <sub>4</sub>	$CH_2CI_2$	72
9	Rh <sub>2</sub> (OAc) <sub>4</sub>	CHCl <sub>3</sub>	28
10	Rh <sub>2</sub> (OAc) <sub>4</sub>	DCE	59
11	Rh <sub>2</sub> (OAc) <sub>4</sub>	THF	trace
12	Rh <sub>2</sub> (OAc) <sub>4</sub>	Hexane	85
13	Rh <sub>2</sub> (OAc) <sub>4</sub>	MeCN	22
14 <sup>d</sup>	Rh <sub>2</sub> (OAc) <sub>4</sub>	Hexane	84
15	-	Hexane	N.R.
16 <sup>e</sup>	Rh <sub>2</sub> (OAc) <sub>4</sub>	Hexane	49
17 <sup>f</sup>	Rh <sub>2</sub> (OAc) <sub>4</sub>	Hexane	38
7 D	1 <b>1</b> (0.2 I)	• (0.4	1) . /=

<sup>*a*</sup> Reaction condition: **1a** (0.2 mmol), **2a** (0.4 mmol), cat. (5 mol%), solvent (4.0 mL), 80 °C, 12 h. <sup>*b*</sup> Isolated yield. <sup>*c*</sup> Using **2a** (0.3 mmol). <sup>*d*</sup> Rh<sub>2</sub>(OAc)<sub>4</sub> (1 mol%). <sup>*e*</sup> Reacted at 50 °C. <sup>*f*</sup> Reacted at room temperature. N.R. = no reaction.



Figure 1. X-ray crystallography of product **3aa** (Thermal ellipsoids are set at 30% probability).

With the optimal reaction conditions in hand, we then explored the scope of the N-aryl-sulfenyl phthalimides **1** in the reaction (Table 2). The electronic effect of the substituents on the aromatic ring of S-Ar group was investigated. To our delight, the substrates bearing either electron-donating (p-Me, p-MeO, m-MeO) or electron-withdrawing (p-F, p-Cl, p-Br) substituents on the aromatic ring of S-Ar underwent the reaction smoothly, affording the corresponding N-S bond insertion products **3aa-3ga** in good yields (entries 1-7, Table 2), and we found the stronger electron-withdrawing substituent of S-Ar decreased the yields of the desired products. When N-(2-naphthyl)-sulfenyl phthalimide **1h** was employed in the

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reaction, the desired product 3ha was obtained in 68% yield (entry 8, Table 1). Next, the scope of the diazo compounds 2 was evaluated (Table 2). First, the electronic and steric effect of the substituents on the benzene ring was investigated. For para-substituted diazo compounds, the reaction either with electron-riched (Me, MeO) or electron-poor (F, Cl, Br) substituents could proceed smoothly, affording the corresponding products in good to excellent yields. However, for the ortho-substituted diazo compounds, such as 2-Me, the reaction worked, but gave the desired products in lower yields (entries 10, Table 2). This result indicates that this [1,2]-C-Nshift (N-S bond insertion) reaction is sensitive to the steric effect of the aromatic substituents. Meanwhile, we found that the stronger electron-withdrawing (e.g. p-F) substituent on the benzene ring of diazo compounds gave the product in high yield (94%). Second, various ester groups of the diazo substrates were examined (entries 16-19, Table 2). It was found that increasing the bulk of the ester groups had little effect on the reaction activity, giving the product yields comparable to other substrates. Comparing the 12 examples in Table 2, 9 of them gave higher yields when 0.1 mol% catalyst used instead of 1 mol%, while 2 of them gave almost identical yields and only one gave slighter lower yield. Clearly, lowering the catalyst loading helps the reaction.

**Table 2.** Reaction of N-aryl-sulfenyl phthalimides **1** with diazo compounds **2**. a

N-SAr	+ , OR <sup>2</sup>	Rh <sub>2</sub> (OAc) <sub>4</sub> (0.1-1 mol%) Hexane, 80 °C, 12 h Ar, seal tube	
1	2 (2.0 equiv.)		3

entry	<b>1</b> , Ar	<b>2</b> , R <sup>1</sup> , R <sup>2</sup>	3	yield (%) <sup>b</sup>
1	<b>1a</b> , C <sub>6</sub> H <sub>5</sub>	<b>2a</b> , H, Me	3aa	85 (91) <sup>c</sup>
2	<b>1b</b> , <i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	<b>2a</b> , H, Me	3ba	82 (87)
3	<b>1c</b> , <i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	<b>2a</b> , H, Me	3ca	83 (89)
4	<b>1d</b> , <i>m</i> -MeOC <sub>6</sub> H <sub>4</sub>	<b>2a</b> , H, Me	3da	93
5	<b>1e</b> , <i>p</i> -FC <sub>6</sub> H <sub>4</sub>	<b>2a</b> , H, Me	3ea	77 (87)
6	<b>1f</b> , <i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	<b>2a</b> , H, Me	3fa	88 (87)
7	<b>1g</b> , <i>p</i> -BrC <sub>6</sub> H <sub>4</sub>	<b>2a</b> , H, Me	3ga	95
8	1h, 2-naphthyl	<b>2a</b> , H, Me	3ha	68 (63)
9	<b>1а</b> , С <sub>6</sub> Н <sub>5</sub>	<b>2b</b> , 4-Me, Me	3ab	96 (95)
10	<b>1a</b> , C <sub>6</sub> H <sub>5</sub>	<b>2c</b> , 2-Me, Me	3ac	44
11	<b>1a</b> , C <sub>6</sub> H <sub>5</sub>	<b>2d</b> , 4-MeO, Me	3ad	83
12	<b>1a</b> , C <sub>6</sub> H <sub>5</sub>	<b>2e</b> , 3,4-(MeO) <sub>2</sub> ,	3ae	81 (85)
		Me		
13	<b>1a</b> , C <sub>6</sub> H <sub>5</sub>	<b>2f</b> , 4-F, Me	3af	94
14	<b>1a</b> , C <sub>6</sub> H <sub>5</sub>	<b>2g</b> , 4-Cl, Me	3ag	79 (83)
15	<b>1a</b> , C <sub>6</sub> H <sub>5</sub>	<b>2h</b> , 4-Br, Me	3ah	77 (85)
16	<b>1a</b> , C <sub>6</sub> H <sub>5</sub>	<b>2i</b> , H, Et	3ai	90
17	<b>1a</b> , C <sub>6</sub> H₅	<b>2j</b> , H, <sup>t</sup> Bu	3aj	85 (89)
18	<b>1a</b> , C <sub>6</sub> H₅	<b>2k</b> , H, Bn	3ak	96
19	<b>1a</b> , C <sub>6</sub> H <sub>5</sub>	<b>2l</b> , 4-Me, <sup>i</sup> Pent	3al	81 (83)

 $^a$  Reaction condition: **1** (0.2 mmol), **2** (0.4 mmol), Rh<sub>2</sub>(OAc)<sub>4</sub> (1 mol%), hexane (4.0 mL), 80 °C, 12 h.  $^b$  Isolated yield.  $^c$  Reaction

Then, to further extend the substrate scope, other N-substituted-sulfenyl imides were examined for this transformation (Scheme 3). When N-benzyl-sulfenyl phthalimide **1i** was employed as the substrate, the reaction proceeded smoothly under the optimal reaction conditions, providing the desired product **3ia** in 96% yield. However, when the substrate **1j** derived from succinimide, the corresponding product **3ja** was obtained in only 21% yield.<sup>[11]</sup> Meanwhile, to demonstrate the practical utility of this transformation, a gram-scale reaction (1.0 gram) was carried out to furnish the desired product **3aa** in 83% yield (Scheme 3), comparable with that obtained in 0.2 mmol scale reaction.



Scheme 3. N-S bond insertion with other substrates and gram-scale reaction.

As shown in Scheme 4, to demonstrate the utility of the N-S bond insertion products. The glycine derivative **9** could be obtained in good yield over 2 steps, cleavage of the phenyl-sulfenyl group under radical conditions and deprotecton of phthalyl group using  $N_2H_a$ - $H_2O$ .



Scheme 4. Transformation of the N-S bond insertion product 3aa.

To gain insights into the reaction mechanism, a crossover experiment was conducted by subjecting an equivalent amount of **1a** and **1j** with **2a** under the optimal reaction conditions (Scheme 5). As expected, only the target products **3aa** and **3ja** were isolated in 83% and 37% yield, respectively. The crossover products **3aa'** and **3ja'** were not detected. From this crossover experiment, we could confirm that the rearrangement of this transformation went through an intramolecular process.

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DOI: 10.1039/C6CC02641A Journal Name



Scheme 5. Crossover experiment of 1a and 1j with 2a.

In conclusion, we have developed a highly regioselective Rh(II)-catalyzed sulfur ylide [1,2]-rearrangement of carbenoids generated from aryldiazoacetates, providing access to tertiary sulfides in moderate to excellent yields. And the product could be easily converted to glycine derivative. This rearrangement went through N-S bond insertion, proceeding with low catalyst loading and broad substrate scope. The metal-catalyzed carbene insertion into other  $\sigma$  bonds are being studied in our laboratory.

Financial support from National Natural Science Foundation of China (grants 81373303, 81473080, 81573299 and 21502230) is gratefully acknowledged. This project was also supported by the Jiangsu Province Natural Science Foundation (BK20150688), and program for Changjiang Scholars and Innovative Research Team in University (IRT1193).

## Notes and references

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- (a) H. M. L. Davies and R. E. J. Beckwith, Chem. Rev., 2003, 103, 2861; (b) H. M. L. Davies, Angew. Chem. Int. Ed., 2006, 45, 6422; (c) H. M. L. Davies and J. R. Manning, Nature, 2008, 451, 417; (d) M. P. Doyle, R. Duffy, M. Ratnikov and L. Zhou, Chem. Rev., 2010, 110, 704; (e) T. Ye and M. A. McKervey, Chem. Rev., 1994, 94, 1091; (f) M. P. Doyle, M. A. McKervey, and T. Ye, In Modern Catalytic Methods for Organic Synthesis with Diazo Compounds; Wiley: New York, 1998. (g) Z. Zhang and J. Wang, Tetrahedron, 2008, 64, 6577.
- For reviews, see: (a) J. B. Sweeney, *Chem. Soc. Rev.*, 2009, 38, 1027; (b) Y. Zhang and J. Wang, *Coord. Chem. Rev.*, 2010, 254, 941; (c) J. Wang, In Comprehensive Organometallic Chemistry III; D. M. P. Mingos and R. H. Crabtree, ed.; Applications II: Transition Metal Compounds In Organic Synthesis 2; Elsevier: Oxford, 2007; Vol. 11, pp 151-178.
- 3 (a) M. P. Doyle, J. H. Griffin, M. S. Chinn and D. van Leusen, J. Org. Chem., 1984, 49, 1917; (b) T. Fukudat, R. Irie and T. Katsuki, Tetrahedron, 1999, 55, 649; (c) D. W. McMillen, N. Varga, B. A. Reed and C. King, J. Org. Chem., 2000, 65, 2532; (d) X. Qu, Z. Zhang, Z. Ma, W. Shi, X. Jin and J. Wang, J. Org. Chem., 2002, 67, 5621; (e) C.-Y. Zhou, W.-Y. Yu, P. W. H. Chan and C.-M. Che, J. Org. Chem., 2004, 69, 7072; (f) H. Zhang, B. Wang, H. Yi, Y. Zhang and J. Wang, Org. Lett., 2015, 17, 3322.
- 4 L. Peng, X. Zhang, M. Ma and J. Wang, Angew. Chem. Int. Ed., 2007, 46, 1905.
- 5 For sulfonium ylides, see: (a) T. Kametani, K. Kawamura and T. J. Honda, Am. Chem. Soc., 1987, 109, 3010; (b) V. Nair, S. M. Nair, S. Mathai, J. Liebscher, B. Ziemer and K. Narsimulu, Tetrahedron Lett., 2004, 45, 5759; (c) K. K. Ellis-Holder, B. P. Peppers, A. Y. Kovalevsky and S. T. Diver, Org. Lett., 2006, 8, 2511; (d) A. J. Price Mortimer, A. E. Aliev, D. A. Tocher and M. J. Porter, Org. Lett., 2008, 10, 5477; (e) A. V. Stepakov, A. P. Molchanov, J. Magull, D. Vidović, G. L. Starova, J. Kopf and

R. R. Kostikov *Tetrahedron*, 2006, **62**, 3610; (f) J.-P. Qu, Z.-H. Xu, J. Zhou, C.-L. Cao, X.-L. Sun, L.-X. Dai and Y. Tang, *Adv. Synth. Catal.*, 2009, **351**, 308.

- For selected oxonium ylides, see: (a) A. Oku, N. Murai and J. J. Baird, Org. Chem., 1997, 62, 2123; (b) F. P. Marmsäter, G. K. Murphy and F. G. West, J. Am. Chem. Soc., 2003, 125, 14724; (c) G. K. Murphy and F. G. West, Org. Lett., 2005, 7, 1801; (d) G. K. Murphy and F. G. West, Org. Lett., 2006, 8, 4359; (e) J. S. Clark, R. Berger, S. T. Hayes, L. H. Thomas, A. J. Morrison and L. Gobbi, Angew. Chem. Int. Ed., 2010, 49, 9867; (f) C. Stewart, R. McDonald and F. G. West, Org. Lett., 2011, 13, 720.
- For selected ammonium ylides, see: (a) A. Padwa, L. S. Beall,
   C. K. Eidell and K. J. Worsencroft, *J. Org. Chem.*, 2001, 66,
   2414; (b) T. M.; Vanecko, J. A. Bott and F. G. West, *J. Org. Chem.*, 2009, 74, 2832.
- 8 (a) M. Liao, L. Peng and J. Wang, *Org. Lett.*, 2008, **10**, 693; (b)
   Y. Li, Y. Shi, Z. Huang, X. Wu, P. Xu, J. Wang and Y. Zhang, *Org. Lett.*, 2011, **13**, 1210.
- 9 Metal-catalyzed carbene insertion into C-C bond: (a) Y. Xia, Z. Liu, Z. Liu, R. Ge, F. Ye, M. Hossain, Y. Zhang and J. Wang, J. Am. Chem. Soc., 2014, **136**, 3013; Sn-Sn and Si-Si bonds: (b) Z. Liu, H. Tan, T. Fu, Y. Xia, D. Qiu, Y. Zhang and J. Wang, J. Am. Chem. Soc., 2015, **137**, 12800.
- 10 CCDC-1416587 contains the supplementary crystallographic data for the product **3aa**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.
- 11 For the low yielding of **3ja**, we found that this reaction could not converted completely. Meanwhile, in contrast to the products derivated from phthalimide, the product **3ja** was not stable under the standard reaction conditions.