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Synthetic studies on strictamine: unexpected oxidation of tertiary amine in Ru-catalyzed ring-closing olefin metathesis

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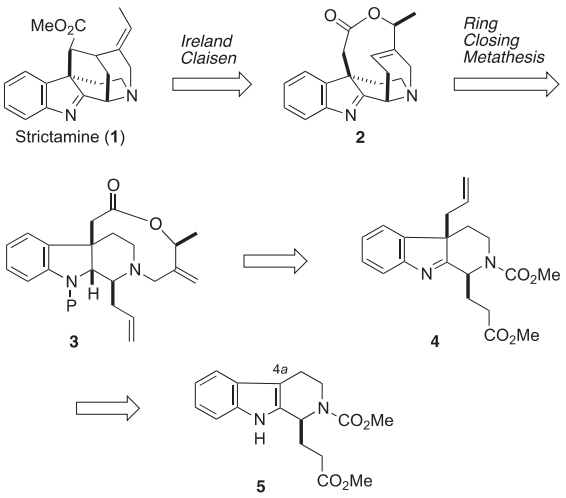
ABSTRACT

During synthetic studies toward strictamine, unexpected oxidation of tertiary amine to enamine was observed in ring-closing olefin metathesis (RCM) using Hoveyda–Grubbs 2nd catalyst. Control experiments under deoxygenated conditions indicated Ru-catalyst and electron deficient 1,4-benzoquinone additive promoted oxidation. The desired RCM reaction took place selectively under microwave irradiation by suppression of oxidation of amine.

Ring-closing olefin metathesis (RCM) catalyzed by ruthenium catalysts[1] has enjoyed a widespread use in the field of total synthesis of natural products due to its high reliability and functional group tolerance. In particular RCM is a powerful tool for the construction of macrocycles taking advantage of its entropically favorable intramolecular process and evolution of ethylene after cyclization. During the course of synthetic studies on the densely fused polycyclic alkaloid, strictamine, we examined the construction of macrocyclic intermediates using RCM. Unexpectedly, however, we observed unprecedented oxidation of tertiary amine to the corresponding enamine as a side reaction in the presence of the Hoveyda–Grubbs 2nd generation catalyst. In this Letter, we describe detailed studies on this unprecedented oxidation reaction regarding factors to promote or suppress this unexpected oxidation in RCM reaction.

Strictamine (**1**),[2] isolated from the flowers of *Alstonia scholaris*, is a member of the *Rhazya* alkaloids,[3] which possesses various activities for the central nervous system and has been used as a folk medicine in India. In addition, Bhattacharya and Bose reported that this compound demonstrates potent inhibitory activity against monoamine oxidase.[4] While compound **1** has attracted considerable interest from the synthetic and biological points of view, the densely fused pentacyclic skeleton has made it difficult to synthesize compound **1** and no total synthesis has been reported to date.

Our synthetic strategy of strictamine (**1**) is shown in Scheme 1. For the crucial construction of the pentacyclic skeleton having *E*-ethylidene moiety, we planned to examine Claisen-Ireland rearrangement[5] of the enolate intermediate generated from lactone **2**. We envisioned that the macrocyclic lactone ring in compound **2** would be accessible by RCM of diene **3**, which should be prepared from allyl indolenine derivative **4** via introduction of an allylic alcohol segment on the secondary amine and formation of the



Scheme 1. Synthetic strategy of strictamine (**1**).

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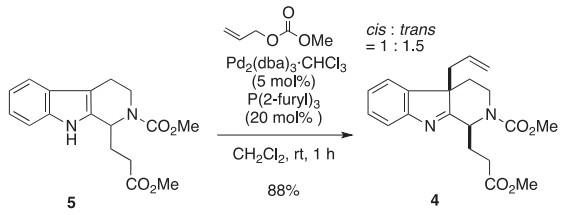
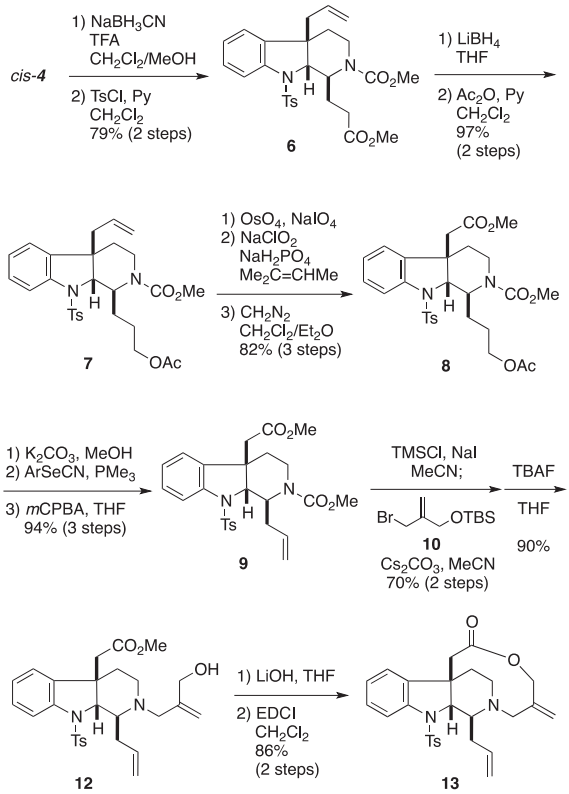


Scheme 2. Palladium catalyzed allylation of tetrahydro-β-carboline derivative **5**.

lactone ring. We decided to construct a quaternary carbon center at the 4*a* position by palladium-catalyzed allylation of the literature-known tetrahydro-β-carboline derivative **5**[6] under the conditions developed by Rawal and co-workers.[7]

We initiated our research by synthesizing diene **13**, the model substrate for the planned RCM reaction. First, tetrahydro-β-carboline derivative **5**,[6] which is readily prepared from tryptamine in a five-step sequence, was subjected to a palladium-catalyzed allylation reaction under the Rawal condition.[7] The expected allylation proceeded regioselectively at the 4*a* position to furnish allyl indolenine **4** as a 1:1.5 mixture of diastereomers (Scheme 2). After separation of the requisite *cis*-isomer **4**, 1,2-reduction of imine from the convex face and tosylation gave *N*-tosyl indoline **6**, which was converted into ester **9** in an eight-step sequence including transformation of the allyl group at the 4*a* position to ester and the ester moiety to terminal olefin (Scheme 3). After introduction of the allylic alcohol segment by removal of the methoxy carbonyl group and N-alkylation with allyl bromide **10**,[8] a 10-membered lactone ring was then formed by desilylation, saponification, and lactonization with EDCI to furnish the desired diene **13**.

With diene **13** in hand, we then examined the key RCM using Hoveyda–Grubbs 2nd generation catalyst (HG-II). Thus, a toluene solution of diene **13** and HG-II (10 mol %) was heated at 80 °C for



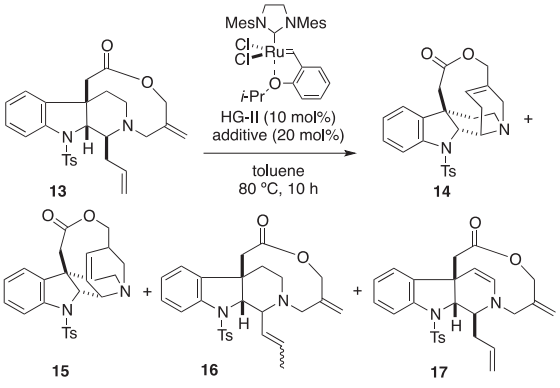
Scheme 3. Synthesis of diene **13**.

10 h. To our disappointment, the reaction gave the desired product **14** in only 16% yield associated with several by-products. Surprisingly, a careful separation of the by-products and determination of their structures based on extensive NMR experiments revealed that the most predominant by-product is enamine **17** (19%), which should be generated by oxidation of tertiary amine of the starting **13**. In addition, **15** (14%) and **16** (9%), as well as the double bond migration product of **14** and **13**, were also isolated. To suppress generation of olefin isomers **15** and **16**, we then examined quinone additives according to Grubbs' report.[9] Addition of 1,4-benzoquinone (BQ) or 2,6-dimethyl-BQ was not effective in suppressing generation of by-products (entries 2 and 3). Generation of enamine **17** substantially increased when the reaction was conducted in the presence of 2,6-dichloro-1,4-BQ (entry 4). In this case, enamine **17** was obtained as a major product without isolation of the desired **14** (entry 4) (See Table 1).

At this point, we executed control experiments to clarify a factor to promote the unexpected oxidation of tertiary amine **13** to enamine **17** (Table 2). First, a toluene solution of **13** was deoxygenated by the freeze-pump-thaw method, purged with argon, and heated without addition of ruthenium catalyst (entry 1). Under these conditions, diene **13** was recovered in 95% with tiny amount (3%) of enamine **17**.[10] Background oxidation due to dissolved oxygen was estimated to be 5–6% based on a result obtained by simply heating the toluene solution of **13** without deoxygenation (entry 2). Similar results were also observed when 1,4-BQ or 2,6-dimethyl-BQ was added to the reaction mixture indicating that these additives did not promote oxidation (entries 3 and 4). In contrast, reaction in the presence of 2,6-dichloro-1,4-BQ gave enamine **17** in 16% yield (entry 5) showing the oxidation of **13** occurred, possibly via SET process, from tertiary amine **13** to 2,6-dichloro-1,4-BQ.

Based on these control experiments, it was concluded that the HG-II plays a critical role in promoting the oxidation process, since the background oxidation due to dissolved oxygen was as low as 5–6% and even 2,6-dichloro-1,4-BQ gave enamine **17** in only 16% yield. Since it is known that amines coordinate the ruthenium metal center of the complex,[11] and Stephenson and co-workers recently reported the ruthenium-catalyzed oxidative coupling of nitroalkanes with tertiary *N*-arylamines through the photo-redox

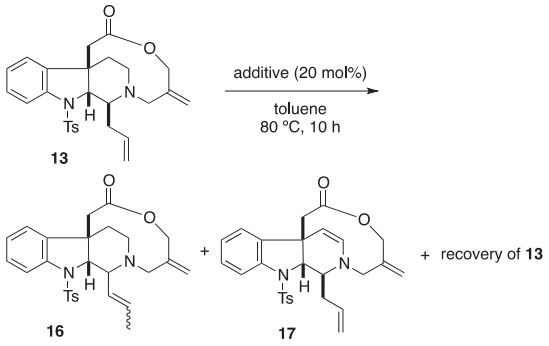
Table 1
Screening of the reaction conditions



Entry	Cat.	Additive	Yield[a] (%)				
			14	**15**	**16**	**17**	**13**
1	HG-II	—	16	14	9	19	13
2	HG-II	1,4-BQ	9	4	8	24	34
3	HG-II	2,6-Dimethyl-1,4-BQ	15	15	8	18	15
4	HG-II	2,6-Dichloro-1,4-BQ	0	15	8	42	0

[a] Isolated yield.

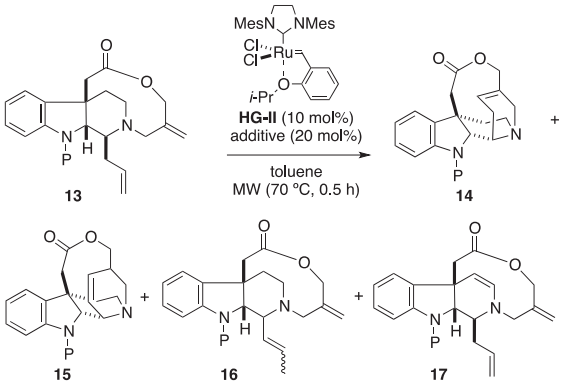
Table 2
Control reactions for conditions



Entry	Deoxygenation	Additive	Yield[a] (%)		
			16	**17**	**13**
1	+	—	—	3	95
2	–	—	—	6	85
3	–	1,4-BQ	—	5	92
4	–	2,6-Dimethyl-1,4-BQ	—	6	90
5	–	2,6-Dichloro-1,4-BQ	—	16	79

[a] Isolated yield.

Table 3
Optimization of RCM under irradiation of microwave



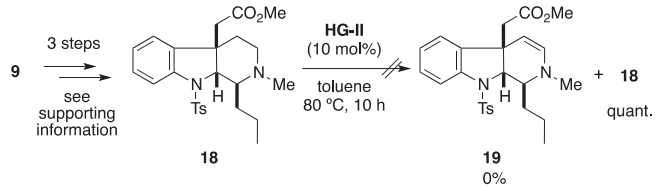
Entry	P	Additive	Yield[a] (%)				
			14	**15**	**16**	**17**	**13**
1	Ts	—	38	6	7	5	3
2	Ts	2,6-Dimethyl-1,4-BQ	37	17	11	9	7
3	Ts	1,4-BQ	45	8	5	5	5
4[b]	CO_2Me	1,4-BQ	52	2	3	4	21

[a] Isolated yield.
[b] HG-II (5 mol %) and 1,4-BQ (10 mol %) were used.

process,[12] possible reaction mechanisms would be HG-II-mediated oxidation initiated by SET process. This process would be accelerated by the highly strained character of the piperidine ring. Actually, exposure of substrate **18** possessing less-strained character of the piperidine ring to ruthenium catalyst did not promote oxidation to the corresponding enamine **19** and starting material **18** was recovered in almost quantitative yield (Scheme 4). To the best of our knowledge, there has been no report on oxidation of tertiary amines with Grubbs' catalysts.

Finally, we performed extensive investigations to maximize the yield of the desired RCM reaction. Expecting acceleration effects for the construction of the highly strained cage-like pentacyclic structure **14**, we examined microwave irradiation[13] (Table 3). Fortunately, we observed acceleration of the reaction rate and improvement of the yield of compound **14** to 38% when a toluene solution of **13** and HG-II (10 mol %) was heated at 70 °C under microwave irradiation (entry 1). In addition, it was found that 1,4-BQ slightly improved the yield to 45%. Further optimization studies on the structure of substrate revealed that a methyl carbamate **13** (P = CO_2Me) is superior to tosyl amide **13** (P = Ts). Thus, treatment with HG-II (5 mol %) and BQ (10 mol %) in toluene at 70 °C under the microwave afforded the desired product in 52% (66% based on the recovered 21% of **13**).

In conclusion, we found that Grubbs' catalysts have a potential for promoting oxidation of tertiary amine to enamine, which might encumber the desired olefin metathesis. Furthermore, we found that microwave irradiation is effective for carrying out RCM for the construction of highly strained nitrogen-containing polycyclic structures with the suppression of oxidation and olefin migration. These observations should be informative for execution of RCM using alkylamine-containing substrates, and for expansion of the scope of RCM for application to a wide range of compounds. Synthetic studies toward strictamine (**1**) based on the strategy described in this Letter are currently under investigation.



Scheme 4. Control reactions for substrate having less-strained piperizine ring.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.10.129.

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