

Article

Tandem Olefin Metathesis/ α -Ketohydroxylation Revisited

Michał Patrzalek, Aleksandra Zasada, Anna Kajetanowicz *  and Karol Grela *

Biological and Chemical Research Centre, Faculty of Chemistry, University of Warsaw, Żwirki i Wigury Street 101, 02-089 Warsaw, Poland; michal.patrz@gmail.com (M.P.); ola.zasada@yahoo.com (A.Z.)

* Correspondence: a.kajetanowicz@uw.edu.pl (A.K.); kl.grela@uw.edu.pl (K.G.)

Abstract: EWG-activated and polar quaternary ammonium salt-tagged ruthenium metathesis catalysts have been applied in a two-step one-pot metathesis-oxidation process leading to functionalized α -hydroxyketones (acyloins). In this assisted tandem process, the metathesis catalyst is used first to promote ring-closing metathesis (RCM) and cross-metathesis (CM) steps, then upon the action of Oxone™ converts into an oxidation catalyst able to transform the newly formed olefinic product into acyloin under mild conditions.

Keywords: olefin metathesis; oxidation; ruthenium; α -ketohydroxylation; acyloins; tandem processes; one-pot

1. Introduction

α -Hydroxyketones (acyloins)—a class of organic compounds that possess a hydroxy group adjacent to a ketone moiety—are not only interesting from a biological point of view (e.g., promoting of cell–cell communication in bacteria [1], exhibiting antibacterial/antifungal properties [2,3] as well as neuroactivity [4], and can be used in the treatment of Alzheimer’s disease [5] and as urease inhibitors [6]) but are also useful building blocks in organic synthesis [7,8]. For example, macrocyclic acyloins are convenient starting materials in the preparation of macrocyclic musk [9,10], and in fact the first industrial synthesis of musk was based on acyloin condensation [11]. In addition to acyloin condensation [7,12–14]—an established methodology in α -hydroxyketones synthesis—other transformations like, e.g., oxidation [15,16], epoxide opening [17,18], the Barbier reaction [19], reduction of 1,2-diketones [20,21], asymmetric reductive coupling of alkynes and aldehydes [22], or CO₂-promoted regioselective hydration of propargylic alcohols [23], can be used. Most of them provide the desired α -hydroxyketones with good to excellent yields but are limited to specific substrates, which are not always easily available. In light of the above, a two-step protocol composed of olefin metathesis (OM) and oxidation reactions offers an interesting level of retrosynthetic orthogonality (Scheme 1a).



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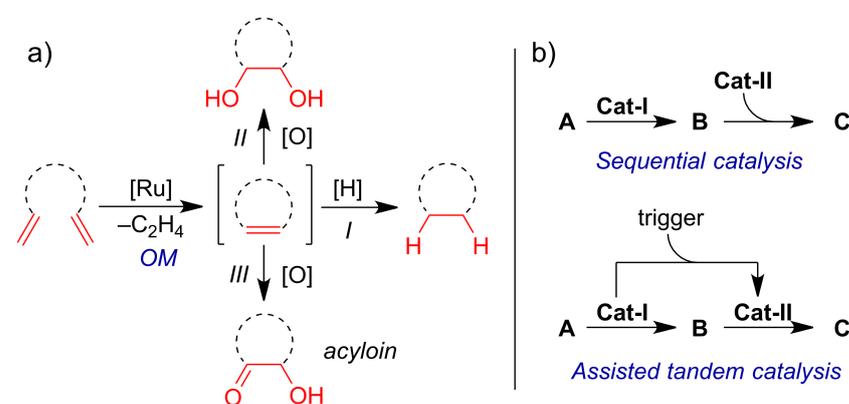
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Scheme 1. (a) Assisted tandem or sequential catalysis involving olefin metathesis (OM) and reduction or oxidation steps. (b) Classification of one-pot processes.

Recently, the Nobel-Prize-winning olefin metathesis reaction catalyzed by well-defined molybdenum- and ruthenium-based catalysts has found widespread application in a diverse range of synthetic protocols [24,25]. Moreover, the Ru-based olefin metathesis catalysts (such as **Ru0–Ru2**, Figure 1) have been found to efficiently promote numerous non-metathetical transformations [26,27]. Interestingly, olefin metathesis can be conveniently combined with such reactions, including reductions (Scheme 1a (I)) [28–30] and oxidations (Scheme 1a (II–III)), conducted in a one-pot step-wise sequence, or in tandem (Scheme 1b) [28,31]. Following this idea, a number of efficient sequential metathesis-dihydroxylation protocols has been developed by Blechert [32], Grubbs [33], and Jarosz [34] (Scheme 1a (II)). At the same time, Plietker reported that various olefins can be oxidized to *cis*-diols or acyloins with the use of RuCl_3 . When the reaction is performed in the presence of NaIO_4 , the in situ formed species “ RuO_4 ” afforded diols in high yields, whereas treatment with Oxone™ (potassium peroxymonosulfate) and NaHCO_3 provided α -hydroxyketones [35–38]. Based on this observation, Snapper et al. described a tandem sequence for the preparation of *cis*-diols and α -hydroxyketones from olefinic precursors, where the Grubbs’ 2nd generation metathesis catalyst **Ru0** (used in 5 to 10 mol% amount) was—after the metathesis step was completed—used to catalyze oxidation of the newly formed C–C double bond utilizing Oxone™ as the stoichiometric oxidant (Scheme 1a (III)) [39].

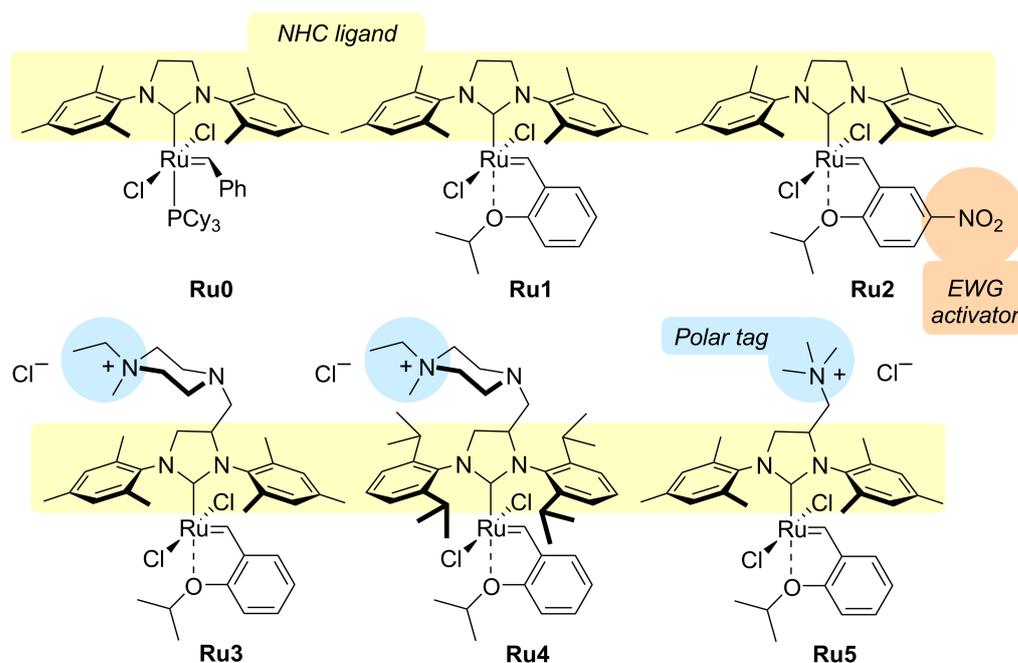


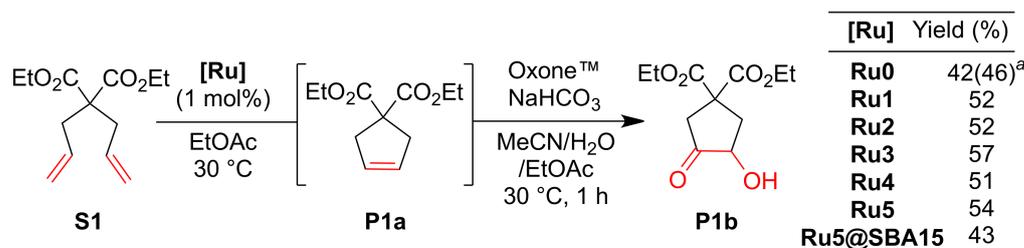
Figure 1. Selected ruthenium olefin metathesis catalysts. Cy = cyclohexyl.

2. Results

Drawing on the availability of Ru metathesis catalysts bearing EWG-activators [40,41] and N-heterocyclic carbene (NHC) ligands with quaternary ammonium tags [42] (Figure 1), we decided to re-investigate the tandem metathesis/ α -keto-hydroxylation of dienes and alkenes. Specifically, we hoped that with the help of modern, commercially available activated **Ru2** and polar catalysts such as AquaMet (**Ru3**), FixCat (**Ru4**), and StickyCat (**Ru5**), we would be able to reduce the loading of the noble metal catalyst, simplify the purification, and extend the scope of the reaction.

To do so, we examined the efficiency of classical **Ru1–Ru2** and tagged **Ru3–Ru5** Ru-catalysts in a model tandem ring-closing metathesis (RCM)/ α -keto-hydroxylation sequence of diethyl diallylmalonate (**S1**) (Scheme 2). On the basis of Plietker’s and Snapper’s observations, the oxidation step was performed by Oxone™ as a stoichiometric oxidant in a 6:6:1 *v/v/v* mixture of MeCN/EtOAc/ H_2O in the presence of NaHCO_3 ; however, we performed this step at room temperature (RT) and using ten- to five-times lower

loading of the Ru catalyst (1 mol%) than it was in the original procedure. As presented in Scheme 2, the best results were found when the tagged catalysts **Ru3** and **Ru5** were employed as the ruthenium source. It is of note that these results are not worse than those previously reported in the literature with 5 mol% of **Ru0** [39]. Interestingly, a heterogeneous system [43], based on **Ru5** immobilized on mesoporous silica SBA-15, which we added to the starters in this competition in the hope of achieving higher catalyst activity and easier purification of the reaction mixture, gave the conversion 11 percent-points lower than the one obtained for **Ru5** under homogeneous conditions (Scheme 2).



Scheme 2. Assisted tandem process involving olefin metathesis and Oxone™ oxidation. Yield determined by GC using durene as an internal standard. Conditions: Metathesis step: Ru-catalyst (1 mol%), 50 °C, 1 h, 0.2 M in EtOAc. Oxidation step: NaHCO₃ (2.5 equiv.), then Oxone™ (5 equiv.), RT, 1 h, 0.08 M in EtOAc/MeCN/H₂O (6/6/1 v/v/v). ^a Result in brackets is taken from ref. [39]. Conditions: **Ru0** (5 mol %), RT, EtOAc, then NaHCO₃, Oxone™, MeCN/H₂O (6:1).

Quaternary ammonium salt tagged-NHC Ru catalysts such as **Ru3–Ru5** offer an additional practical benefit of easier purification [44,45]. When the RCM/oxidation reaction of **S1** was conducted with a polar catalyst (**Ru5**), we noted that both the reaction mixture and the product **P1b** isolated by aqueous extraction and column chromatography on silica were visibly less colored (Figure 2) as compared with the same reaction made with the classical Grubbs benzylidene complex **Ru0** (previously used in this transformation) [39].

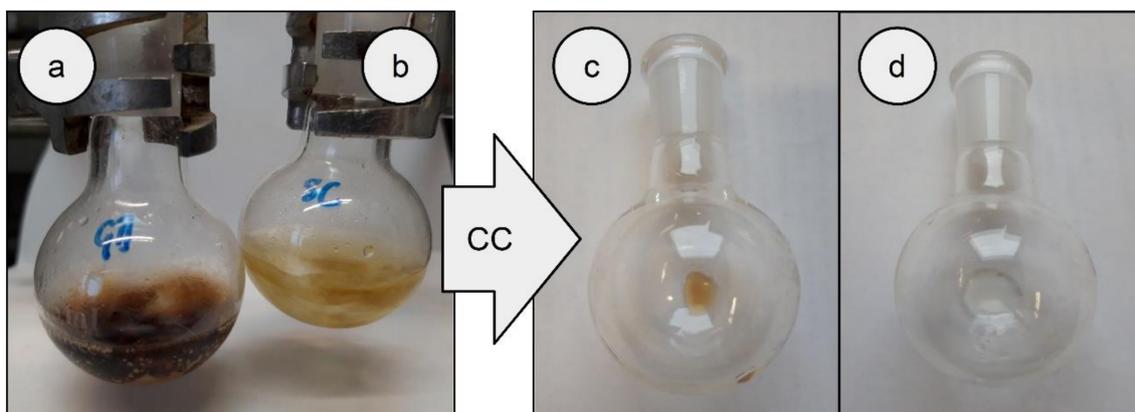
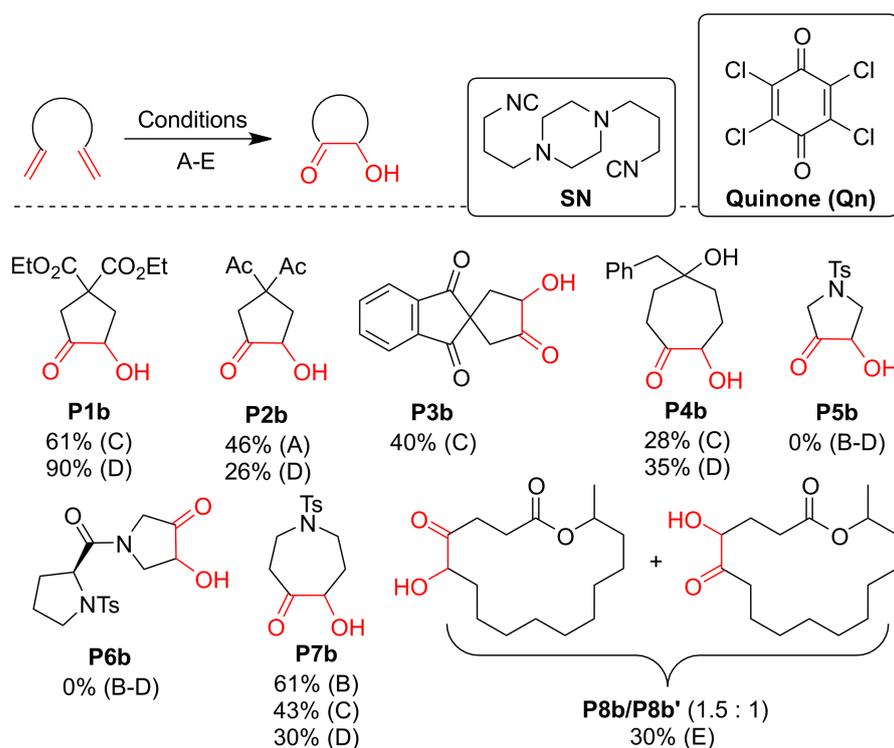


Figure 2. Reaction mixture after RCM and oxidation of **S1** conducted under identical conditions using (a) Grubbs **Ru0** and (b) StickyCat catalyst **Ru5**. Product **P1b** isolated by column chromatography (CC) from (c) reaction with **Ru0** and (d) with **Ru5**.

Following the initial trial with diethyl diallylmalonate (**S1**), the RCM/ α -ketohydroxylation sequence was tested with other dienes (Scheme 3). Essentially, we proceeded according to the protocol developed previously (Scheme 2); however, we made a number of small alterations. A diene substrate was treated with 1 mol% of the corresponding Ru catalysts (Conditions A = **Ru2**; Conditions B = **Ru3**; C–E = **Ru5**) in ethyl acetate at RT. The RCM was $\geq 95\%$ complete within 1 h. Next, MeCN and H₂O were added and the mixture was treated with NaHCO₃ and solid Oxone™ at RT. After the oxidation step was completed (1 h), the solvents were evaporated and the resultant crude product was purified by column chromatography on silica gel. In Procedure D, an Ru scavenger **SN** (4.4 mol%) [46–48] was added after the metathesis step to

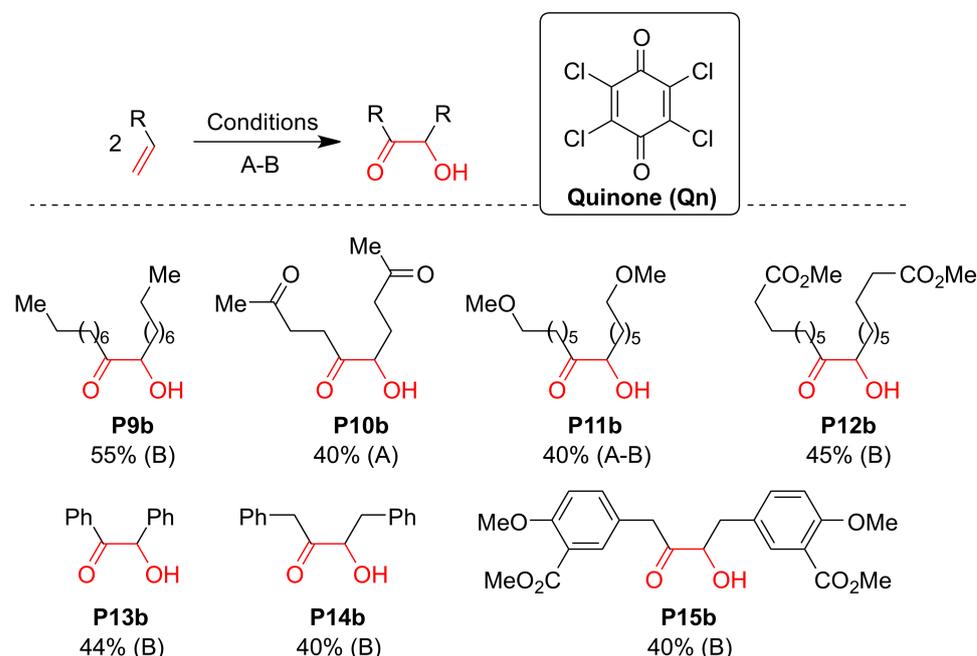
fully deactivate the catalyst and see if it facilitated the purification of the reaction mixture. The acyloins were isolated in 26–90% overall yields. In Scheme 3 only the representative conditions individually optimized for each substrate are presented (for full set of optimization data, see SI, Scheme S6 and Table S3). We were pleased to note that 5-, 7-, and 16-membered carbocyclic acyloins (**P1b**, **P2b**, **Pb3**, **P4b**, **P8b/8b'**) were obtained in moderate to good yields. Interestingly, two low-molecular-weight 3-pyrroline derivatives (**P5b**, **P6b**) were not formed (substrate was not recovered), while a 2,3,6,7-tetrahydro-1*H*-azepine derivative (**P7b**) was obtained in a 61% yield. As anticipated [39], in the case of an unsymmetrical diene, a mixture of regioisomers (**P8b** and **P8b'**) was formed with 1.5:1 regioselectivity (for other example of macrocyclic acyloin formation, see SI, Scheme S6 and Table S3). In this case, an additive—quinone **Qn**—was used in the RCM reaction to block the C–C double bond isomerization (shift) that was previously noted during similar RCM macrocyclizations [49] (Conditions E, Scheme 3).



Scheme 3. Scope and limitations in one-pot process involving RCM and oxidation steps. Conversion in RCM step $\geq 90\%$ in all cases. Conditions: A = Metathesis step: **Ru2** (1 mol%), 50 °C, 1 h, 0.2 M in EtOAc. Oxidation step: NaHCO₃ (2.5 equiv.), then Oxone™ (5 equiv.), RT, 1 h, 0.08 M in EtOAc/MeCN/H₂O (6/6/1 v/v/v). B = Metathesis step: **Ru3** (1 mol%), 50 °C, 1 h, 0.2 M in EtOAc. Oxidation step: NaHCO₃ (2.5 equiv.), then Oxone™ (5 equiv.), RT, 1 h, 0.08 M in EtOAc/MeCN/H₂O (6/6/1 v/v/v). C = Metathesis step: **Ru5** (1 mol%), 50 °C, 1 h, 0.2 M in EtOAc. Oxidation step: NaHCO₃ (2.5 equiv.) then Oxone™ (5 equiv.), RT, 1 h, 0.08 M in EtOAc/MeCN/H₂O (6/6/1 v/v/v). D = Metathesis step: **Ru5** (1 mol%), 50 °C, 1 h, 0.2 M in EtOAc, then SnachCat™ (**SN**, 4.4 mol%). Oxidation step: NaHCO₃ (2.5 equiv.) then Oxone™ (5 equiv.), RT, 1 h, 0.08 M in EtOAc/MeCN/H₂O (6/6/1 v/v/v). E = Metathesis step: **Ru5** (2 mol%), 50 °C, 1 h, 10 mM in EtOAc, quinone (**Qn**, 4 mol%), then concentration to 0.2 M. Oxidation step: NaHCO₃ (2.5 equiv.) then Oxone™ (5 equiv.), RT, 1 h, 0.08 M in EtOAc/MeCN/H₂O 6/6/1 (v/v/v).

The above established conditions were also used in in situ oxidation of cross-metatheses (CM) products. The results presented in Scheme 4 demonstrate that a variety of functionalized products including acyloins with aliphatic (e.g., **P9b–P12b**) and aromatic substituents (e.g., **P13b–P15b**) and decorated by various functionalities (e.g., **P10b**, **P11b**, **P12b**, **P15b**) can be obtained in tandem CM/oxidation (for full data please see SI: Scheme S7 and Table S4). As previously in the case of RCM, the transformation involving CM is opera-

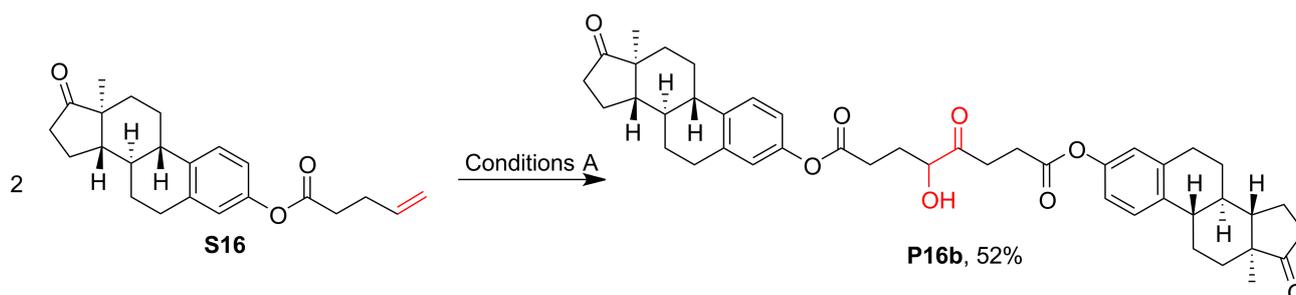
tionally simple, involving EtOAc as a solvent for CM followed by admixing of two other co-solvents leading to the formation of linear acyloins in 40–55% yields over two steps.



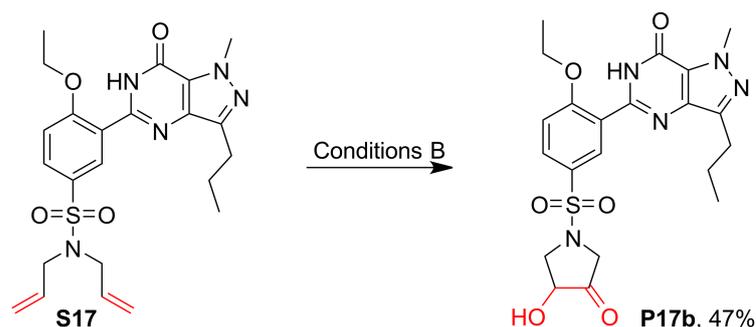
Scheme 4. Scope and limitations in one-pot process involving CM and oxidation. Conditions: A = Metathesis step: **Ru2** (1 mol%), **Qn** (4 mol%), 50 °C, 1 h, 0.5 M in EtOAc. Oxidation step: RT, 1 h, 0.08 M in EtOAc/MeCN/H₂O (6/6/1 v/v/v), NaHCO₃ (2.5 equiv.), then Oxone™ (5 equiv.). B = Metathesis step: **Ru5** (1 mol%), **Qn** (4 mol%), 50 °C, 1 h, 0.5 M in EtOAc. Oxidation step: NaHCO₃ (2.5 equiv.) then Oxone™ (5 equiv.), RT, up to 1 h, 0.08 M in EtOAc/MeCN/H₂O (6/6/1 v/v/v).

To show compatibility of the worked-out metathesis/ α -ketoxylation conditions, we decided to convert a more advanced substrate—an estrone-alkene derivative—into substituted acyloin **P16b**. Despite the complexity of the steroid **S16**, the reaction proceeded in a surprisingly clean manner and required only a short silica gel pad to provide an analytically pure product **P16b** in a 52% yield over two steps (Scheme 5).

We next tackled an even more complex substrate **S17**, a derivative of Sildenafil (Viagra™), a drug used to treat erectile dysfunction and primary pulmonary hypertension [50]. This compound, in addition to numerous functional groups, contains *N,N*-diallylsulfonamide moiety which, when present in **S5** and **S6** substrates, was found to completely suppress the oxidation step and formation of the desired acyloin. Fortunately, substrate **S17** proved to be susceptible to oxidation reaction, and we were able to obtain a new Sildenafil analogue **P17b** with a satisfactory yield of 47% (over two steps, Scheme 6).



Scheme 5. One-pot CM and oxidation of estrone derivative **S16**. Conditions A = Metathesis: **Ru5** (1 mol%), 50 °C, 1 h, 0.5 M in EtOAc. Oxidation: NaHCO₃ (2.5 equiv.), Oxone™ (5 equiv.), RT, 0.5 h, 0.08 M in EtOAc/MeCN/H₂O (6/6/1 v/v/v).



Scheme 6. One-pot CM and oxidation of an active pharmaceutical ingredient (API) derivative **S17**. Conditions B = Metathesis: **Ru5** (1 mol%), 50 °C, 1 h, 0.2 M in EtOAc. Oxidation step: NaHCO₃ (2.5 equiv.), Oxone™ (5 equiv.), RT, 1 h, 0.08 M in EtOAc/MeCN/H₂O (6/6/1 v/v/v).

3. Conclusions

In summary, a ruthenium-catalyzed assisted tandem transformation for the preparation of functionalized α -hydroxyketones has been re-investigated. As the catalyst for this transformation, the EWG-activated nitro-Hoveyda–Grubbs complex (**Ru2**) and the polar ammonium tagged Ru-complexes (**Ru3–Ru5**) were used at room temperature without extra additives, or in the presence of quinone and/or isocyanide metal-scavenger. Importantly, it was possible to reduce the catalyst loading from 5 (in the case of RCM) to 10 times (in the case of CM), still allowing the diversely functionalized acyloins, including a heterocyclic analogue of Sildenafil, to be produced in moderate to good yields. In addition, we found that the tandem processes involving CM of alkenes can be performed in ethyl acetate as opposed to the original conditions [39] where this reaction was made in DCM, which was then evaporated and replaced with EtOAc before the oxidation step. Owing to its ease of use and retrosynthetic simplicity, together with the small optimization steps introduced by us, we believe that the Snapper’s metathesis/ α -keto-hydroxylation of alkenes and dienes will allow access to functionalized densely oxygenated products in a cost-effective and friendly manner.

Supplementary Materials: The following are available online at <https://www.mdpi.com/article/10.3390/catal11060719/s1>. Scheme S1. General scheme of RCM reaction (first step in tandem metathesis/ α -keto-hydroxylation); Scheme S2. General scheme of macroRCM reaction (first step in tandem metathesis/ α -keto-hydroxylation); Scheme S3. General scheme of selfCM reaction (first step in tandem metathesis/ α -keto-hydroxylation); Scheme S4. General scheme of oxidation reaction (second step in tandem metathesis/ α -keto-hydroxylation); Scheme S5. Tandem metathesis/ α -keto-hydroxylation of DEDAM (**S1**); Scheme S6. Tandem metathesis/ α -keto-hydroxylation of dienes; Scheme S7. Tandem metathesis/ α -keto-hydroxylation of olefins; Table S1. Influence of time on the oxidation step in tandem metathesis/ α -keto-hydroxylation of DEDAM (**S1**) in the presence of 1 mol% of catalyst; Table S2. Influence of time on the oxidation step in tandem metathesis/ α -keto-hydroxylation of DEDAM (**S1**) in the presence of 0.1 mol% of catalyst; Table S3. Results of tandem RCM/ α -keto-hydroxylation reactions; Table S4. Results of tandem selfCM/ α -keto-hydroxylation reactions.

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Conflicts of Interest: The authors declare no conflict of interest.

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