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Olefin Metathesis of Amine-Containing Systems: Beyond the Current Consensus

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Abstract: Olefin metathesis is one of the most powerful synthetic tool to access amine-containing heterocycles and alkaloids. A major drawback associated with the use of amines concerns their ability to coordinate to metal-alkylidene complexes and to interfere unproductively with catalytic activity. Based on literature precedents, it has been established as a "dogma" that efficient metathesis reactions are suppressed in the presence of basic amines and that such substrates must invariably be deactivated by conversion of the amines to the corresponding carbamates or ammonium salts. However, an increasing number of examples of amine-containing compounds that are good substrates for metathesis is being reported in the literature. How can this "non-classical" reactivity be rationalized and exploited? The purpose of this review is to provide an overview of successful metathesis reactions performed with amine-containing compounds in order to allow some guidelines to be formulated. A special emphasis is placed on the different parameters that may influence the outcome of the reaction such as steric effects, amine basicity, and the nature of the catalyst.

Keywords: amines; metathesis; natural products; nitrogen heterocycles; synthetic methods

1 Introduction

Over the last decade, olefin metathesis has become a major element in the synthetic chemist's toolbox.[1–3] The advantages and opportunities offered by this catalytic carbon-carbon bond forming reaction are indeed numerous. High levels of chemo-, regio-, and stereoselectivity may be attained. The olefin substrates are generally easier to prepare and more stable than those, such as aldehydes, halides or triflates, used in other C–C bond forming processes. In addition, the olefinic products obtained offer many synthetic opportunities for further structural elaboration including, for example, dihydroxylation, epoxidation, halogenation and cycloaddition. As a consequence, the olefin metathesis reaction has had a profound impact on the way organic chemists approach synthesis and has opened up unprecedented synthetic possibilities.[4] Ring-closing metathesis (RCM) is finding an exponential number of applications for the synthesis of various heterocycles in the fields of natural products, medicinal chemistry or material science.[5–7] This process has been particularly useful for the construction of nitrogen-containing compounds.[7–9] Not surprisingly, most applications have been reported for the synthesis of functionalized pyrrolidines and piperidines which constitute major classes of biologically active molecules.[10] These heterocycles are found in many alkaloid natural products, glycomimetics (iminosugars)[11] and drug candidates. It has been reported that during a recent 10-year period there were over 12,000 piperidine compounds mentioned in clinical and preclinical studies.[12] Despite its effectiveness, the major issue with the use of the metathesis reaction for the synthesis of amine-containing systems is linked to the structure of the target itself and the presence of basic amino groups that may interfere unproductively with catalytic activity in several ways. Based on many reports, it has been indeed established as a "dogma" that unsaturated amines are poor sub-

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strates for the metathesis reaction. Consequently, strategies have been developed to prevent coordination of the electron pair on the nitrogen atom with metal-alkylidene complexes. The most obvious and efficient one is based on suitable protection of the amino group by conversion into a carbamate, sulfonamide or amide function.[7–9] However, this approach may add protection group manipulations and reduce the efficiency of the whole synthetic sequence. Formation of unproductive metallacycle intermediates by chelation of metal complexes by the carbonyl oxygen of the protected amines may also occur.[13] Other strategies consist in deactivating the substrate by protonation of the amine. The metathesis reaction was carried out on the corresponding ammonium salt[14–24] or with the free amine in the presence of *p*-toluenesulfonic or camphorsulfonic acid.[25–27] These approaches may be incompatible with acid-sensitive substrates and are not always successful.[28,29] Very recently, Xiao and Yu disclosed that RCM of diallylamines using a ruthenium-based catalyst could be performed in the presence of 20 mol% of $Ti(O\text{-}i\text{-}Pr)_4$.[29–32] It is of course too soon to evaluate the benefit of this method but first applications appear to give contrasting results.[33] The nature of the catalyst seems to play an important role when the reaction is performed with tertiary amines. Although molybdenum catalysts, such as **1**, are more sensitive to atmospheric oxygen and moisture than ruthenium catalysts **2** and **3**, they do better tolerate substrates containing tertiary amino group[8,34] (Figure 1). This result may be explained by the relatively crowded pseudo-tetrahedral coordination sphere of molybdenum metal centre.[34]

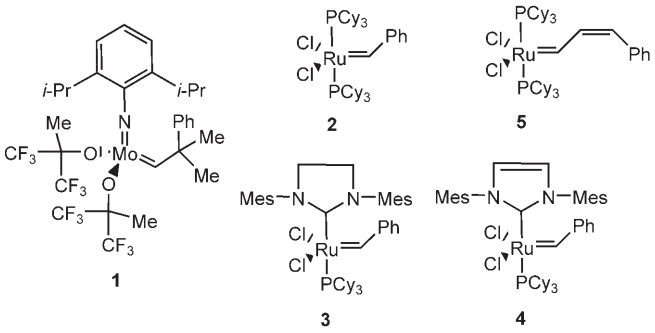


Figure 1.

Based on literature precedents and on the efforts devoted to prevent coordination to the catalyst, can we conclude that amines are not suitable for metathesis? The answer is not obvious considering the increasing number of examples of amine-containing compounds that are good substrates for metathesis. What are the structural and electronic factors that may explain this "non-classical" reactivity? The purpose of this review is to provide an overview of successful metathesis reactions performed with amine-containing compounds in order to allow some guidelines to be formulated. A special emphasis is placed on the different parameters that may influence the outcome of the reaction such as steric effects, amine basicity, and the nature of the catalyst.

2 Ruthenium-Catalyzed Metathesis of Hindered Amines

The majority of examples of amine-containing compounds that are good substrates for metathesis concern RCM of hindered tertiary amines. This is a consequence of the fact that steric hindrance in aminodiene derivatives probably prevents coordination of the amino group to the catalyst's metal centre. Some examples of ruthenium-catalyzed RCM of crowded secondary amines have even been reported in the literature.

2.1 Acyclic Amines

Access to iminosugars of biological interest[11] has been recently developed by way of RCM of aldose-

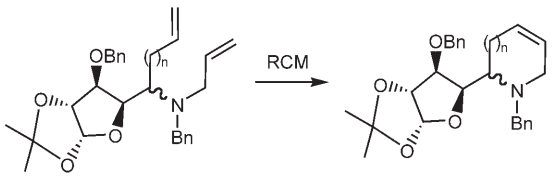
derived dienes (Scheme 1, Scheme 2, Scheme 3). The nature of the hydroxy protecting groups in amino diols **6** was found to affect significantly the yield of the key RCM step.[35] Isopropylidenes **6a** and **6c** provided the expected pyrrolidines more efficiently than the corresponding di-*O*-benzyl derivatives (Scheme 1). The more active second generation Grubbs' catalyst **3** was found to be superior than the classical catalyst **2** in forming the azacycle. Remarkably, similar yields were obtained for the RCM of amines **6a** and **b** and the RCM of the corresponding amides **6c** and **d**. These results suggest that steric hindrance is sufficient to prevent coordination of the amino group's electron pair on the ruthenium catalyst.

Substrate	R^1	R^2	X	Reaction conditions	Product	Yield
6a	$C(CH_3)_2$		H,H	8 mol % **2**, CH_2Cl_2, r.t.	**7a**	85%
6a	$C(CH_3)_2$		H,H	5 mol % **3**, CH_2Cl_2 Δ	**7a**	97%
6b	Bn	Bn	H,H	8 mol % **2**, CH_2Cl_2, r.t.	**7b**	60%
6c	$C(CH_3)_2$		O	8 mol % **2**, CH_2Cl_2, Δ	**7c**	85%
6c	$C(CH_3)_2$		O	5 mol % **3**, CH_2Cl_2, Δ	**7c**	98%
6d	Bn	Bn	O	8 mol % **2**, CH_2Cl_2, r.t.	**7d**	50%
6d	Bn	Bn	O	5 mol % **3**, CH_2Cl_2, r.t.	**7d**	85%

Scheme 1.

Substrate	n	R	Reaction conditions	Product	Yield
8a	1	H	8 mol % **3**, toluene, 70 °C	**9a**	50%
8a	1	H	8 mol % **2**, CH_2Cl_2 Δ	**9a**	70%
8b	2	H	8 mol % **3**, toluene, 70 °C	**9b**	66%
8c	2	$C(CH_3)_2$	5 – 10 mol % **3** or **2**, CH_2Cl_2	**9c**	–
8c	2	$C(CH_3)_2$	8 mol % **3**, toluene, 70 °C	**9c**	72%

Scheme 2.



Substrate	n	Reaction conditions	Product	Yield
10	0	10 mol % **2**, CH_2Cl_2, r.t.	**12**	82 – 84%
11	1	5 mol % **2**, C_6H_6, Δ	**13**	81%

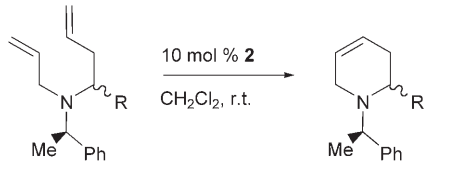
Scheme 3.

A similar example was reported by Genisson et al. from amino triols **8** (Scheme 2).[36] Good results were obtained with substrates bearing three non-protected hydroxy groups such as **8a** and **b**. The greater reactivity of second generation Grubbs' catalyst **3** was in this case detrimental to the yield of the RCM reaction since compound **9a** was obtained in moderate yield accompanied by oligomeric products. Experimental conditions were found to play a key role in the RCM of partially protected triol **8c**. When the reaction was performed in toluene at 70 °C, compounds **9c** was obtained in 72 % yield, whereas no cyclized product was obtained after treatment with Grubbs I or Grubbs II catalyst in refluxing CH_2Cl_2.

An efficient access to quinolizidine and indolizidine alkaloids has been recently developed by Dhavale et al. by way of RCM of D-glucose derived aminodienes **10** and **11** (Scheme 3).[37]

RCM reactions of more crowded amines bearing an *N*-α-methylbenzyl, an *N*-diphenylmethyl or an *N*-triphenylmethyl (trityl) protecting group are depicted in Scheme 4, Scheme 5, Scheme 6, Scheme 7, Scheme 8 and Scheme 9.[38–42] Comparisons of yields obtained under similar conditions from dienes **14**, **16** and **18** indicated clearly that the efficiency of the RCM increases with the steric hindrance around the amino group (see also Scheme 30).

Reactions with secondary amines could even been performed in moderate yields using an *N*-α-methylbenzyl group[41] and in good yields using the bulky triphenylmethyl protecting group[42] (Scheme 7 and



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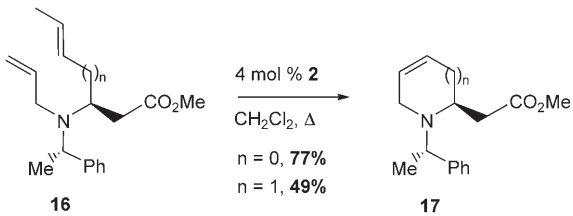
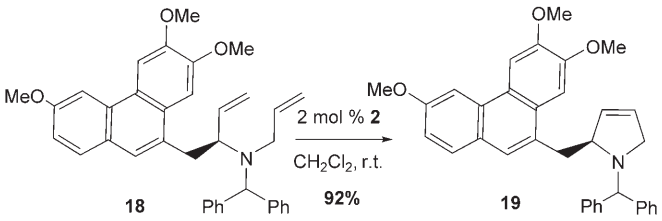
Scheme 4.

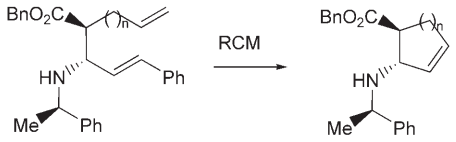


16 **17**

Scheme 5.

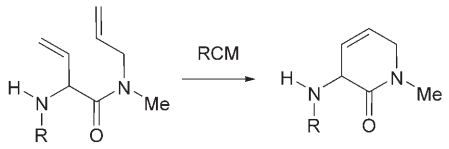


Scheme 6.



Substrate	n	Reaction conditions	Product	Yield
20	1	15 mol % **2**, toluene, 55 °C	**22**	56%
21	2	20 mol % **2**, toluene, 55 °C	**23**	46%

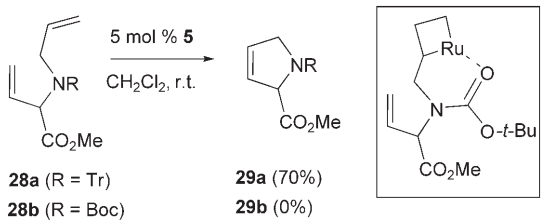
Scheme 7.



Substrate	R	Reaction conditions	Product	Yield
24	Boc	5 mol % **5**, benzene, Δ	**26**	41% (-)[a]
25a	Bn	5 mol % **5**, benzene, Δ	**27a**	0% (58%)[a]
25a	Bn	5 mol % **5**, TFA, benzene, Δ	**27a**	45% (23%)[a]
25b	Tr	5 mol % **5**, benzene, Δ	**27b**	65% (-)[a]
25b	Tr	5 mol % **5**, CH_2Cl_2, Δ	**27b**	67% (15%)[a]

[a] Yield of recovered starting material after purification.

Scheme 8.

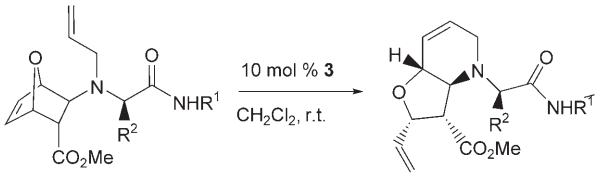


Scheme 9.

Scheme 8). Protonation of *N*-benzylamine **25a** was found to be less efficient than the use of the corresponding *N*-trityl derivative **25b** under neutral conditions (Scheme 8). These results constitute a rare example of secondary amines that are good substrates for metathesis reactions (see also Schemes 40, 41, 44 and 48). As will be shown in Section 3, the presence of an adjacent amide electron-withdrawing group in **24–25** may also favour the RCM by decreasing the electron density at the nitrogen atom.

RCM of α-amino esters **28** further highlights advantages of *N*-trityl derivatives.[42] Cyclized compound **29a** was obtained in 70% yield from *N*-trityl aminodiene **28a** whereas its *N*-Boc-protected analogue **28b** did not undergo any RCM reaction (Scheme 9). This result may be explained by a coordination of the carbamate carbonyl oxygen to the ruthenium complex formed in the first step of the metathesis, leading to an unreactive six-membered chelate ring.

In 2006, Guanti et al. reported a diversity-oriented synthesis of polycyclic scaffolds by way of ring-opening metathesis (ROM)/RCM of 7-oxabicyclo-[2.2.1]heptene derivatives (Scheme 10).[43] A dramatic



Substrate	R^1	R^2	Product	Yield
30a	*t*-Bu	*i*-Bu	**31a**	61%
30b	*t*-Bu	4-NO_2-C_6H_4	**31b**	71%
30c	Bn	*i*-Bu	**31c**	88%
30d	cyclohexyl	*i*-Pr	**31d**	87%
30e	*t*-Bu	4-Cl-C_6H_4	**31e**	95%

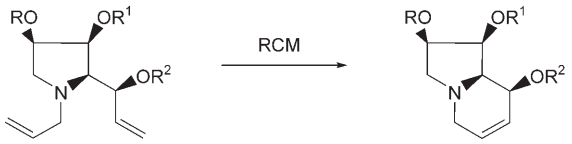
Scheme 10.

difference of reactivity was observed between ruthenium catalysts **2** and **3**. The use of the first generation Grubbs' catalyst resulted in very poor yields of the desired products **31**. Similar results were obtained when the reaction is performed with (substrates **30c–e**) or without ethylene (substrates **30a** and **b**).

2.2 Endocyclic Amines

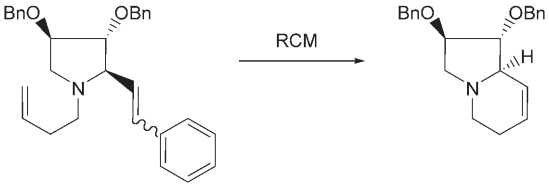
2.2.1 α-Substituted Azacycles

The construction of the indolizidine skeleton was efficiently performed by an RCM reaction on *N*-allyl- or *N*-homoallylpyrrolidines **32** and **34** (Scheme 11 and Scheme 12). The second generation Grubbs' catalyst **3** was found to promote better results than **2**.[44–46] The nature of the hydroxy protecting groups plays also an important role in the outcome of the reaction probably by decreasing pyrrolidine ring flexibility (isopropylidene group) or by increasing steric hindrance (TBS group).



Substrate	R	R^1	R^2	Reaction conditions	Product	Yield
32a	Bn	Ac	Ac	10 mol % **2**, CH_2Cl_2, r.t.	**33a**	82%
32b	$C(CH_3)_2$	TBS		**2** cat., CH_2Cl_2	**33b**	–
32b	$C(CH_3)_2$	TBS		20 mol % **3**, CH_2Cl_2, Δ	**33b**	70%

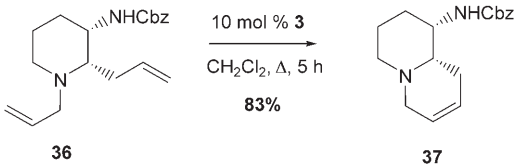
Scheme 11.



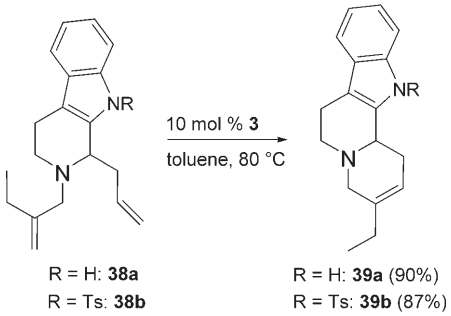
Substrate	Reaction conditions	Product	Yield
34	**2** cat., CH_2Cl_2, Δ	**35**	10%
34	**3** cat., CH_2Cl_2, Δ	**35**	56%
34	10 mol % **3**, toluene, 70 °C	**35**	86%

Scheme 12.

RCM of 2-allyl-*N*-alkenylpiperidines **36** and **38** afforded the quinolizidine skeleton of two natural products, epiquinamide and mitralactonine, in good yields (Scheme 13 and Scheme 14).[47,48] No protection of the indole nitrogen atom was required to prevent coordination to the ruthenium catalyst since the heteroatomic lone pair is involved in maintaining the indole aromaticity (Scheme 14).

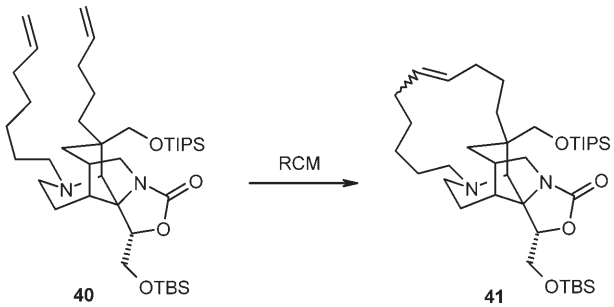


Scheme 13.



Scheme 14.

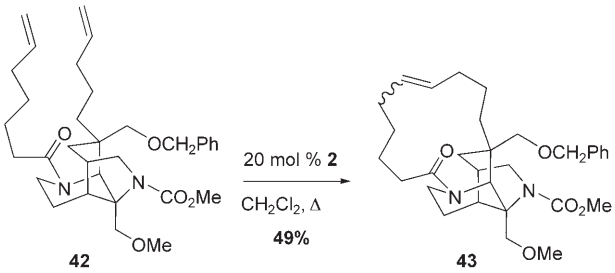
In 2005, Overman et al. used an efficient reductive amination/RCM sequence to install the saturated macrocycle of sarain A, a natural product isolated from the sponge *Reniera sarai*.[49a] Closure of the macrocylic ring catalyzed by **3** afforded the desired 13-membered ring macrocycle **41** in only 17% yield. The major products obtained in 61% combined yield incorporated two units of the starting material **40**. To minimize secondary metathesis reactions that were supposed to convert the 13-membered product **41** to 26-membered ring macrocyclic dimers, the authors successfully employed the less active first generation Grubbs's catalyst **2** to afford **41** in 80% yield (Scheme 15). Interestingly, a much lower yield was observed for the formation of the related lactam **43** (Scheme 16).[49b] This result may be due to subtle structural effects related to the introduction of an amide function that likely decreases the flexibility of the RCM substrate.



40 41

Reaction conditions	Product	Yields
15 mol% **3**, CH_2Cl_2, Δ	**41**	17%
5 mol% **2**, CH_2Cl_2, Δ	**41**	80%

Scheme 15.



42 43

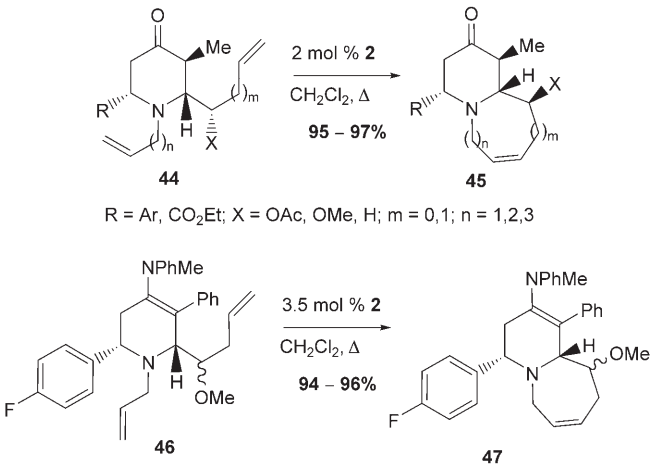
Scheme 16.

2.2.2 α,α′-Disubstituted Azacycles

Endocyclic amines of 2,6-disubstituted piperidines and 2,5-disubstituted pyrrolidines are known to be

particularly crowded. As a consequence, difficulties in functionalizing such amines have been reported in the literature.[27d,50] In addition, yields reported in this section are generally higher than the ones observed for RCM of the corresponding less hindered 2-substituted pyrrolidines or piperidines.

Various azabicycloalkane derivatives were obtained in nearly quantitative yields by way of RCM of dienes **44** (Scheme 17).[51] Both isomers of unsaturated



Scheme 17.

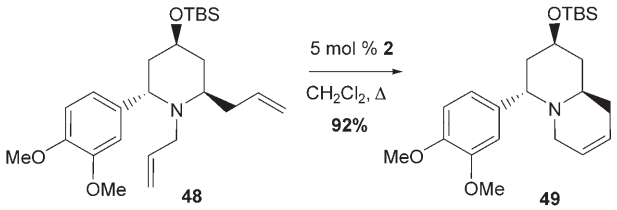
amines **46** reacted also successfully with first generation Grubb's catalyst **2** to provide the desired RCM products **47**. Following a similar approach, Davis et al. prepared trisubstituted indolizidine derivatives of biological interest.[52]

Access to quinolizidines derivatives were performed from 2-allyl-6-substituted *N*-allylpiperidines **48** and **50** (Scheme 18).[53,54] The less sterically hindered piperidine **50** required the use of the more active catalyst **4** to undergo RCM.[53] Following a similar approach, indolizidine **53** was obtained in good yield from *N*-allylpyrrolidine **52** (Scheme 19).[55]

RCM construction of the alkaloid (−)-205B ring system was performed in high yields from indolizidines **54** (Scheme 20).[56] The polycyclic skeleton of another complex alkaloid, (−)-tuberostemonine, was efficiently obtained by way of RCM of **56** in the presence of 5 mol% of catalyst **3** (Scheme 21).[27c]

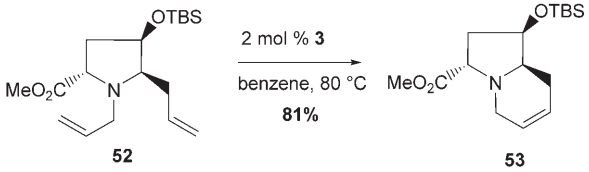
2.2.3 Neopentylic Endocyclic Amines

Dienes and dienynes containing a neopentylic amino group have been found to be good substrates for RCM reactions. In this type of structure, steric hindrance around the nitrogen atom is exacerbated by the neopentylic character of the amine. Clark and Middelton have recently developed a new strategy for

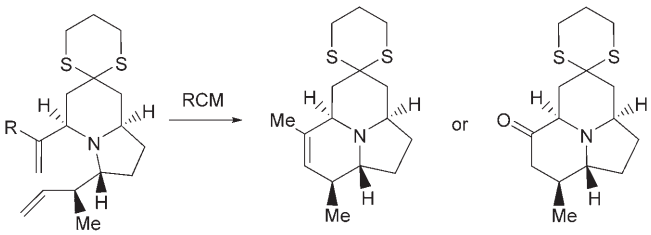


Reaction conditions	Product	Yields
2 cat., CH_2Cl_2, Δ	**51**	trace
1 mol % **4**, toluene, 80 °C	**51**	77%

Scheme 18.

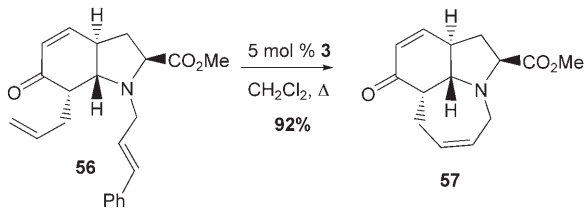


Scheme 19.



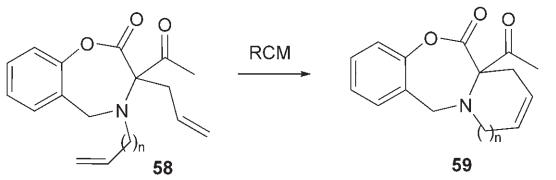
Substrate	Reaction conditions	Product	Yields
54a	5 mol % **3**, CH_2Cl_2, Δ	**55a**	99%
54b	10 mol % **3**, benzene, 65 °C	**55b**	81%

Scheme 20.



Scheme 21.

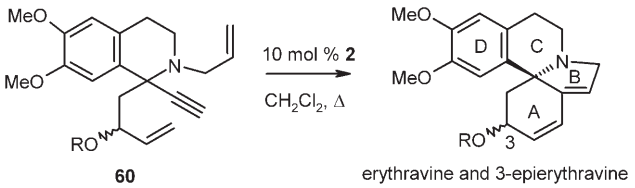
the synthesis of protected cyclic amino acids by RCM of dienes **58**.[57] Better yields were obtained with the more reactive catalyst **3** than with the first generation Grubbs' catalyst **2** (Scheme 22).



Substrate	*n*	Reaction conditions	Product	Yields
58a	1	10 mol % **2**, CH_2Cl_2, r.t.	**59a**	92%
58b	2	10 mol % **2**, CH_2Cl_2, r.t.	**59b**	74%
58b	2	10 mol % **3**, toluene, 80 °C	**59b**	87%
58c	3	10 mol % **2**, CH_2Cl_2, r.t.	**59c**	57%
58c	3	10 mol % **3**, toluene, 80 °C	**59c**	83%

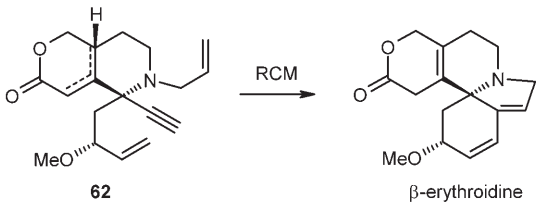
Scheme 22.

The group of Hatakeyama has achieved the total synthesis of two *Erythrina* alkaloids, erythravine[58] and β-erythroidine[59] (Scheme 23 and Scheme 24). This family of compounds is classified in two groups according to the D ring structure which can be aromatic or an unsaturated lactone. The efficient construction of the erythrinan skeleton relied on tandem RCM of dienyne precursors which provided the expected A,B,C ring system. Results obtained with RCM precursors **60**, **62**, **64**, **66**, **68** and **71** reveal that the mode of metathesis depends on the structure of the substrates and that subtle structural changes may significantly affect the yield and the outcome of the reaction (Scheme 23, Scheme 24, Scheme 25, Scheme 26 and Scheme 27). A striking example is shown in Scheme 26, in which compound **68a** and its epimer display a strong difference of reactivity.



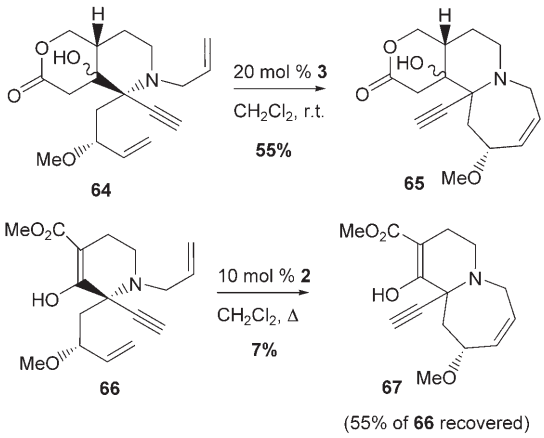
R	Product	Yield
H	**61a**	–
Ac	**61b**	78%
TES	**61c**	63%

Scheme 23.

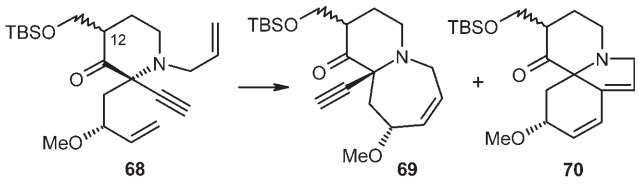


Reaction conditions	Product	Yield
10 mol % **2**, CH_2Cl_2, r.t.	**63**	42%
10 mol % **3**, CH_2Cl_2, r.t.	**63**	< 30%

Scheme 24.

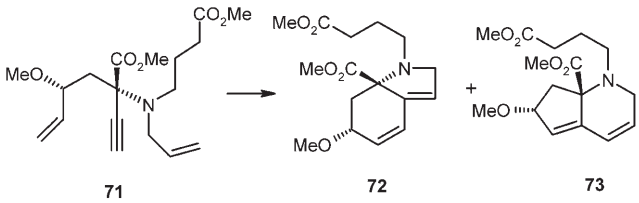


Scheme 25.



68	Reaction conditions	Yield 69	70	68
68a (12*S*)	20 mol % **2**, CH_2Cl_2, Δ	27%	–	9%
68b (12*R*)	20 mol % **3**, CH_2Cl_2, r.t.	–	66%	–

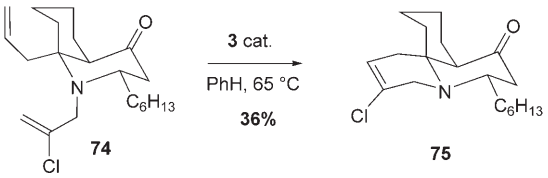
Scheme 26.



Reaction conditions	Yield 72	73
10 mol % **2**, CH_2Cl_2, Δ	27%	–
10 mol % **3**, CH_2Cl_2, Δ	57%	15%

Scheme 27.

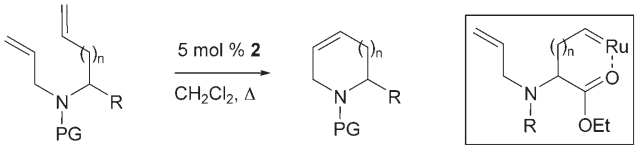
Construction of tricyclic pyridoquinoline framework of cylindricines B and J has been performed using vinyl chloride RCM methodology recently developed by the group of Weinreb.[60] The neopentylic endocylic amine of 2-phenyl-4-piperidone **74** is in this case particularly hindered. Exposure of this diene to second generation Grubbs' catalyst **3** afforded the expected RCM product **75** in 36% unoptimized yield (Scheme 28).



Scheme 28.

3 Ruthenium-Catalyzed Metathesis of Amines α-Substituted by an Electron-Withdrawing Group

Various examples of protected α-amino acids and analogues that are substrates of RCM have been reported in the literature. The poisoning or deactivation of the ruthenium catalyst by the amino group is probably avoided by the presence of the electron withdrawing group which decreases the electron density on the nitrogen atom. Sterically crowded amines of this type have been presented in Section 2 (Schemes 8–10, 17-19, 21-22, 26 and 27). In this section, we will focus on unhindered derivatives to better study the influence of the electron-withdrawing group. It is noteworthy that this effect is not always sufficient to achieve efficient metathesis reactions (see Scheme 8, Scheme 29 and Scheme 34).

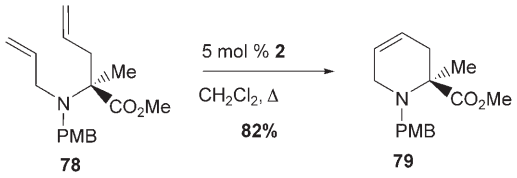


Substrate	n	PG	R	Product	Yield
76a	1	H	CO_2Et	**77a**	–
76b	1	PMB	CO_2Et	**77b**	54%
76c	1	Bn	CF_3	**77c**	95%[a]
76d	1	Cbz	CF_3	**77d**	98%[a]
76e	1	CH_2Fer	CO_2Et	**77e**	18%
76f	1	Boc	CO_2Et	**77f**	93%
76g	2	PMB	CO_2Et	**77g**	94%
76h	2	CH_2Fer	CO_2Et	**77h**	87%

[a] Reaction performed at room temperature.
Fer = Ferrocenyl.

Scheme 29.

Trifluoromethylamine- and amino acid-derived dienes have been found to be useful starting materials in RCM reactions to give six- and seven-membered rings (Scheme 29 and Scheme 30).[61] This process was

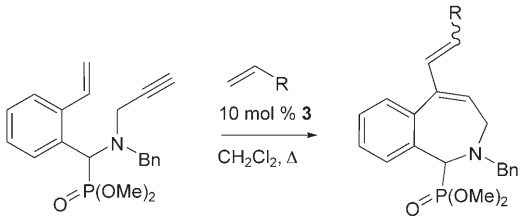


Scheme 30.

particularly efficient for the formation of piperidines substituted by a strong electron-withdrawing group (CF_3).[61b] When $R = CO_2Et$, lower yields observed for $n = 1$ may be due to the formation of a six-membered chelate ring that suppress catalytic turnover. Formation of an analogous seven-membered metallacycle ($n = 2$) is indeed believed to be less favoured (Scheme 29). Comparison of yields obtained with α-amino ester **76b** and the corresponding α-methyl analogue **78** nicely highlights the decisive influence of increasing steric bulk around the RCM substrate nitrogen atom (Scheme 29 and Scheme 30).[61a]

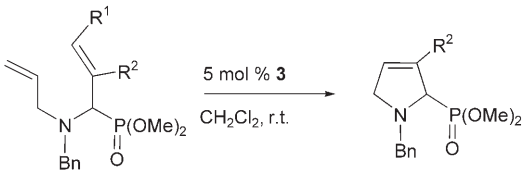
A short approach towards phosphonylated benzazepines has been recently developed by the group of Stevens by way of a domino enyne metathesis-cross metathesis sequence between *N*-benzyl α-amino phosphonate **80** and various olefins (Scheme 31).[62] This study is a rare example of cross-metathesis performed with amine-containing substrates (see also Scheme 40).

Phosphonopyrrolines **83** could be obtained from *N*-benzylaminoalkenyl phosphonates **82** in reasonable to good yields by treatment with 5 mol% of catalyst **3** (Scheme 32).[63] An enyne-metathesis approach from dienyne analogues of compounds **82** has been also reported by the same group.[63b]



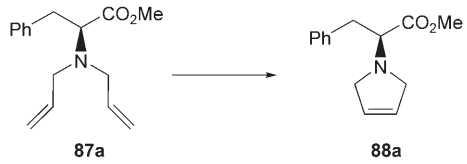
Substrate	R	Product	Yield	*E*/*Z*
80	Ph	**81a**	78%	100/0
80	CH_2SiMe_3	**81b**	74%	66/34
80	$(CH_2)_2COMe$	**81c**	68%	67/33

Scheme 31.



Substrate	R^1	R^2	Product	Yield
82a	Ph	H	**83a**	44%
82b	Ph	Me	**83b**	58%
82c	Me	Bn	**83c**	62%
82d	Ph	isoamyl	**83d**	70%
82e	Me	Ph	**83e**	54%

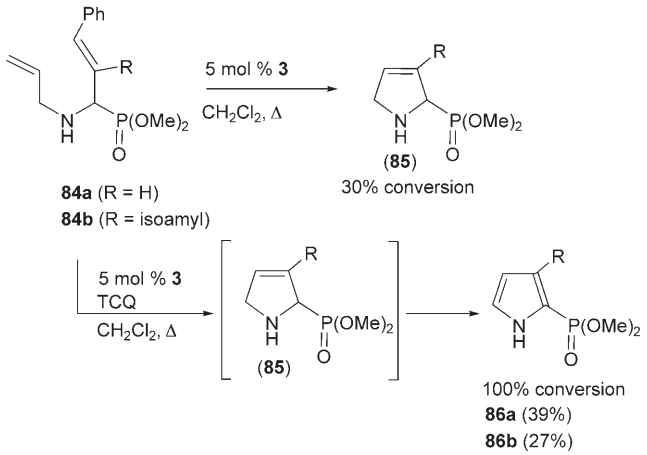
Scheme 32.



Reaction conditions	Lewis Acid	Yield
5 mol % **2**, CH_2Cl_2, Δ	–	0%
5 mol % **3**, CH_2Cl_2, Δ	–	24%
5 mol % **4**, CH_2Cl_2, Δ	=	17%
5 mol % **3**, DCE, Δ	–	27%
5 mol % **3**, toluene, Δ	–	19%
5 mol % **3**, CH_2Cl_2, Δ	20 mol % Ti(O-*i*-Pr)$_4$	93%

Scheme 34.

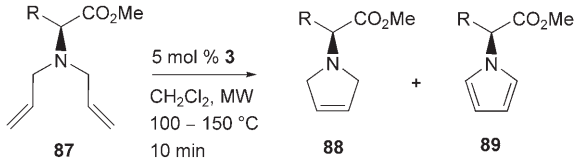
Ring closing of phosphonates **84** bearing a free secondary amine were studied under various conditions and were found to be much less efficient (Scheme 33).[63] A maximum conversion of 30% was reached in the RCM of dienes **84**. Experimental kinetic data suggested catalyst inhibition by the RCM product **85** rather than by the starting material. A similar reaction in the presence of tetrachloroquinone (TCQ) afforded pyrroles **86** which resulted from the oxidation of the pyrroline intermediates.



Scheme 33.

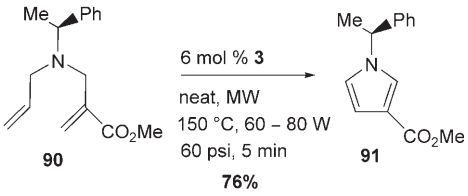
A systematic study has been recently performed by Xiao and Yu to identified optimized experimental conditions for the RCM of diallylamines (Scheme 34). This work has led to the discovery that metathesis of amine-containing substrates could be performed in the presence of substoichiometric amount of Lewis acid.[29] Results presented in Scheme 34 indicated that cyclized product **88a** may nevertheless be obtained in 17–27% yield in the absence of Lewis acid by treatment with a reactive ruthenium catalyst such as **3** or **4**. It would be interesting to explore the same reaction with the allylamine analogue of **87** bearing one or two stronger electron-withdrawing groups such as CF_3 or a ketone with the hope of increasing RCM yields.

The same group has established an efficient method for the RCM of diallylamines **87** using microwave activation. Under these conditions, pyrrole derivatives **89** were generally obtained as the major product along with pyrrolines **88** (Scheme 35). One of the interests of this process is that it can be carried out without deactivation of the amino-group or without using Lewis acid.[64] The decisive influence of microwave activation is nicely highlighted by the result obtained with compound **87a** under classical thermal conditions (24% yield, Scheme 34) and the one obtained under microwave activation (97% yield, Scheme 35). Pyrrole formation using RCM under microwave irradiation has also been reported from hindered *N*-α-methylbenzyl diallylamines **90** (Scheme 36).[65]



Substrate	R	Yield 88	Yield 89
87a	Bn	40%	57%
87b	Me	10%	75%
87c	CH_2CO_2Me	75%	16%
87d	*i*-Bu	35%	53%
87e	3-indolyl	39%	54%

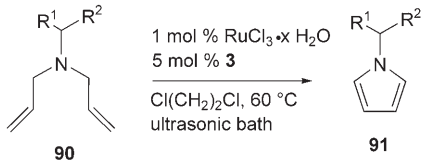
Scheme 35.



90 91

Scheme 36.

The group of Stevens has reported a straightforward pyrrole synthesis from diallylamines by way of a tandem RCM/dehydrogenation reaction using a combination of Grubbs' catalyst **3** and $RuCl_3$ (Scheme 37).[66] The ultrasonic bath is expected to favour the formation of a fine dispersion of $RuCl_3 \cdot x\,H_2O$ in the reaction mixture, thus greatly increasing its active surface, and consequently the efficiency of the dehydrogenation step.



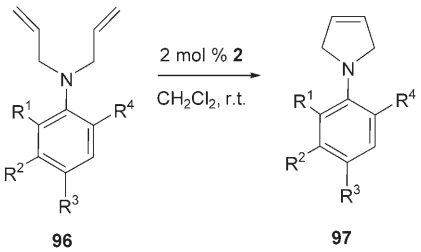
90 91

Substrate	R^1	R^2	Product	Yield
90a	CO_2Me	H	**91a**	63%
90b	CO_2Et	Me	**91b**	57%
90c	$P(O)(OEt)_2$	H	**91c**	60%
90d	CN	H	**91d**	0%
90e	CH_2CN	H	**91e**	30%
90f	Ph	H	**91f**	55%

Scheme 37.

4 Ruthenium-Catalyzed Metathesis of Phenylamines and Analogues

Not surprisingly, phenylamines and analogues which are in general weakly basic have been found to be good substrates of RCM. The decrease of the electron density on nitrogen is due, *inter alia*, to the fact that the nitrogen lone pair is partially conjugated into the benzene ring. Electron-withdrawing groups on the aromatic ring are thus expected to further decrease the availability of the lone pair and consequently to improve the efficiency of the metathesis process. Conversely, electron-donating groups should lead to lower yields. This effect was demonstrated by the study performed by Grigg et al. on RCM of *N,N*-diallylaniline derivatives.[67] For example, low conversion was observed for RCM of 2,4-dimethoxyaniline derivative **96c** whereas the corresponding 2,4-dibromoaniline **96b** provided the expected cyclized product **97b** almost quantitatively (Scheme 38). Access to *N*-phenylpiperidines such as **99** was also described by the same group (Scheme 39). RCM of aniline analogues of **90** was enabled through microwave irradiation and provided carboxymethyl-substituted dihydropyrroles.[65] *N,N*-Diallylaniline derivatives have also been shown to be substrates for the synthesis of various pyrroles using microwave or ultrasound activation.[64,66]

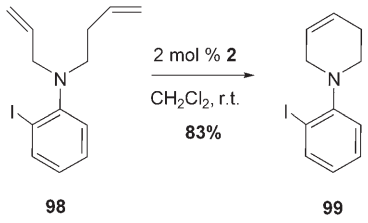


96 97

Substrate	R^1	R^2	R^3	R^4	Product	Yield
96a	Et	H	H	H	**97a**	44%[a]
96b	Br	H	Br	H	**97b**	98%
96c	OMe	H	OMe	H	**97c**	–[b]
96d	H	H	OMe	H	**97d**	65%
96e	H	H	CO_2Me	H	**97e**	83%
96f	H	NO_2	H	Me	**97f**	88%
96g	H	OMe	H	Me	**97g**	70%

[a] 69% yield based on recovered **96a**.
[b] Low conversions.

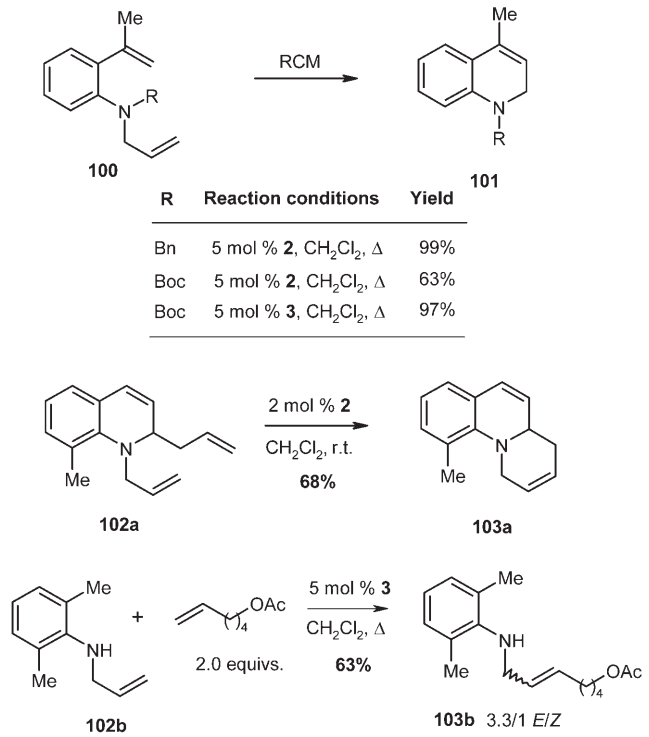
Scheme 38.



98 99

Scheme 39.

Syntheses of dihydroquinolines **101**[68] and **103a**[67] were described using RCM catalyzed by first-generation Grubbs' catalyst **2** (Scheme 40). A better yield was observed for RCM of *N*-benzylamine **100** than for its *N*-Boc-protected analogue, probably because of the formation of chelated intermediates between ruthenium complexes and the Boc carbonyl oxygen. The higher reactivity of catalyst **3** was sufficient to overcome this difficulty and *N*-Boc-dihydroquinoline **101** was obtained in 97% yield.[68] Secondary phenylamine **102b** was found to be a good partner in cross-metathesis reactions (Scheme 40).[4i] Much more complex derivatives have been used as substrates for metathesis reactions. Zimmerman et al. demonstrated that phenylamine-containing dendrimers bearing allyl



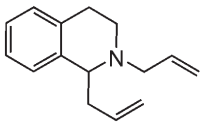
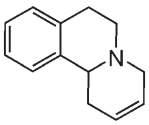
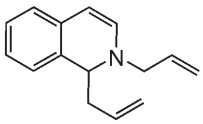
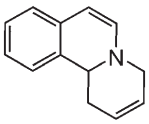
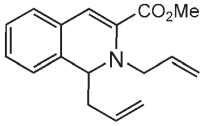
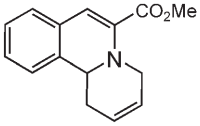
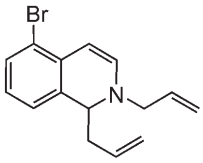
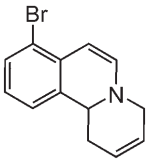
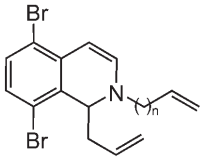
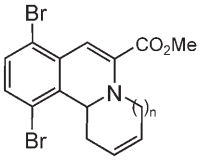
Scheme 40.

ether peripheral groups could undergo efficiently RCM-mediated cross-linking.[69]

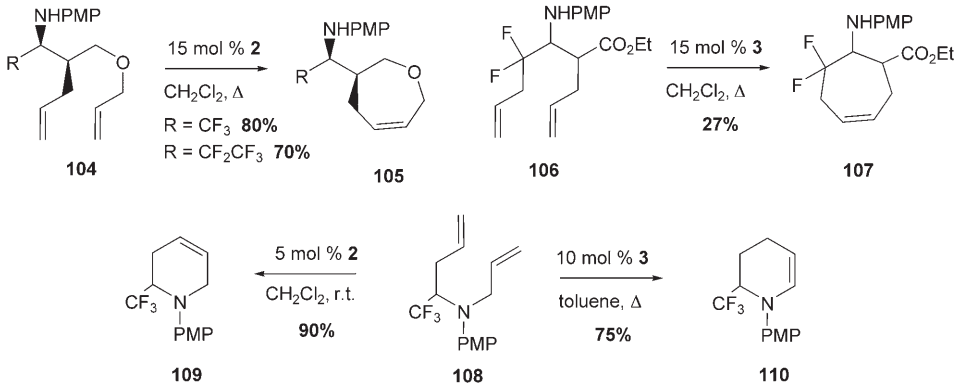
Fustero et al. have reported the synthesis of various fluorinated nitrogen-containing six or seven-membered rings by way of RCM (Scheme 41).[70–72] Reactions performed from secondary amines **104** and **106** protected with a *p*-$MeOC_6H_4$ (PMP) group afforded the expected cyclized products in low to good yields. Formation of unproductive six-membered metallacycle intermediates by chelation of ruthenium complexes and the ester carbonyl oxygen may partly explain the difference of reactivity between **104** and **106**. According to the experimental conditions used, diene **108** is transformed into the expected RCM product **109** or into the isomerised tetrahydropiperidine **110**.[61b,72] The PMP group can be removed under mild conditions by ammonium cerium(IV) nitrate (CAN).

Enamines have basicity comparable to aniline derivatives. An interesting study performed by Grigg et al. on isoquinolines has shown that the efficiency of the RCM process was closely related to the calculated basicity of starting materials **111** (Table 1).[73] Other examples of enamine-containing substrates for RCM

Table 1. RCM of isoquinolines **111**.[a]

Substrate **111**	pK_a (calcd.)	Product **112**	Yield
	7.80		0%
	6.57		80%
	4.56		98%
	5.10		89%
	4.37 ($n=1$) 5.20 ($n=2$)		97% ($n=1$) 93% ($n=2$)

[a] *Reaction conditions:* 5 mol% **2**, CH_2Cl_2, room temperature.



Scheme 41.

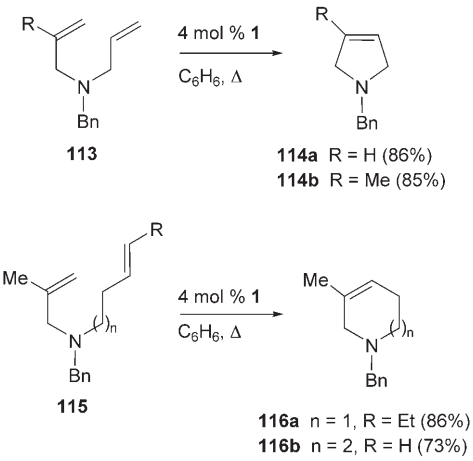
have been described in the literature.[74] Aromatic *N*-heterocycles such as indole, pyridine and thiazole may also be used in conjunction with ruthenium catalysts related to **2** and **3**.[7,8,15,48,75]

5 Molybdenum-Catalyzed Metathesis of Amines

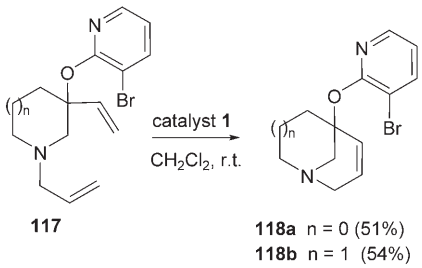
Commercially available molybdenum-based complex **1** is relatively tolerant of a wide range of functionalities including tertiary amines but is not compatible with free alcohols, acetate groups or enones.[8,34] Schrock's catalyst **1** generally gives higher yields and shorter reaction times than first-generation Grubbs' catalyst **2**. However, catalysts such as **2** or **3** are much more convenient to use since they are less sensitive to atmospheric oxygen and moisture. In this section, we will focus on molybdenum-catalyzed metathesis reaction of basic amines that are not sterically hindered. The first examples of synthesis of cyclic amines *via* RCM of dienes were reported by Grubbs and Fu in 1992.[34a] Pyrrolines **114**, tetrahydropyridine **116a** and tetrahydroazepine **116b** were generated efficiently by treatment with complex **1** (Scheme 42).[34a]

More complex polycyclic bridgehead amines were prepared using the same methodology (Scheme 43). 1-Azabicyclo[3.3.1]nonane and 1-azabicyclo-[3.2.1]octane ring systems were obtained in 54% and in 51% yields, respectively, when dienes **117** were reacted with complex **1**.[76]

Enantioenriched piperidine derivatives were synthesized from trienes **119** and **122** by treatment with chiral molybdenum catalysts **121** in benzene.[77] Under these conditions, tertiary amines and neopentylic unprotected secondary amines readily underwent asymmetric RCM in good yields and enantioselectivities (Scheme 44).



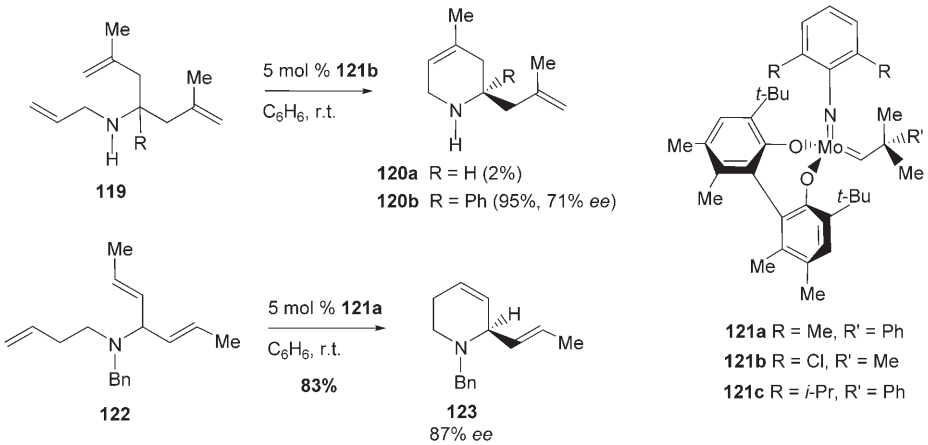
Scheme 42.



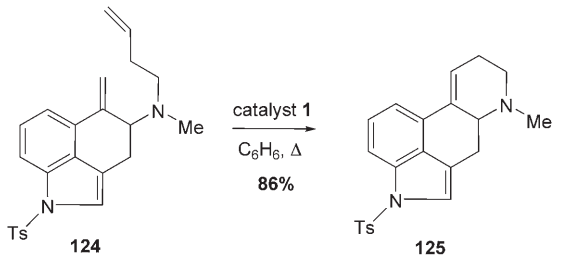
Scheme 43.

A novel entry to the tetracyclic structure of the *Ergot* alkaloids has been recently developed by Martin et al.[78] RCM of diene **124** using complex **1** was found to proceed in very good yield whereas Grubbs' catalyst **2** gave only trace amount of the expected tetracycle **125** (Scheme 45).

Amines which are directly adjacent to a quaternary carbon centre or to an electron-withdrawing-group have been shown to be good substrates for molybde-

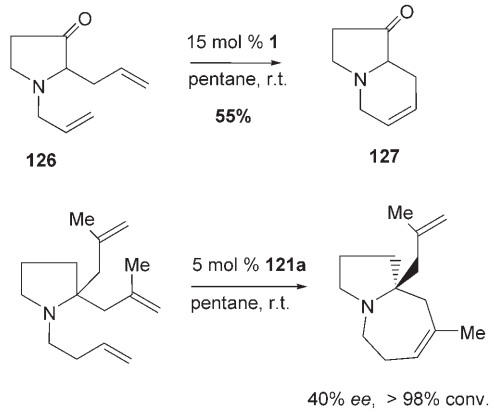


Scheme 44.



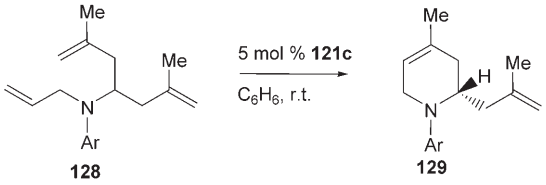
Scheme 45.

num-catalyzed RCM.[77,79,80]. Examples are depicted in Scheme 46. It is noteworthy that RCM of diene **126** using Grubbs' catalyst **2** failed to provide indolizidine **127**.[79]



Scheme 46.

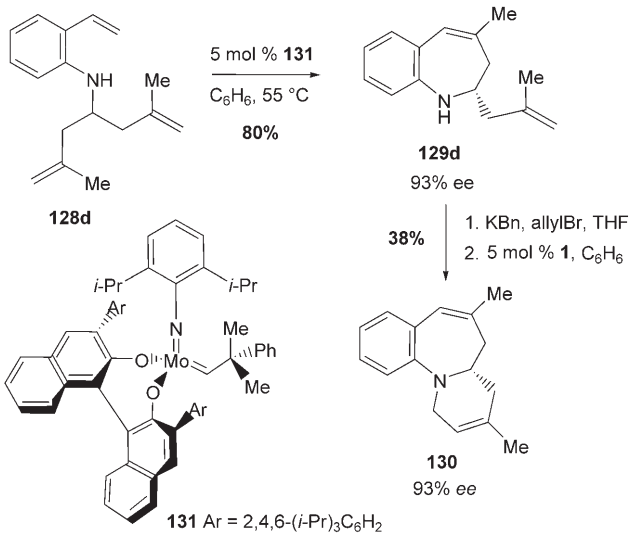
As was described for ruthenium-catalyzed metathesis, phenylamine-containing dienes are generally efficiently converted to the expected RCM products in the presence of molybdenum complexes such as **1** or **121**.[80–82] However, in this case, there is no notable variation in reaction rate between electron-deficient arylamines and their corresponding electron-rich derivatives (Scheme 47).[80,81] These results indicate that coordination of the amino group to metal-alkylidene



Substrate	Ar	Yield	*ee*
128a	Ph	78%	98%
128b	*p*-$MeOC_6H_4$	81%	97%
128c	*p*-BrC_6H_4	81%	98%

Scheme 47.

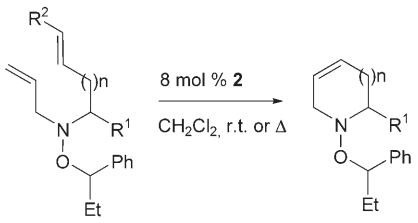
complexes is much less operative in theses instances than for ruthenium-catalyzed metathesis reactions of the analogous substrates (Scheme 38). The synthetic power of this strategy has been demonstrated by the efficient synthesis of enantioenriched tricyclic amines, such as **130**, by way of two RCM reactions (Scheme 48).[80]



Scheme 48.

6 Miscellaneous

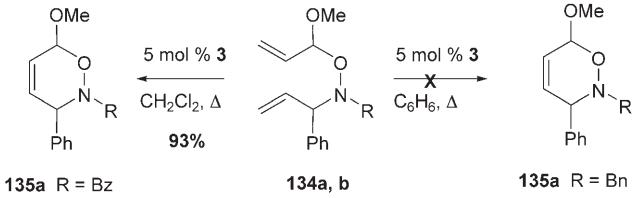
The synthesis of N-O heterocyles from protected hydroxylamine derivatives **132** have been reported by way of RCM (Scheme 49).[83] These examples further highlight the decisive influence of nitrogen atom basicity on the outcome of metathesis reactions. *N*-Alkoxyamines are expected to be less basic than the corresponding amines because of the inductive electron-



Substrate	n	R^1	R^2	Product	Yield
132a	0	$BnO(CH_2)_4$	H	**133a**	35%
132b	1	*n*-Pr	H	**133b**	90%
132c	1	Ph	H	**133c**	53%
132d	0	Ph	Ph	**133d**	51%
133e	0	*n*-Bu	Ph	**133e**	78%
133f	0	*i*-Bu	Ph	**133f**	74%

Scheme 49.

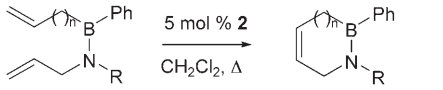
withdrawing effect of the adjacent oxygen atom.[84] However, further deactivation of the nitrogen atom by an electron-withdrawing protecting group is necessary in some cases to obtain the desired RCM product as shown by Cossy et al. (Scheme 50).[33c]



Scheme 50.

Access to pyrroloazepines from acetoxyamine-containing dienes in the presence of second generation Grubbs' catalyst has also been described in the literature.[83d] The N–O bond cleavage may be efficiently performed by reduction under various conditions such as PtO_2/H_2, $Pd/C/H_2$ or Zn/AcOH and provide the corresponding amine function.

The group of Ashe has reported that amino-borane derivatives such as **136** could be readily converted into the corresponding five- or six- membered B-N heterocycles by treatment with 5 mol% of **2** (Scheme 51).[85] This result may be explained by the nature of the aminoborine N–B bond which has a considerable double bond character, resulting primarily from resonance $R_1R_2B{-}NR_3R_4 \leftrightarrow R_1R_2B^{-}{=}N^{+}R_3R_4$.[85,86] This feature has also been exploited to perform RCM reaction of catechol-protected secondary amines.[77]

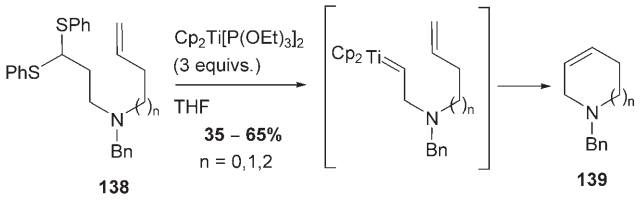


Scheme 51.

Alternative approaches to classical RCM reaction have been reported by the group of Takeda;[87] various saturated nitrogen heterocycles such as **139** have been obtained in modest to good yields by titanocene(II)-promoted cyclization of thioacetals **138** (Scheme 52).

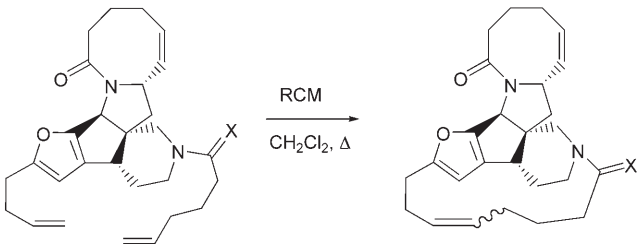
7 Conclusion

Considering the ubiquity of amines in organic compounds and the synthetic power of metathesis, efficient strategies to increase amino group compatibility



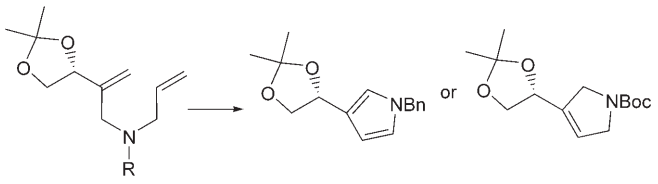
Scheme 52.

with metal-alkylidene complexes have to be developed and discovered. Examples reported in the literature indicated that two principal tactics may be considered. One concerns the exploitation of steric hindrance around the nitrogen atom. Systematic deactivation of an hindered amine by a carbamate or an amide function may not be the first solution to be envisaged in a retrosynthetic analysis as such protection may not be necessary.[88] The use of *N*-α-methylbenzyl, *N*-diphenylmethyl or *N*-triphenylmethyl (trityl) may represent an interesting alternative that avoids potential formation of unproductive metallacycle due to the presence of a chelating carbonyl group. The second strategy is aimed at decreasing the electronic density around the nitrogen atom by using adjacent electron-withdrawing groups, by exploiting the lower basicity of phenylamine derivatives (PMP protecting group) or by working with alkoxyamines. However, exceptions to these rules do exist as shown in Scheme 53, Scheme 54 and Scheme 55.[89–93] The basic amino groups of compounds **140a** and **142a** do not seem to be particularly hindered since the nitrogen atoms are attached to three adjacent secondary carbons. Surprisingly, these substrates underwent RCM in good to almost quantitative yields. In addition, there is no notable variation in reaction efficiency between amines **140a** and **142a** and their corresponding amide derivatives **140b** and **142b**. However, concerning the RCM of **140a**, it should be noted that a large amount of catalyst is used (40 mol%) suggesting that such process may be difficult to perform.[89] Converse-



Substrate	X	Catalyst	Product	Yield	*E*/*Z*
140a	H,H	40 mol % **2**	**141a**	66%	5/3
140b	O	30 mol % **2**	**141b**	70%	5/3

Scheme 53.

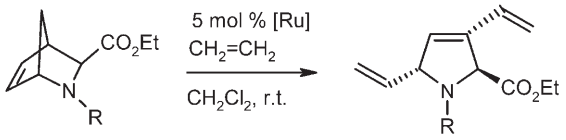


142a (R = Bn)
142b (R = Boc)

143a **143b**

Substrate	Reaction conditions	Product	Yields
142a	1 mol % **3**, CH_2Cl_2, Δ	**143a**	99%
142b	1 mol % **3**, CH_2Cl_2, r.t.	**143b**	100%

Scheme 54.



Substrate	[Ru]	R	Product	Yields
144a	**2**	CHMePh	**145a**	15%
144a	**4**	CHMePh	**145a**	30%
144b	**2**	Boc	**145b**	70%

Scheme 55.

ly, ring-opening metathesis/cross metathesis reaction of α-amino ester **144a** gave poor results whereas the corresponding *N*-Boc derivative **145b** afforded the expected trisubstituted pyrrolidines in 70% yield (Scheme 55).[91] In this case, steric hindrance around the nitrogen atom and the presence of an adjacent ester electron-withdrawing group were not sufficient to prevent coordination to ruthenium-alkylidene complexes.

Theses exceptions serve as reminders that many other synthetic examples are required to better understand the electronic and structural factors that influence the outcome of this process. However, studies presented in this review strongly highlight that, contrary to the current consensus, tertiary and even secondary amines are not necessarily incompatible with metathesis. Efficient metathesis reactions are not always suppressed in the presence of amines and such substrates must not invariably be deactivated by conversion of the amines to the corresponding carbamates or ammonium salts. This classical dogma must be reconsidered carefully in light of the structural and electronic properties of the metathesis substrate. Regarding the importance of amine-containing compounds in organic and medicinal chemistry, it is hoped that insights gained from examples presented in this review and future studies will help to further expand the synthetic scope of metathesis. Development of new catalysts, such as phosphine-free catalysts, should be also of great benefit by analogy with results already obtained for example with acrylonitrile derivatives.[94] As pointed out by R. H. Grubbs, much remains to be done; "the history of metathesis has been an exciting period of discovery […]. We are now entering a new phase where the promise of metathesis will finally be realized".[95]

Note Added in Proof

While this review was being processed for publication, the following articles of related interest have come out in the literature:

1) J. E. Antoline, R. P. Hsung, J. Huang, J. Huang, Z. Song, G. Li, Highly stereoselective [4+3] cycloadditions of nitrogen-stabilized oxyallyl cations with pyrroles. An approach to parvineostemonine, *Org. Lett.* **2007**, *9*, 1275-1278.

2) Q. Yang, H. Alper, W.-J. Xiao, Efficient method for the synthesis of chiral pyrrolidine derivatives via ring-closing enyne metathesis reaction, *Org. Lett.* **2007**, *9*, 769-771.

3) S. D. Nielsen, T. Ruhland, L. K. Rasmussen, Ruthenium-catalysed isomerisation of allylhydrazines: a new entry to the Fisher indole synthesis, *Synlett* **2007**, 443-446.

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