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Synthesis of substituted 1,2-dihydroquinolines and quinolines using ene–ene metathesis and ene–enol ether metathesis

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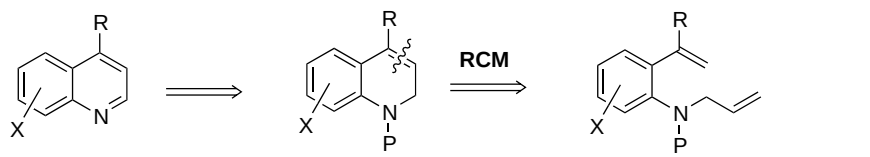
Abstract—We describe a novel and convenient method for quinoline synthesis using ring-closing olefin metathesis (RCM), ene–ene metathesis, and ene–enol ether metathesis. We also report the first example of enol silyl ether–ene metathesis to produce cyclic enol silyl ether. Using this method, versatile substituted quinoline derivatives were readily prepared in excellent yield from anthranilic acid derivatives.

The quinoline ring system is an important structural unit in naturally occurring quinoline alkaloids, therapeutics, and synthetic analogues with interesting biological activities. Therefore, the development of a new and efficient synthetic route to the quinoline ring system is of interest in both synthetic organic and medicinal chemistry. Versatile methods for synthesis of the quinoline ring system have been developed;[1,2] however, the reaction conditions have some drawbacks, such as the need for high temperature and/or strongly acidic conditions. Additionally, regioisomers are usually formed during intramolecular electrophilic substitution of unsymmetrically substituted aniline derivatives to the quinoline ring, which is the most common method used for synthesis of the quinoline ring system. Therefore, synthesis of the quinoline ring with a variety of substituents remains to be resolved. In our continuing study of the RCM reaction[3–7] and in our approach to the synthesis of novel anti-malarial agents,[8] we were intrigued by the possibility of exploiting an RCM reaction of dienes, *N*-allyl-*N*-protected-*o*-aminostyrene, to 1,2-dihydroquinolines and quinolines (Scheme 1). We synthesized the requisite diene, *N*-allyl-*N*-protected-*o*-aminostyrene, from anthranilic acid derivatives as shown in Schemes 2 and 3. This communication reports a novel method for the synthesis of substituted 1,2-dihydroquinolines and quinolines using RCM, including enol silyl ether–ene metathesis.

We first examined the RCM reaction of **1**, derived from commercially available 2-isopropenylaniline, using 30 mol% of commercially available Grubbs' catalyst (**A**). Diene **1** readily reacted at rt for 3 h to give 1,2-dihydroquinoline **2** in 94% yield (Table 1, run 1). When the amount of catalyst was reduced to 5 mol%, the yield of **2** decreased to 72% (run 2). The yield improved to 92% when heated at 50°C for 1 h (run 3). General procedure: Ru-benzylidene catalyst (5 mol%; **A**) was added to a stirring solution of **1** in CH_2Cl_2 (0.01 M). The mixture was degassed using the freeze–pump–thaw (FPT) cycle method and stirred at 50°C for 1 h under an Ar atmosphere. The reaction mixture was concentrated to give a crude residue that was subjected to column chromatography (*n*-hexane:AcOEt = 1:1) to



Scheme 1. Our strategy for the synthesis of substituted 1,2-dihydroquinolines and quinolines.

Keywords: 1,2-dihydroquinoline; quinoline; quinoline alkaloid; ring-closing metathesis; ene–ene metathesis; enol silyl ether–ene metathesis; ene–enol ether metathesis.

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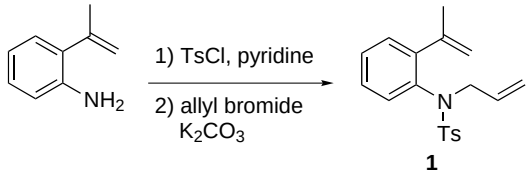


Scheme 2. Preparation of RCM precursor **1**.

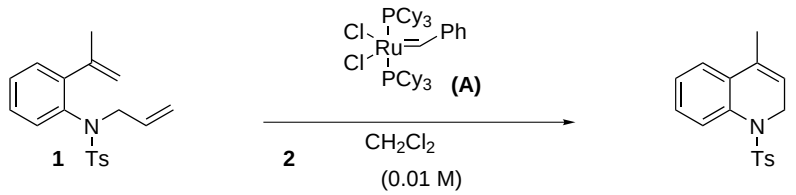
give **2** (92%) as a colorless oil.[9] Various dienes **3**–**7**, prepared from anthranilic acid (Scheme 3), were subjected to the above optimal reaction conditions to investigate the scope and limitations of the system. The results are summarized in Table 2. Substrates with an electron-donating group such as -OMe (runs 2 and 3) as well as those with a weak electron-withdrawing group (-Cl, runs 4–6), gave the corresponding quinolines **8**–**11** in excellent yield. Diene **7** was also successfully transformed to benzoquinoline (run 7). In the reaction of **6**, catalyst **B** proved to be superior to the classical Grubbs catalyst **A**, and gives **11** in quantitative yield, consistent with recent reports (runs 5 and 6).[10] In the present method, since *o*-aminostyrene is the RCM precursor, no regioisomers were formed. In addition, a diene such as **3**, with a sterically hindered substituent at the position *ortho* to aniline, also gave the corresponding 1,2-dihydroquinoline (run 2).[2]

These results prompted us to screen similar RCM reactions of dienes such as **13** and **14** to construct other related heterocycles such as benzoazepine and benzoazocine. Dramatic differences were observed when **13** and **14** were subjected to the above conditions using catalysts **A** and **B** (Table 3). When catalyst **A** was used for RCM of **13** and **14**, only the corresponding dimeric compounds **15** and **17** were obtained. In sharp contrast, the expected cyclization occurred to give benzoazepine **16** and benzoazocine **18**, respectively, using catalyst **B**.

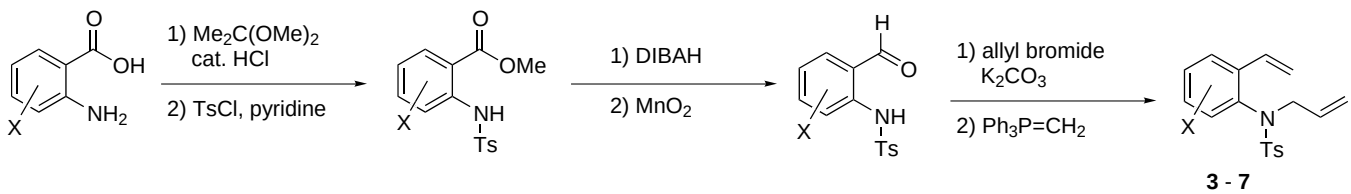
We also examined the effect of protective groups on nitrogen. Dienes **19**–**21** were prepared in essentially the same manner (Scheme 3) and treated with catalysts **A** and **B**. The reaction of the *N*-benzyl derivative **19** using catalyst **A** gave **22** quantitatively (Table 4, run 1). The *N*-acetyl derivative **20** did not give any product in the presence of catalyst **A** (run 2), whereas the *N*-Boc derivative **21** cyclized to quinoline **24** under similar conditions in moderate yield (run 4). Catalyst **A** probably coordinated with the terminal double bond of **20** to form a chelated intermediate **25**, which could not convert to **23**. On the other hand, the higher reactivity of catalyst **B** overcame this problem, and **23** was obtained in 98% yield (run 3). Protective groups on products **22**–**24** were readily removed by silica gel column chromatography followed by spontaneous air oxidation to give quinoline **26** quantitatively.

We also investigated the synthesis of 4-methoxy- and 4-siloxy-1,2-dihydroquinolines by ene–enol metathesis of diene (**27** and **28**) from *o*-aminoacetophenone, since 4-substituted quinolines are key intermediates for the synthesis of quinoline derivatives, such as chloroquine and quinine (Table 5). Enol methyl ether (**27**)[11] and enol *tert*-butyldimethylsilyl (TBDMS) ether (**28**) were prepared by standard methods and treated with ruthenium catalysts **A** and **B**, respectively, under similar

Table 1. Synthesis of 1,2-dihydroquinoline **2** using the RCM method

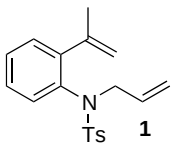
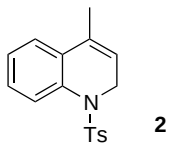
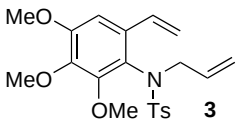
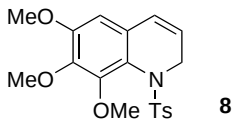
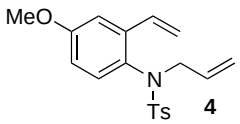
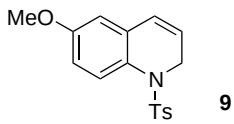
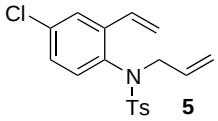
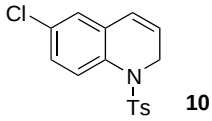
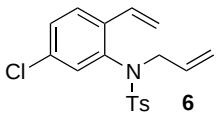
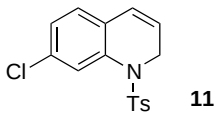
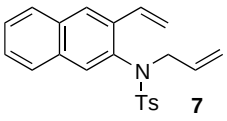
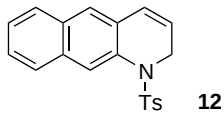


Run	Catalyst (mol%)	Temp. (°C)	Reaction Time (h)	Product (%)
1	30	rt	3	94
2	5	rt	3	72
3	5	50	1	92



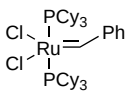
Scheme 3. Preparation of RCM precursors **3**–**7**.

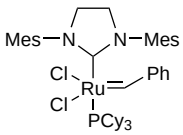
Table 2. RCM of dienes **1**–**7** using catalysts **A** and **B**[a]

Run	Substrate	Ru-catalyst[b]	Product	Yield (%)[c]
1	 **1**	**A**	 **2**	92
2	 **3**	**A**	 **8**	90
3	 **4**	**A**	 **9**	95
4	 **5**	**A**	 **10**	90
5	 **6**	**A**	 **11**	74
6		**B**		100
7	 **7**	**A**	 **12**	98

a) All reactions are carried out at 50 °C, 1 h, using 5 mol% of ruthenium catalyst, in CH_2Cl_2 (0.01 M).

b)

Catalyst **A**: 

Catalyst **B**: 

c) Isolated yields.

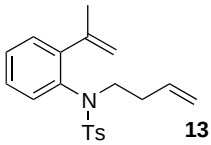
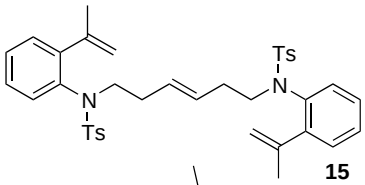
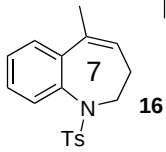
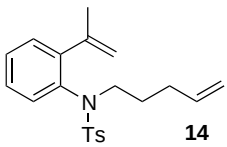
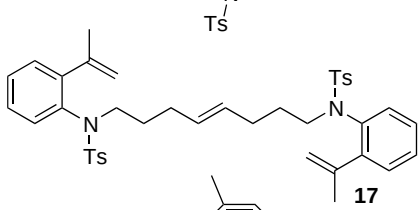
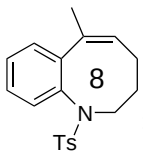
conditions. When catalyst **A** was used, the RCM reaction of **27** gave no cyclized product at all and the starting material was recovered unchanged. On the other hand, treatment of **27** with catalyst **B** gave the corresponding 1,2-dihydro-4-methoxyquinoline **29** in excellent yield (run 1 and 2).

We next investigated the enol silyl ether–ene RCM and found that the enol TBDMS ether **28** was an excellent substrate for RCM. Enol TBDMS ether **28** successfully underwent cyclization to give the expected 4-siloxy-1,2-dihydroquinoline **30** in excellent yield through enol silyl ether–ene metathesis with catalyst **B**, while catalyst **A** was not effective (run 3 and 4). These results can be applied to significantly enhance the utility of the RCM reaction for the synthesis of heterocyclic compounds. To the best of our knowledge, this is the first report of the synthesis of 4-hydroxyquinoline derivatives using an enol silyl ether–ene metathesis methodology.[12] This novel method is currently being applied to the total synthesis of natural products in our laboratory.

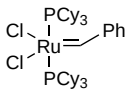
Acknowledgements

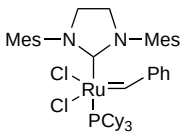
This research was supported by a Grant-in-Aid for Scientific Research on Priority Areas (A) 'Exploitation of Multi-Element Cyclic Molecules' from the Ministry of Education, Culture, Sports, Science, and Technology, Japan. We also thank Ms. R. Hara at the Analytical Center, Chiba University, for performing the mass spectroscopy.

Table 3. Synthesis of 2,3-dihydro-1*H*-benzo[*b*]azepine and 1,2,3,4,5,6-hexahydrobenzo[*b*]azocine using RCM[a]

Run	Substrate	Ru-catalyst[b)]	Product	Yield (%)[c)]
1	 **13**	**A**	 **15**	100
2		**B**	 **16**	100
3	 **14**	**A**	 **17**	95
4		**B**	 **18**	99

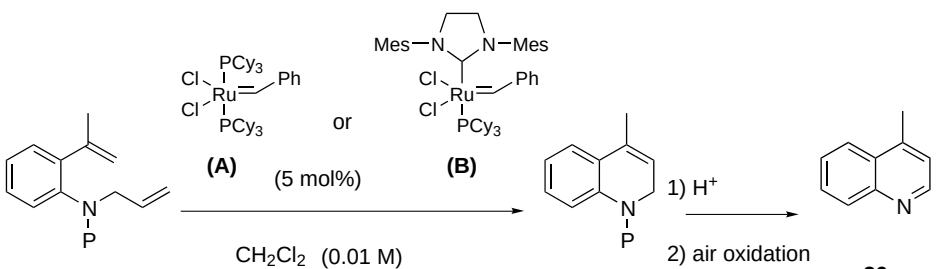
a) All reactions are carried out at 50 °C, 1 h, using 5 mol% of ruthenium catalyst, in CH_2Cl_2 (0.01 M).
b)

Catalyst **A**: 

Catalyst **B**: 

c) Isolated yields.

Table 4. Effect of protective groups on nitrogen



Run	Substrate		Catalyst	Product		
		P			P	%
1	**19**	Bn	**A**	**22**	Bn	99
2	**20**	Ac	**A**	**23**	Ac	0
3	**20**	Ac	**B**	**23**	Ac	98
4	**21**	Boc	**A**	**24**	Boc	63
5	**21**	Boc	**B**	**24**	Boc	97

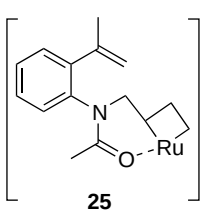


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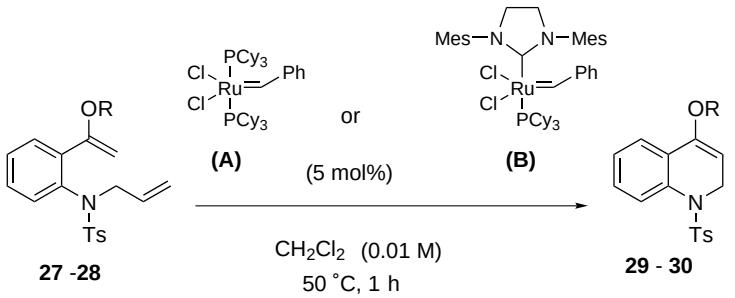
Table 5. Ene–enol metathesis to 4-methoxy- and 4-siloxy-1,2-dihydroquinolines



Run	Substrate		Catalyst	Product		
		R			R	%
1	**27**	Me	**A**	**-**	-	0
2	**27**	Me	**B**	**29**	Me	95
3	**28**	TBS	**A**	**-**	-	0
4	**28**	TBS	**B**	**30**	TBS	95

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9. Recently, Fukuyama and co-workers also reported the preparation of 1,2-dihydroquinolines (e.g. **2**), through acid-mediated cyclization of 3-(*N*-aryl-*N*-sulfonylamino)propionaldehydes, which were efficiently converted to quinolines (KOH, DMSO, 80°C). See: Ref. 2a.
10. For example, see: Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012–3043.
11. Several examples of ene–alkyl enol ether metathesis have been reported. See: (a) Rainier, J. D.; Cox, J. M.; Allwein, S. P. *Tetrahedron Lett.* **2001**, *42*, 179–181; (b) Postema, M. H. D.; Calimente, D.; Liu, L.; Behrmann, T. L. *J. Org. Chem.* **2000**, *65*, 6061–6068; (c) Clark, J. S.; Kettlle, J. G. *Tetrahedron* **1999**, *55*, 8231–8248; (d) Dirat, O.; Vidal, T.; Langlois, Y. *Tetrahedron Lett.* **1999**, *40*, 4801–4802; (e) Nicolaou, K. C.; Postema, M. D. H.; Claiborne, C. F. *J. Am. Chem. Soc.* **1996**, *118*, 1565–1566.
12. Recently, Shibasaki and co-workers reported their independent work on the synthesis of cyclic enol ethers from acyclic enol silyl ethers using RCM. See: Okada, A.; Ohshima, T.; Shibasaki, M. *18th International Congress of Heterocyclic Chemistry (Yokohama, Japan), Abstracts*, 2001; p. 363.