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COMMUNICATION

$PdBr_2$-catalyzed acetal formation of carbonyl compounds using diazophenanthrenequinone: utility of 9,10-phenanthrenedioxy acetal

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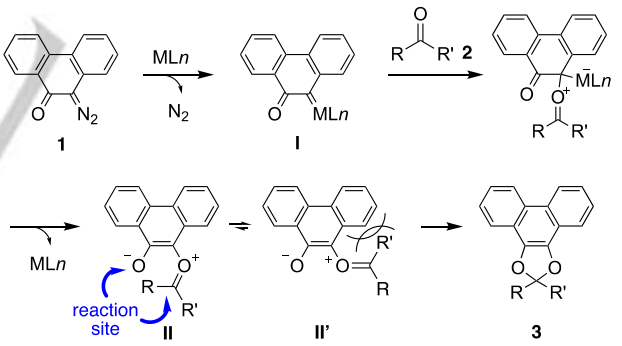
Abstract: We developed a new acetalization method of ketones and aldehydes under non-acidic conditions using diazophenanthrenequinone and $PdBr_2$. The formed acetals that have a phenanthrene skeleton withstand under mild acidic conditions. Removal of acetals was successfully proceeded under strong acidic or oxidation conditions using aqueous ceric ammonium nitrate (CAN) to afford corresponding ketones and aldehydes.

For the synthesis of complex and functional organic compounds, the carbonyl group is one of the useful functional groups. They are used as both nucleophiles and electrophiles, and various carbon–carbon bond formation reactions using carbonyl compounds are reported.[1] For example, carbonyl groups suffer nucleophilic attacks at carbon atoms of carbonyl groups owing to carbon nucleophiles such as organometallic reagents and enolates. In contrast, enolates and enols formed by deprotonation and tautomerization from corresponding carbonyl compounds are used as carbon nucleophiles that react with carbon electrophiles such as alkyl halides and carbonyl compounds. However, such high reactivity of carbonyl compounds sometimes interrupts the desired reaction in the multistep synthesis of organic compounds. Side reaction of a carbonyl group can be inhibited *via* protection/deprotection processes in the group, and acetal is usually used to protect the carbonyl group.[2]

Acetalization of carbonyl compounds is generally conducted *via* dehydration reaction of alcohol under acidic conditions.[2] However, when the carbonyl compounds have an acid-sensitive functional group, acidic acetalization is difficult to apply to the molecules. Therefore, various methods are being introduced in developing non-acidic acetalization,[3-6] and several practical methods have been developed, such as iodine promoted reaction,[3] base-catalyzed reaction,[4] and metal-catalyzed reaction.[5]

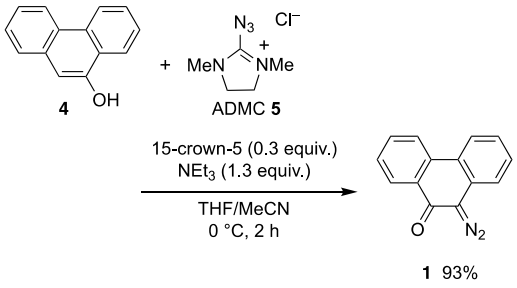
We have studied the reaction of metal carbene formed from diazoquinones.[7,8] We envisioned that a practical acetal formation could be developed *via* the reaction between diazoquinones and carbonyl compounds in the presence of a metal catalyst and therefore experimented. In this letter, we describe the outcome of the abovementioned investigation.

In Scheme 1, the outline of our strategy toward acetalization of carbonyl compounds under non-acidic reaction conditions is depicted and conducted using diazoquinone **1** and a metal catalyst. Diazoquinone **1** reacts with metal catalysts to form metal carbene **I**,[9] that is attacked with a carbonyl compound **2** to form oxonium ylide **II**.[10] Internal cyclization proceeds to afford the corresponding acetal **3**. As the diazoquinone for the acetalization, diazophenanthrenequinone **1** was chosen because two outside benzene rings in phenanthrene are responsible for the cyclization to force the reaction sites close, as shown in **II** (*vs* **II'**). Moreover, the acetal carbon in acetal **3** is not a chiral center, which helps in the multistep transformation so that it does not lead to the formation of a diastereomer *via* the protection step (acetalization).



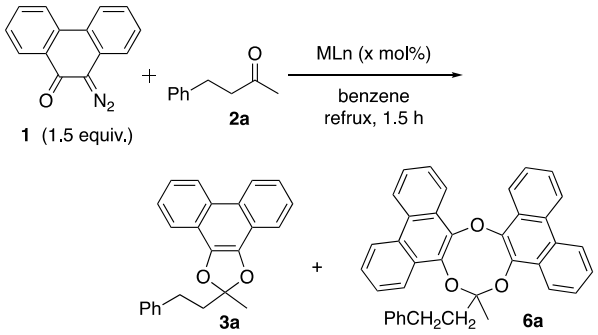
Scheme 1. Plan of metal-catalyzed acetalization using diazophenanthrenequinone **1**.

Diazophenanthrenequinone **1** was prepared by diazo-transfer reaction of 9-phenanthrol **4** with 2-azido-1,3-dimethylimidazolinium chloride (ADMC **5**) in good yield (Scheme 2).[11]



Scheme 2. Preparation of diazophenanthrenequinone **1**.

Table 1. Optimization study of metal-catalyzed acetalization using diazophenanthrenequinone **1**.[a]

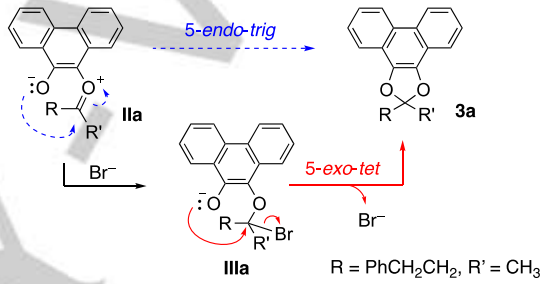


		yield (%)[c]	
Run	MLn (x mol%) [b]	**3a**	**6a**
1	$PdBr_2$ (10)	68	10
2	$PdCl_2$ (10)	55	5
3	PdI_2 (10)	50	12
4	$Pd(acac)_2$ (10)	16	trace
5	$Pd(OAc)_2$	26	5
6	$Pd_2(dba)_3$ (10)	23	18
7	$Pd_2(dba)_3$ (10), PPh_3 (40)	0	0
8	$Rh_2(OAc)_4$ (3)	trace	0
9	$Rh_2(oct)_4$ (3)	6	0
10	$Rh_2(esp)_2$ (3)	34	trace
11	$Cu(CF_3\text{-}acac)_2 \cdot H_2O$	trace	0

[a] Reaction conditions: **2a** (0.3 mmol), **1** (0.45 mmol), MLn (3-10 mol%) in benzene (1.5 mL) at reflux for 1.5 h. [b] dba = dibenzylideneacetone, acac = acetoacetonato, oct = octanoate, esp = α,α,α',α'-tertramethyl-1,3-benzenedipropionate, CF_3-acac = hexafluoroacetylacetonato. [c] Isolated yield.

An initial trial of the metal-catalyzed acetalization using diazophenanthrenequinone **1** was conducted with 4-phenyl-2-butanone (**2a**) (Table 1). The desired acetalization proceeded efficiently with $PdBr_2$ (Run 1). When diazophenanthrenequinone **1** (1.5 equiv) in benzene was slowly added to a mixture of ketone **2a** and 10 mol% of $PdBr_2$ in benzene at reflux, acetalization proceeded smoothly to afford acetal **3a** in 68% yield. Other palladium(II) halide and palladium(II) salts were ineffective for acetalization compared with $PdBr_2$ (Runs 1–5). In the reaction with tris (dibenzylideneacetone)dipalladium, acetal **3a** was formed (Run 6), and the formation of **3a** was well suppressed in the presence PPh_3 (Run 7). Although several Rh catalysts were examined, remarkable increase in the yield of acetal **3a** was not observed (Runs 8–10). Cyclization of carbonyl compounds and 2-diazo-1,3-dicarbonyl compounds using Cu(II) salt has been reported[5b]; however the Cu salt was not effective for the cyclization using diazophenanthrenequinone **1** (Run 11). Additionally, trioxocin derivative **6a** was formed as a by-product in some cases.

The efficiency of $PdBr_2$ may be attributed to the role of Br^-. Since 5 *endo-trig* cyclization is highly disfavored commonly,[12] acetal **3a** is not formed directly from oxonium ylide **IIa**, but is formed by 5-*exo-tet* cyclization of **IIIa** which was formed by the reaction of **IIa** and Br^- (Scheme 3).

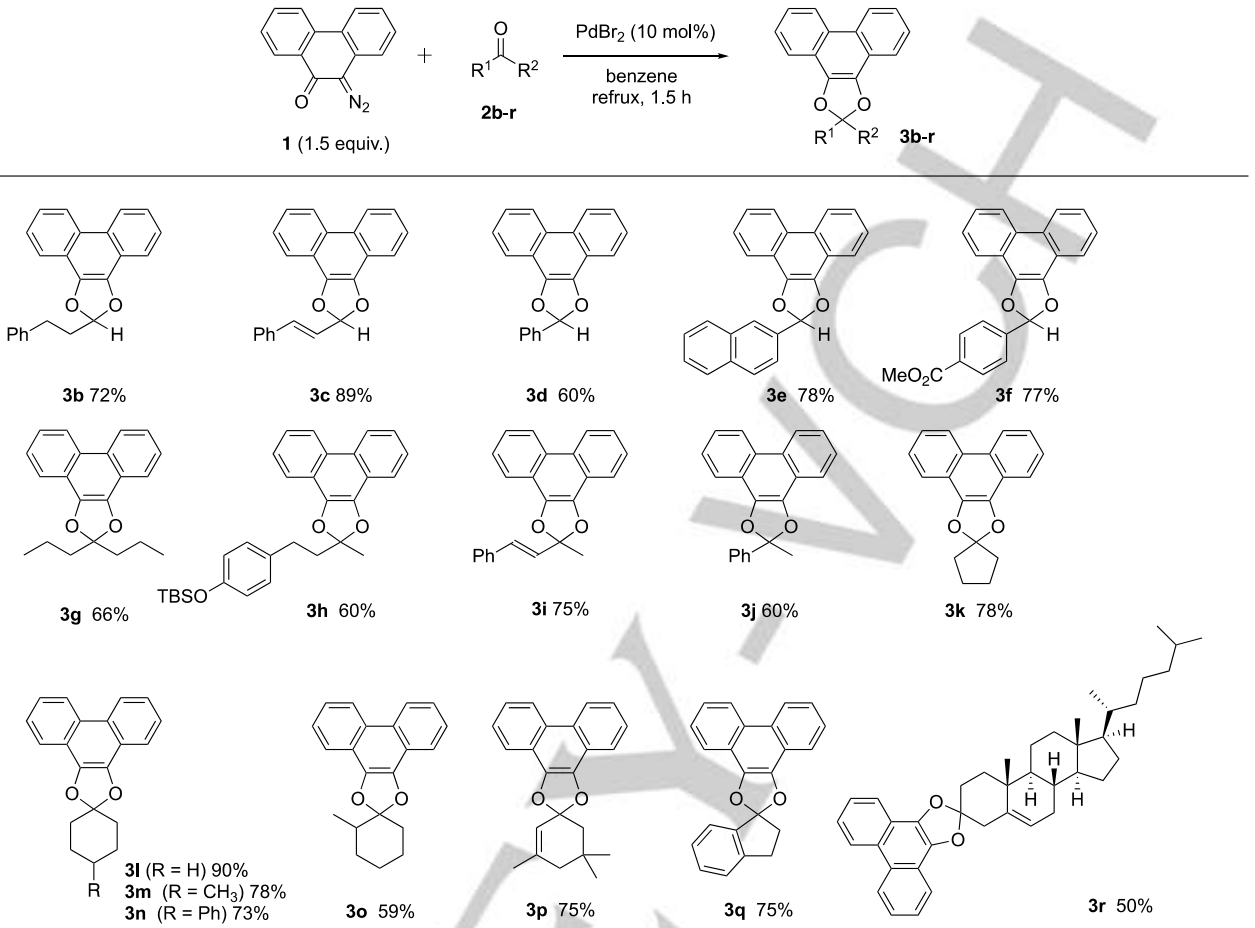


Scheme 3. Efficiency of Br^- for the cyclization.

Next, a variety of aldehydes and ketones were examined for the $PdBr_2$-catalyzed acetalization using diazophenanthrenequinone **1** (Table 2). Both the alkyl and aryl aldehydes were transformed to corresponding acetals in good to high yields. In the series of ketones, cyclic ketones were effective for the acetalization than acyclic ketones in most cases. It is important to note that acid-sensitive TBS group is tolerated under the reaction conditions as shown in the formation of **3h**.

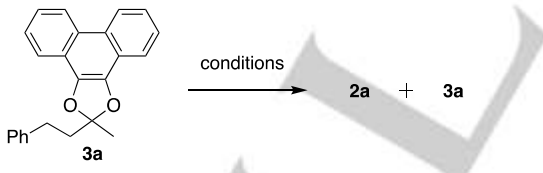
Subsequently, experiment on stability under various conditions and deprotection of acetal **3** was performed (Table 3). **3a** was stable under general conditions in which common acetal survive [with piperidine (base), Bu_4NF (F^-), and $LiAlH_4$ (hydride)]. Interestingly, **3a** withstood mild acidic conditions (Table 3, Runs 1-4). Deprotection reaction of **3a** was successfully proceeded under stronger acidic conditions (2 M HCl aq.in 1,4-dioxane at 80 °C) or oxidation conditions with aqueous ceric ammonium nitrate (CAN) to afford corresponding ketone **2a** in high yields (Runs 5 and 6).[13]

Table 2. $PdBr_2$-acetalization of various aldehydes and ketiones with diazophenanthrenequinone **1**.[a]



[a] Reaction conditions: **2**/**1**/ $PdBr_2$ = 1/1.5/0.1. Benzene (0.2 M for **2**). Reflux for 1.5 h.

Table 3. Examination of the stability of acetal **3a** under various conditions.[a]



Run	Conditions	Temp	Time	Yield (%)	
				2a	**3a**
1	*p*-TsOH (20 mol%), THF/H_2O = 1:1	r.t.	5	0	88
2	2 M HCl aq./1,4-dioxane = 1:1	r.t.	5	0	90
3	10% H_2SO_4 aq./THF = 1:1	r.t.	5	0	90
4	CH_3CO_2H	r.t.	5	0	92
5	2 M HCl aq./1,4-dioxane =1/1	80 °C	8	82	6
6[b]	CAN (2.0 eq.), CH_3CN/H_2O=1/1	0 °C	5	84	0

[a] Reaction was carried out for 5 h. [b] CAN: $(NH_4)_2[Ce(NO_3)_6]$.

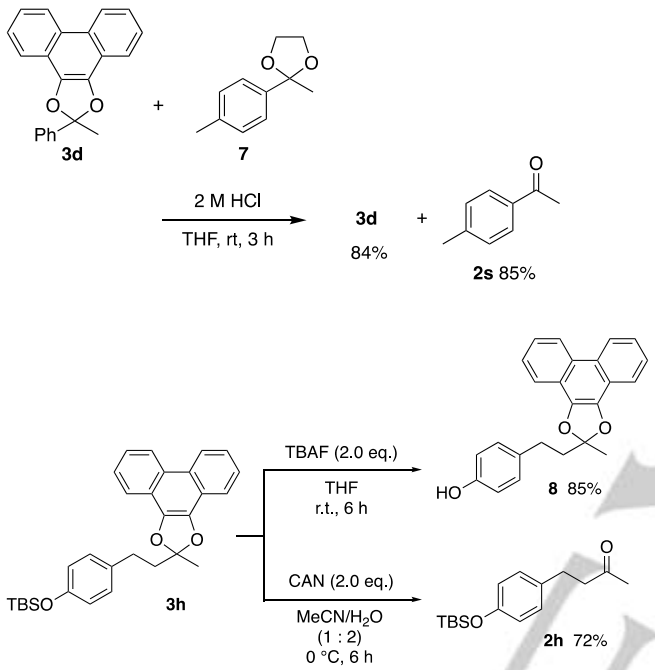
In Table 4, the results of the deprotection reaction of various 9,10-phenanthrenedioxy acetals **3** are shown. Since several carbonyl compounds **2** were over oxidized with the aqueous CAN solution, the yields were low (Runs 3 and 6).

Table 4. Deprotection of acetal **3**.[a]

Run	Acetal **3**	Product **2**	Yield (%) [Time (h)]	
			Method A	Method B
1	**3a**	**2a**	82 [8]	84 [5]
2	**3c**	**2c**	80 [1]	80 [2.5]
3	**3e**	**2e**	82 [12]	40 [9][b]
4	**3i**	**2i**	90 [5][c]	100 [5]
5	**3n**	**2n**	24 [15][d]	78 [1.5][b]
6	**3q**	**2q**	80 [3]	38 [6][b]

[a] Reaction conditions. Method A: In 1,4-dioxane/2 M HCl=1/1 at 80 °C. Method B: CAN (2 equiv.) in CH_3CN/H_2O=1/2 at 0 °C. [b] In $CHCl_3/H_2O$=1/2. [c] In $CHCl_3$/2 M HCl=1/1. [d] **3n** was recovered in 63% yield.

In Scheme 4, demonstration of synthetic utility of the 9,10-phenanthrenedioxy acetal are shown. When 2 M HCl aqueous solution was treated to a mixture of 9,10-phenanthrenedioxy acetal **3d** and ethylenglycol acetal **7** at room temperature in THF, ethylenglycol acetal **7** was selectively deprotected and 9,10-phenanthrenedioxy acetal was isolated in 84% yield. **3h** possesses two kinds of acid sensitive protective groups such as *tert*-butyldimethylsilyl group and 9,10-phenanthrenedioxy acetal, these protective groups are selectively removed by treatment using tetrabutylammonium fluoride and CAN to afford phenol **8** and ketone **2h**, respectively.



Scheme 4. Demonstration of selective deprotection.

In conclusion, we developed the $PdBr_2$-catalyzed acetal formation reaction with diazophenanthrenequinone under non-acidic conditions. The acetal that has a phenanthrene skeleton has good stability against mild acidic reaction conditions and was transformed to the corresponding carbonyl compound under strong acidic or oxidation conditions using aqueous CAN.

Acknowledgements

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Keywords: acetal • diazo compounds • palladium • protective group

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[13] 9,10-Phenanthrenequinone was formed as by-product in the deprotection reaction.

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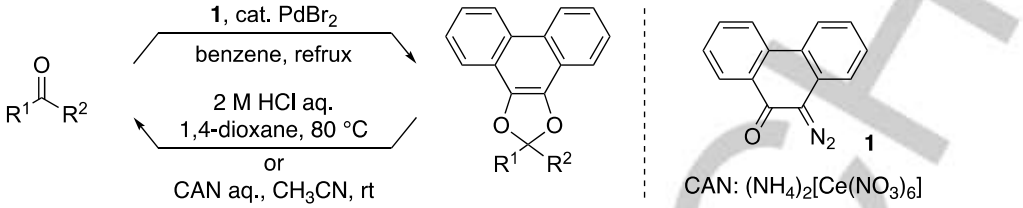

A new acetalization method of ketones and aldehydes under non-acidic conditions was developed using diazophenanthrenequinone and $PdBr_2$. The formed acetals that have a phenanthrene skeleton withstand under mild acidic conditions. Removal of acetals was successfully proceeded under strong acidic or oxidation conditions using aqueous ceric ammonium nitrate (CAN).

Key topic

Acetal Formation