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Rh(II)/Phosphine-cocatalyzed Synthesis of Dithioketal Derivatives from Diazo Compounds through Simultaneous Construction of Two Different C-S Bonds

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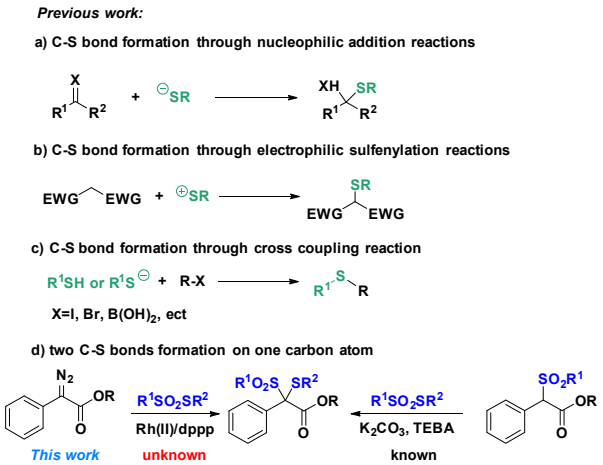
Rhodium(II)/phosphine-cocatalyzed bis-sulfuration of α-diazocarbonyl compounds using thiosulfonates as the sulfenylating agent which provided two sulfur-containing moieties was developed via simultaneous inter- and intra-molecular C–S bonds formation. This novel protocol provides a rapid synthetic route to dithioketal derivatives in moderate to good yields in an atom-economic process. The transformation is proposed to proceed through phosphine ylide formation followed by S(O_2)–S bond cleavage and rearrangement.

The synthesis of organic sulfur compounds has attracted significant attentions owing to the wide occurrence of sulfur skeletons in natural and various biological systems.[1] Meanwhile, sulfur-containing molecules could also serve as important intermediates and ligands in organic synthesis.[2] In the past few decades, great efforts have been devoted to develop new methods for the construction of C–S bonds. Representative strategies include a) C-S bond-formation through nucleophilic addition reaction (Scheme 1a);[3] b) C-S bond-formation through electrophilic sulfenylation reactions (Scheme 1b);[4] c) C-S bond formation through cross coupling reaction (Scheme 1c).[5] Despite these advances, simultaneous construction of two C-S bonds has rarely been explored, especially the two newly-built C-S bonds are on the same carbon atom.[6] In 1996, a synthesis of α-alkylsulfanyl-α-phenylsulfonyl carboxylic esters via benzyltriethylammonium chloride-catalyzed sulfanylation was achieved in a solid/liquid phase transfer system.[7] Given that dithioketal derivatives have drawn much attention[8] because of their unique motifs, and this framework is embodied in many drug candidates, including those used in cancer chemotherapy or as a nontoxic oral hypocholesterolemic agent, therefore, it becomes highly desirable to find a facile and efficient strategy to construct this scaffold.[9]

Diazo compounds are versatile and powerful synthetic building blocks that have been extensively explored in modern synthetic organic chemistry and their rich chemistry has attracted great interest.[10] One of main reasons is that diazo compounds can generate carbenes or metal carbenoids in situ,[11] which are reactive intermediates that could undergo a wide range of synthetically useful reactions including C-H[12] and X-H insertion reaction (X= N, O, S, P, Si),[13] cyclopropanation reactions[14] and ylide formation.[15] Recently, the metal-catalyzed insertion of carbenoids into X–Y (X, Y= C, N, O, Si, S, etc.) bonds has become a powerful method for the construction of versatile chemical frameworks.[16] Inspired by these works, we envision that diazo compounds could be right starting points to build two C-S bonds simultaneously with a specific disulfur compounds, namely, sulfenylating agent. At this point, S-methyl benzenesulfonothioate catches our eyes, since it contains two different types of sulfur atom and usually it serves as thiolating reagent with benzenesulfonyl moiety as a leaving group which was usually discarded as a waste. In the past decades, diazo compounds have become a readily available and widely employed precursor to access carbenes. When it is subjected to S-methyl benzenesulfonothioate, two different types of C-S bonds might be resulted simultaneously on the same carbon atom.



Scheme 1. Patterns for the construction of C-S bonds

In order to examine our hypothesis, diazoacetate **1a** and S-methyl benzenesulfonothioate (**2a**) were chosen as model substrates. To our delight, we observed that when a 2:1 mixture of diazoacetate **1a** and S-methyl benzenesulfonothioate (**2a**) was catalyzed by 5 mol % of $CuCl_2$, α-methylsulfanyl-α-phenylsulfonyl carboxylic ester (**3a**) was

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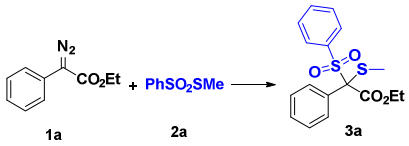
obtained in 16% yield with 10 mol% tricyclohexyl phosphine as cocatalyst in DCE at 70 °C for 12 h (Table 1, entry 1). Subsequent metal screening suggested that $Rh_2(OAc)_4$ was the optimal one among $CuCl_2$, $Cu(acac)_2$, $Cu(OAc)_2$, $Pd(OAc)_2$, and $Pd_2(dba)_3$ (see the Supporting Information). Temperature examination revealed that higher temperature has deteriorate effect on the reaction, and 25 °C gave the best yield of the desired product **3a** (Table 1, entries 4-5). Further fine tuning on the loading of catalysts as well as the combination of substrate **1a** and **2a** indicated that 1.5:1 of **1a**:**2a** with 1 mol% of $Rh_2(OAc)_4$ rendered the optimal result (Table 1, entries 6-8). In view that the choice of cocatalyst is crucial for the success of this transformation, several commonly used electron-rich organophosphine compounds, such as tricyclohexyl phosphine, triphenylphosphine (PPh_3), 1,4-bis(diphenylphosphino)butane (dppb) and 1,3-bis(diphenylphosphino)propane (dppp) were tested, and 1,3-bis(diphenylphosphino)propane (dppp) appeared to be the best choice for the reaction (Table 1, entries 7, 8–11).

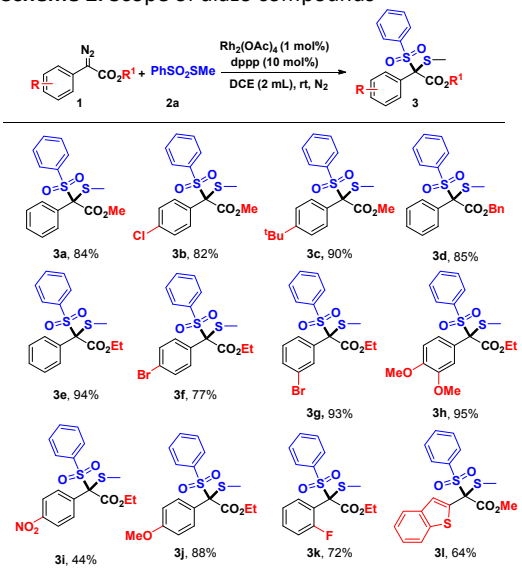
Table 1. Optimization of the reaction conditions



entry	**1a**:**2a**	Catalyst [x mol%]	Cocatalyst [10 mol%]	T[°C]/[h]	Yield[a][%]
1	2:1	$CuCl_2$/5	Cy_3P	70/12	16
2	2:1	$Rh_2(OAc)_4$/5	Cy_3P	70/12	75
3	2:1	$Rh_2(OAc)_4$/2.5	Cy_3P	70/12	79
4	2:1	$Rh_2(OAc)_4$/1	Cy_3P	70/12	80
5	2:1	$Rh_2(OAc)_4$/1	Cy_3P	25/12	94
6	2:1	$Rh_2(OAc)_4$/1	Cy_3P	25/3	89
7	1.5:1	$Rh_2(OAc)_4$/1	Cy_3P	25/3	89
8	1:1	$Rh_2(OAc)_4$/1	Cy_3P	25/3	71
9	1.5:1	$Rh_2(OAc)_4$/1	PPh_3	25/3	25
10	1.5:1	$Rh_2(OAc)_4$/1	dppb	25/3	82
11	**1.5:1**	**$Rh_2(OAc)_4$/1**	**dppp**	**25/3**	**94**

Reaction conditions: **2a** (0.2 mmol), in DCE (2.0 mL), N_2. [a] Isolated yields.

Scheme 2. Scope of diazo compounds[a]

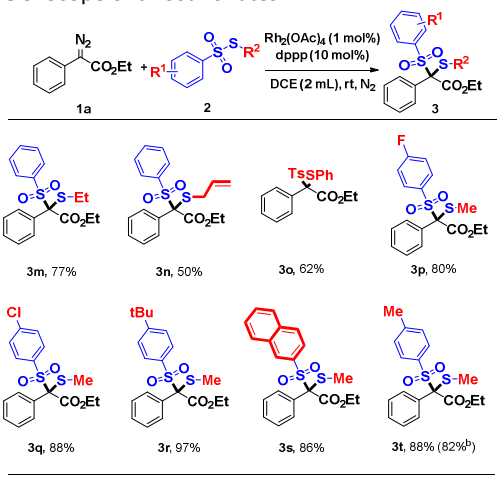


[a] Unless otherwise noted, all reactions were run with **1** (0.3 mmol), **2a** (0.2 mmol), $Rh_2(OAc)_4$ (1 mol%), dppp (10 mol%), DCE (2 mL) in a Schlenk tube under N_2 atmosphere at 25 °C for 3 h.

Next, we proceeded to explore the generality of the reaction under the optimized reaction conditions. As shown in Scheme 2, a series of diazo compounds could be employed as substrates in the reaction with **2a**, affording the corresponding dithioketal derivatives **3a-3l** efficiently. It is noteworthy that both electron-withdrawing and electron-donating groups (fluoro, chloro, bromo, NO_2, ^{t}Bu, and methoxyl) on the aromatic ring of **1** were well tolerated under the reaction conditions, and the position of substituents has little influence on the efficiency of the transformation (Scheme 2, **3b-3c, 3f-3k**). Most remarkably, heteroaryl acetate derived diazo compounds, such as benzothiophene was also compatible under the standard conditions, leading to desired product **3l** in 64% yield.

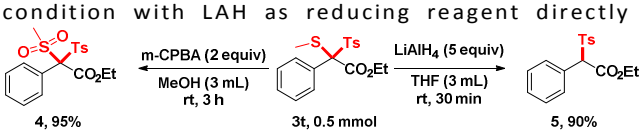
Furthermore, the scope of thiosulfonate derivatives were investigated (Scheme 3). Not surprisingly, a variety of thiosulfonates underwent the insertion smoothly and afforded the target products in good yields.

Scheme 3. Scope of thiosulfonates[a]



[a] Unless otherwise noted, all reactions were run with **1a** (0.3 mmol), **2** (0.2 mmol), $Rh_2(OAc)_4$ (1 mol%), dppp (10 mol%), DCE (2 mL) in a schlenk tube under N_2 atmosphere at 25 °C for 3 h. [b] scale up to 5 mmol.

The easy availability of dithioketal derivative **3t**, which was obtained in 82% yield when scaled up to 5 mmol, opens new synthetic opportunities for a suitable functionalization on the S-methyl group due to its well-known reactivity upon different conditions. For example, methyl-sulfonyl derivative **4** was readily obtained in almost quantitative yield under oxidizing condition with *m*-CPBA as an oxidant; meanwhile, a reductive condition with LAH as reducing reagent directly



Scheme 4. Further synthetic elaborations of **3t** under different redox conditions

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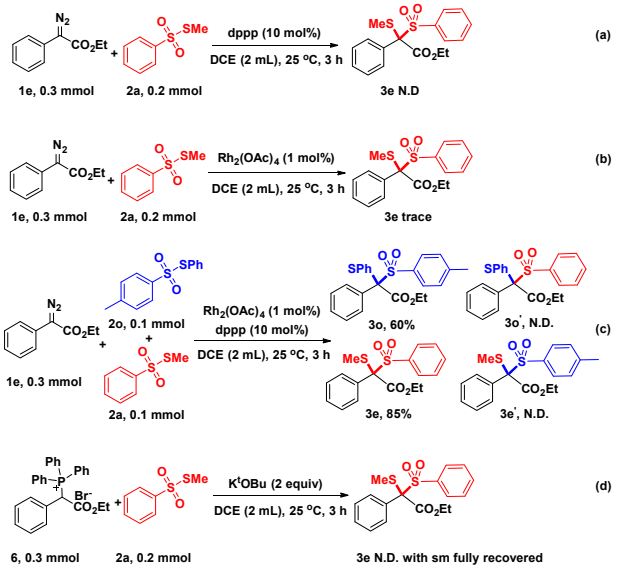
converted **3t** into 2-tosyl-phenylacetate **5**, with the substitution of MeS group by a hydride from LAH (Scheme 4).

In order to gain insights into the efficient $S(O_2)$-S bond insertion into the diazo compounds, a series of control reactions were carried out. First, in the absence of Rh (II) catalyst, desired product **3e** was not detected (Scheme 5a). When the reaction was performed without co-catalyst dppp, no **3e** was ever obtained (Scheme 5b) and the material was fully recovered. These two experiments indicated that both Rh (II) catalyst and dppp play key roles for the success of this transformation. To further confirm that an intramolecular-concerted process was involved in the transformation via the cleavage of $S(O_2)$-S bond and simultaneous insertion of carbene moiety, a crossover reaction was run with two different thiosulfonates and only the corresponding target products **3o** and **3e** were obtained (60% and 85% yields respectively) and no crossover intermolecular products **3o'** and **3e'** were ever detected (Scheme 5c). Therefore this result ruled out the S_N1 pathway, strongly supporting a concerted cleavage-attack route. When the reaction was performed with Wittig reagent **6** and thiosulfonate **2a** in the presence of K^tOBu, no **3e** was ever obtained (Scheme 5d) and the material was fully recovered. This experiment suggested that phosphine ylide itself could not promote this transformation, therefore it further underscored the importance of both Rh(II) salt and cocatalyst 1,3-bis(diphenylphosphino)propane (dppp) for the reaction.



Scheme 5. Control experiments

To further elucidate the mechanism of such a dual-catalyst system, we carried out several reactions with ^{31}P NMR spectroscopic analyses on the experimental processes (Fig. 1, ^{31}P NMR). The ^{31}P NMR spectroscopy studies provide further supports for the assumed key catalytic active species in the reaction. The cocatalyst dppp alone showed a ^{31}P peak at -17.5 ppm. (Fig. 1a); the shift of this signal has not changed when dppp was mixed with $Rh_2(OAc)_4$ (1:1) (Fig. 1b), indicating that dppp does not serve as a ligand with Rh(II) salt, it should be a cocatalyst. There is a new peak at 26.1 ppm appeared, when dppp was mixed with diazo compound **1a** and $Rh_2(OAc)_4$ (1:1:0.05) (Fig. 1c). This new resonance was assigned to a zwitterion intermediate. Moreover, when TsSMe was added to the above solution of diazo compound **1a**, dppp and $Rh_2(OAc)_4$, and the mixture was stirred for 3 hours, we can see two new peaks at -17.5 ppm and 32.6 ppm shown up, undoubtedly, the peak at -17.5 ppm is the recovery of catalyst dppp, and the one at 32.6 ppm represents the oxidized phosphine compound that derived by dppp (Fig. 1d, ^{31}P NMR), which has been proven by the reaction between TsSMe and dppp only, in this reaction, 1,3-bis(diphenylphosphino)propane was fully oxidized into oxyphosphine (Fig. 1e, ^{31}P NMR). It is of note that

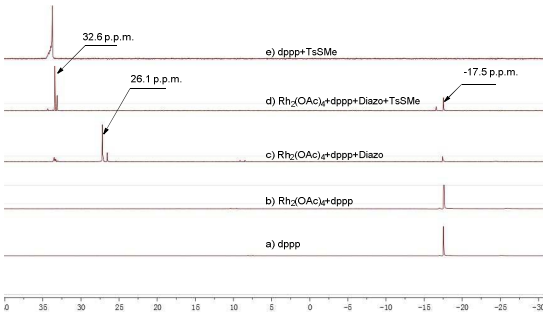
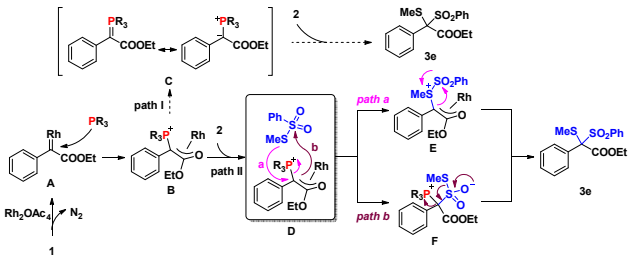


Figure 1. ^{31}P NMR and in CDCl3. (^{31}P NMR-a) dppp ; (^{31}P NMR-b) dppp:$Rh_2(OAc)_4$ =(1:1); (^{31}P NMR-c) dppp: Diazo:$Rh_2(OAc)_4$ =0.2:1:0.05; (^{31}P NMR-d) dppp:Diazo:TsSMe:$Rh_2(OAc)_4$ =0.2:1:1:0.05; (^{31}P NMR-e) dppp: TsSMe= 1:1

On the basis of previous reports as well as our own experimental observations, a plausible mechanism for the formation of **3e** is depicted in Scheme 6. The formation of the observed product is first initiated by the Rh(II)-catalyzed decomposition of diazo-compound **1** to afford the corresponding Rh(II)-carbenoid intermediate **A** via the loss of N_2. Carbenoid **A** subsequently reacts with dppp to form a rhodium-containing phosphorus ylide **B**, which might undergo two reaction pathways (path I and II). However, the phosphorus ylide **C**, which is generated from intermediate **B** by the release of Rh salt, can be excluded as the possible reaction intermediate by the control experiment **d** in Scheme 5 (path I).



Scheme 6. Proposed mechanism for the formation of **3e**

In terms of Path II, as shown in the reaction details **D**, two possible pathways might be occurred leading to the desired product. Given that the strong leaving ability of the $^+PR_3$ motif on intermediate **B**, the sulfur ylide **E** is obtained via direct nucleophilic substitution reaction between the sulfur atom of the thiosulfonate **2** and intermediate **B**, generating final product **3e** through a Stevens-type rearrangement (path a). On

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the other hand, intermediate **B** attacks on the $PhSO_2$-motif of thiosulfonate **2** rendering intermediate **F**, which produces **3e** via the SMe 1, 2-migration and the departure of 1,3-bis(diphenylphosphino)propane (path b).

In summary, we have developed an unprecedented rhodium(II)-catalyzed direct sulfenylation reaction between thiosulfonates with diazo compounds which simultaneously build dual C-S bonds by sulfur ylide formation followed by $S(O_2)$–S bond cleavage and rearrangement. A series of dithioketal derivatives were obtained in moderate to high yields by the metal-catalyzed insertion of carbenoids into $S(O_2)$–S. Most importantly, the substrate scope was extended by successful execution of α-diazocarbonyl compounds and thiosulfonates as suitable substrates for this transformation. The present protocol provides a versatile method to establish two important functional groups which are key structural elements and are frequently encountered in many natural products and biomolecules.

Conflicts of interest

The authors declare no competing financial interest.

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