Tandem Reactions

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Synthesis of Heterocycles through a Ruthenium-Catalyzed Tandem Ring-Closing Metathesis/Isomerization/N-Acyliminium Cyclization Sequence**

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Olefin metathesis is an extremely powerful and general method for carbon–carbon bond formation in organic synthesis.[1] For example, ruthenium alkylidene catalyzed metathesis has been widely used to construct a variety of alkenes for applications in chemistry, materials science, and chemical biology. A key asset of the metathesis process is the unique olefin functional group selectivity mediated by robust and well-defined catalytic systems.

Over the years, however, unexpected non-metathetic reactions have been observed under metathesis conditions.[2] Although these reactions typically are highly substrate dependent, associated with specific reaction conditions, and possibly caused by ill-defined metal-catalytic species, they represent a unique opportunity for the development of tandem processes.[3] It is well recognized that tandem reactions offer major advantages in the synthesis of valuable target compounds. In this context, metathesis mediated by ruthenium alkylidene catalysts **1e** and **1k** (Grubbs first- and second-generation catalysts; Figure 1) has successfully been coupled to nonmetathetic transformations, such as double-bond isomerization,[4–6] hydrogenation,[7–9] cyclopropanation,[10] dihydroxylation,[11,12] keto-hydroxylation,[12] and Kharasch addition reactions.[13]

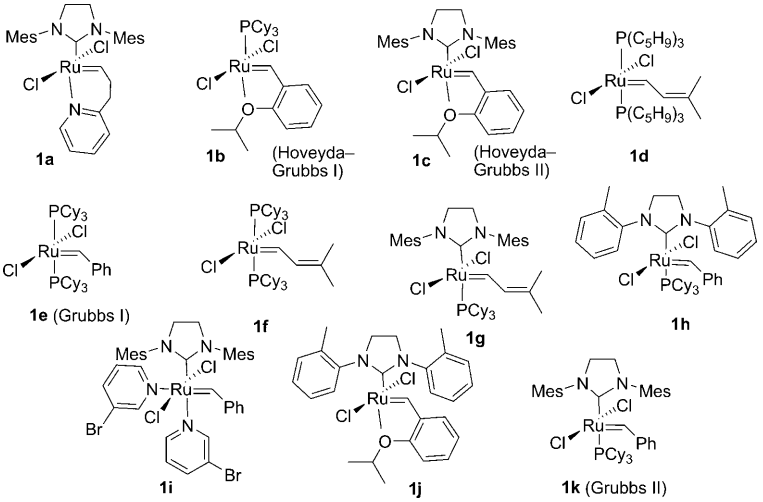
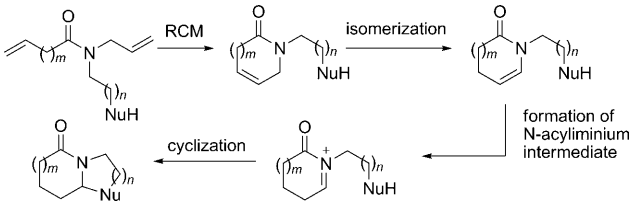


Figure 1. Ruthenium alkylidene catalysts commonly used in metathesis. Cy = cyclohexyl, Mes = 2,4,6-trimethylphenyl.

Only a few reports have dealt with the tandem ring-closing metathesis (RCM)/ double-bond isomerization. Notable works by the groups of Snapper[4] and Schmidt[5] have independently shown how cyclic allyl ethers can isomerize into 2,3-dihydropyrans. Schmidt and co-workers have also shown the beneficial effect of added hydride to favor the isomerization step. Inspired by the work of Fustero et al. (RCM/isomerization),[14] and Pérez-Castells and co-workers (RCM/isomerization/cyclopropanation),[15] we speculated that enamides generated in the event of a RCM/isomerization sequence could be further isomerized into reactive N-acyliminium intermediates (Scheme 1).[16] The presence of a suitably tethered nucleophile could then bring about a second cyclization step.



Scheme 1. Tandem RCM/isomerization/N-acyliminium cyclization.

Initial investigations were focused on substrate **2** (see, Table 1), which contains an indole moiety as a potentially reactive π nucleophile. The resulting product has a tetracyclic indolizinoindole core that is present in a range of pharmacologically interesting compounds, such as GPCR antagonists,[17] antibacterial,[18] and antiparasitic agents.[19] Access to enantiopure indolizinoindole derivatives has also been widely pursued in recent efforts in asymmetric catalysis.[20] We started out by screening ruthenium catalysts **1a–k** (Figure 1), in toluene at reflux (Table 1). The reactions were generally very clean, as indicated by UPLC-MS and ^{1}H NMR spec-

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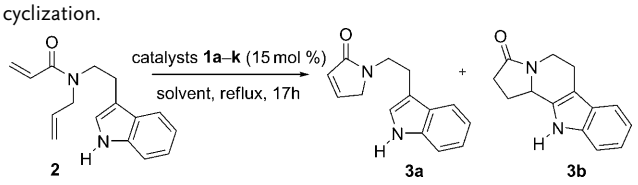
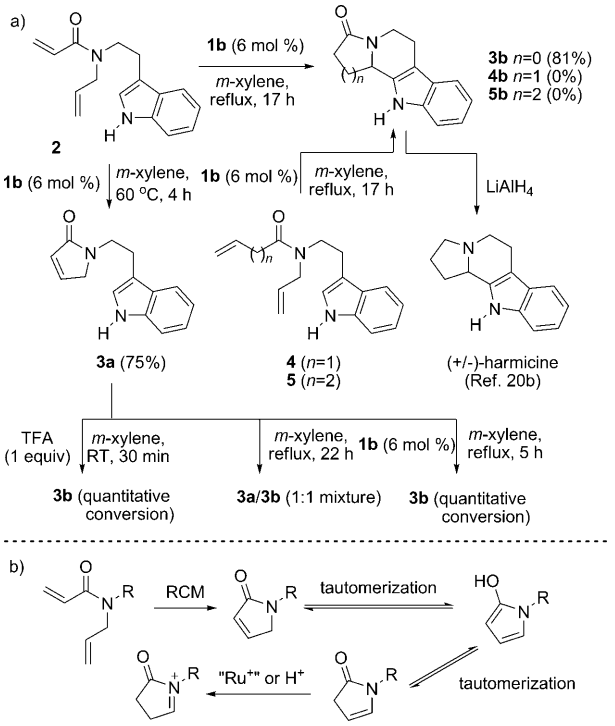
Table 1: Screening of catalysts for RCM/isomerization/N-acyliminium cyclization.



Entry	Catalyst	Solvent	**2**/**3a**/**3b**[a]
1	**1a**	toluene	100:0:0
2	**1b**	toluene	0:2:98
3	**1b**	*m*-xylene	0:0:100
4[b]	**1b**	*m*-xylene	0:5:95
5	**1c**	toluene	0:26:74
6	**1c**	*m*-xylene	0:0:100
7[b]	**1c**	*m*-xylene	0:10:90
8	**1d**	toluene	83:3:14
9	**1e**	toluene	54:6:40
10	**1f**	toluene	36:0:64
11	**1f**	*m*-xylene	0:0:100
12[b]	**1f**	*m*-xylene	38:0:62
13	**1g**	toluene	0:12:88
14	**1g**	*m*-xylene	0:0:100
15[b]	**1g**	*m*-xylene	0:5:95
16	**1h**	toluene	61:4:35
17	**1i**	toluene	25:38:37
18	**1j**	toluene	3:14:83
19	**1j**	*m*-xylene	0:0:100
20[b]	**1j**	*m*-xylene	7:13:80
21	**1k**	toluene	0:70:30

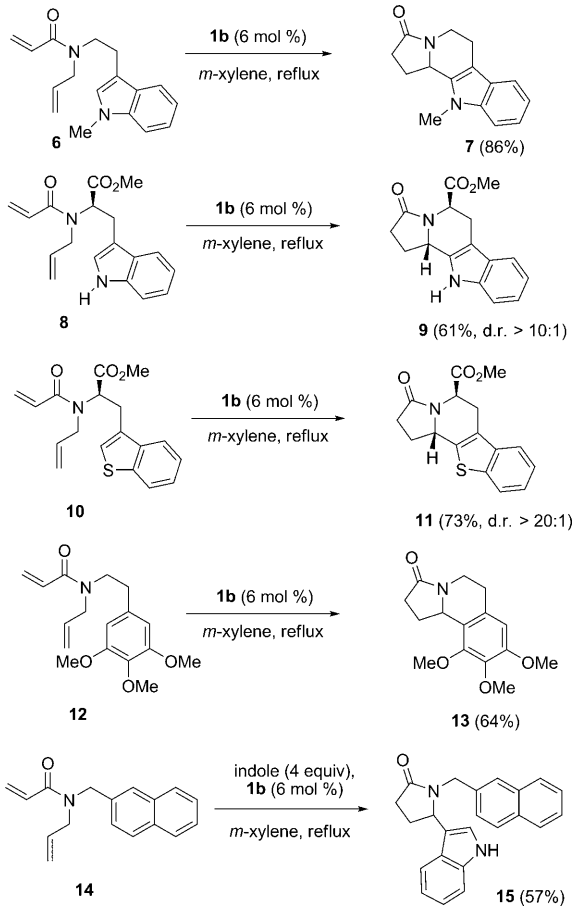
[a] With the exception of entry 17, product mixtures were generally clean (>85% of **2**/**3a**/**3b** in the reaction mixture as indicated by RP-HPLC analysis). [b] The reaction was carried out with 5 mol% of catalyst.



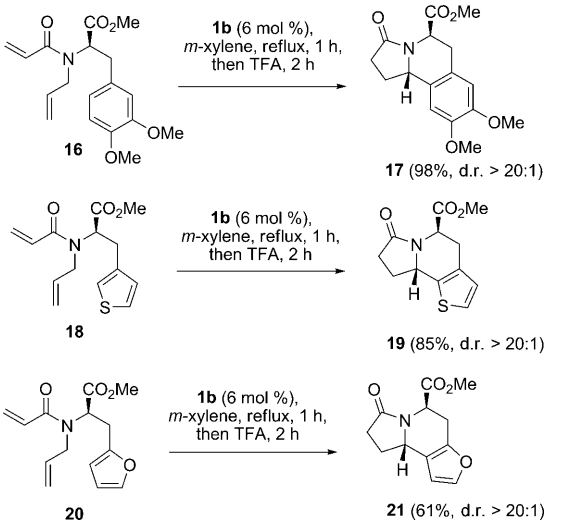
Scheme 2. a) Optimized reaction conditions, and b) proposed mechanism for formation of N-acyliminium intermediate. TFA = trifluoroacetic acid.

troscopy, and the proposed enamide intermediate was never detected.[21] Notably, with 15 mol% of catalyst in *m*-xylene at reflux, several catalysts brought about clean conversion into the desired product **3b** (entries 3, 6, 11, 14, and 19). When the amount of catalyst was lowered to 5 mol%, the Hoveyda–Grubbs catalyst **1b** gave the cleanest and highest conversion (95%) of **2** into **3b** (entry 4). When the catalyst loading was raised to 6 mol%, the reaction was complete in 17 hours (Scheme 2a), and gave **3b** in 81% yield. When **2** was subjected to the same reaction conditions at lower temperature (60°C), the metathesis product **3a** could be isolated in 75% yield. After careful removal of trace amounts of ruthenium,[22] the conversion of **3a** into **3b** was investigated under various reaction conditions. When **3a** was treated with catalyst **1b**, the desired product formed quantitatively in less than 5 hours. The same experiment without catalyst led to a 1:1 mixture of **3a** and **3b**, thus indicating a thermal background reaction, but also unambiguously demonstrating the beneficial effect of the catalyst in the nonmetathetic part of the tandem sequence. The synthesis of **3b** represents a formal total synthesis of the antiparasitic natural product harmicine.[19,20b] The homologous substrates **4** and **5** were not converted into the tetracycles **4b** and **5b** under the optimized conditions (although they still underwent RCM reactions) and TFA rapidly converted **3a** into **3b** (Scheme 2a); together these findings suggest to us that the nonmetathetic role of the ruthenium does not necessarily involve a ruthenium hydride intermediate, but somehow promotes favorable tautomerization events during the isomerization (Scheme 2b). In additional experiments, we also noted that the conversion of **2** into **3b** can be catalyzed cleanly with **1b** in the presence of 1–2% TFA or $BF_3{\cdot}Et_2O$ (added at the beginning of the reaction) in *m*-xylene heated at reflux, thus shortening the reaction times to less than 1 hour but giving slightly lower yields (70–75%; Scheme 2a).

The reaction using the N-methylated indole **6** gave an increased yield of 86% (Scheme 3). The introduction of a substituent, as present in the tryptophan (**8**) and benzothienylalanine (**10**) derivatives, effectively directed the formation of the new stereocenter with excellent *trans* diastereoselectivity at the ring junction. The trimethoxybenzene derivative **12** also underwent the tandem reaction sequence to give the tetrahydroisoquinoline derivative **13** in good yield (64%). The methodology was also extended to an intermolecular variant, wherein indole acted as the nucleophile in the reaction with the N-acyliminium intermediate that was derived from **14**, in good yield (57%). Under these reaction conditions, however, the reaction required the addition of 4 equivalents of indole. If **14** was instead treated with **1b** at reflux for 1 hour, followed by the addition of indole (1 equiv) and TFA (1 equiv) and additionally reacted for 1 hour, then **15** could be isolated in 84% yield. The nucleophilicity of the aromatic ring is highly important, as evident for substrates **16**, **18**, and **20** (Scheme 4), which were not converted into the corresponding tricycles under reaction conditions similar to those used in Scheme 3. Ring-closing metathesis occurred smoothly for these substrates but further conversion was better mediated by the subsequent addition of 1–4 equiva-



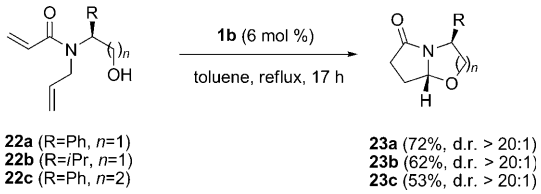
Scheme 3. Tandem RCM/isomerization/N-acyliminium reactions.



Scheme 4. RCM and acid-mediated isomerization/N-acyliminium cyclization.

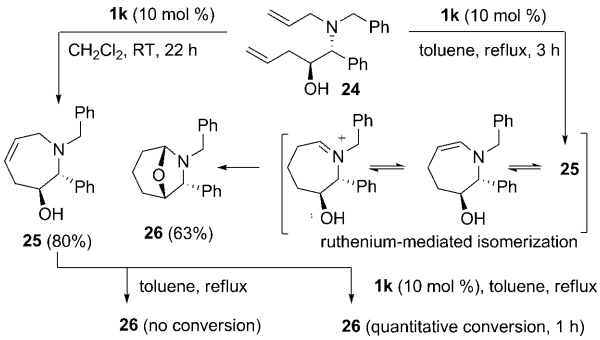
lents of TFA to the reaction mixture. In this way, tricyclic compounds **17**, **19** and **21** were obtained in good to excellent yields.

Furthermore, the extension of the methodology to heteroatom nucleophiles was briefly examined by using substrates **22a–c**, and, rewardingly, hemiaminals **23a–c** were formed in good yield and with excellent diastereoselectivity (Scheme 5).



Scheme 5. Tandem RCM/somerization/N-acyliminium cyclization reactions of alcohols.

The tandem methodology presented herein, presumably involves the generation of an N-acyliminium species. Therefore, it was natural to also investigate whether N-alkyliminium ions could be formed during a similar tandem process. In a preliminary study on amino alcohol **24**, treatment with 10 mol% of the Grubbs second-generation catalyst **1k** resulted in a tandem metathesis/isomerization/cyclization sequence to give the bicyclic product **26** in good yield (Scheme 6). Notably, carefully purified cyclic alkene **25** does not convert into **26** under thermal conditions whereas the addition of **1k** rapidly effects the isomerization steps.



Scheme 6. Ruthenium-catalyzed tandem RCM/isomerization/N-acyliminium cyclization.

In summary, an efficient ruthenium-catalyzed tandem ring-closing metathesis/isomerization/N-acyliminium cyclization sequence has been developed. In this tandem process, two new rings are formed in a single synthetic operation, which proceeds through a metathesis reaction and attack of tethered carbon and heteroatom nucleophiles on iminium intermediates. The resulting bi-, tri-, and tetracylic ring systems are generally formed in good to excellent yields with excellent diasteroselectivities. We believe that our findings point in a promising direction for future metathesis research.

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