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Mild Functionalization of Tetraoxane Derivatives via Olefin Metathesis: Compatibility of Ruthenium Alkylidene Catalysts with Peroxides

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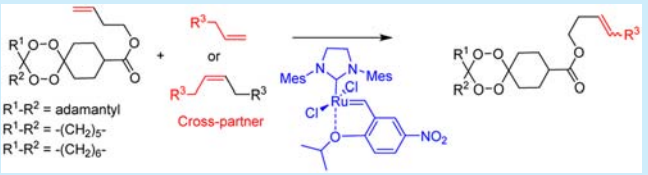
Supporting Information

ABSTRACT: An easy and mild functionalization method of tetraoxane derivatives via olefin metathesis is reported. This reaction offers a new method to afford fully functionalized tetraoxanes in high yields. This method is also utilized in the functionalization of bioactive compounds.



Malaria is one of the most threatening diseases in the tropical and subtropical regions. It is caused by infection with parasites of genus *Plasmodium* and affects billions of people worldwide every year.[1] The natural product, artemisinine (ART, **1**), isolated from Chinese medicinal plant *Artemisia annua*, is established as the best antimalarial to treat *Plasmodium faliparum* related infections.[2] The importance of "*the isolation and application of Artemisia annua*" has been recognized by the award of the Nobel Prize in Medicine for 2015 to Tu Youyou.[3] Due to poor pharmacokinetic properties,[4] high cost, and the limited bioavailability of artemisinine, its semisynthetic derivatives (Figure 1) are being used against *P. faliparum*, but

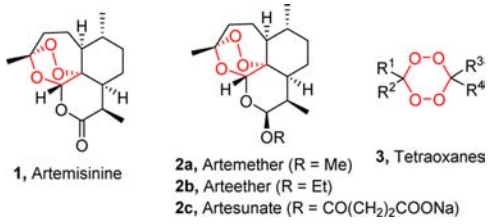


Figure 1. Antimalarial drugs.

emergence of resistance to the most available drugs has stimulated a search for its replacements—synthetic peroxides as potential antimalarial drugs.[5] The search for new drugs has brought renewed attention to 1,2,4,5-tetraoxanes,[6] a class of peroxides that combine high antimalarial activity with remarkable chemical stability. However, chemical diversity in this class of compounds has yet to be developed, as functionalized tetraoxanes remain relatively unexplored.[6]

Although several approaches[7] have been reported for constructing a tetraoxanes, methods for their postsynthetic functionalization of tetraoxane derivatives are limited in number and scope.[6c−f] Therefore, developing practical and general methods to prepare libraries of such compounds is of importance. Since 1995, when the first well-defined ruthenium carbene complexes such as **4** were introduced by Grubbs (Figure 2), olefin metathesis has become a routine process in the manipulation of C−C double bonds. Nowadays, olefin meta-

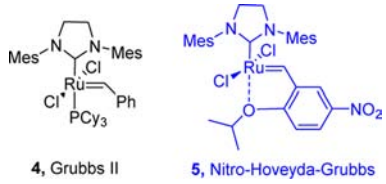


Figure 2. Catalysts for olefin metathesis.

thesis has emerged as a versatile and powerful tool for target-oriented organic synthesis as well as in biological and material science.[8] However, with one exception,[9] this phenomenal reaction has not yet been used for the functionalization of peroxides. Due to their instability and highly oxidizing power, applications of peroxides as substrates for metathesis reaction is a challenging and rather underrepresented area. On the contrary, peroxides were used in easy, rapid, and efficient removal of ruthenium residues produced from metathesis reaction.[10]

Therefore, in the current study, we decided to explore the applicability and the generality of functionalization of tetraoxane substrates via olefin metathesis. As the examples of conducting metathesis reaction with organic peroxides are rare,[9] in the first phase of our research we sought to explore reactivity of different organic peroxides toward popular commercial ruthenium olefin metathesis catalysts in order to reveal potential incompatibility between Ru catalysts and peroxide substrates.

For this study, we tested the compatibility of two representative catalysts: Grubbs second-generation catalyst **4** and nitro-Hoveyda−Grubbs catalyst **5** with selected peroxides such as *m*-CPBA, benzoyl peroxide, di-*tert*-butyl peroxide, *tert*-hydroperoxide, 1,2,3,4-tetraoxne **9**, and hydroperoxide **10**. To check how different peroxide additives influence the catalytic

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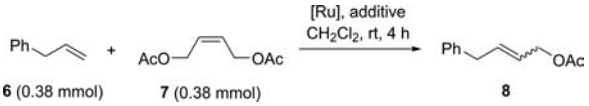
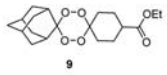
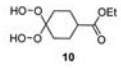
activity of these Ru complexes, we used a model[11] cross-metathesis reaction (CM) of allylbenzene **6** and *cis*-1,4-diacetoxy-2-butene **7** (see Table 1). This reaction in the absence of any additives proceeds in 85% conversion. Results in Table 1 (entries 2−6, 12, and 13) show that additives as hydroperoxides and a peroxyacid apparently destroyed both of the Ru catalysts tested, as no conversion in the model CM reaction was observed. On the other hand, nitro-Hoveyda−Grubbs catalyst **5** exhibited some limited catalytic activity in the presence of benzoyl peroxide (entry 7), though Grubbs carbene **4** was unable to show any activity in the presence of this additive. Importantly, organic peroxides like *tert*-butyl peroxide (entries 8 and 9) and 1,2,3,4-tetraoxne (entries 10 and 11) had no effect on CM of alkene **6**.

Table 1. Influence of Peroxy Additives on Model CM Reaction



6 (0.38 mmol) **7** (0.38 mmol) **8**

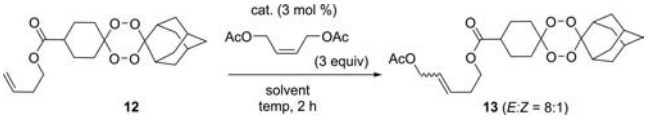
entry	additive	[Ru]	conversion[a,b] (%)
1	no additive	**4**	85
2	*m*-CPBA	**4**	nr
3	*m*-CPBA	**5**	nr
4	*tert*-Butylhydroperoxide	**4**	nr
5	*tert*-Butylhydroperoxide	**5**	nr
6	Benzoyl peroxide	**4**	nr
7	Benzoyl peroxide	**5**	34
8	di-*tert*-Butylperoxide	**4**	85
9	di-*tert*-Butylperoxide	**5**	80
10	 **9**	**4**	84
11	**9**	**5**	80
12	 **10**	**4**	nr
13	**10**	**5**	nr

[a]Reaction conditions: allylbenzene (**6**), (*Z*)-but-2-ene-1,4-diyl diacetate (**7**), additive (0.3 equiv), [Ru] 2.5 mol %, CH_2Cl_2, 4 h, rt. [b]Conversion of allylbenzene determined by GC using durene as an internal standard; nr = no reaction.

We are not attempted to characterize products of oxidation of Ru catalysts **4** and **5** with peroxides.[12] However, during CM performed in the presence of additive **10**, cyclohexanone derivative **11** was identified in the reaction mixture. To characterize better this transformation, we mixed **10** with catalytic amount of complex **4** (3 mol %) and as result a clean formation of cycloxexanone **11** (Scheme 1) together with RuO_2.[10] Significantly, 1,2,3,4-tetraoxne **9** was not destroyed by either **4** or **5** in an analogous experiment.

The fundamental structural functionality within artemisinin and synthetic highly potent 1,2,4-trioxanes and 1,2,3,4-tetraoxanes is the endoperoxide bridge. Although the mechanism of action of artemisinins and other endoperoxides is still unknown[13] it is supposed that the radicals formed in the presence of high concentrations of iron(II) accumulated inside the parasite food vacuole after the digestion of large quantities of host hemoglobin can alkylate several targets in the parasite, leading to its death. Among the different types of endoperoxides, 1,2,3,4-tetraoxnes have significantly higher stability[14] than their 1,2,4-trioxolane or 1,2,4-trioxane counterparts. Dispirotetraoxanes bearing the adamantyl fragment, which increases stability of the endoperoxide motif, are characterized by enhanced bioactivity.[15] Some of them showed improved pharmacokinetic profiles compared to those of ART derivatives.[14b] Based on this analysis, we envisaged tetraoxane **12** as a prototypical substrate for functionalization via olefin metathesis, leading to new endoperoxide derivatives (for the synthesis of 1,2,3,4-tetraoxane substrates, see the Supporting Information). Cross-metathesis of the tetraoxane-bearing alkene **12** with (*Z*)-1,4-diacetoxy-2-butene **7** was chosen to check the feasibility of this transformation (Table 2). At first, tetraoxane **12** was treated with cross-metathesis partner **7** at room temperature in the presence of 3 mol % of Grubbs catalyst **4** in dichloromethane (DCM) under an atmosphere of argon for 2 h. The cross-metathesis product **13** was obtained in 50% yield (Table 2, entry 1) as the mixture of two geometrical isomers (*E*/*Z* = 8:1). To improve the yield, further optimization was conducted. In the case of Grubbs II generation catalyst **4**, the yield of the reaction was increased when dimethyl carbonate (DMC) was used as a solvent (entry 3). Switching to Hoveyda−Grubbs catalyst **5** instantly increased the yield from 50 to 87% (entry 2), independent of the solvent used. The yield was further increased when reaction was conducted at 45 °C (entries 5 and 6).

Table 2. Optimization of Reaction Conditions for the Cross-Metathesis



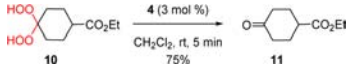
12 **13** (*E*:*Z* = 8:1)

entry	catalyst	solvent	temp (°C)	yield[a] (%)
1	**4**	CH_2Cl_2	rt	50
2	**5**	CH_2Cl_2	rt	87
3	**4**	$(MeO)_2CO$	rt	78
4	**5**	$(MeO)_2CO$	rt	87
5	**5**	$(MeO)_2CO$	45	90
6	**5**	CH_2Cl_2	45	90

[a]Isolated yield after flash chromatography, *E*/*Z* ratio was determined by ^{1}H NMR spectroscopy.

More tetraoxane substrates were synthesized (see the Supporting Information) in order to peruse the scope and limitations study. Thus, in an optimized experimental procedure a mixture of tetraoxane-derived alkene (1 equiv), cross-partner (3 equiv), and nitro catalyst **5** (3 mol %) were refluxed at 45 °C. As tetraoxane derivatives are in general thermally unstable, DCM was used as a solvent for the metathesis reactions due to its low boiling point. After evaporation of DCM, column chromatography over silica gel provided the pure product. A wide range of CM partners underwent reactions with tetraoxane-bearing alkenes, leading to diversely substituted tetraoxane derivatives as shown in Table 3. For example, when the tetraoxane **12** was refluxed with (*Z*)-but-2-ene-1,4-diyl diacetate in the presence of 3 mol % of nitro-Hoveyda−Grubbs catalyst **5** for 2 h, acetate **13** was obtained in 90% yield as a mixture of *E*- and *Z*-isomers in an

Scheme 1. Decomposition of 10 Promoted by Ru-carbene 4



10 **11**

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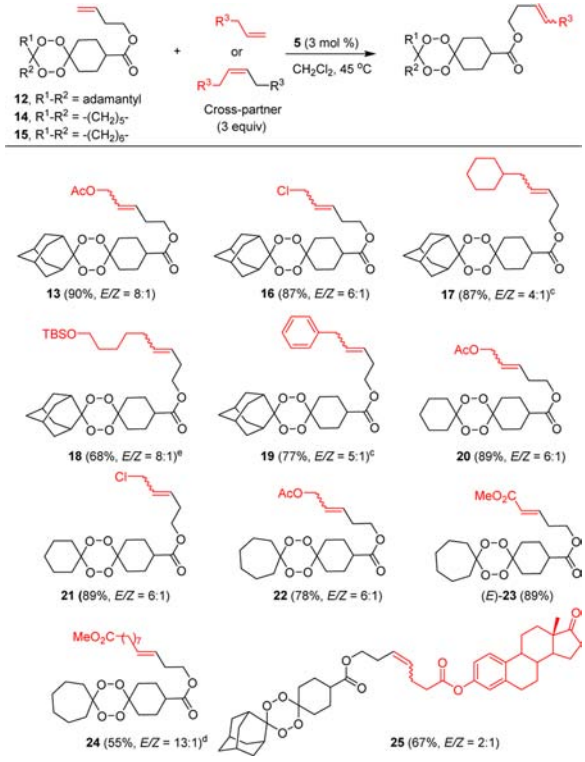
Table 3. CM Functionalization of Tetraoxanes with Various Alkenes[a,b]

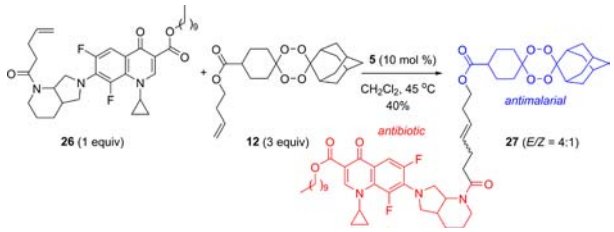


[a]Conditions: CH_2Cl_2 (nondegassed), 45 °C, catalyst **5** (3 mol %). [b]Isolated yields after flash chromatography. *E*/*Z* ratio was determined by ^{1}H NMR spectroscopy or HPLC. [c]With 5 mol % of **5**. [d]With 7 mol % of 5. [e]With 10 mol % **5**.

8:1 ratio. Similarly, when (*Z*)-1,4-dichlorobut-2-ene was used as cross-partner, the corresponding product**16** was isolated in 87% yield. Furthermore, when allyl benzene and allylcyclohexane were employed to react with **12**, benzyl- and cyclohexylmethyl-substituted tetraoxanes **19** and **17** were afforded, respectively. Tetraoxane **15** also worked well with the cross-partner (*Z*)-but-2-ene-1,4-diyl diacetate and gave product **22** in 78% yield. Interestingly, CM proceeded efficiently in the case of electron-poor substrates, such as methyl acrylate, leading to the corresponding disubstituted α,β-unsaturated ester (*E*)-**23** in 89% yield. Notably, CM of the dispiroperoxides **12** and **15** with long-chain alkenes such as TBS-protected hex-5-en-1-ol and methyl dec-9-enoate (9-DA) proceeded efficiently, leading to corresponding products in good yield. Next, we decided to prove that this methodology can be used to combine a fragile dispiroperoxide fragment not only with small molecules like (*Z*)-but-2-ene-1,4-diyl diacetate or acrylate but also with more elaborate compounds and biomolecules. We were therefore pleased to see that CM reaction of **12** with estrone derivative gave product **25** in 67% yield.

Having successfully demonstrated the practicality of tetraoxane CM with simpler substrates (Table 3), we decided to apply the methodology to more complicated compounds of potential medicinal interest. To do so, we attempted the CM reaction of potentially antimalarial dispiroperoxide **12** with ester **26**,[16] a distant relative of the fluoroquinolone antibacterial agent moxifloxacin (Scheme 2). At first, compound **26** and 3 equiv of tetraoxane derivative **12** were dissolved in dichloromethane and refluxed at 45 °C for 12 h in the presence of 5 mol % of

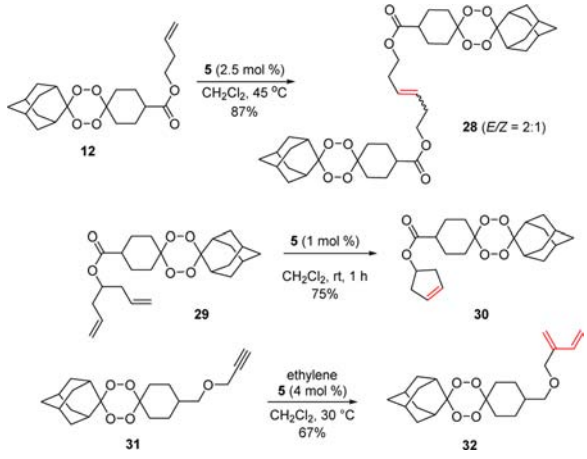
Scheme 2. Preparation of a Tetraoxane−Drug Conjugate



ruthenium catalyst **5**. Then, another 5 mol % of the catalyst was added and the mixture refluxed for another 12 h. The reaction produced the desired dispiroperoxide drug conjugate **27** in 40% yield. The purification of the reaction mixture was challenging as the formed CM product was highly polar and insoluble in most of the common solvents, and unfortunately, the isolated yield was low.

To further extend the application of the studied protocol, other important classes of olefin metathesis transformation, such as self-CM reaction (a.k.a. "dimerization"),[8d,e] ring-closing metathesis (RCM),[8d,e] and enyne metathesis[8d,e] reactions were investigated (Scheme 3). At first, self-CM reaction was

Scheme 3. Self-CM, RCM, and Enyne Metathesis of Tetraoxane Derivatives



attempted. A solution of compound **12** in dichloromethane was refluxed at 55 °C in the presence of catalyst **5** (2.5 mol %) for 6 h. The expected "dimeric" product **28** containing two tetraoxane fragments was formed in excellent yield as 2:1 *E*/*Z* mixture. Then the RCM precursor **29** was synthesized from the corresponding carboxylic acid by an esterification reaction with hepta-1,6-dien-4-ol in 73% yield. Upon treatment of diene **29** with catalyst **5** (1 mol %), ring-closing metathesis proceeded smoothly to form cyclopentene derivative **30** in outstanding yield. Finally, enyne cross-metathesis was studied using dispiroperoxide **31**. Therefore, we focused on the synthesis of the substrate of enyne metathesis **31**. To this end, ester **9** was reduced by adding lithium aluminum hydride to afford the corresponding alcohol, which was alkylated by treatment of propargyl bromide and sodium hydride. The alkylated product **31** was obtained in 50% yield as the only isolable product. The alkyne **31** was subjected to enyne metathesis with ethylene at 4 atm pressure at 30 °C for 4 h in the presence of catalyst **5** to result in tetraoxane-embedded diene **32** in 67% yield.

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In summary, it was found that 1,2,3,4-tetraoxanes, unlike hydroperoxides and benzoyl peroxide, are fully compatible with popular Ru olefin metathesis catalysts. As a result, we have developed an easy and mild functionalization method for tetraoxane derivatives via olefin metathesis. A number of peroxide derivatives bearing various substituents were obtained by self-CM, CM, RCM, and enyne cross-metathesis with ethylene. We expect that the developed transformation can serve as a convenient platform for preparing drug conjugates containing antimalarial peroxide pharmacophore. Due to the potential utility of the resulting functionalized dispiroperoxides and the mild conditions employed, we expect this method to be of utility in medicinal chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03688.

Experimental procedures and compound characterization data (PDF)
NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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