Rhodium(III)-Catalyzed Oxidative Alkenylation of 1,3-Dithiane-Protected Arenecarbaldehydes via Regioselective C−H Bond Cleavage

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S *Supporting Information*

ABSTRACT: A Rh(III)-catalyzed direct alkenylation of 2-aryl-1,3-dithiane derivatives with alkenes has been developed. The 1,3-dithiane group can serve as an effective directing group for the exclusively monoselective alkenylation under mild oxidative conditions. The directing group is readily removable after the coupling event.

1,3-Dithianes are attractive building blocks in organic synthesis because of their utility as unique umpolung acyl anionic synthons.[1] Since the Corey and Seebach groups reported their elegant work on dithiane carboanion chemistry (Scheme 1, left),[1]

Scheme 1. 1,3-Dithiane-Based C−C Bond-Forming Reaction

these umpolung synthons have been applied in various synthetic sequences, especially in natural product synthesis.[2] After nearly a half century since the first disclosure, 1,3-dithiane chemistry still plays a significant role in C−C bond-forming reactions, and considerable efforts have continuously been made to uncover the new application of 1,3-dithianes.[3] For example, Smith and co-workers developed anion-relay chemistry using 2-silyl-1,3-dithiane derivatives.[2b,3a−d] More recently, Schmink[3e] and Walsh[3f] independently reported the palladium-catalyzed arylation of the relatively acidic 2-position of 2-aryl-1,3-dithianes.

Meanwhile, the transition-metal-catalyzed direct functionalization reactions of non- or less acidic C−H bonds have recently been regarded as powerful synthetic tools from atom- and step-economical points of view and extensively studied, especially for the last two decades.[4] Among them, the chelation-assisted regioselective version with the aid of a directing group to enable regioselective functionalization is highly useful in precise synthesis.[4,5] So far, a variety of functional groups containing oxygen and nitrogen atoms have been utilized as effective directing groups in a wide range of reactions. However, the use of sulfur-containing directing groups has been less explored[6,7] because it is generally believed that they coordinate metal centers too strongly to suppress the catalytic activity. In particular, the coordination of a sulfide sulfur is known to be tight. Recently,

Sheppard and co-workers have reported that a 1,3-dithiane moiety can act as a directing group to allow the regioselective acetoxylation of 2-homoallyl-1,3-dithianes by using a stoichiometric amount of $Pd(OAc)_2$.[8] In the context of our continuous studies on rhodium-catalyzed C−H bond functionalization,[4m,n,ac,9] we have succeeded in utilizing this directing group to a catalytic transformation. Thus, the direct alkenylation of 2-aryl-1,3-dithianes and their analogues is achievable at their ortho-position selectively (Scheme 1, right). In addition, the 1,3-dithiane group has been found to be readily removable after the directed alkenylation. These new findings are described herein.

First, we carried out optimization studies using 2-phenyl-1,3-dithiane (**1a**) and n-butyl acrylate (**2a**) as model substrates (Table 1). In an initial attempt, **1a** (0.25 mmol) was treated with **2a** (0.5 mmol) in the presence of $[Cp^*Rh(MeCN)_3(SbF_6)_2]$ (0.005 mmol, 2 mol %) and $Cu(OAc)_2 \cdot H_2O$ (0.5 mmol) in diglyme at 100 °C under N_2 for 12 h. As a result, the desired dehydrogenative coupling product **3a** was formed in 22% GC yield (entry 1). $[Cp^*RhCl_2]_2$ was inactive in this reaction (entry 2). The yield of **3a** was somewhat improved at a lower temperature of 60 °C (entry 3). However, a further decrease of temperature to 40 °C reduced the yield (entry 4). Next, various solvents were screened (entries 5−10). Among them, THF gave the best result to afford **3a** in 45% yield. AgOAc was totally ineffective as oxidant (entry 11). Eventually, the desired coupling product **3a** was obtained in 92% yield (87% isolated yield) by a higher loading of $[Cp^*Rh(MeCN)_3(SbF_6)_2]$ (8 mol %) and the elongation of reaction time (entry 13).

With the effective conditions in hands (entry 13 in Table 1), we next examined the substrate scope of this reaction (Scheme 2). A number of (4-substituted phenyl)dithianes **1b−f** underwent coupling with alkene **2a** smoothly to afford the
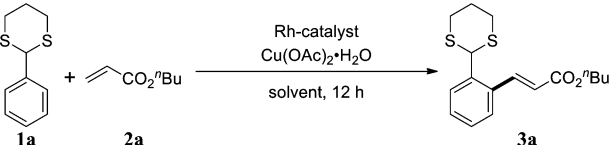
Table 1. Optimization Studies for Rh-Catalyzed Direct Alkenylation of 2-Phenyl-1,3-dithiane 1a[a]

entry	Rh catalyst (mol %)	solvent	temp (°C)	yield[b] (%)
1	[Cp*Rh(MeCN)$_3$][SbF$_6$]$_2$ (2)	diglyme	100	22
2	[Cp*RhCl$_2$]$_2$ (1)	diglyme	100	trace
3	[Cp*Rh(MeCN)$_3$][SbF$_6$]$_2$ (2)	diglyme	60	31
4	[Cp*Rh(MeCN)$_3$][SbF$_6$]$_2$ (2)	diglyme	40	16
5	[Cp*Rh(MeCN)$_3$][SbF$_6$]$_2$ (2)	DCE	60	8
6	[Cp*Rh(MeCN)$_3$][SbF$_6$]$_2$ (2)	PhCF$_3$	60	12
7	[Cp*Rh(MeCN)$_3$][SbF$_6$]$_2$ (2)	MeOH	60	6
8	[Cp*Rh(MeCN)$_3$][SbF$_6$]$_2$ (2)	acetone	60	37
9	[Cp*Rh(MeCN)$_3$][SbF$_6$]$_2$ (2)	MeCN	60	2
10	[Cp*Rh(MeCN)$_3$][SbF$_6$]$_2$ (2)	THF	60	45
11[c]	[Cp*Rh(MeCN)$_3$][SbF$_6$]$_2$ (2)	THF	60	trace
12	[Cp*Rh(MeCN)$_3$][SbF$_6$]$_2$ (4)	THF	60	51
13[d]	[Cp*Rh(MeCN)$_3$][SbF$_6$]$_2$ (8)	THF	60	92 (87)

[a]Reaction conditions: **1a** (0.25 mmol), **2a** (0.5 mmol), Rh catalyst, Cu(OAc)$_2$·H$_2$O (0.5 mmol), solvent (2 mL) under N$_2$ for 12 h. [b]GC yield. Yield after purification is given in parentheses. [c]AgOAc (0.5 mmol) was used as oxidant instead of Cu(OAc)$_2$·H$_2$O. [d]For 24 h.

corresponding alkenylated products **3b−f** in fair to good yields.[10] Notably, Cl and Br groups were intact under the reaction conditions to enable the further functionalization of products **3c** and **3d**. It is known that an acetyl function also acts as directing group that leads to ortho-alkenylation under rhodium catalysis.[11] However, the observed selective formation of **3f** from **1f** indicates that 1,3-dithiane is a more effective directing group than acetyl under the present catalytic system. The reactions of 4-nitro **1g** and 4-methoxy **1h** substrates were sluggish to give compounds **3g** and **3h** in 40% and 16% yield, respectively, under standard conditions. In the latter case, a significant amount of deprotected anisaldehyde was formed due to the instability of **1h**. Therefore, the reaction conditions for this substrate were reexamined briefly (see the Supporting Information for details). As a result, the use of the [Cp*Rh(MeCN)$_3$(SbF$_6$)$_2$] (8 mol %)/Cu(OAc)$_2$·H$_2$O (20 mol %)/activated MnO$_2$ (2 equiv) system improved the yield up to 42%. Under similar conditions, 4-methylthio-substituted substrate **1i** was also converted to **3i** with reasonable efficiency.

Naphthyl-containing substrate **1j** reacted with **2a** at the less hindered position to produce **3j** exclusively. Treatment of 3-methoxy- (**1k**) and 3-phenoxy- substituted (**1l**) substrates predominantly gave **3k** and **3l**, in which the alkenylation took place at sterically less hindered positions, along with minor amounts of **3k′** and **3l′**. In contrast, the reaction of piperonal-derived **1m** gave more congested **3m′** preferentially, probably due to an additional directing effect by the tethered oxygen atom.[12] 2-Methyl-substituted substrate **1n** showed low reactivity probably because of steric repulsion between the methyl group and the bulky dithiane moiety. Interestingly, the use of a less hindered five-membered 1,3-dithiolane as the directing group made the reaction efficient even with 2-substituted substrates. Thus, 2-(2-methylphenyl)-1,3-dithiolane (**1o**) and 2-(2-fluoro-phenyl)-1,3-dithiolane (**1p**) coupled with **2a** to give **3o** and **3p** in 78 and 90% yields, respectively. The present procedure was also

Scheme 2. Reaction of 2-Aryl-1,3-dithianes and Dithiolanes 1 with Alkenes 2a[a]
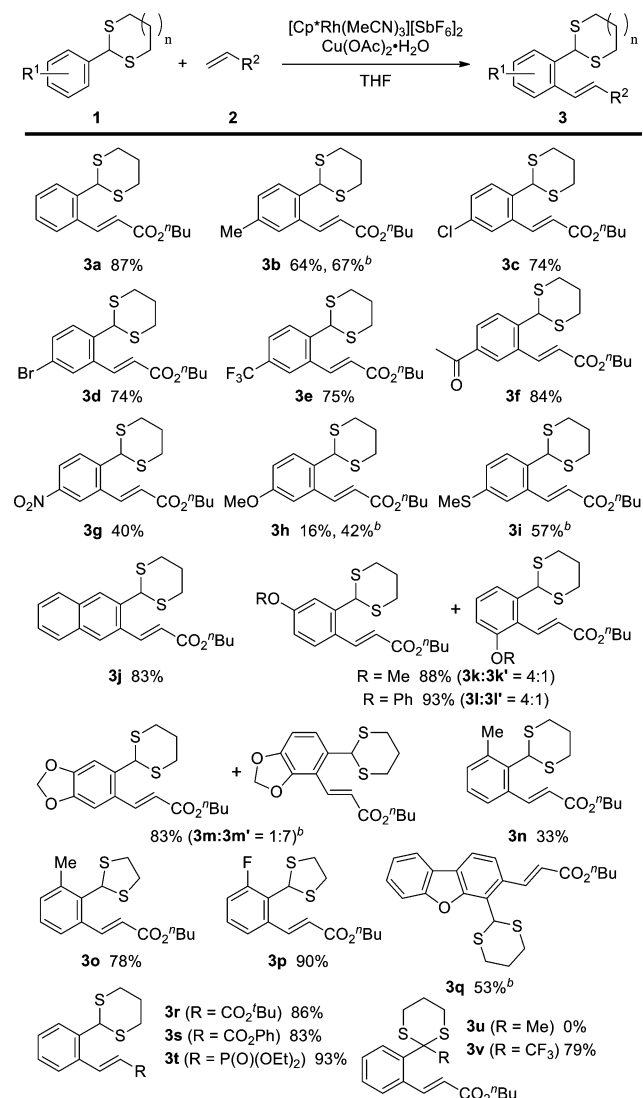
[a]Reaction conditions: **1** (0.25 mmol), **2** (0.5 mmol), [Cp*Rh-(MeCN)$_3$][SbF$_6$]$_2$ (0.02 mmol), Cu(OAc)$_2$·H$_2$O (0.5 mmol), in THF (2 mL) at 60 °C under N$_2$ for 24 h. Isolated yields are shown. [b]With Cu(OAc)$_2$·H$_2$O (0.05 mmol) and activated MnO$_2$ (0.5 mmol) instead of Cu(OAc)$_2$·H$_2$O (0.5 mmol).

effective for the C3 selective alkenylation of a dibenzofuran framework to produce **3q** selectively. Other alkenes such as tert-butyl acrylate (**2b**), phenyl acrylate (**2c**), and diethyl vinyl-phosphonate (**2d**) could be employed in place of **2a** in the reaction of **1a** to give **3r−t** in 83−93% yields. In addition, the reactions of ketone-derived substrates were examined. Aceto-phenone-derived **1u** was completely decomposed under the reaction conditions to form a significant amount of acetophe-none. On the other hand, trifluoroacetophenone-derived **1v** smoothly reacted with **2a** to afford **3v** in 79% yield. This suggests that the CF$_3$ group stabilizes the starting material to suppress a cationic decomposition pathway.[13]

This Rh catalysis was also applicable to a substrate bearing a cyclic monosulfide (Scheme 3).[6d] Treatment of cyclic sulfide **4** with **2a** under standard conditions resulted in the formation of monoalkenylated product **5** and dialkenylated product **6** in 10% and 82% yield, respectively. In this reaction, both **5** and **6** could

Scheme 3. Reaction of Cyclic Sulfide 4 with Alkene 2a

m = 2, n = 2	10%	82%
m = 1, n = 2	73%	10% (NMR)
m = 3, n = 3	0% (NMR)	94%
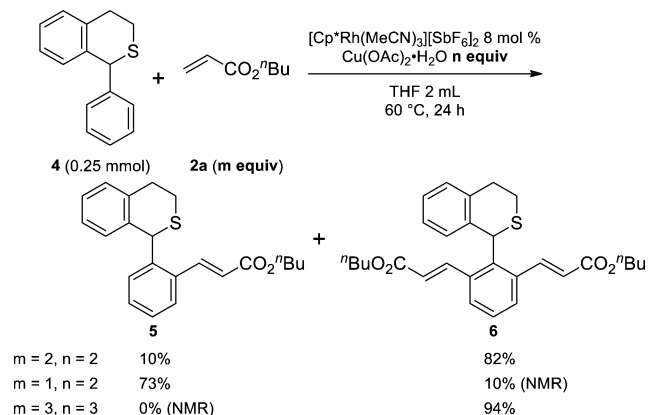
be selectively prepared by using the appropriate amounts of alkene **2a** and oxidant $Cu(OAc)_2 \cdot H_2O$. Thus, reducing the amount of **2a** gave monoalkenylated product **5** predominantly and increasing the amounts of **2a** and the Cu salt gave **6** exclusively.

A plausible mechanism for the reaction of 2-phenyl-1,3-dithiane (**1a**) with alkene **2** is illustrated in Scheme 4.

Scheme 4. Plausible Reaction Mechanism
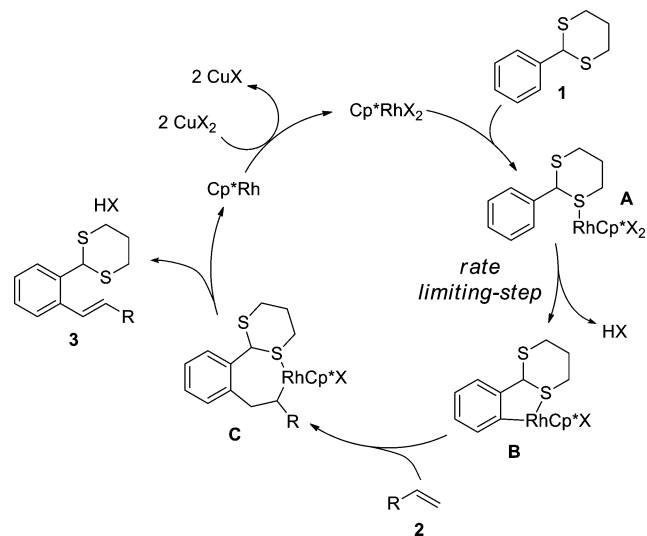
Coordination of the dithiane moiety of **1a** to a Rh(III) center and subsequent C–H bond cleavage at the ortho position of a resulting intermediate **A** take place to form a five-membered rhodacycle intermediate **B**.[6d,7a] Then, alkene insertion and subsequent β-hydrogen elimination via an intermediate **C** may occur to produce alkenylated product **3**. The resulting Rh(I) species seems to be oxidized by a Cu(II) oxidant to regenerate a Rh(III) active species.

To provide further mechanistic insight, we carried out some deuterium-labeling experiments (see the Supporting Information for details).[14] The kinetic isotope effects were examined through the reactions of **1a**-d_0 and **1a**-d_5 with alkene **2a**. The k_H/k_D values were found to be 4.1 (two parallel reactions: Figure S1, Supporting Information) and 4.0 (intermolecular competition: eq S3, Supporting Information). Moreover, when **1a**-d_5 was treated with or without alkene **2a** under standard conditions for 100 min, no D/H exchange at the ortho positions of **1a**-d_5 and

product **3a**-d_4 was observed (eqs S4 and S5, Supporting Information). These results suggest that the cyclometalation step of **A** to **B** is irreversible and is the rate-limiting step of this coupling.

Finally, the further reactions of an alkenylated product were carried out. Treatment of **3s** with 2 equiv of the Dess–Martin periodinane reagent in a $MeCN/CH_2Cl_2/H_2O$ cosolvent system at room temperature[15] resulted in deprotection to furnish aldehyde **7** in an excellent yield (eq 1). It should be noted that the
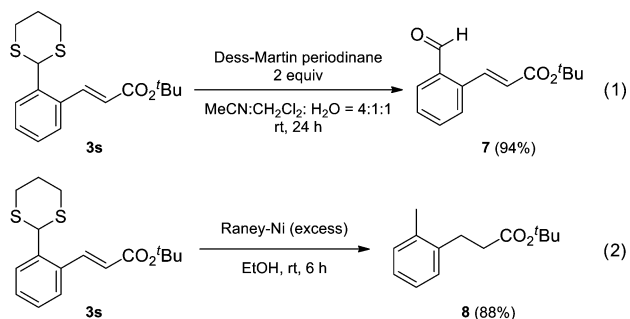
direct ortho-alkenylation of aromatic aldehydes is still challenging.[16] Jeganmohan[16a] and Prabhu[16b] independently reported Ru(II)-catalyzed versions though the scope is limited to electron-rich aromatic aldehydes. Therefore, the present procedure appears to be a useful alternative for synthesizing a wide range of ortho-alkenylated aromatic aldehydes. Moreover, the reductive desulfurization/alkene reduction of **3s** was also achieved by a simple treatment with Raney-Ni to afford **8** in 88% yield (eq 2).

In summary, we have demonstrated that the rhodium-catalyzed direct ortho-alkenylation of 2-phenyl-1,3-dithiane and its analogues can be conducted efficiently. This provides a new strategy for dithiane-based C–C bond-forming chemistry. Further development of sulfur-assisted catalytic transformation reactions is now in progress in our laboratory.

■ ASSOCIATED CONTENT

ⓢ Supporting Information

Experimental procedures, additional results, and characterization data of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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