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**Mn(OAc)$_3$ catalyzed intermolecular oxidative peroxycyclization of naphthoquinone**

Alex MeyeBiyogo,$^a$ Christophe Curti,$^a$ Hussein El-Kashef,$^b$ Omar Khoumeri,$^a$ Thierry Terme$^a$ and Patrice Vanelle*$^a$

Manganese(III) acetate-mediated peroxycyclization between 2-hydroxy-3-methylnaphthoquinone and various alkenes was performed to obtain dihydronaphtho[2,3-c][1,2]dioxine-5,10(3H,10aH)-diones. The reactivity of symmetrical or unsymmetrical 1,1-disubstituted alkenes and monosubstituted alkenes allowed the synthesis of more than 50 original molecules. Focusing on the excellent reactivity of 2-hydroxy-3-methylnaphthoquinone, we describe the first example of Mn(OAc)$_3$ reactivity with nitro-substituted alkenes. The scope, limitations and stereochemistry of the products synthesized are discussed. Starting from monosubstituted alkenes, the instability of a pair of diastereoisomers was observed, leading to ring opening.

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**Introduction**

Manganese(III) acetate is a useful tool in organic chemistry, but remains underestimated in medicinal chemistry. Over the past four decades, the literature has contained accounts of its applications in C-C bond-forming reactions starting from various substrates.$^1$ Among these substrates, the reactivity of quinones was studied under anaerobic conditions with stoichiometric quantities of Mn(OAc)$_3$. Under aerobic conditions was also described as an efficient catalytic system, leading to C-C bond formation and oxygen insertion via a radical pathway, yielding 1,2-dioxane derivatives.$^3$ Saturated heterocyclic endoperoxides, such as 1,2-dioxane, were described as powerful antiparasitic compounds. In addition to the well-known commercial drug artemisinin,$^4$ trioxolane arteplane and artefenomel,$^5$ a wide variety of 1,2-dioxanes showed potential antimalarial activity.$^6$ Quinone derivatives have important biological applications, mainly as anticancer$^7$ and antiparasitic$^8$ compounds. The 2-hydroxy-3-alkynaphthoquinone Lapachol derivatives antimalarial activity encouraged us to seek an easily reproducible procedure to obtain chimeric 2-hydroxy-3-alkynaphthoquinone / endoperoxidemolecules.

Expanding on our previous work on the synthesis of antiparasitic compound$^9$ and Mn(OAc)$_3$ reactivity,$^{10,11}$ we present herein the first example of this original reactivity on 2-hydroxy-3-methylnaphthoquinone with various alkenes, under Mn(OAc)$_3$ catalytic conditions.

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**Results and Discussion**

First, best reaction conditions were studied with 1,1-diphenylethylene (Scheme 1). According to previous Mn(OAc)$_3$ reactivity studies, good yields can be obtained with this alkene, as the intermediate benzylic tertiary radical is highly stabilized.$^{12}$ 2-Hydroxynaphthoquinones were chosen both without and with a methyl in position 3. Results are summarized in Table 1.

**Scheme 1.** Mn(OAc)$_3$ mediated cyclization of 2-hydroxynaphthoquinones with 1,1-diphenylethylene under aerobic conditions

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Table 1. Mn(OAc)$_3$ mediated cyclization of 2-hydroxynaphthoquinones and

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Starting from 2-hydroxynaphthoquinone in the presence of Mn(OAc)$_3$ at 65 °C, dihydrofuranophthoquinone was obtained in moderate yields (Entry 1) according to a previously reported mechanism.$^5$ We obtained lower yields (52%) than those reported with similar 1,1-di aromatic alkenes, perhaps due to the presence of oxygen under our conditions. Catalytic quantities of Mn(OAc)$_3$ only decreased yields without any oxygen insertion (Entry 4), and lower temperature (RT) left the unchanged starting material (Entries 2, 3). With 2-hydroxy-3-methyl naphthoquinone in the presence of 2.5 equiv. of Mn(OAc)$_3$ at 65 °C, product 2 was formed, without traces of 1,2-dioxane ring formation (Entry 5). This structure was obtained via the same mechanism observed for product 1, but the presence of a methyl group in position 3 did not allow cyclization. Instead, acetate reacted with the intermediate carbocation to form product 2. Reactivity allowing the purification of product 3 in very good yields was finally observed with catalytic quantities of Mn(OAc)$_3$ at room temperature in only 1 h (Entry 6). When Mn(OAc)$_3$ quantities were doubled to 0.4 equiv, time reaction was decreased to 30 min with a moderate yield decrease (Entry 7).

Temperature was previously reported to influence the Mn(OAc)$_3$ reactivity, appearing to be an important parameter leading to the formation of the 1,2-dioxane ring of product 3. The influence of the alkyl groups on Mn(OAc)$_3$ reactivity was previously studied, for example with α-alkyl-β-keto esters versus unsubstituted-β-ketoesters as summarized in Scheme 3.$^{13}$

Scheme 3. Mn(OAc)$_3$ reactivity with β-ketoesters.$^{13}$

Methyl group substitution in position 3 of naphthoquinone highly influenced Mn(OAc)$_3$ reactivity, appearing to be an important parameter leading to the formation of the 1,2-dioxane ring of product 3. The influence of the alkyl groups on Mn(OAc)$_3$ reactivity was previously studied, for example with α-alkyl-β-keto esters versus unsubstituted-β-ketoesters as summarized in Scheme 3.$^{13}$

Scheme 2. Naphthoquinone / Mn(OAc)$_3$ proposed reactivity mechanism.
The reaction was extended to various substrates, starting from symmetrical alkenes (Scheme 4). Results are summarized in Table 2.

Table 2. Symmetrical alkenes reactivity.

| Entry | R          | Product (yield) |
|-------|------------|-----------------|
| 1[b]  | -Ph        | 3 (90%)         |
| 2[b]  | -4-Cl-Ph   | 4 (86%)         |
| 3[b]  | -4-F-Ph    | 5 (79%)         |
| 4[b]  | -CH₂-CH₃   | 6 (54%)         |
| 5[b]  | -[(CH₂)₃]- | 7 (40%)         |

[a] Isolated yields based on number of alkenes equiv. [b] Reaction conditions: 2-hydroxy-3-methylnaphthoquinone (1 equiv), alkene (1 equiv).

Cis-substitution was observed for every product obtained from aromatic and aliphatic symmetrical alkenes. Yields obtained ranged from excellent with aromatic alkenes (Entries 1-3), even when they carried electron-withdrawing substituents such as -Cl or -F, to moderate (Entries 4-5) with aliphatic alkenes. This can be explained by the stability of intermediate radical formed during the reaction just after the C-C bond formation. For each type of alkene, a tertiary radical was formed, sufficiently stabilized to react with oxygen, but for aromatic alkenes the stability of this tertiary benzylic radical was increased by resonance.

From these promising results, we extended this reactivity to 1,1-disubstituted unsymmetrical alkenes, in order to generate a new asymmetric center (Scheme 5). Results are summarized in Table 3.

Table 3. Unsymmetrical 1,1-disubstituted alkenes reactivity.

| Entry[a] | R₁     | R₂     | Products diastereoisomeric ratio[b] (yields; diastereoisomeric ratio) |
|----------|--------|--------|-----------------------------|
| 1        | -Ph    | -4-NO₂-Ph | 8 / 8' (83%; 75/25)         |
| 2        | -CH₂   | -Ph    | 9 / 9' (83%; 55/45)         |
| 3        | -CH₂   | -4-CH₃-Ph | 10 / 10' (82%; 60/40)       |
| 4        | -CH₂   | -3-OCH₂-Ph | 11 / 11' (59%; 60/40)       |
| 5        | -CH₂   | -4-Cl-Ph | 12 / 12' (80%; 60/40)       |
| 6        | -CH₂   | -2,5-diCl-Ph | 13 / 13' (63%; 60/40)       |
| 7        | -CH₂   | -4-CN-Ph  | 14 / 14' (70%; 60/40)       |
| 8        | -CH₂   | -4-NO₂-Ph | 15 / 15' (75%; 60/40)       |
| 9        | -CH₂   | -3-NO₂-Ph | 16 / 16' (58%; 60/40)       |
| 10       | -CH₂   | -2-NO₂-Ph | -                           |

[a] Reaction conditions: 2-hydroxy-3-methylnaphthoquinone (1 equiv), alkene (0.5 equiv). [b] Isolated yields based on number of alkenes equiv.

As expected, the reactivity of 2-hydroxy-3-methylnaphthoquinone and unsymmetrical alkenes led to a mixture of diastereoisomers. Two fractions were easily separable by column chromatography. The first fraction corresponded to products with the R₁ and 4-methyl group cis-substituted (8-16), and the second fraction to products with the R₂ and 4-methyl group trans-substituted (8'-16').

These results are evidence of the excellent reactivity of 2-hydroxy-3-methylnaphthoquinone for Mn(OAc)₃ C-C bond forming reactions, even with deactivated alkenes such as nitro- (Entries 1, 7) or nitro-(Entries 1, 8, 9) substituted alkenes. Mn(OAc)₃ reactivity of the double bond decreases with aromatic substitution of electron-withdrawing substituents. To our knowledge, this is the first example of a C-C bond forming reaction mediated with Mn(OAc)₃ and nitro-substituted alkenes. We did not observe reactivity for 1-nitro-2-(prop-1-en-2-y)benzene (Entry 10), probably because of steric hindrance due to the proximity of nitro and methyl groups with a double bond. Methoxy-substituted alkenes allowed the synthesis of products 12 / 12' (Entry 4) in lower yields than other alkenes. This phenomenon was already observed with methoxy-substituted alkenes, and an interaction between oxygen and Mn(OAc)₃ was hypothesized. Under conditions involving stoichiometric quantities of manganese, this limitation dealt by increasing manganese equivalents, but it remains problematic with catalytic quantities.
The structure of products 15/15' was confirmed by X-ray crystallography and an ORTEP view is reported in Figure 2.

![ORTEP view of products 15 / 15'.](image)

**Figure 2.** ORTEP view of products 15 / 15'.

As previously described for 1,1-disubstituted symmetrical alkenes, 10-hydroxyl and 4-methyl groups were cis-substituted. Moreover, for product 15, the R₂ substituent and 4-methyl group were also cis-substituted, while they were trans-substituted for product 15'. We noticed a slight stereoselectivity, with a diastereoisomeric excess for products cis substituted with 10-hydroxyl and R₂ substituents. Similar selectivity was previously described and discussed for radical induced peroxycyclization.35

Next, given the excellent reactivity of 2-hydroxy-3-methylnaphthoquinone, we extended reactivity to monosubstituted terminal alkenes (Scheme 6). Several vinyl derivatives reacted with methylnaphthoquinone in moderate to excellent yields. Results are summarized in Table 4.

**Scheme 6.** Mn(OAc)₃ catalyzed cyclization of 2-hydroxy-3-methylnaphthoquinone and monosubstituted alkenes under aerobic conditions

Starting from styrene or monosubstituted alkenes bearing electron-donating substituents, diastereoisomer products were synthesized in good yields in a similar way to that described previously. Surprisingly, stereoselectivity was not observed for styrene (Entry 1). *Para*-substitution for alkenes led to better yields than *meta*- or *ortho*-substitution (Entries 2, 3 and 5). When alkenes bearing electron-withdrawing substituents were used as starting material, only one diastereoisomeric product was purified and a major product identified as a ring opening structure (Entries 6-12). To confirm whether this new product came from a secondary reaction or from the degradation of peroxycyclized products, a reaction that only yielded to diastereoisomeric products was left under stirring for 3 hours (Entry 4). Similar formation of ring opening product 19'' was observed, clearly indicating that diastereoisomer 19' was totally cleaved.

Decomposition of a 1,2-dioxane ring to afford γ-diketones was previously described.46 Thus, the formation of the ring opening structure could be explained by the acid-catalyzed rearrangement of the less stable diastereoisomer (Scheme 7).

**Scheme 7.** Acid-catalyzed decomposition of peroxycyclized diastereoisomer.

Electron-withdrawing substituents on the benzene ring decrease the stability of the 1,2-dioxane ring by their influence on O-O bond stability and on benzylic hydrogen acidity. Therefore, spontaneous decomposition of peroxycyclized products could occur.

**Table 4.** Monosubstituted alkenes reactivity.

| Entry | R          | Diastereoisomer Products (yield; diastereoisomeric ratio) | Ring opening products (yield) |
|-------|------------|----------------------------------------------------------|------------------------------|
| 1     | -Ph        | 17 / 17' (88%; 50/50)                                     |                              |
| 2     | -4-CH₃Ph   | 18 / 18' (80%; 60/40)                                     |                              |
| 3     | -3-CH₃Ph   | 19 / 19' (58%; 60/40)                                     |                              |
| 4     | -3-CH₃Ph   | 19 (23%)                                                 | 19'' (31%)                   |
| 5     | -2-CH₂Ph   | 20 / 20' (52%; 65/35)                                     |                              |
| 6     | -4-Cl-Ph   | 21 (28%)                                                 | 21'' (40%)                   |
| 7     | -4-F-Ph    | 22 (23%)                                                 | 22'' (34%)                   |
| 8     | -4-CN-Ph   | 23 (22%)                                                 | 23'' (33%)                   |
| 9     | -3-Br-Ph   | 24 (25%)                                                 | 24'' (37%)                   |
| 10    | -4-NO₂-Ph  | 25 (29%)                                                 | 25'' (43%)                   |
| 11    | -3-NO₂-Ph  | 26 (24%)                                                 | 26'' (35%)                   |
| 12    | -2-NO₂-Ph  | 27 (22%)                                                 | 27'' (32%)                   |

[a] Reaction conditions: 2-hydroxy-3-methylnaphthoquinone (1 equiv.), alkene (0.5 equiv.). [b] Isolated yields based on number of alkenes equiv. [c] Reaction was left under stirring for 2 hours after starting material consumption.
The structure of products 27/ 27” was confirmed by X-ray crystallography and an ORTEP view is shown in Figure 3.

Figure 3. ORTEP view of products 27 / 27”.

Peroxyxycyclized product trans-substituted with 10-hydroxyl and R substituent appeared to be less stable than trans-substituted ones. This difference in stability may also explain the stereochemistry of the observed peroxide cyclization. Moreover, starting from monosubstituted alkenes, when R bears an electron withdrawing substituent, trans-substituted diastereoisomers were probably spontaneously cleaved with ketoformer formation. On the other hand, if R is substituted by an electron-donating group, its increased reaction time could lead to the same decomposition on trans-substituted diastereoisomers.

Conclusions

A new protocol of manganese(III) acetate catalyzed peroxycyclization of 2-hydroxy-3-methyl-naphthoquinone was established and extended to a wide variety of alkenes. The high reactivity of quinones allowed deactivated alkenes to react with good yields. Thus, we report herein the first example of nitro-substituted alkene Mn(OAc)₃ radical reactivity. Symmetrical or unsymmetrical 1,1-disubstituted alkenes and monosubstituted alkenes allowed the synthesis of 26 original molecules as a mixture of diastereoisomers or enantiomers. Differences in stability between diastereoisomers could explain stereoselectivity. Moreover, reactivity of monosubstituted alkenes bearing an electron-withdrawing group led to ring opening of the less stable diastereoisomers.

Experimental Section

Typical procedure for the synthesis of 3

A solution of 2-hydroxy-3-methyl-1,4-naphthoquinone (1.06 mmol, 200 mg, 1 equiv.) in 25 mL of glacial acetic acid was stirred at room temperature in an open vessel. 1.1-Diphenylethylene (0.53 mmol, 96 mg, 0.5 equiv.) and manganese(III) acetate dihydrate (0.21 mmol, 57 mg, 0.2 equiv.) were added and the reaction was controlled by TLC until consumption of alkene. After 1 h, the reaction mixture was poured into 60 mL of cold water and extracted with dichloromethane (3 x 20 mL). The organic extracts were collected and dried (Na₂SO₄). Solvent was evaporated under reduced pressure and crude product was purified by column chromatography (CH₂Cl₂/petroleum ether, 70/30), and the product obtained was recrystallized to afford product 3 (202 mg, 95%) as a white solid, mp = 167-168°C (petroleumether/CH₂Cl₂, 9:1).

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