Rh(II)-catalyzed formal [3+3] cycloaddition of diazonaphthoquinones and propargyl alcohols: Synthesis of 2,3-dihydronaphtho-1,4-dioxin derivatives

Rh(II)-catalyzed formal [3+3] cycloaddition of diazonaphthoquinones and propargyl alcohols: Synthesis of 2,3-dihydronaphtho-1,4-dioxin derivatives

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Abstract

A Rh(II)-catalyzed formal [3+3] cyclization of diazonaphthoquinones and propargyl alcohol is reported to afford 2,3-dihydro-1,4-benzodioxins. Various terminal propargyl alcohols react with diazonapthoquinone in the presence of $Rh_2(OAc)_4$ to give the corresponding dihydrodioxins in good to high yields. However, dihydrodioxins are not formed in the reaction of internal propargyl alcohols, and the O–H insertion product and 2,5-dihydrofurans are formed as the main product(s) depending on the terminal substituent. 2,3-Dihydro-1,4-benzodioxins are proposed to be formed *via* Rh(II)-catalyzed intermolecular oxonium ylide formation and subsequent 6-*exo*-*dig* cyclization with the internal alkynyl group.

Keywords:

Cyclization

Diazo compounds

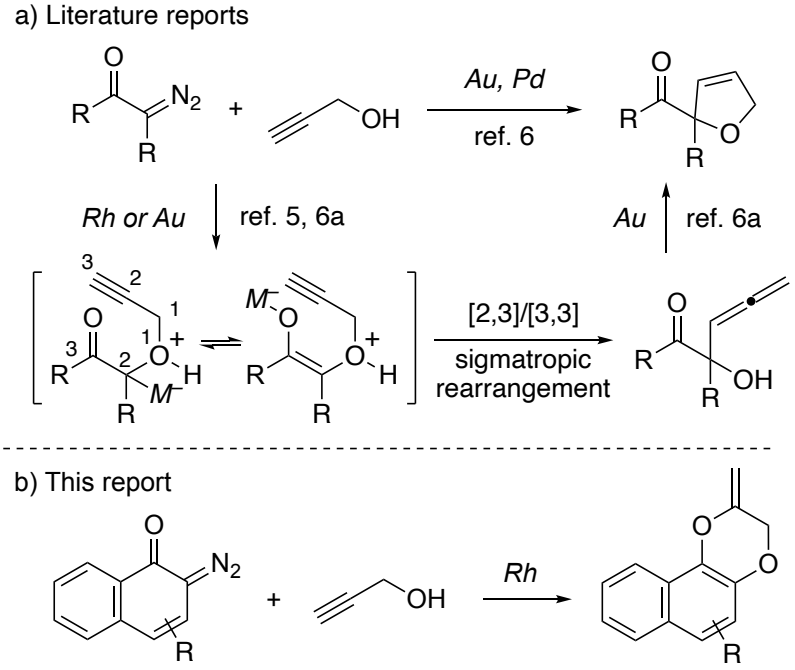
Diazonaphthoquinone

Propargyl alcohol

Rhodium

Introduction

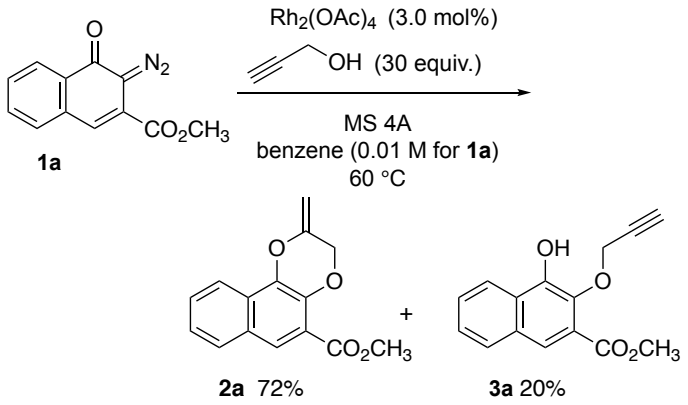
α-Diazocarbonyl compounds react with various metal complexes to form metal carbenes, which are widely used as intermediates in organic synthesis [1]. One of the useful reactions of metal carbenes is the insertion reaction into X–H bonds (X = heteroatom) [1,2]. In particular, O–H insertion reactions between metal carbenes and alcohols are well studied [3], and the reaction mechanism is proposed to proceed *via* formation of an oxonium ylide followed by a proton transfer reaction [4]. Interestingly, when propargylic alcohols are used for the reaction with metal carbenes, allenes are occasionally formed *via* a tandem oxonium ylide formation followed by [2,3]/[3,3]-sigmatropic rearrangement (Scheme 1) [5]. Further cyclization of the formed allenes has been examined for the synthesis of heterocycles, namely, 2,5-dihydrofurans [6].



Scheme 1. Metal-catalyzed reaction of α-diazocarbonyl compounds and propargyl alcohol.

Previously, we developed an efficient synthetic method for the preparation of diazonaphthoquinones *via* diazo-transfer with 2-azido-1,3-dimethylimidazolinium salt [7], and we have subsequently been investigating a series of metal-catalyzed reactions using these products [8,9]. In the study of the Rh(II)-catalyzed O–H insertion reaction of diazonaphthoquinone and alcohols, we observed the formation of formal [3+3] cycloaddition product **2a** (2,3-dihydronaphtho[1,2-b]-1,4-dioxin) along with the expected O–H insertion product **3a** when 2-propyn-1-ol was used (Scheme 2) [9h]. Such formal

[3+3] cycloaddition had not been previously reported for the metal-catalyzed reaction of diazocarbonyl compounds and propargyl alcohol. Only a related reaction was reported by Katukojvala and co-workers, which consists of the formation of 1,4-oxazines by the cooperative Rh(II)/Bronsted acid and Au(I)-catalyzed cyclization of enal diazocarbonyl compounds and propargylamine *via* a dienamine intermediate [10].



Scheme 2. Unexpected result in the Rh-catalyzed reaction of diazonaphthoquinone **1a** and propargyl alcohol.

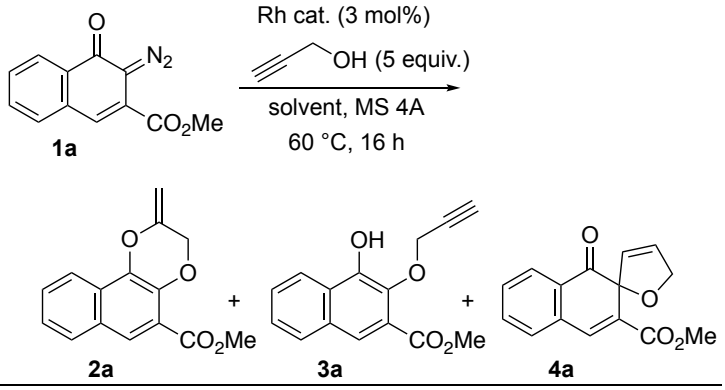
We were intrigued by this unexpected formal [3+3] cycloaddition and anticipated that this transformation could be a new and simple method for the synthesis of 2,3-dihydronaphtho[1,2-b]-1,4-dioxin derivatives, which are potentially attractive bioactive compounds similar to 2,3-dihydro-1,4-benzodioxins [11]. Therefore, the generality and efficiency of the Rh-catalyzed reaction of diazonaphthoquinones with propargylic alcohols were explored. In this letter, we describe these results in detail.

Results and Discussion

Initially, the model reaction of diazonaphthoquinone **1a** with 2-propyn-1-ol was examined in the presence of a Rh catalyst at 60 °C for 16 h (Table 1). When the reaction was carried out with $Rh_2(OAc)_4$ (3 mol%) in benzene under several concentrations (0.01–0.2 M for **1a**) (Entries 1–4), dihydrodioxin **2a** was obtained in the highest yield (94%) at the concentration of 0.1 M (Entry 3). Nonpolar solvents were particularly suitable for the reaction (Entries 3 and 5–9), and benzene was determined to give the best results (Entry 3). In the screening of ligands for the Rh catalyst (Entries 3 and 10-14), $Rh_2(OAc)_4$ gave the best result for the formation of **2a** (Entry 3), and O–H insertion product **3a** was observed when the Rh catalyst contained electron-withdrawing ligands such as trifluoroacetate and perfluorobutyrate (Table 1, Entries 13 and 14).

Table 1.

Optimization of the formation of **2a** by the Rh-catalyzed reaction of **1a** and 2-propyn-1-ol.[a]



Entry	Solvent	Conc. (M)	Rh. cat.[b]	Yield (%)[c]		
				2a	**3a**	**4a**
1	Benzene	0.01	$Rh_2(OAc)_4$	51	0	1
2	Benzene	0.05	$Rh_2(OAc)_4$	81	0	6
3	Benzene	0.1	$Rh_2(OAc)_4$	94	0	1
4	Benzene	0.2	$Rh_2(OAc)_4$	79	0	15
5	CH_3CN	0.1	$Rh_2(OAc)_4$	0	0	0
6	THF	0.1	$Rh_2(OAc)_4$	0	0	0
7	CH_2Cl_2	0.1	$Rh_2(OAc)_4$	41	18	0
8	CH_2ClCH_2Cl	0.1	$Rh_2(OAc)_4$	67	0	0
9	Toluene	0.1	$Rh_2(OAc)_4$	81	5	0
10	Benzene	0.1	$Rh_2(oct)_4$	76	0	0
11	Benzene	0.1	$Rh_2(esp)_2$	76	0	0
12	Benzene	0.1	$Rh_2(TPA)_4$	71	0	0
13	Benzene	0.1	$Rh_2(TFA)_4$	0	22	0
14	Benzene	0.1	$Rh_2(pfb)_4$	6	61	0

[a] Reagents and conditions: **1a** (0.3 mmol), 2-propyn-1-ol (1.5 mmol), $Rh_2(OAc)_4$ (3 mol%), solvent, 60 °C, 16 h.

[b] oct = octanoate, esp = α,α,α',α'-tetramethyl-1,3-benzenedipropionate, TPA = triphenylacetate. TFA = trifluoro-acetate, pfb = perfluorobutyrate.

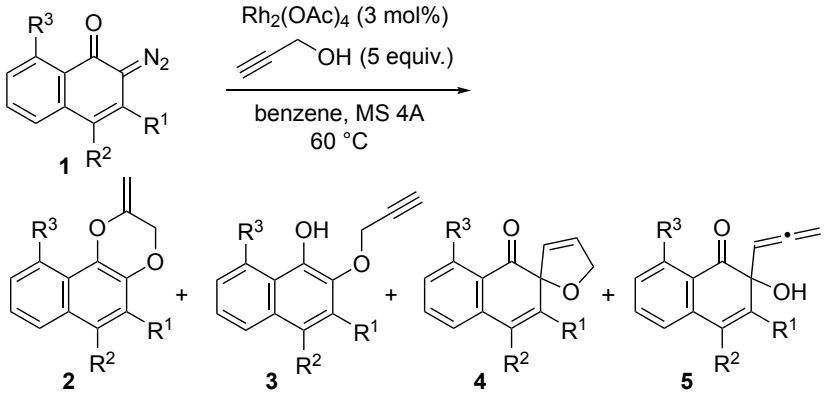
[c] Isolated yield.

Then, having established the optimized reaction conditions [5 equiv. of propargylic alcohol, 3 mol% $Rh_2(OAc)_4$ in benzene (0.1 M for **1**) at 60 °C], the scope of the Rh-catalyzed cyclization reaction of alkynes and diazonaphthoquinones was explored.

First, the reaction between various substituted diazonaphthoquinones **1** and 2-propyn-1-ol was examined (Table 2). The cyclization was strongly affected by the C-3 substituents of the diazonaphthoquinones **1**. When the C-3 substituent R^1 was a carbonyl group, the formal [3+3] cyclization proceeded efficiently (Entries 1–7). 3-Cyano- and alkoxylmethyl-substituted diazonaphthoquinones **1** also cyclized to dihydrodioxin **2** in good yields (Entries 8 and 9). However, the reaction of unsubstituted or alkyl-substituted diazonaphthoquinones **1** gave **2** in lower yields, and O–H insertion product **3** and/or oxy-spiro compounds **4** were mainly formed (Entries 10–12). In addition, the formation of allene **5m** was observed in the reaction of isopropyl-substituted diazonaphthoquinone (Entry 12). Interference in the dioxane formation was not observed upon introducing a methyl group at the C-4 position or a methoxy group at the C-8 position (Entries 13 and 14).

Table 2.

Rh-catalyzed reaction of various diazonaphthoquinones **1** and 2-propyn-1-ol.[a]



Entry	R^1	R^2	R^3	Time (h)	Yield (%)[b]
1	CO_2Et	H	H	18	**2b** 90
2	CO_2Pr	H	H	17	**2c** 92
3	CO_2Ph	H	H	12	**2d** 76, **3d** 5
4	CO_2NHPh	H	H	24	**2e** 79
5	CHO	H	H	16	**2f** 54
6	COMe	H	H	12	**2g** 81
7	COPh	H	H	14	**2h** 82
8	CN	H	H	8	**2i** 40, **4i** 4
9	CH_2OMe	H	H	9	**2j** 60, **3j** 4, **4j** 14
10	H	H	H	6	**2k** 17, **3k** 33
11	Me	H	H	6	**2l** 31, **3l** 40, **4l** 25
12	^{i}Pr	H	H	16	**2m** 26, **3m** 33, **4m** 21, **5m** 17
13	CO_2Me	Me	H	12	**2n** 87
14	CO_2Me	H	OMe	18	**2o** 78, **3o** 6, **4o** 7

[a] Reagents and conditions: **1** (0.3 mmol), 2-propyn-1-ol (1.5 mmol), $Rh_2(OAc)_4$ (3 mol%), benzene (3 mL), 60 °C.

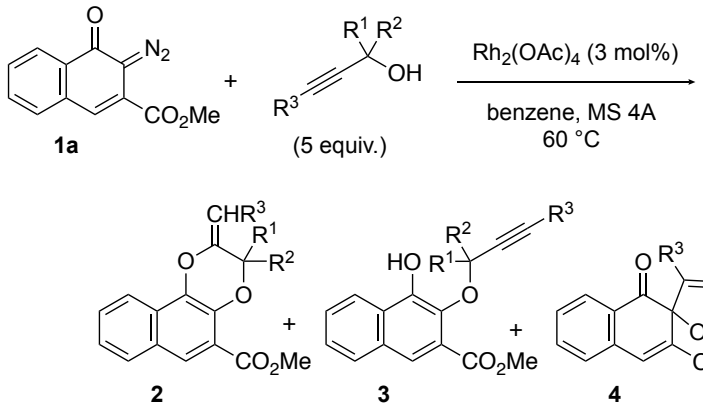
[b] Isolated yield.

Next, the effect of substituents at the terminal and internal positions of the propargylic alcohol was examined (Table 3).

In the reaction of 1-substituted-2-propyn-1-ol derivatives (terminal alkynes) with **1a**, dihydrodioxins **2** were formed exclusively. The yield of **2** decreased when the number of substituents increased (Entries 1 and 2).

In contrast, dihydrodioxins **2** were not obtained in the reaction of internal propargyl alcohols (Entries 3–7). Propargyl alcohols containing methyl, phenyl, or 1-alkynyl groups as the terminal substituent R^3 reacted with **1a** to afford a mixture of O–H insertion product **3** and spiro-compounds **4** (Entries 3–5). O–H insertion product **3** was formed as the only product in the reaction of 3-trimethylsilyl-2-propyn-1-ol (Entry 6). When the terminal substituent R^3 was a hydroxymethyl group, dihydrodioxines **2** were formed as a sole product (Entries 7).

Table 3. Substrate scope for internal propargyl alcohols.



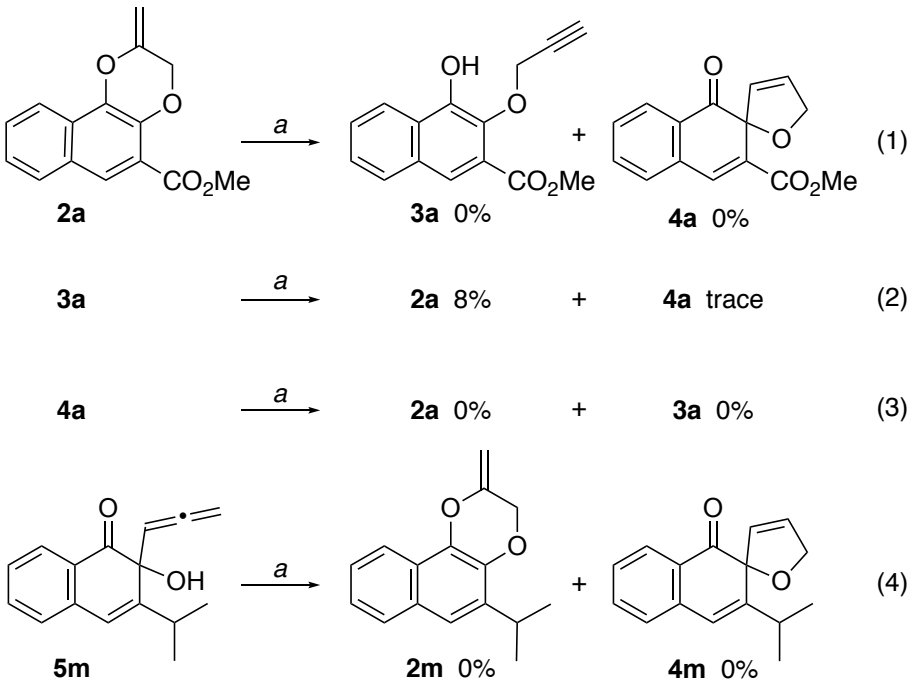
Entry	R^1	R^2	R^3	Time (h)	Yield (%)
1	CH_3	H	H	16	**2p** 66
2	CH_3	CH_3	H	16	**2q** 31
3	H	H	Me	17	**3r** 38, **4r** 34
4	H	H	Ph	16	**3s** 22, **4s** 6
5[b]	H	H	$C{\equiv}C(CH_2)_3CH_3$	10	**3t** 21, **4t** 23
6	H	H	TMS	16	**3u** 88
7[c]	H	H	CH_2OH	14	**2v** 58[d]

[a] Reagents and conditions: **1a** (0.3 mmol), propargylic alcohol (1.5 mmol), $Rh_2(OAc)_4$ (3 mol%), benzene (3 mL), 60 °C.

[b] 1.2 equiv. of propargylic alcohol was used.

[c] $ClCH_2CH_2Cl$ was used as the solvent.

[d] Single geometric isomer. Geometry of alkenyl part in **2v** is not assigned.



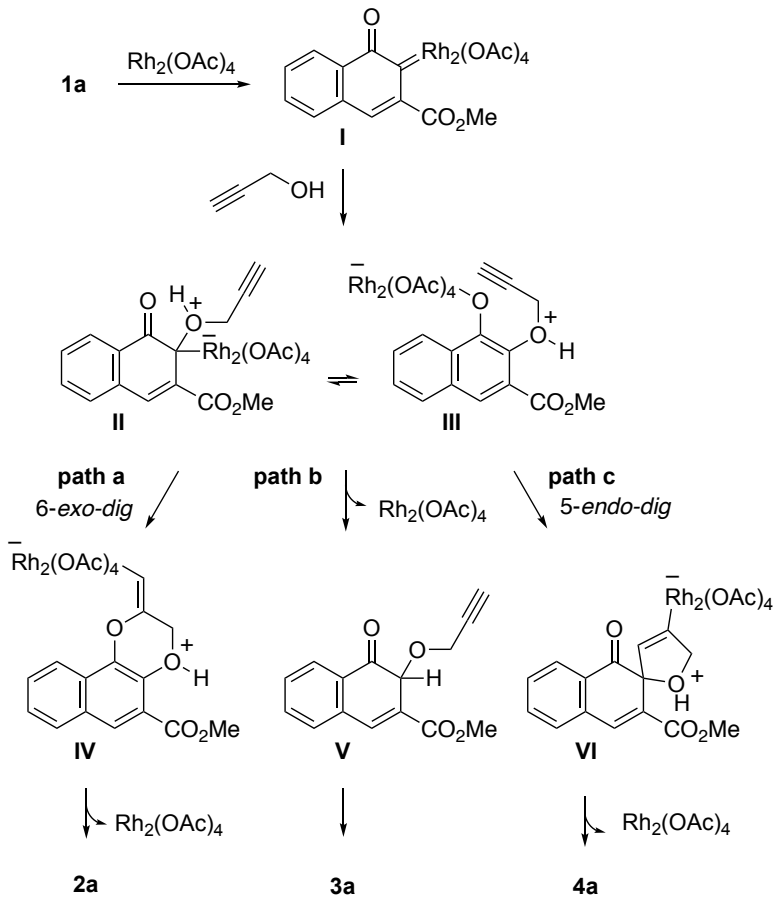
a: $Rh_2(OAc)_4$ (3 mol%), CH≡C–CH_2OH (5 equiv.), benzene, 60 °C, 12 h.

Scheme 3. Investigation of the reaction mechanism.

To gain insight into the reaction mechanism, several control experiments were conducted (Scheme 3). First, the three products **2a, 3a**, and **4a** were treated under the standard reaction conditions to investigate the occurrence of interconversion or transformation processes (Eq. 1–3). Compounds **2a** and **4a** were not converted to other forms (Eq. 1 and 3). In the case of O–H insertion product **3a**, formation of **2a** and **4a** was observed, albeit in low yields (Eq. 2). These results suggest that the three products **2**, **3**, and **4** are not intermediates in the reaction. In the metal-catalyzed formation of 2,5-dihydrofuran derivatives *via* the reaction of diazo-compounds and propargyl alcohol, α-hydroxy allenes were suggested as intermediates [5,6]. However, we ruled out the formation of hydroxy allene as intermediate in the reactions leading to cyclic compounds **2** and **4** because dihydrodioxin **2m** and spiro-compound **4m** were not formed from hydroxy allene **5m** (Eq. 4).

On the basis of the above results and literature reports, a plausible reaction mechanism for the Rh-catalyzed reaction of propargylic alcohol and diazonaphthoquinones **1a** is presented in Scheme 4. In the first step, the Rh(II) catalyst reacts with **1a** to form rhodium–carbene complex **I**. Then, the nucleophilic attack of propargylic alcohol on carbene complex **I** proceeds to form oxonium ylide **II**, which may be in equilibrium with

Rh naphtholate **III**. In path a, dihydrodioxin **2a** is formed by oxy rhodation *via* 6-*exo-dig* cyclization. Meanwhile, **3a** and **4a** are formed from oxonium ylide **II** *via* a 1,2 proton shift (path b) and migratory insertion of the C≡C triple bond into the Rh-C bond (5-*endo-dig* cyclization, path c), respectively. Since transformation from **3a** to **2a** occurs in low yield as shown in Eq. 2, this interconversion would not be a main pathway for the formation of **2a**.



Scheme 4. Possible reaction mechanism.

Conclusion

We have developed a novel $Rh_2(OAc)_4$-catalyzed formal [3+3] cyclization of diazonaphthoquinones and propargyl alcohol to afford 2,3-dihydro-1,4-benzodioxins, which are formed *via* an oxonium ylide and subsequent 6-*exo-dig* cyclization. In the reaction of terminal propargyl alcohols, dihydrodioxins are formed in good to high yields. However, in the reaction of internal propargyl alcohols, dihydrodioxins **2** were not necessarily formed, and the O–H insertion product and 2,5-dihydrofurans were formed as the main product(s) depending on the terminal substituent.

Acknowledgements

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