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Ring-Rearrangement Metathesis of Nitroso Diels–Alder Cycloadducts

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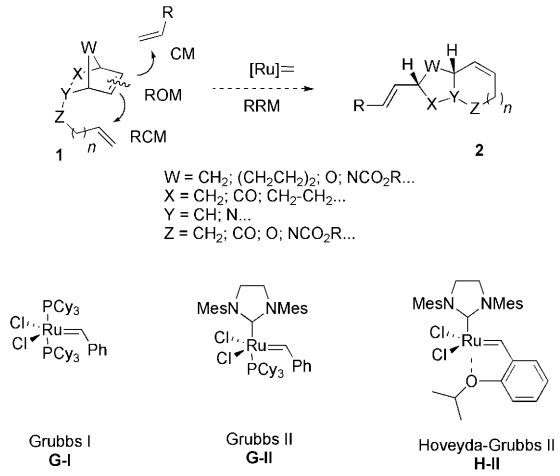
Abstract: Strained nitroso Diels–Alder bicyclo[2.2.1] or [2.2.2] adducts functionalized with alkene side chains of diverse length undergo a ring-rearrangement metathesis process with external alkenes and Grubbs II or Hoveyda–Grubbs II ruthenium catalysts, under microwave irradiation or classical heating, to deliver *cis*-fused bicycles of various ring sizes, which contain a N–O bond. These scaffolds are of synthetic relevance for the generation of molecular diversity and to the total synthesis of alkaloids. The observation of unexpected reactions, such as epimerization or one-carbon homologation of the alkene side chain, is also reported.

Keywords: cycloaddition · Diels–Alder · metathesis · nitroso compounds · rearrangement

Introduction

Recently, ruthenium-catalyzed ring-rearrangement metathesis (RRM) has been recognized as a powerful tool for the creation of molecular complexity. This domino process combines successive metathesis reactions with the same carbene catalyst to transform a cycloolefin connected with an exocyclic olefin into a new ring.[1] In this context, the domino sequence of ring-opening metathesis (ROM)/ring-closing metathesis (RCM)/cross metathesis (CM) of strained bicyclo[2.2.1],[2–6] [2.2.2],[7] and [3.2.1][8] systems **1** has received considerable attention for the synthesis of fused five-, six-, and seven-membered rings **2** (Scheme 1). The pioneering studies from the groups of Grubbs[2] and Blechert[3] were followed by considerable amounts of work from other research groups.[4–8] The transfer of the stereoinformation contained in the starting bicyclic olefin to the rearranged product is of particular interest. The utility of RRM has been highlighted in the total syntheses of several natural products.[9] The ring-strain release is presumably the driving force of this transformation. Thus, highly strained bicyclo[2.2.1] systems are particularly reactive and have been widely employed.[2–7] However, the analogous bicyclo[2.2.2] systems suffer from a lack of strain and are, therefore, less reactive. Consequently, they have scarcely been studied as domino metathesis substrates.[7,9c,h]



Scheme 1. Ring-rearrangement metathesis.

Although RRM has been largely utilized for the synthesis of bicycles that contain one or more heteroatoms, there were no reports of such processes in substrates with two contiguous heteroatoms before our involvement in this field. In this context, we were interested to study the domino metathesis of bicyclo[2.2.*n*] systems ($n=1$, 2) that contained a N–O bond, because our research group has previously been involved in the development and synthetic application of the nitroso Diels–Alder (NDA) reaction.[10,11] This cycloaddition, between a diene **4** and a nitroso reagent **3**, allows the straightforward synthesis of 3,6-dihydro-1,2-oxazines. It seemed evident that the strained NDA cycloadducts **5–8** arising from cyclopentadienes or 1,3-cyclohexadienes could be suitable substrates for RRM. This strategy would lead to the rare *cis*-bicyclo[*x*,*y*,0]systems ($x=3$, 4; $y=3$–5) **9–12**, which contain an N–O bond (Scheme 2). In 2002, Ellis and King described the domino ROM/CM of strained bicyclo-

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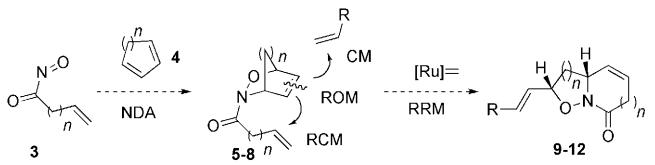
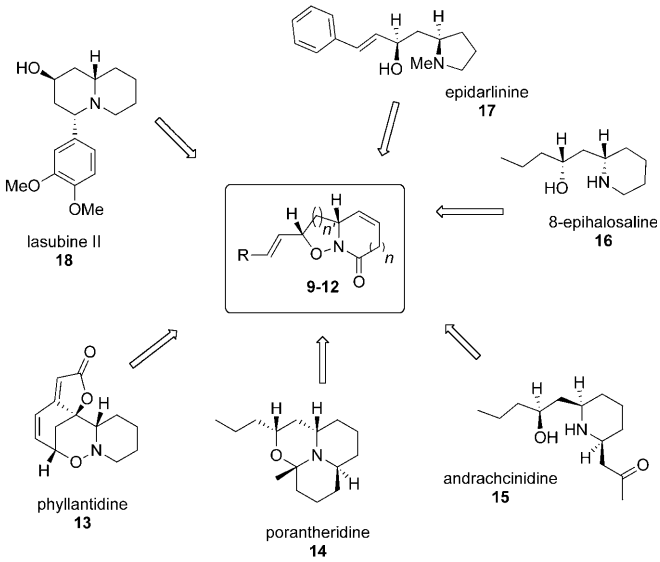


Scheme 2. Ring-rearrangement metathesis of NDA cycloadducts.

[2.2.1]dihydrooxazines[12] and, in 2007, our group published the preliminary results of a study of the ROM/RCM/CM RRM of a bicyclo[2.2.1] NDA cycloadduct with Grubbs II catalyst, which yielded tetrahydroisoxazolo[2,3-*a*]pyridin-7-ones.[13]

Moreover, this NDA/RRM method seems suitable to access several natural products that contain tetrahydrooxazino[2,3-*a*]piperidine scaffolds (phyllantidine; **13**[14a]), 1,3-*cis*-amino-alcohol skeletons (porantheridine; **14**,[14b] andrachcinidine; **15**,[14c] 8-epihalosaline; **16**,[14c] and epidarlinine; **17**[14d]), or quinolizinol moieties (lasubine II; **18**[14e]) (Scheme 3). Indeed, we have recently completed the total synthesis of **16** and the formal synthesis of **14** based on this strategy.[15]

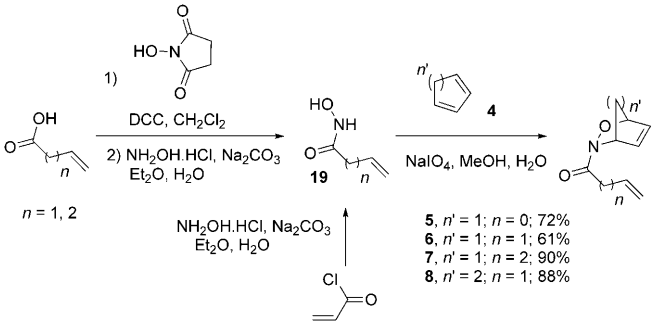


Scheme 3. Potentially accessible natural products from the ring-rearrangement metathesis of NDA cycloadducts.

The purpose of the present report was to further expand the scope of the NDA/RRM sequence with respect to the cyclic diene, the length of the alkene side chain, and the nature of the CM partner. The use of microwave irradiation to shorten the reaction times was also investigated.[16]

Results and Discussion

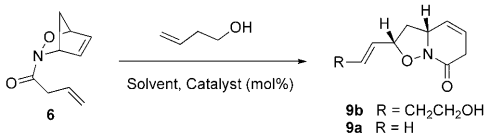
The strained 3,6-dihydro-1,2-oxazines **5**–**8** were easily obtained from the cycloaddition between cyclic dienes **4** (cyclopentadiene or 1,3-cyclohexadiene) and acylnitroso reagents **3**, obtained in situ from the oxidation of the corresponding hydroxamic acids **19** with sodium periodate. The hydroxamic acids were derived from the commercially available but-3-enoic acid, pent-4-enoic acid, or acryloyl chloride (Scheme 4).



Scheme 4. Preparation of NDA cycloadducts **5**–**8**.

We then explored the RRM of the bicyclo[2.2.1] NDA cycloadduct **6** with but-3-en-1-ol to find suitable reaction conditions under microwave irradiation, to shorten the reaction time reported in our precedent communication. The desired ROM/RCM/CM compound **9b** was obtained, as well as the ROM/RCM product **9a**. Microwave irradiation improved the ratio of **9b/9a** relative to classical thermal conditions (Table 1, entry 2 versus 1). After further optimization, we found that the Grubbs II catalyst (**G-II**, Table 1, entry 4) was superior to the Hoveyda II catalyst (**H-II**, Table 1, entry 11), whereas the Grubbs I catalyst (**G-I**) was ineffective for this process (Table 1, entry 10). A large excess of the CM partner (4 equiv) promoted the formation of the desired ROM/RCM/CM product **9b** over the ROM/RCM product **9a** (Table 1, entries 2 and 3). The reaction was best

Table 1. Optimization of the ring-rearrangement metathesis.[a]



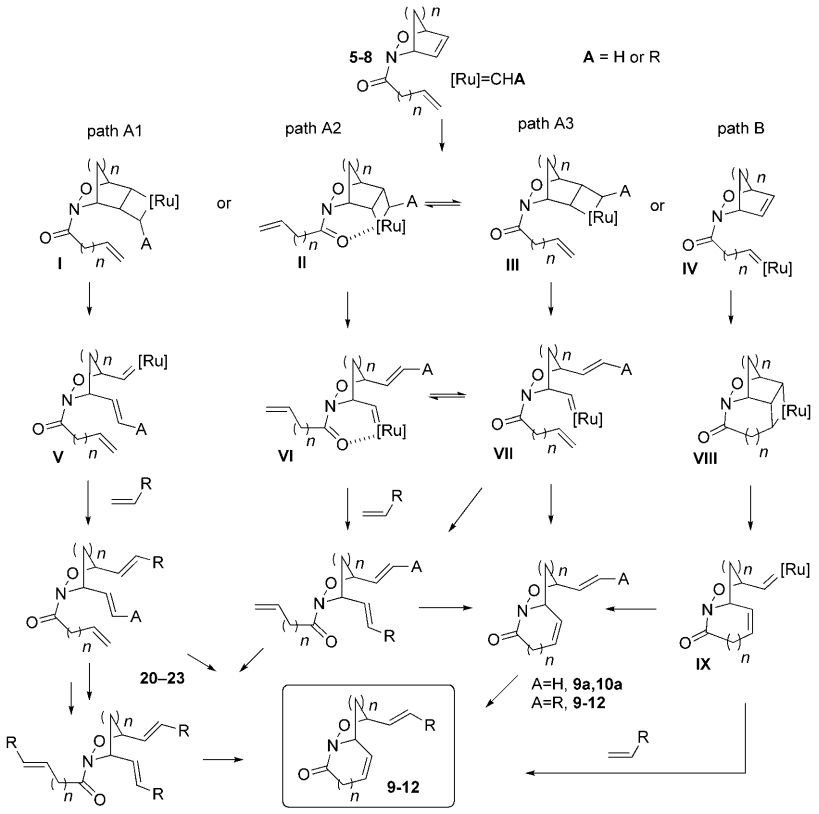
	Cat.	Solvent (concentration [M])	*T* [°C]	**9b** [%]	**9a** [%]
1	**G-II**	toluene (0.05)	80[b]	51	36
2	**G-II**	toluene (0.05)	80	64	22
3[c]	**G-II**	toluene (0.05)	80	39	35
4	**G-II**	toluene (0.1)	80	67	18
5	**G-II**	toluene (0.2)	80	49	9
6	**G-II**[d]	toluene (0.1)	80	59	19
7	**G-II**	toluene (0.1)	60	62	25
8	**G-II**	toluene (0.1)	100	62	11
9	**G-II**	CH_2Cl_2 (0.1)	80	63	13
10	**G-I**	toluene (0.1)	80	0	0
11	**H-II**	toluene (0.1)	80	52	15
12[e]	**G-II**[f]	toluene (0.1)	80	70	8

[a] Conditions: Alkene (4 equiv), cat. (10 mol%), microwave irradiation, 0.5 h. [b] Oil bath heating. [c] 2 equiv of alkene used. [d] 5 mol% catalyst used. [e] Reaction time 2×20 min. [f] Catalyst added in 2×5 mol% portions.

performed in toluene (Table 1, entries 4 and 9), at 80 °C (Table 1, entries 4, 7, and 8), and at a concentration of 0.1 M (Table 1, entries 2, 4, and 5). Finally, the addition of **G-II** (10 mol %) in two portions proved to be beneficial to the yield of **9b** (Table 1, entry 12).

In this RRM process different reaction pathways may be operative, dependent on various factors (Scheme 5).[4c]

Initial cyclobutanametallation of the endocyclic double bond (path A, Scheme 5, intermediates **I**–**III**) would lead to two regioisomeric ring-opened intermediates, **V** (path A1, Scheme 5) and **VI** or **VII** (paths A2 and A3, Scheme 5). Intermediate **V** should undergo CM to give **20**–**23**, whereas intermediates **VI** and **VII** could afford the RCM (**9**–**12**) or CM products (**20**–**23**). It is postulated that coordination of the Ru carbene by the exocyclic carbonyl (**VI**) would prevent RCM, thus, CM would be favored. Eventually, the ROM/CM products **20**–**23** could react further to yield the RCM compounds **9**–**12**.



Scheme 5. Potential pathways for the ring-rearrangement metathesis of NDA cycloadducts.

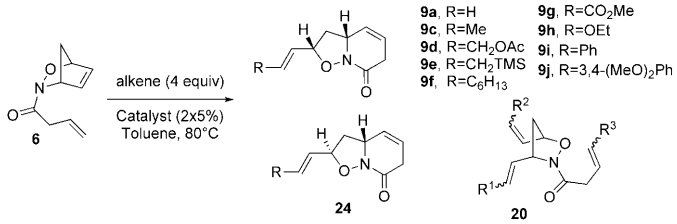
Considering the nature of the active catalyst ([Ru]=CHA; A = H or R), the isolation of significant amounts of ROM/RCM products **9a** and **10a** (see Table 3 below) alongside the ROM/RCM/CM compounds led us to believe that the ruthenium methylidene ([Ru]=CH_2) is a propagating species. If the ruthenium alkylidene intermediate ([Ru]=CHR) was the only active catalyst, only ROM/CM/RCM or ROM/CM products would have been isolated.

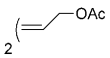
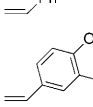
On the other hand, reaction of the active Ru–carbene complex with the exocyclic double bond (path B, Scheme 5) would generate reactive intermediate **IV**, which would undergo ROM/RCM and finally CM. No ROM/CM products are expected to arise from this pathway.

We propose to examine the variations in the preferred pathway with the level of ring strain in the bicyclic NDA cycloadduct, the length of the alkene side chain, and the nature of the CM partner.

With optimized conditions in hand, we turned our attention to the reactivity of bicyclo[2.2.1]-3,6-dihydro-1,2-oxazine (**6**) towards various CM partners (Table 2). In the absence of an external alkene, the bicyclo[4.3.0] compound **9a** was obtained in 17% yield (Table 2, entry 1). Polymeric substances were the major side products, which most probably arose from a ring-opening metathesis polymerization (ROMP) process. Under an ethylene atmosphere the polymerization was suppressed and **9a** was obtained with an improved yield of 54% (Table 2, entry 2). Reaction with gaseous but-2-ene at 80 °C led to the formation of the ROM/RCM/CM product **9c** (68%, Table 2, entry 3).[17] Surprisingly, a minor amount of the epimerized compound **24c** was also isolated. The mechanism of formation of this compound is unclear and will be discussed later (see Scheme 6 below). When the same reaction performed at a lower temperature (60 °C, Table 2, entry 4) the formation of **24c** was suppressed and a good yield of **9c** was obtained (75%). Reaction with allyl acetate (Table 2, entry 5) led to a 1:1 mixture of **9d** (ROM/RCM/CM) and **9a** (ROM/RCM) in 52% yield. It is known that CM processes might be improved by using a dimer of one of the partners.[18] Accordingly, we ran the reaction with but-2-enyl diacetate (Table 2, entry 6). The ratio of **9d**/**9a** was improved to 4:1, but was accompanied by a decreased yield of 29%. In this case, a large amount of ROM/CM product **20d** was obtained. Allyltrimethylsilane (Table 2, entry 7) and oct-1-ene (Table 2, entry 8) led to good yields of the desired rearranged bicycles **9e** and **9f** (ROM/RCM/CM), respectively, as mixtures with **9a** (ROM/RCM). When methyl acrylate (Table 2, entry 9) was tested no ROM/RCM/CM product **9g** was recovered. Only 25% of the ROM/RCM product **9a** was obtained, along with polymer formation, indicative that methyl acry-

Table 2. Formation of tetrahydroisoxazolo[2,3-*a*]pyridin-7-ones **9**.



	Alkene	Cat.	**9** (Yield [%])	Other products (Yield [%])
1	none	**G-II**[a]	**9a** (17)	polymers
2	$H_2C=CH_2$	**G-II**[b]	**9a** (54)	–
3		**G-II**[b]	**9c** (68) **24c** (3)	–
4		**G-II**[c]	**9c** (75)	–
5		**G-II**[a]	**9d/9a** 1:1 (52)	–
6		**G-II**[a]	**9d/9a** 4:1 (29)	**20d** (44–28) $R^1,R^2,R^3=$ CH_2OAc or H
7		**G-II**[a]	**9e/9a** 3.5:1 (70)	–
8		**G-II**[a]	**9f/9a** 1.4:1 (77)	–
9		**G-II**[a]	**9g/9a** 0:1 (25)	polymers
10		**H-II**[a]	**9g/9a** 1:1.6 (31)	polymers
11		**G-II**[a]	none	**20h** (72) $R^1,R^3=H;R^2=OEt$ or $R^1=OEt;R^2,R^3=H$
12		**G-II**[a]	**9i/9a/24i** 1:1:1.3 (65)	–
13		**G-II**[a]	**9j/9a/24j** 1.3:1:1.3 (71)	–

[a] Microwave irradiation, 2×20 min, $c=0.1$ M. [b] Oil bath heating, 2×2 h, $c=0.05$ M. [c] Oil bath heating, 60 °C, 2×2 h, $c=0.05$ M.

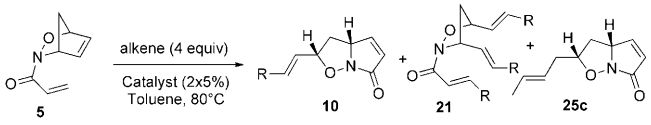
late is spectator in the reaction. The Hoveyda ruthenium species **H-II** is known to be the catalyst of choice for CM with alkenes that contain an electron-withdrawing group. Indeed, with the **H-II** catalyst (Table 2, entry 10), a 1:1.6 mixture of the desired **9g** with **9a** was obtained in a modest yield of 31%. Pyridin-7-one **9h** was not obtained upon reaction with the electron-rich ethyl vinyl ether (Table 2, entry 11). The product **20h**, the result of a ROM/CM sequence, was recovered in this case.

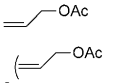
The reactions of styrene (Table 2, entry 12) and 3,4-dimethoxystyrene (Table 2, entry 13) led to the expected pyridin-7-ones **9i** and **9j** (ROM/RCM/CM products), respectively. The products were obtained as mixtures with **9a** (ROM/RCM) and large amounts of the respective epimeric ROM/RCM/CM products **24i** and **24j** that were only observed in minor amounts previously (**24c**, Table 2, entry 3). We were surprised by the importance of this phenomenon; consequently we ran some control experiments (Scheme 6). When the CM between **9c** and 3,4-dimethoxystyrene was attempted, the same epimeric mixture of **9j** and **24j** was observed. During the formation of the macrocycle of BILN2061 by RCM with catalyst **G-I**, a team at Boehringer Ingelheim Pharmaceuticals previously observed a related epimerization.[19] Moreover, when pure **9j** was heated in toluene with catalyst **G-II** the two epimers, **9j** and **24j**, were recovered in a 1:1 ratio. Thus, we can postulate that the epimerization takes place after **9j** is formed. One could also postulate that the decomposition of the metathesis catalyst into a hydride–ruthenium species is a trigger for the epimerization.[20] A C–H insertion of the ruthenium carbene could also be invoked. The mechanism of this side reaction has not been elucidated, but the presence of an aromatic ring on the alkene seems to be of high importance. It is also worth noting that **24j** epimerized slowly to **9j** on standing for several weeks in $CDCl_3$. This reverse epimerization process might be induced by participation of the aromatic ring, as depicted in Scheme 6. Tetrahydroisoxazolo[2,3-*a*]pyridin-7-one (**9j**) is a potential precursor of **18**, in accordance with the synthesis of quinolizinones previously reported by our group.[13]

The presence, in some cases, of polymeric substance or ROM/CM compounds is indicative of initiation at the internal double bond (paths A1–3, Scheme 5), but does not rule out initiation at the external double bond (path B, Scheme 5); the two pathways might be simultaneously operative.

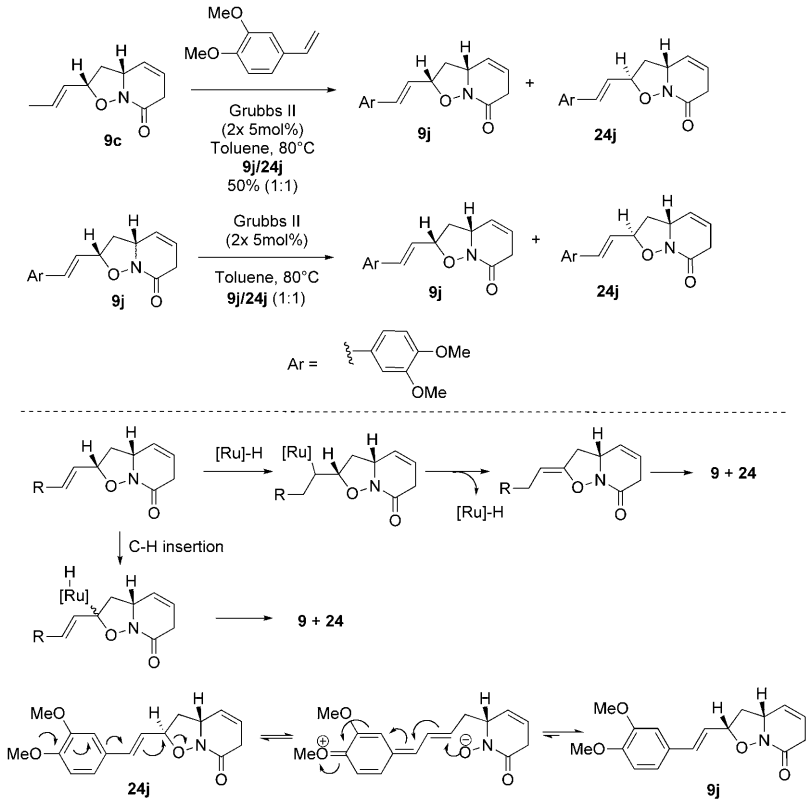
Subsequently, we examined the formation of tetrahydroisoxazolo[2,3-*a*]pyrrol-6-ones **10** from NDA substrates **5** that contained an acrylic side chain (Table 3). Because the RCM step involves an electron-withdrawing

Table 3. Formation of tetrahydroisoxazolo[2,3-*a*]pyrrol-6-ones **10**.



	Alkene	Cat.	*c* [M][d]	**10** (Yield [%])	Other products (Yield [%])
1	none	**H-II**[a]	0.1	**10a** (0)	polymers
2	$H_2C=CH_2$	**H-II**[b]	0.05	**10a** (40)	**21a** (12)
3		**H-II**[b]	0.05	**10c** (53–44)	**21c** (23) **25c** (7–0)
4		**G-II**[a]	0.1	**10f/10a** 0:1 (<10)	**21f** (50–45)
5		**H-II**[a]	0.1	**10f/10a** 1.4:1 (50)	**21f** (25–20)
6		**H-II** $[Ti(OiPr)_4]$ (30%)[a,c]	0.1	**10f/10a** 2.3:1 (40)	**21f** (25–20)
7		**H-II**[a]	0.05	**10f/10a** 1.5:1 (52)	**21f** (25–20)
8		**H-II**[a]	0.1	**10d/10a** 2:1 (30)	**21d** (40–30)
9		**H-II**[a]	0.1	**10d** (31)	**21d** (40–30)
10		**H-II**[a]	0.1	**10e/10a** 10:1 (27)	**21e** (50–40)
11		**G-II**[a]	0.1	**10i/10a** 2:1 (37)	**21i** (20–15)

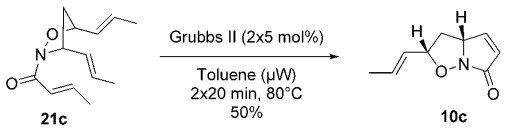
[a] Microwave irradiation, 2×20 min. [b] Oil bath heating, 2×2 h. [c] Ti($OiPr$)$_4$ additive (4 equiv). [d] Concentration of **5**.



Scheme 6. Epimerization of tetrahydroisoxazolo[2,3-*a*]pyridin-7-ones **9** and postulated mechanisms.

group, the catalyst of choice was complex **H-II** in preference to **G-II** (Table 3, entry 4 versus 5). In the absence of a CM partner only polymeric products were produced (Table 3, entry 1). Under an ethylene atmosphere, the bicyclo[3.3.0] rearranged compound **10a** was obtained in 40% yield (Table 3, entry 2). Reaction with gaseous but-2-ene led to the formation of the ROM/RCM/CM product **10c** (53%, Table 3, entry 3); the homologation product **25c** was sometimes observed from the reaction on a larger scale. The mechanism of formation of **25c** will be discussed later (in analogy with **29c**, Scheme 11 below). Reaction with oct-1-ene, allyl acetate, allyltrimethylsilane, or styrene (Table 3, entries 5, 7, 8, 10, and 11) gave moderate yields of mixtures of the ROM/RCM compound **10a** with the ROM/RCM/CM products **10f**, **10d**, **10e**, and **10i**. To improve the ratio of **10d**/**10a**, reaction with the dimeric alkene but-2-enyl diacetate was examined and the ROM/RCM/CM product **10d** was exclusively obtained (Table 3, entry 9). In all cases, the ROM/CM byproducts **21** were recovered in large amounts. A reasonable hypothesis would be that ROM is the first step to occur, followed by CM (paths A1 and 2, Scheme 5). The RCM event would be slower due to the presence of the electron-withdrawing group on the side chain. The RCM step could be further decelerated if it involves a disubstituted alkene after the CM step (path A2, Scheme 5). If an external alkene is not present to intercept the ROM intermediate it is evident that the rate of polymerization is superior to the rate of the RCM (Table 3, entry 1). This is in contrast with the Ru-catalyzed reaction of *N*-acryloyl-2-azabicyclo[2.2.1]hept-5-en-3-ones in the absence of external alkenes or ethylene, which led cleanly to the desired rearranged bicycles, as described by Aljarilla and Plumet.[4e] It was previously postulated that coordination of the Ru–carbene by the exocyclic carbonyl moiety would stabilize the intermediate **VI** (Scheme 5) and, thus, slow the rate of RCM. To prevent the undesired formation of this hypothetical coordinate complex, [Ti(O*i*Pr)$_4$] was added to induce coordination the carbonyl group to titanium and, thus, regenerate an active Ru–carbene moiety.[21] Unfortunately, the yield of **10f** was not improved in the presence of this additive (Table 3, entry 6).

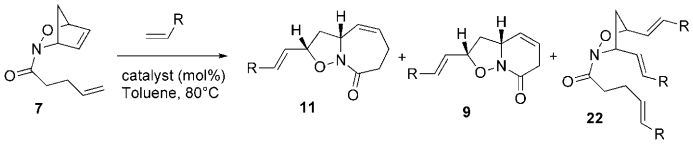
The tetrahydroisoxazolo[2,3-*a*]pyrrol-6-ones **10** were obtained in moderate yields. It was possible to recycle the ROM/CM byproduct **21c** in a RCM process to yield **10c** (50%), which improves the overall efficiency of this process (Scheme 7). Overall, **10c** was obtained in 64% yield from **5**, over two metathesis cycles.



Scheme 7. Ring-closing metathesis of ROM/CM product **21c**.

The synthesis of tetrahydroisoxazolo[2,3-*a*]azepin-8-ones **11** from **7** proved to be less rewarding (Table 4). In the absence of any alkene, only polymerization was observed (Table 4, entry 1). If an external alkene was added, ROM/CM was the major pathway. After ROM, the formation of seven-membered rings by RCM seems to be highly disfavored relative to CM or polymerization. However, reaction with but-2-ene afforded the desired bicyclo[3.5.0] rearranged compound **11c** in 15% yield, with 15% of the bicyclo[3.4.0] compound **9c** (from isomerization of the external double bond, followed by the more favored six-membered ring formation by RCM) (Table 4, entry 2). Cycloadduct **11e** was obtained in 7% yield when 4 equiv of allyltrimethylsilane were used (Table 4, entry 3). To decelerate the rate of CM relative to RCM, only two equivalents of allyltrimethylsilane were used, or the concentration was lowered to 0.05 M

Table 4. Formation of tetrahydroisoxazolo[2,3-*a*]azepin-8-ones **11**.

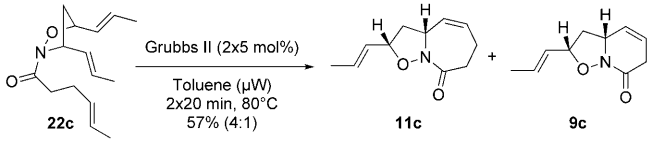


	Alkene	Cat.	*c* [M][e]	Products (Yield [%]) **11**	**9**	**22**
1	none	**G-II**[a]	0.1	–		only polymers
2		**G-II**[b]	0.05	**11c** (15)	**9c** (15)	**22c** R = Me (42)
3[c]	TMS	**G-II**[a]	0.1	**11e** (7)	–	**22e** R = CH_2TMS, H (35–0)
4[d]	TMS	**G-II**[a]	0.1	**11e** (15)	–	**22e** R = CH_2TMS, H (30–20)
5[d]	TMS	**G-II**[a]	0.05	**11e** (12)	**9e** (3)	**22e** R = CH_2TMS, H (50–30)

[a] Microwave irradiation, 2×20 min. [b] Oil bath heating, 2×2 h. [c] 4 equiv of alkene used. [d] 2 equiv of alkene used. [e] Concentration of **7**.

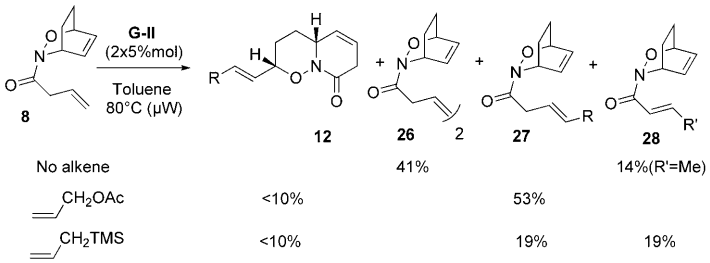
(Table 4, entries 4 and 5). Accordingly, slightly better yields of **11e** (15 and 12%, respectively) were obtained. Addition of [Ti(O*i*Pr)$_4$] to avoid the formation of the postulated unproductive chelate **VI** (Scheme 5) did not lead to any improvement. Allylacetate and but-2-enyl diacetate were also examined as reaction partners, but with no success.

To obtain acceptable amounts of **11**, the ROM/CM byproduct **22c** was engaged in a subsequent RCM process to yield 57% of a 4:1 mixture of **11c** and **9c** (Scheme 8).



Scheme 8. Ring-closing metathesis of ROM/CM product **22c**.

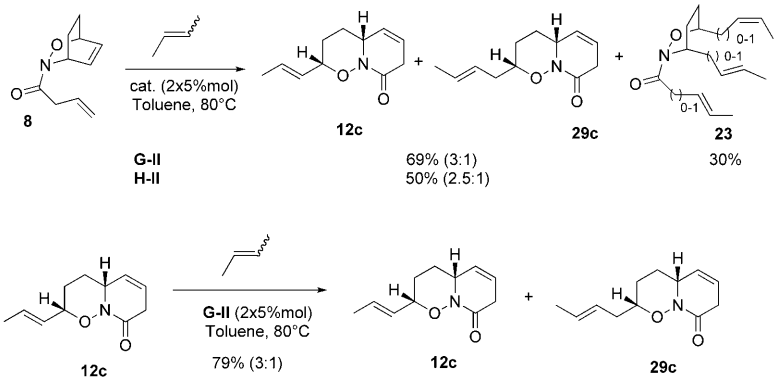
Next, we turned our attention to the challenging ring rearrangement of the bicyclo[2.2.2] NDA cycloadduct **8** (Scheme 9). Usually the ROM reactions of bicyclo[2.2.2] compounds are known to be difficult due to the less-strained nature of the framework. Phillips and co-workers described the RRM of bicyclo[2.2.2]octenes with all-carbon-atom frameworks.[7a] However, there are very few examples of RRM with bicyclo[2.2.2] frameworks that contain heteroatoms and those reported are usually accompanied by variable yields.[7b,9h] Our first attempts did not meet with great success. In the absence of any alkene, the external double bond was the only reactive site; we observed isomerization of this double bond or dimerization. No ROM of the oxaazabicyclo[2.2.2]octene **8** was observed. When allyltrimethylsilane or allylacetate were added, the major process was CM with the external double bond. However, trace amounts of the RRM products were obtained.



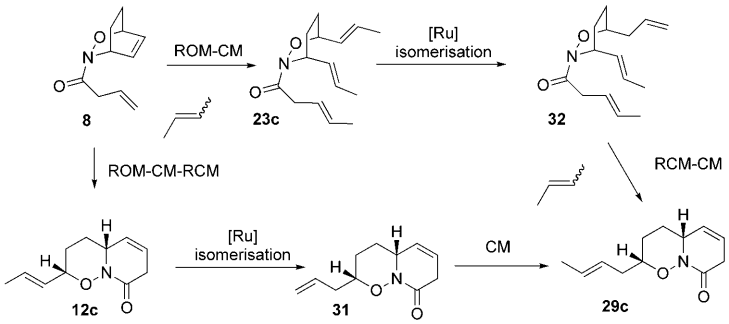
Scheme 9. Failed ring-rearrangement metathesis of bicyclo[2.2.2] NDA cycloadduct **8**

Finally, when we operated the reaction in presence of but-2-ene, we observed that the internal alkene of the bicyclic system was reactive (Scheme 10). Thus, the desired hexahydrooxazino[2,3-*a*]pyridin-8-one **12c** was obtained in 69% yield as a 3:1 mixture with the unexpected hexahydrooxazino[2,3-*a*]pyridin-8-one **29c**, which contained an extra carbon atom on the side chain (analogous to **25c**). Compounds **23**, the products of ROM/CM, were also isolated, which suggests initiation at the internal double bond (path A, Scheme 5). The ROM/CM products **23** also contained extra carbon atoms in part. When the pure desired heterocycle **12c** was resubmitted to the RRM conditions a 3:1 mixture of **12c** and **29c** was recovered.

These results imply that this carbon homologation is operative either on the ROM product or the formed hexahydrooxazino[2,3-*a*]pyridin-8-one **12**. Different pathways may account for the carbon homologation (Scheme 11). Our main hypothesis relies on an unusual ruthenium-catalyzed isomerization[20] of the external disubstituted double bond of **12c** into the terminal alkene **31**, followed by CM with but-2-ene to access **29c**. Such an isomerization/CM sequence could also be applied to the ROM/CM substrate **32**; subsequently **29c** would be delivered by RCM.



Scheme 10. Successful ring-rearrangement metathesis of bicyclo[2.2.2] NDA cycloadduct **8**; synthesis of the phyllantidine (**13**) framework.



Scheme 11. Tentative explanation for the formation of compound **29c**.

The synthesis of **12c** featured in a straightforward route to the N–O containing bicyclo[4.4.0] scaffold of **13**.[22]

Conclusion

We have demonstrated that the ring rearrangement of NDA bicyclo[2.2.1] or [2.2.2] adducts with external alkenes, in presence of Grubbs II or Hoveyda–Grubbs II ruthenium catalysts under microwave or classical heating, deliver rare *cis*-bicyclo[*x*,*y*,0] systems ($x=3,4$; $y=3$–5) that contain an N–O bond. The scaffolds obtained are of significant interest for the synthesis of alkaloids. Studies towards the synthesis of natural products by this strategy will be reported in due course.

During our investigations of this domino metathesis process, we discovered interesting side reactions, such as an intriguing epimerization and a one-carbon homologation of the alkene side chain of the metathesis products. Research to elucidate the mechanisms involved is underway.

Experimental Section

Typical procedure A—synthesis of the NDA cycloadducts: Dicyclohexyl carbodiimide (1.05 equiv) and but-3-enoic acid or pent-4-enoic acid (1 equiv) were added to a solution of *N*-hydroxysuccinimide (1.1 equiv) in CH_2Cl_2 (0.7 M) at 0 °C. The mixture was stirred for 2 h before the insoluble dicyclohexyl urea formed was removed by filtration. The filtrate was concentrated in vacuo and the crude product was solubilized in Et_2O/H_2O (1:1, 0.5 M). Hydroxylamine hydrochloride (2.5 equiv) and sodium carbonate (1.7 equiv) were added successively at 0 °C and the mixture was stirred for 12 h. The heterogeneous mixture was then filtered with EtOAc. The filtrate was concentrated in vacuo to yield the crude hydroxamic acid. MeOH and water (30:1, 0.7 M) were added to the crude hydroxamic acid and cyclopentadiene or 1,3-cyclohexadiene (3–5 equiv) and sodium periodate (1.5 equiv) were added successively at 0 °C. The reaction was stirred for 30 min at 0 °C, then 1.5 h at RT. The reaction was quenched with aqueous saturated $NaHCO_3$ solution and extracted with EtOAc (×2). The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (20–50 % EtOAc/cyclohexane) to yield the desired NDA cycloadduct.

Typical procedure B—RRM with ethylene or but-2-ene under classical heating: The metathesis catalyst (5 mol %) was added to the NDA cycloadduct (1 equiv) in degassed toluene (0.05 M) under an argon atmosphere at −78 °C. But-2-ene or ethylene was bubbled through the reaction mixture at −78 °C for 2 min. The mixture was then heated at 80 °C by using an oil bath for 2 h. A second portion of the metathesis catalyst (5 mol %) was added and the mixture was heated at 80 °C for a further 2 h. After cooling, the reaction mixture was concentrated in vacuo and the crude product was directly purified by flash column chromatography on silica gel.

Typical procedure C—RRM under microwave irradiation: The alkene partner (4 equiv) and the metathesis catalyst (5 mol %) were added to the NDA cycloadduct in degassed toluene (0.05 M) under an argon atmosphere. The mixture was then irradiated at 80 °C for 20 min. A second portion of the metathesis catalyst (5 mol %) was added and the mixture was irradiated at 80 °C for a further 20 min. After cooling, the crude product was directly purified by flash column chromatography on silica gel.

Oxazine 7: Following procedure A, compound **7** (1.586 g, 90 %) was obtained from pent-4-enoic acid (1 mL, 9.79 mmol) and cyclopentadiene (1.6 mL, 19.6 mmol): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=6.56$–6.48 (br, 1H), 6.36–6.29 (br, 1H), 5.84–5.72 (m, 1H), 5.32–5.22 (m, 2H), 4.99 (d, $J=17.6$ Hz, 1H), 4.94 (d, $J=10.0$ Hz, 1H), 2.41–2.25 (m, 4H), 1.98–1.90 (br, 1H), 1.81 ppm (app. d, $J=8.6$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=$ 176.8, 137.2, 136.4, 132.6, 115.0, 84.2, 62.0, 48.3, 34.1, 27.8 ppm; IR (neat, NaCl): $\tilde{\nu}=$ 2961, 1670, 1388, 1328, 1173, 919, 849, 734 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{20}H_{27}O_4N_2$: 359.1965 $[2M+H]^+$; found: 359.1971.

Oxazine 8: Following procedure A, compound **8** (1.94 g, 88 %) was obtained from but-3-enoic acid (1 mL, 11.77 mmol) and 1,3-cyclohexadiene (3.m mL, 37 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=6.55$ (dd, $J=8.0$, 6.4 Hz, 1H), 6.44 (dd, $J=8.0$, 6.0 Hz, 1H), 5.90–5.75 (m, 1H), 5.18 (br, 1H), 5.07–5.00 (m, 2H), 4.69 (br, 1H), 3.03 (ddt, $J=16.2$, 6.8, 1.4 Hz, 1H), 2.94 (ddd, $J=16.2$, 6.8, 1.1 Hz, 1H), 2.18–1.97 (m, 2H), 1.42 ppm (app. d, $J=8.7$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=170.5$, 133.0, 131.3, 130.8, 117.9, 71.9, 46.4, 38.2, 23.5, 21.0 ppm; IR (neat, NaCl): $\tilde{\nu}=$ 2939, 1650, 1432, 1364, 1166, 1085, 988, 923, 833, 712 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{10}H_{13}O_2NNa$: 202.0838 $[M+Na]^+$; found: 202.0847.

Oxazine 5: $NaHCO_3$ (1.55 g, 18.4 mmol) was added portionwise to hydroxylamine hydrochloride (427.7 mg, 6.15 mmol) in Et_2O (10 mL) and water (1 mL) at 0 °C. Acryloyl chloride (0.5 mL, 6.15 mmol) was added dropwise over 10 min at 0 °C and the mixture was stirred for 4 h. The heterogeneous mixture was then filtered with EtOAc. The filtrate was concentrated in vacuo to yield the crude hydroxamic acid. Methanol (10 mL) and water (2 mL) were added to the crude material, then cyclopentadiene (1 mL, 12.3 mmol) and sodium periodate (1.49 g, 7.4 mmol) were added successively at 0 °C. The reaction was stirred for 30 min at 0 °C, then 1.5 h at RT. The reaction was then quenched with aqueous saturated $NaHCO_3$ solution and extracted with EtOAc (×2). The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (20–50 % EtOAc/cyclohexane) to yield the desired NDA cycloadduct **5** (669 mg, 72 %). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=6.38$–6.12 (m, 4H), 5.50 (d, $J=10.1$ Hz, 1H), 5.28–5.10 (br, 2H), 1.85 (d, $J=8.8$ Hz, 1H), 1.70 ppm (d, $J=8.8$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=167.7$, 132.6, 128.0, 127.7, 84.3, 48.0 ppm; IR (neat, NaCl): $\tilde{\nu}=2962$, 1652, 1411, 1260, 1019, 845, 802 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{16}H_{18}O_4N_2Na$: 325.1159 $[2M+Na]^+$; found: 325.1166.

Pyridin-7-one 9c: Following procedure B, compound **9c** (682.0 mg, 75 %) was obtained from dihydrooxazine **6** (840.0 mg, 5.09 mmol), but-2-ene, and **G-II** (2×216.0 mg, 2×0.254 mmol) in toluene (100 mL). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=5.90$–5.72 (m, 3H), 5.49 (dd, $J=15.0$, 7.5 Hz, 1H), 4.74 (q, $J=8.2$ Hz, 1H), 4.52–4.45 (m, 1H), 3.19 (ddt, $J=21.5$, 5.0, 2.2 Hz, 1H), 2.98 (dt, $J=21.2$, 3.6 Hz, 1H), 2.65 (dt, $J=11.8$, 6.3 Hz, 1H), 1.80 (dd, $J=11.8$, 9.0 Hz, 1H), 1.71 ppm (d, $J=6.4$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=161.6$, 131.6, 128.5, 123.0, 122.5, 81.6, 60.3, 40.9, 33.8, 17.7 ppm; IR (neat, NaCl): $\tilde{\nu}=2925$, 1671, 1448, 1404, 1303, 966, 858, 737, 702 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{10}H_{13}O_2NNa$: 202.0844 $[M+Na]^+$; found: 202.0850.

Pyridin-7-one 9d: Following procedure C, compounds **9d** (*E*/*Z*, 10:1) and **9a** were obtained as a 1:1 mixture (33.1 mg, 52 %) from dihydrooxazine **6** (52.3 mg, 0.317 mmol), allyl acetate (0.137 mL, 1.267 mmol), and **G-II**

(2×13.4 mg, 2×0.01584 mmol) in toluene (3.2 mL). ^{1}H NMR (300 MHz, $CDCl_3$): δ=5.94–5.69 (m, 4H, *E* + 4H, *Z*), 4.83–4.69 (m, 1H, *E* + 1H, *Z*), 4.58 (d, *J*=5.4 Hz, 2H, *Z*), 4.54 (d, *J*=5.4 Hz, 2H, *E*), 4.52–4.41 (m, 1H, *E* + 1H, *Z*), 3.23–3.12 (m, 1H, E + 1H, Z), 3.02–2.92 (m, 1H, *E* +1H, *Z*), 2.79–2.67 (m, 1H, *E* + 1H, *Z*), 2.05 (s, 3H, *E*), 2.04 (s, 3H, *Z*), 1.87–1.74 ppm (m, 1H, *E* + 1H, *Z*); ^{13}C NMR (75 MHz, $CDCl_3$): δ= 170.7, 132.2, 131.1, 128.8, 127.8, 123.2, 122.3, 80.5, 63.6, 60.2, 41.5, 41.0, 33.8, 20.9 ppm; IR (neat, NaCl): $\tilde{\nu}$=2929, 1738, 1667, 1403, 1236, 1031, 971 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{12}H_{15}O_4NNa$: 260.0899 [*M*+Na]$^+$; found: 260.0895.

Pyridin-7-ones 9j and 24j: Following procedure C, compounds **9j**, **24j**, and **9a** were obtained as a 1.3:1.3:1 mixture (50.7 mg, 71%) from dihydrooxazine **6** (44.9 mg, 0.272 mmol), 3,4-dimethoxystyrene (179 mg, 1.09 mmol), and **G-II** (2×11.5 mg, 2×0.0136 mmol) in toluene (2.7 mL). IR (neat, NaCl): $\tilde{\nu}$=2925, 1685, 1515, 1265, 1140, 1024, 457 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{17}H_{19}O_4N_1Na$: 324.1206 [*M*+Na]$^+$; found: 324.1212.

*Compound **9j***: ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.94 (s, 1H), 6.91 (d, *J*= 8.2 Hz, 1H), 6.79 (d, *J*=7.6 Hz, 1H), 6.60 (d, *J*=15.8 Hz, 1H), 6.04 (dd, *J*=15.8, 8.2 Hz, 1H), 5.91–5.75 (m, 2H), 4.96 (q, *J*=8.2 Hz, 1H), 4.62–4.48 (m, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.23 (ddt, *J*=21.0, 5.0, 2.5 Hz, 1H), 3.02 (dt, *J*=21.0, 3.3 Hz, 1H), 2.75 (dt, *J*=12.0, 6.3 Hz, 1H), 1.94 ppm (dd, *J*=12.0, 8.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ= 161.9, 149.4, 149.0, 134.2, 128.9, 124.6, 123.3, 122.3, 120.4, 111.0, 108.9, 81.9, 60.5, 55.9, 41.3, 33.8 ppm.

*Compound **24j***: ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.94–6.90 (m, 2H), 6.81 (d, *J*=8.8 Hz, 1H), 6.65 (d, *J*=15.8 Hz, 1H), 6.05 (dd, *J*=15.8, 7.6 Hz, 1H), 5.91–5.73 (m, 2H), 4.91 (q, *J*=7.6 Hz, 1H), 4.63–4.51 (m, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.22 (ddt, *J*=21.5, 5.1, 2.5 Hz, 1H), 3.00 (dt, *J*= 21.5, 3.8 Hz, 1H), 2.45 (ddd, *J*=12.0, 8.2, 5.1 Hz, 1H), 2.29 ppm (dd, *J*= 12.0, 9.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=163.8, 149.5, 149.1, 134.5, 123.5, 123.2, 122.7, 120.2, 111.1, 108.9, 80.9, 59.4, 55.9, 40.9, 33.8 ppm.

Compounds 10c and 21c: Following procedure B, compounds **10c** (34.2 mg, 53%) and ROM/CM product **21c** (19.9 mg, 23%) were obtained from dihydrooxazine **5** (58.9 mg, 0.390 mmol), but-2-ene, and **H-II** (2×12.2 mg, 2×0.0195 mmol) in toluene (7.8 mL).

*Compound **10c***: ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.27 (dd, *J*=6.4, 1.9 Hz, 1H), 6.04 (dd, *J*=6.4, 1.3 Hz, 1H), 5.77 (dd, *J*=15.1, 6.3 Hz, 1H), 5.45 (ddd, *J*=15.1, 8.2, 1.3 Hz, 1H), 5.01 (td, *J*=8.2, 5.7 Hz, 1H), 4.51 (td, *J*=8.9, 1.9 Hz, 1H), 2.56 (ddd, *J*=12.6, 6.9, 5.7 Hz, 1H), 1.67 (dd, *J*= 6.3, 1.3 Hz, 3H), 1.60 ppm (dt, *J*=12.6, 8.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=177.7, 148.9, 132.1, 128.3, 126.2, 89.8, 65.0, 38.1, 17.7 ppm; IR (neat, NaCl): $\tilde{\nu}$=2919, 1723, 1447, 1208, 1033, 966, 865, 820, 796, 627 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_9H_{11}O_2NNa$: 188.0687 [*M*+Na]$^+$; found: 188.0687.

*Compound **21c***: ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.99 (dd, *J*=15.2, 6.9 Hz, 1H), 6.49 (dd, *J*=15.2, 1.9 Hz, 1H), 5.98–5.70 (m, 2H), 5.49 (dd, *J*=15.2, 7.3 Hz, 2H), 4.91 (q, *J*=7.3 Hz, 1H), 4.35–4.23 (m, 1H), 2.69–2.55 (m, 1H), 1.91 (dd, *J*=6.9, 1.9 Hz, 3H), 1.88–1.80 (m, 1H), 1.78 (d, *J*=7.3 Hz, 3H), 1.71 ppm (d, *J*=7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=166.8, 142.5, 133.1, 130.0, 127.5, 126.6, 121.0, 83.0, 58.8, 41.4, 18.2, 17.9, 17.6 ppm; IR (neat, NaCl): $\tilde{\nu}$=2918, 1666, 1446, 1410, 1377, 1354, 965, 921 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{13}H_{20}O_2N$: 22.1494 [*M*+H]$^+$; found: 222.1493.

Pyrrol-6-ones 10f and 10a: Following procedure C, compounds **10f** and **10a** were obtained as a 1.5:1 mixture (27.7 mg, 52%) from dihydrooxazine **5** (39.1 mg, 0.259 mmol), oct-1-ene (0.162 mL, 1.036 mmol), **H-II** (2× 8.1 mg, 2×0.01295 mmol) in toluene (5.2 mL).

*Compound **10f***: ^{1}H MR (300 MHz, $CDCl_3$): δ=7.27 (dd, *J*=6.3, 1.5 Hz, 1H), 6.05 (d, *J*=6.3 Hz, 1H), 5.81–5.71 (m, 1H), 5.44 (dd, *J*=15.5, 8.2 Hz, 1H), 5.03 (td, *J*=8.2, 5.7 Hz, 1H), 4.52 (td, *J*=7.6, 1.8 Hz, 1H), 2.61–2.51 (m, 1H), 2.01–1.96 (m, 2H), 1.68–1.57 (m, 1H), 1.39–1.02 (m, 8H), 0.86–0.83 ppm (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=177.7, 148.8, 137.4, 126.8, 126.3, 89.9, 65.0, 38.2, 32.2, 31.7, 28.8, 28.7, 22.6, 14.1 ppm. IR (neat, NaCl): $\tilde{\nu}$=2927, 1728, 1455, 1265, 1032, 967, 819, 797 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{15}H_{21}O_2NNa$: 236.1645 [*M*+Na]$^+$; found: 236.1641.

*Compound **10a***: ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.29 (dd, *J*=6.1, 1.8 Hz, 1H), 6.06 (dd, *J*=6.1, 1.1 Hz, 1H), 5.85 (ddd, *J*=17.3, 10.2, 7.2 Hz, 1H), 5.33 (d, *J*=17.3 Hz, 1H), 5.22 (d, *J*=10.2 Hz, 1H), 5.05 (q, *J*=7.2 Hz, 1H), 4.55 (td, *J*=8.2, 1.1 Hz, 1H), 2.67–2.56 (m, 1H), 1.77–1.67 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=177.9, 149.0, 135.4, 126.4, 119.4, 89.6, 64.7, 37.5 ppm; IR (neat, NaCl): $\tilde{\nu}$=2924, 1722, 1428, 1262, 1036, 988, 818, 795 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{16}H_{18}O_4N_2Na$: 325.1159 [2*M*+Na]$^+$; found: 325.1163.

Compound 11c: Following procedure B, compounds **11c** (7.1 mg, 15%), **9c** (6.5 mg, 15%), and ROM/CM product **22c** (25.0 mg, 42%) were obtained from dihydrooxazine **7** (42.8 mg, 0.239 mmol), but-2-ene, and **G-II** (2×10.1 mg, 2×0.0119 mmol) in toluene (4.8 mL).

*Compound **11c***: ^{1}H NMR (300 MHz, $CDCl_3$): δ=5.87 (dd, *J*=15.4, 6.4 Hz, 1H), 5.86–5.78 (m, 1H), 5.61 (dd, *J*=11.8, 1.8 Hz, 1H), 5.49–5.42 (m, 1H), 4.93–4.85 (m, 1H), 4.59–4.52 (m, 1H), 2.75–2.65 (m, 2H), 2.55–2.26 (m, 3H), 2.05 (dd, *J*=21.8, 10.0 Hz, 1H), 1.71 ppm (d, *J*=6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=165.9, 133.2, 131.0, 126.0, 125.9, 79.6, 56.2, 42.9, 32.9, 24.3, 17.9 ppm; IR (neat, NaCl): $\tilde{\nu}$=2930, 1660, 1446, 1142, 1026, 966 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{11}H_{16}O_2N$: 194.1181 [*M*+H]$^+$; found: 194.1177.

*Compound **22c***: ^{1}H NMR (300 MHz, $CDCl_3$): δ=5.86 (dd, *J*=15.2, 6.4 Hz, 1H), 5.71 (ddd, *J*=15.2, 6.4, 0.8 Hz, 1H), 5.61–5.39 (m, 4H), 4.80 (q, *J*=7.2 Hz, 1H), 4.27–4.19 (m, 1H), 2.61–2.28 (m, 5H), 1.84 (ddd, *J*= 12.4, 10.2, 7.2 Hz, 1H), 1.74 (dd, *J*=6.4, 1.5 Hz, 3H), 1.68 (d, *J*=6.4 Hz, 3H), 1.63 ppm (dd, *J*=3.8, 0.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ= 173.7, 133.1, 130.0, 129.9, 127.5, 126.5, 125.7, 82.7, 58.6, 41.7, 32.8, 27.5, 18.0, 17.9, 17.6 ppm; IR (neat, NaCl): $\tilde{\nu}$=2919, 1667, 1447, 1379, 964 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{15}H_{24}O_2N$: 250.1807 [*M*+H]$^+$; found: 250.1802.

Pyridin-8-ones 12c and 29c: Following procedure B, compounds **12c** and **29c** were obtained as a 3:1 mixture (41.0 mg, 69%) from dihydrooxazine **8** (55.2 mg, 0.308 mmol), but-2-ene, and **G-II** (2×13.0 mg, 2× 0.0154 mmol) in toluene (6.1 mL).

*Compound **12c***: ^{1}H NMR (300 MHz, $CDCl_3$): δ=5.76–5.71 (m, 2H), 5.65–5.92 (m, 1H), 5.54–5.47 (m, 1H), 4.74–4.66 (m, 1H), 4.34–4.22 (m, 1H), 3.08–3.02 (m, 2H), 2.22–2.08 (m, 1H), 1.88–1.64 ppm (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=162.7, 129.7, 127.5, 125.0, 121.2, 79.3, 59.2, 33.3, 27.8, 26.8, 18.2 ppm; HRMS (ESI): *m*/*z* calcd for $C_{11}H_{15}O_2NNa$: 216.1000 [*M*+Na]$^+$; found: 216.0997.

*Compound **29c***: ^{1}H NMR (300 MHz, $CDCl_3$): δ=5.77–5.38 (m, 4H), 4.34–4.24 (m, 1H), 4.24–4.16 (m, 1H), 3.12–3.08 (m, 2H), 2.66–2.49 (m, 1H), 2.39–2.29 (m, 1H), 2.10–1.98 (m, 1H), 1.82–1.68 (m, 3H), 1.66 ppm (d, *J*=6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=168.5, 128.4, 126.6, 125.1, 121.3, 79.5, 59.2, 33.4, 33.0, 26.5, 25.7, 18.1 ppm; HRMS (ESI): *m*/*z* calcd for $C_{12}H_{17}O_2NNa$: 230.1157 [*M*+Na]$^+$; found: 230.1151.

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