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Phosphine-free cationic rhodium(I) complex-catalyzed disulfide exchange reaction: convenient synthesis of unsymmetrical disulfides

Ken Tanaka* and Kaori Ajiki

Department of Applied Chemistry, Tokyo University of Agriculture and Technology,
2-24-16, Nakacho, Koganei, Tokyo 184-8588, Japan

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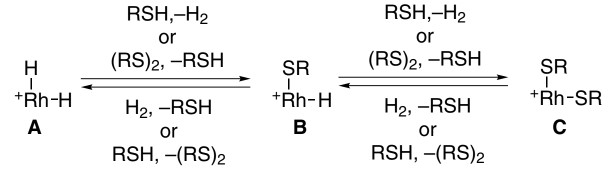
Abstract—A phosphine-free cationic rhodium(I) complex, $[Rh(cod)_2]BF_4$, is an effective catalyst for disulfide exchange reaction of symmetrical disulfides to unsymmetrical disulfides under inert atmosphere. This reaction could be carried out using unpurified commercial grade solvents under air without decrease of yields and reaction rates.

Disulfides are important compounds for both chemical and biological processes.[1] The synthesis of symmetrical disulfides can be carried out by selective oxidative coupling of thiols to disulfides.[2] On the other hand, for the synthesis of unsymmetrical disulfides, disulfide exchange reaction is one of the useful methods to eliminate the use of thiols, which have unpleasant odour.[3] The existing methods of disulfide exchange reactions require severe reaction conditions to generate sulfur radicals,[4] cations,[5] or anions,[6] which react with disulfide to cleave the disulfide bond. In order to overcome these problems, Arisawa and Yamaguchi reported that $RhH(PPh_3)_4$/*p*-tol_3P/trifluoromethanesulfonic acid combination catalyst is highly effective for disulfide exchange reaction and two structurally different disulfides rapidly reach equilibrium composition to give unsymmetrical disulfides.[7,8]

During our program of the utilization of cationic rhodium(I) complexes for the variety of synthetic reactions, we recently discovered that $[Rh(cod)_2]BF_4/PPh_3/H_2$ catalyst[9] is the effective catalyst for the dehydrogenation of thiols to symmetrical disulfides (Eq. 1).[10,11]

$$\mathrm{RSH} \xrightarrow[\substack{\mathrm{CH_2Cl_2,\ under\ Ar} \\ 4\ ^\circ\mathrm{C,\ 1\ h}}]{\substack{5\%\ [\mathrm{Rh(cod)_2}]\mathrm{BF_4}/ \\ 8\ \mathrm{PPh_3/H_2}}} \mathrm{(RS)_2 + H_2} \qquad (1)$$



Scheme 1.

The mechanistic studies revealed that dehydrogenation of thiols is reversible process.[12] Plausible mechanism of this reaction is illustrated in Scheme 1. Presumably, all the steps shown in Scheme 1 are reversible and the reaction proceeds via complexes **A**, **B** and **C**. Therefore, if disulfides are used as substrates instead of thiols in the presence of rhodium hydride complex, disulfide exchange reaction may proceed via generation of catalytic amount of thiol.[13]

We first examined the disulfide exchange reaction of dibenzyl disulfide and di-*n*-butyl disulfide in the presence of $[Rh(cod)_2]BF_4/PPh_3/H_2$ catalyst[9] in CH_2Cl_2 at 25 °C for 1 h, and found that disulfide exchange smoothly proceeded to give benzyl *n*-butyl disulfide in 48% yield (Eq. 2).

$$\mathrm{(PhCH_2S)_2} + (n\text{-}\mathrm{BuS})_2 \xrightarrow[\substack{\mathrm{CH_2Cl_2,\ under\ Ar} \\ 25\ ^\circ\mathrm{C,\ 1\ h}}]{\substack{5\%\ [\mathrm{Rh(cod)_2}]\mathrm{BF_4}/ \\ 8\ \mathrm{PPh_3/H_2}}} \underset{48\%}{\mathrm{PhCH_2{-}S{-}S{-}}n\text{-}\mathrm{Bu}} \qquad (2)$$

Keywords: Disulfide; Disulfide exchange; Phosphine-free; Rhodium.

* Corresponding author. Tel./fax: +81-42-388-7037; e-mail: tanaka-k@cc.tuat.ac.jp

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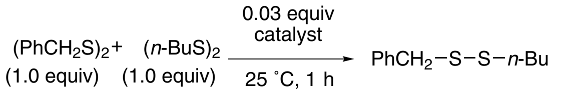
Table 1. Screening of reaction conditions for rhodium(I)-catalyzed disulfide exchange of symmetrical disulfides[a]



$$\underset{(1.0\ \text{equiv})}{(\text{PhCH}_2\text{S})_2} + \underset{(1.0\ \text{equiv})}{(n\text{-BuS})_2} \xrightarrow[25\ ^\circ\text{C},\ 1\ \text{h}]{0.03\ \text{equiv catalyst}} \text{PhCH}_2\text{–S–S–}n\text{-Bu}$$

Entry	Catalyst	Solvent	Yield (%)[b,c]
1[d]	$[\text{Rh(cod)}_2]\text{BF}_4/4\text{PPh}_3/\text{H}_2$	CH_2Cl_2	48
2	$[\text{Rh(cod)}_2]\text{BF}_4/4\text{PPh}_3$	CH_2Cl_2	49
3	$[\text{Rh(cod)}_2]\text{BF}_4$	CH_2Cl_2	48
4[e]	$[\text{Rh(cod)Cl}]_2/8\text{PPh}_3$	CH_2Cl_2	47
5[e]	$[\text{Rh(cod)Cl}]_2$	CH_2Cl_2	1
6[e]	$[\text{Ir(cod)Cl}]_2/8\text{PPh}_3$	CH_2Cl_2	40
7	$[\text{Rh(cod)}_2]\text{BF}_4$	Acetone	17
8	$[\text{Rh(cod)}_2]\text{BF}_4$	THF	3
9	$[\text{Rh(cod)}_2]\text{BF}_4$	CH_3CN	0
10	$[\text{Rh(cod)}_2]\text{BF}_4$	Toluene	0
11	—	CH_2Cl_2	0

[a] The reaction was conducted using $(\text{PhCH}_2\text{S})_2$ (0.25 mmol), $(n\text{-BuS})_2$ (0.25 mmol), catalysts (0.0075 mmol) and solvents (2 mL) under Ar.

[b] Yield based on the PhCH_2S group.

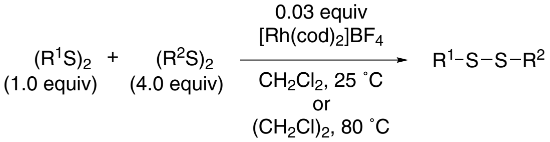
[c] Determined by ^{1}H NMR using hexamethylbenzene as an internal-standard.

[d] The catalyst was prepared by mixing $[\text{Rh(cod)}_2]\text{BF}_4$ and PPh_3 in CH_2Cl_2 followed by hydrogenation (1 atm, rt, 0.5 h).

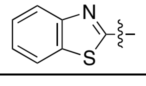
[e] $[\text{Rh(cod)Cl}]_2$ (0.0038 mmol) or $[\text{Ir(cod)Cl}]_2$ (0.0038 mmol) were used.

Various rhodium(I) catalysts were examined to facilitate this transformation as shown in Table 1. In the case of cationic rhodium(I) complex, treatment of catalyst with hydrogen and addition of phosphine were not essential (entries 1–3). On the other hand, addition of phosphine was essential for neutral rhodium(I) complex (entries 4 and 5). Although the catalytic activity was lower than rhodium(I) complex, iridium(I) complex also catalyzed disulfide exchange (entry 6). Among the solvent examined, CH_2Cl_2 was the most effective (entries 3 and 7–10). In the absence of rhodium catalyst no reaction was observed (entry 11).

Table 2. Phosphine-free cationic rhodium(I) complex-catalyzed disulfide exchange of symmetrical disulfides[a]



$$\underset{(1.0\ \text{equiv})}{(\text{R}^1\text{S})_2} + \underset{(4.0\ \text{equiv})}{(\text{R}^2\text{S})_2} \xrightarrow[\text{CH}_2\text{Cl}_2,\ 25\ ^\circ\text{C or } (\text{CH}_2\text{Cl})_2,\ 80\ ^\circ\text{C}]{0.03\ \text{equiv}\ [\text{Rh(cod)}_2]\text{BF}_4} \text{R}^1\text{–S–S–R}^2$$

Entry	R^1	R^2	Condition	Yield (%)[b,c]
1	PhCH_2	n-Bu	25 °C, 3 h	79
2	p-MeOC_6H_4	n-Bu	25 °C, 1 h	81
3	PhCH_2	Cy	80 °C, 1 h	79
4	p-MeOC_6H_4	Cy	80 °C, 1 h	79
5	p-MeOC_6H_4	Ph	80 °C, 5 h	74
6		n-Bu	80 °C, 3 h	95

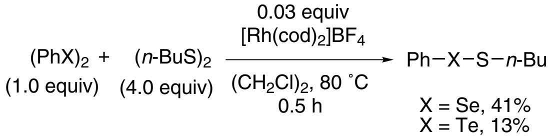
[a] The reaction was conducted using $(\text{R}^1\text{S})_2$ (0.25 mmol), $(\text{R}^2\text{S})_2$ (1.0 mmol), $[\text{Rh(cod)}_2]\text{BF}_4$ (0.0075 mmol) and solvent (2 mL) under Ar.

[b] Yield based on the R^1S group.

[c] Isolated yield.

The phosphine-free cationic rhodium(I) complex-catalyzed disulfide exchange of structurally diverse disulfides, $(\text{R}^1\text{S})_2$ (1 equiv) and $(\text{R}^2\text{S})_2$ (4 equiv), was investigated in detail as shown in Table 2. The disulfide exchange of two different primary alkyl disulfides or primary alkyl disulfide and aryl disulfide proceeded at 25 °C to give corresponding unsymmetrical disulfides (entries 1 and 2). The reaction of secondary alkyl disulfide and primary alkyl disulfide or aryl disulfide proceeded at 80 °C (entries 3 and 4). The reaction of two different aryl disulfides also proceeded at 80 °C (entry 5). The heteroaryl disulfide, which is used for rubber industry could be employed (entry 6).

Exchange reaction of disulfide and diselenide or ditelluride could be accomplished using phosphine-free cationic rhodium(I) complex to give corresponding selenosulfide or tellurinosulfide (Eq. 3).[14,15]

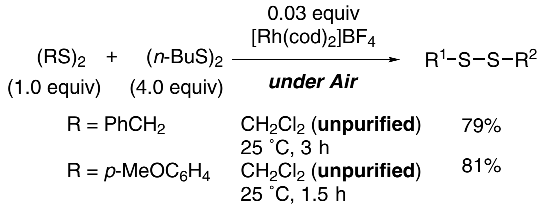


$$\underset{(1.0\ \text{equiv})}{(\text{PhX})_2} + \underset{(4.0\ \text{equiv})}{(n\text{-BuS})_2} \xrightarrow[(\text{CH}_2\text{Cl})_2,\ 80\ ^\circ\text{C},\ 0.5\ \text{h}]{0.03\ \text{equiv}\ [\text{Rh(cod)}_2]\text{BF}_4} \text{Ph–X–S–}n\text{-Bu} \qquad (3)$$

X = Se, 41%
X = Te, 13%

Scheme 2 depicts a plausible mechanism of the phosphine-free cationic rhodium(I) complex-catalyzed disulfide exchange reaction. Because the reaction proceeds in the absence of hydride complex, the reaction presumably proceeds via complex **D**.

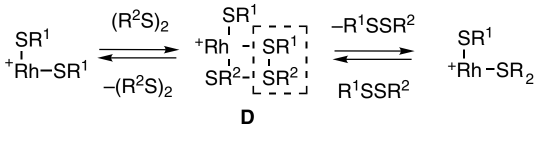
Importantly, this phosphine-free cationic rhodium(I) complex-catalyzed disulfide exchange reaction could be carried out using unpurified commercial grade solvents under air without decrease of yields and reaction rates (Eq. 4).[16] We believe that this feature represents a practical usefulness of this catalytic process.



$$\underset{(1.0\ \text{equiv})}{(\text{RS})_2} + \underset{(4.0\ \text{equiv})}{(n\text{-BuS})_2} \xrightarrow[\textbf{under Air}]{0.03\ \text{equiv}\ [\text{Rh(cod)}_2]\text{BF}_4} \text{R}^1\text{-S-S-R}^2 \qquad (4)$$

R = PhCH_2 — CH_2Cl_2 **(unpurified)**, 25 °C, 3 h — 79%
R = p-MeOC_6H_4 — CH_2Cl_2 **(unpurified)**, 25 °C, 1.5 h — 81%

In conclusion, we have determined that a phosphine-free cationic rhodium(I) complex is an effective catalyst for disulfide exchange reaction of symmetrical disulfides to unsymmetrical disulfides. This reaction takes place under completely neutral conditions without any additional reagents except commercially available cationic rhodium(I) complex, $[\text{Rh(cod)}_2]\text{BF}_4$. In addition, this process is highly practical due to the usable of commercial grade solvents without purification under air.



Scheme 2.

Future work will include elucidation of the role of phosphine and cationic character of rhodium for this reaction, and further utilization of cationic rhodium(I) complexes to a variety of organosulfur chemistry processes.

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15. Exchange reaction of di-*n*-butyl disulfide (1 equiv) and diphenyl diselenide (4 equiv) proceeded in the same reaction conditions (CH_2Cl_2, 80 °C, 0.5 h) to give corresponding selenosulfide in 43% yield.
16. Sample procedure (Eq. 4): Under air, to a CH_2Cl_2 (Wako 130-02457, 1.0 mL) solution of bis(*p*-methoxyphenyl)disulfide (278.4 mg, 1.00 mmol) and di-*n*-butyl disulfide (713.4 mg, 4.00 mmol) was added a CH_2Cl_2 (7.0 mL) solution of $[Rh(cod)_2]BF_4$ (12.2 mg, 0.030 mmol). The resulting solution was kept at 25 °C for 1.5 h under air. The solution was concentrated and purified by silica gel chromatography (hexane/EtOAc = 20:1), which furnished *n*-butyl *p*-methoxyphenyl disulfide (370.8 mg, 1.62 mmol, 81%).