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One-Pot Ring-Closing Metathesis (RCM)/Oxidation by an Assisted Tandem Ruthenium Catalysis for the Synthesis of 2-Quinolones

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Abstract: We have developed a one-pot ring-closing metathesis (RCM)/oxidation methodology to yield various 2-quinolines from 2-vinyl-*N*-allylaniline derivatives. This is a first example of an oxidation involving methylene (CH_2) groups with modified Grubbs-type ruthenium complexes. Hence, this adds an example of a non-methathesis reaction using a ruthenium carbene catalyst.

Keywords: heterocycles; metathesis; oxidation; 2-quinolones; ruthenium

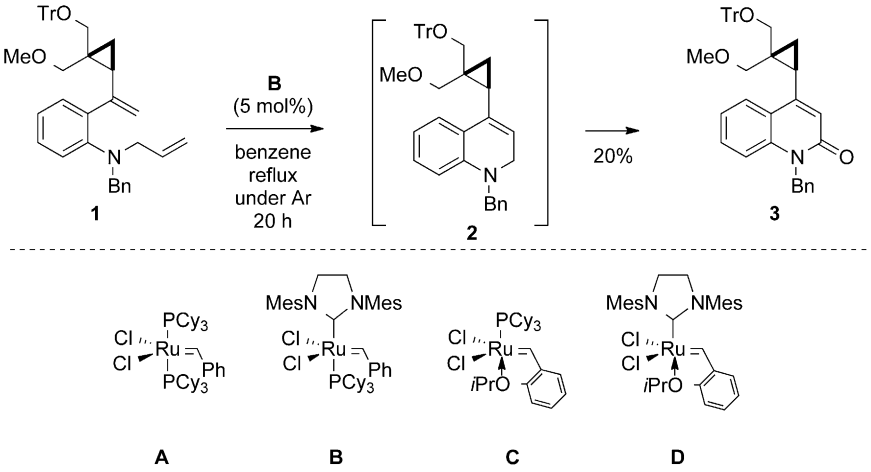
Advances in the field of transition metal catalysis have revolutionized organic synthesis. Numerous examples of catalyst efficiency can be found in which a catalyst is used to conduct two or more mechanistically similar reactions, including cascade/domino reactions and those involving either a specific order of reagent addition or a differential reactivity of functional groups. A particularly valuable tandem or domino process occurs when fundamentally different transformations are mediated by the same catalytic precursor.[1] The principal limitation of assisted tandem catalysis is the requirement for intervention.[1b]

In this regard, ruthenium alkylidenes **A**[2], **B**[3], **C**[4] and **D**[5], which are widely used for olefin metathesis, have been shown to function as procatalysts[6] in olefin isomerizations,[7] hydrogenations,[8] radical reactions,[9] activation of silanes,[10] cyclopropanations,[11] epimerization of cyclopropanes,[12] [3+2]cycloadditions[13] and cycloisomerizations.[14]

2-Quinolinone derivatives have attracted considerable attention due to their use as anti-inflammatory, antihypertensive, analgesic and antipsychotic agents. Although many methods have been developed for the synthesis of quinolones and their derivatives, most are not completely satisfactory with respect to yield, reaction conditions, generality, or operational simplicity. Therefore, the development of better synthetic approaches to 2-quinolones remains an active research area.[15]

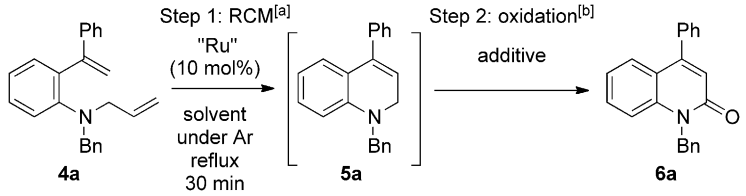
In this communication, we report an assisted tandem Ru catalysis system which promotes a one-pot ring-closing metathesis[16] (RCM)/oxidation providing 2-quinolones. Although there are some related tandem reactions involving metathesis as the first step,[17] an oxidation involving CH_2 with modified Grubbs-type ruthenium complexes is unprecedented.[18] It is noteworthy that oxidation of the α-methylene group of amines to give the corresponding amides[19] is very difficult and only one example of an efficient catalytic oxygenation of primary amines into the corresponding amides using a supported ruthenium hydroxide catalyst has been reported so far by the Mizuno group in 2008.[20]

In our work on medicinal chemistry with cyclopropanes as the key conformationally restricted unit,[21] we observed that the reaction of an α,ω-diene, *N*-allyl-*N*-benzyl-2-vinylaniline, derivative **1**, with 5 mol% of **B** in refluxing benzene under an argon balloon for 20 h and subsequent silica gel column chromatography purification led to 2-quinolone **3** in 20% yield instead of the expected 1,2-dihydroquinoline **2**[22] (Scheme 1). When the same reaction and purification were carried out in a glove box, where the concentrations of H_2O and O_2 were less than 1 ppm, the dihydroquinoline **2** was obtained quantitatively. The purified compound **2** was not readily oxidized to **3** under an air or oxygen atmosphere. These results suggested that a ruthenium species might catalyze a novel non-metathesis reaction, i.e., oxidation of **2** into



Scheme 1. RCM-oxidation one-pot reaction to give 2-quinolinone derivatives.

Table 1. RCM-oxidation one-pot reaction to give 2-quinolinone derivatives.



Entry	Solvent	Step 1	Step 2				Yield [% over 2 steps]
		"Ru"	Temperature [°C]	Time [h]	Atmosphere[e]	Oxidant (equiv.)	
1	benzene	**B**	reflux	5	air	–	42
2	benzene	**B**	reflux	5	O_2	–	52
3	benzene	**B**	reflux	5	ar	–	trace
4	dioxane[c]	**B**	80	5	air	–	35
5	AcOH[d]	**B**	90	5	air	–	trace
6	CCl_4	**B**	reflux	5	air	–	no reaction
7	CH_2Cl_2	**B**	reflux	5	air	–	trace
8	benzene	**A**	reflux	5	air	–	–[f]
9	benzene	**C**	reflux	5	air	–	trace
10	benzene	**D**	reflux	5	air	–	–[f]
11	benzene	**B**	reflux	1/6[g]	Ar	H_2O_2 (10)	32
12	benzene	**B**	reflux	1/6[g]	Ar	*m*CPBA (10)	trace
13	benzene	**B**	reflux	1/6[g]	Ar	$PhCO_3$-*t*-Bu (10)	32
14	benzene	**B**	reflux	1/6[g]	Ar	*t*-BuOOH (10)	64
15	benzene	**B**	reflux	1/6[g]	Ar	*t*-BuOOH (2)	71
16	benzene	**B**	reflux	1/6 [g]	Ar	*t*-BuOOH (1.5)	55
17	benzene	**B**	reflux	1	Ar	*t*-BuOOH (2)	71
18	benzene	**B**	reflux	3	Ar	*t*-BuOOH (2)	77
19	benzene	**B**	50	1	Ar	*t*-BuOOH (2)	79
20	benzene	**B**	r.t.	1	Ar	*t*-BuOOH (2)	84

[a] On TLC, **4a** was completely converted to **5a** except for entries 8 and 10.[22]
[b] The same solvent which was used in Step 1 was also used in Step 2.
[c] Step 1 was carried out at 80 °C (bath temperature).
[d] Step 1 was carried out at 90 °C (bath temperature).
[e] A balloon was used (*ca.* 1 atm).
[f] Step 1 was not completed.
[g] 1/6 hour means 10 min.

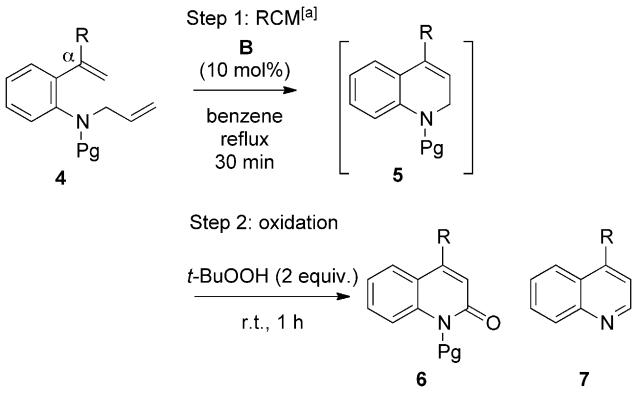
3.[23] Consequently, we decided to continue to explore this chemistry further.

To examine this reaction in detail, we used a simplified substrate **4a** instead of **1** (Table 1). In the first step, **4a** was treated with the ruthenium carbene catalyst (**A**–**D**: 5 mol%) in refluxing benzene or another solvent for 30 min under an argon atmosphere to give **5a**.[22] The subsequent step, which involved oxidation of the resulting **5a** without purification, was investigated under various conditions. In entries 1–3, the first reaction, the RCM of **4a** with **B** in refluxing benzene for 30 min under an argon atmosphere, proceeded to give **5a**. The subsequent reaction under 1 atm of air, oxygen or argon, gave the corresponding oxidation product **6a** in yields of 42%, 52% and a trace amount, respectively. Among the solvents examined, benzene was better than the others (entries 4–7). The other ruthenium carbene catalysts, **A**, **C** or **D** (entries 8–10), were less effective compared to **B** (entry 1). We next examined the effect of oxidants in the second step. Although H_2O_2, *m*CPBA, and $PhCO_3$-*t*-Bu did not improve it, the yield of **6a** was increased to 64% with 10 equivalents of *t*-BuOOH (entries 11–14). Clearly, *t*-BuOOH was the most favorable oxidant examined for the second step. Upon further research, we found that 2 equivalents of *t*-BuOOH and 1 hour of reaction time at room temperature in benzene were appropriate conditions for the second reaction (entries 14–20). In entry 20, the isolated yield of **6a** was 84% in the one-pot 2-step reaction. Therefore, chemical yield of **6** from **4** was dramatically changed with changing reaction conditions. It should be noted that purified **5a** was not oxidized to **6a** in the presence of 2 equivalents of *t*-BuOOH.

We next examined the effect of protecting groups on the nitrogen and substituents at the α position of the styrene (Table 2). The acetyl, mesyl and methoxycarbonyl protecting groups on the nitrogen are easily removed under the second reaction conditions and the corresponding quinoline **7a** without the protecting group was produced in 49%, 54% and 44% yield, respectively (entries 2–4), probably because the oxidation of the carbon adjacent to the nitrogen did not proceed efficiently in these cases. Therefore, the benzyl group is a more favorable protecting group on the nitrogen atom for our one-pot reaction system (entry 1), and the protection of the nitrogen atom is required for the subsequent oxidation. Through entries 1 and 5–8, it became clear that substrate **4** needed substituents, such as Ph, *i*-Pr, or *c*-Pr at the α position of the styrene, to be converted to the corresponding 2-quinolone **6**.

We next examined the substituent effect on the benzene ring with the substrates **4j**–**4n**, and the results are shown in Table 3. It was observed on TLC that compounds **4j**–**4n** were almost completely converted to the corresponding 1,2-dihydroquinolines **5j**–**5n** by

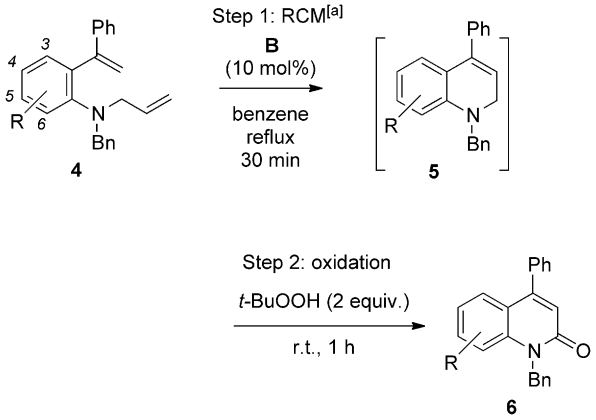
Table 2. RCM-oxidation one-pot reaction: substituent effects (I).



Entry	Substrate	R	Pg	Product (isolated yield,%, 2 steps)	
1[b]	**4a**	Ph	Bn	**6a** (84)	–
2	**4b**	Ph	Ac	–	**7a** (49)
3	**4c**	Ph	Ms	–	**7a** (54)
4	**4d**	Ph	CO_2Me	**6d** (22)	**7a** (44)
5	**4e**	Me	Bn	trace	–
6	**4f**	Et	Bn	trace	–
7	**4g**	*i*-Pr	Bn	**6g** (50)	–
8	**4h**	*c*-Pr	Bn	**6h** (57)	–

[a] On TLC, **4** was completely converted to **5**.[22]
[b] The entry 20 in Table 1.

Table 3. RCM-oxidation one-pot reaction: substituent effects (II).



Entry	Substrate	R	Isolated yield of **6** (%, 2 steps)
1[b]	**4a**	H	84
2	**4j**	3-Me	69
3	**4k**	4-Me	80
4	**4l**	5-Me	68
5	**4m**	6-Me	55
6	**4n**	4-Br	74

[a] On TLC, **4** was completely converted to **5**.
[b] The entry 20 in Table 1.

RCM. We successfully transformed these substrates, **5j**–**5l**, **5n**, into the corresponding 2-quinolones **6j**–**6l**, **6n** in good to excellent yields. However, **4m**, with a substituent on the 6-position, was converted to the corresponding 2-quinolone in moderate yield (entry 5), probably due to steric hindrance. Therefore, this is a substrate-dependent reaction.

These results suggest that after the RCM process, the Ru carbene catalyst seems to be converted to another Ru species, which might catalyze the oxidation of the methylene adjacent to the nitrogen of the 1,2-dihydroquinoline.

Finally, the best conditions (Table 1, entry 20) were applied to our medicinal substrate **1**. As a result, the expected **3** was successfully obtained in 83% yield.

In summary, we have developed a one-pot RCM/oxidation methodology to produce various 2-quinolones from 2-vinyl-*N*-allylaniline derivatives. This is another example of a non-metathesis reaction using a ruthenium carbene catalyst.

Experimental Section

General Procedure for the Preparation of 2-Quinolone Derivatives

To a solution of an α,ω-diene (0.1 mmol) in benzene (10 mL) was added catalyst **B** (8.5 mg, 10 mol%) and the mixture was refluxed for 30 min under argon. The mixture was cooled to room temperature and TBHP (68% in water; 0.029 mL, 0.2 mmol) was added. After 1 hour, the solvent was evaporated under reduced pressure. The obtained residue was subjected to column chromatography (neutral silica gel, hexane/AcOEt = 5:1) to give the products.

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