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Azabicycloalkenes as Synthetic Intermediates – Synthesis of Azabicyclo[X.3.0]alkane Scaffolds

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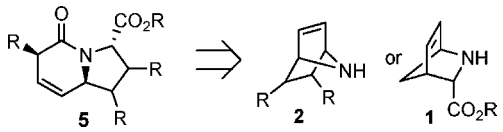
ABSTRACT



A general method to synthesize functionalized azabicyclo[X.3.0]alkane scaffolds 5 is reported. Key intermediates are azabicycloalkenes such as 1 and 2, which are acylated with unsaturated carboxylic acids and subsequently submitted to tandem olefin metathesis. The resulting bicyclic heterocycles are versatile intermediates for different dipeptide mimetics and can be used as intermediates for natural products with indolizidine scaffolds or analogues thereof.

Conformationally constrained dipeptide mimetics based on azabicyclo[X.Y.0]alkane scaffolds have found numerous applications in medicinal and bioorganic chemistry.[1] In addition, the azabicycloalkane structural motif forms the core of many natural products with pharmacological relevance such as indolizidine and quinolizidine alkaloids and aza-sugars.[2] In consequence, a number of groups have developed efficient syntheses of these bicyclic heterocycles.[3]

Ring-closing metathesis (RCM) and tandem metathesis[4] have been particularly successful strategies for the assembly of common natural product scaffolds.[5] Application of RCM to the synthesis of peptide mimetics was first described by Grubbs[6] and later extended by several other groups.[7] Key intermediates in these approaches are often alkenyl-substituted pyrrolidines, which are N-acylated with an unsaturated carboxylic acid and submitted to ring-closing metathesis (RCM).

Inspired by the elegant concept of intramolecular ring-opening/ring-closing metathesis (RORCM) established by the groups of Blechert, Grubbs, and Hoveyda,[8] we wanted to

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use N-acylated 2-[9] and 7-azabicycloalkenes **1** and **2** as precursors for azabicyclo[X.3.0]alkanes **5**. This is part of a general synthetic concept using azabicycloalkenes as masked analogues of functionalized pyrrolidines or piperidines.[10]

In particular, symmetrical derivatives of 7-azabicycloalkenes **2** are in this context very interesting substrates because they can be desymmetrized by either diastereoselective or enantioselective metathesis. Both 2- and 7-azabicycloalkenes are easy to synthesize[11] via Diels−Alder reaction, and a stereoselective catalytic approach to **1** has been recently reported by our group, giving access to enantiomerically pure scaffolds **5** (Figure 1).[12]

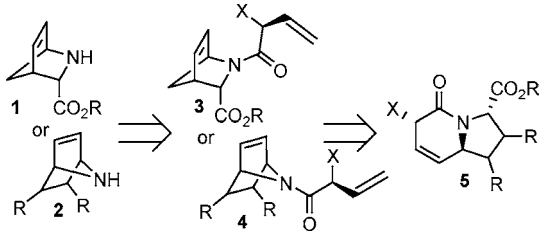
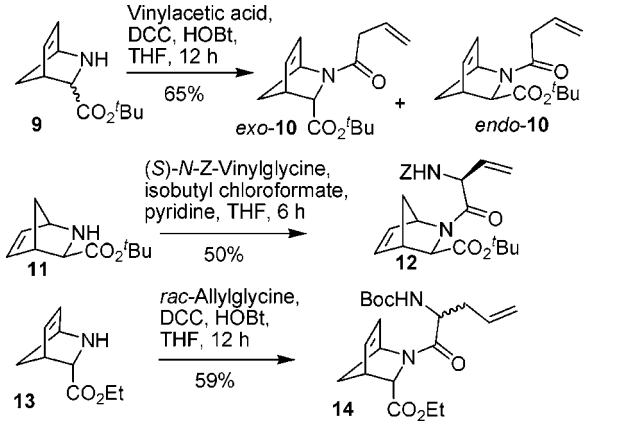


Figure 1. Retrosynthetic analysis of indolizidine scaffold **5**.

Synthesis of suitable metathesis precursors was achieved according to Scheme 1 by acylation of the racemic dia-

Scheme 1. Acylation of 2-Azabicycloalkenes **9**, **11**, and **13**



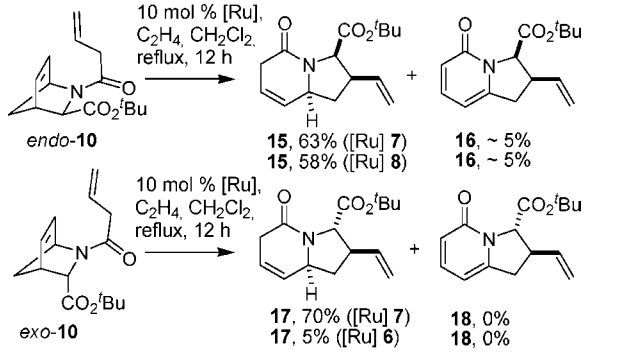
stereomeric mixture **9** and enantiomerically enriched azabicycloalkanes **11** and **13**, which were synthesized by an enantioselective catalytic *imino* Diels−Alder reaction.[12] As acyl compounds, we chose vinylacetic acid for model studies, Cbz-vinylglycine, and Boc-allylglycine for the synthesis of dipeptide mimetics.

The choice of educt **9** was due to stereochemical reasons because we wanted to evaluate endo and exo isomers of 3-substituted 2-azabicycloalkene scaffolds. Therefore, azabicycloalkene **9** was an ideal starting material because it can be synthesized as a racemic mixture of (at this point unseparable) endo and exo isomers. However, both diastereoisomers are easily separated by column chromatography after acylation with vinylacetic acid, giving *exo*-**10** and *endo*-**10**.

Our catalytic approach gives enantiomerically enriched azabicycloalkenes **11** and **13** with high exo selectivity. Metathesis precursor **12**, resulting from coupling of (*S*)-vinylglycine to **11**, is therefore an excellent intermediate for the synthesis of enantiomerically pure dipeptide mimetics of general structure **5**.

Olefin metatheses were performed according to Scheme 2. Careful control of reaction conditions was essential for successful conversions. Ruthenium precatalysts **7** and **8** (Figure 2) gave comparable results and were more effective

Scheme 2. Olefin Metathesis of Bisolefins **10**



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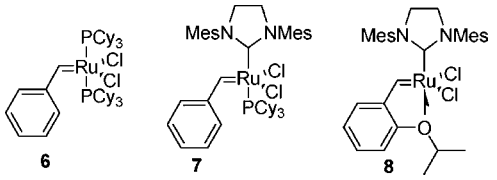


Figure 2. Ruthenium-based precatalysts for olefin metathesis.

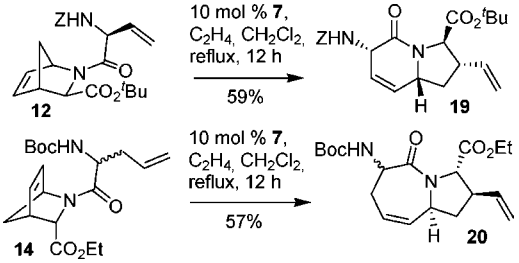
than **6**, which gave significantly lower yields. An important parameter for the synthesis of azabicycloalkanes **15** and **17** is temperature. If substrates **10** are treated with precatalysts **7** or **8** at room temperature, the conversion to **15** or **17** is clean but yields are low (<20% of **15** or **17** along with unreacted starting material **10**). In refluxing dichloromethane, yields for indolizidines **15** or **17** are better. However, these conditions require a relatively high catalyst loading (10 mol %) and lead to the formation of side products, which have been identified by NMR as pyridone **16** and products derived from olefin isomerization of products **15** or **17**.

In some cases, the benzylidene ligand of precatalyst **7** was incorporated by cross metathesis into the olefinic side chain of target structures **15** or **17**.[13] Metathesis products derived from *endo*-**10** were particularly prone to rapid aromatization, and a substantial amount (~5%) of pyridone **16** was observed by NMR immediately following the reaction. Within hours, the amount of pyridone **16** grows significantly, if the sample is not strictly excluded from air. Most likely, this type of aromatization occurs via a peroxide pathway from either **15** or the α,β-unsaturated bicyclic lactam that is generated by isomerization of **15**. In consequence, **15** needs to be stored under a strict inert atmosphere if it is to be used for further conversions. Similar side reactions were observed for olefin metathesis of *exo*-**10**, although aromatization to **18** was much slower in this case.

Concentration is another important parameter because concentrated solutions of **10** in dichloromethane gave significant amounts of oligomerized products. However, educt concentrations of 0.01 M were found to give indolizidines **15** and **17** in good yields for endo and exo precursors. In addition, it was essential to perform all metatheses of azabicycloalkenes **10** under an ethylene atmosphere to enhance catalyst initialization.

Having established suitable reaction conditions for olefin metathesis, we turned our attention to the synthesis of bicyclic dipeptide mimetics. As depicted in Scheme 3, azabicycloalkene dipeptides **12** and **14** were submitted to the standard conditions for olefin metathesis. Desired bicyclic dipeptide mimetics **19** and **20** were thus obtained in good yields, respectively. However, increased amounts of side products were noted for the metathesis of bisolefin **12** compared to the corresponding reaction starting from *exo*-

Scheme 3. Synthesis of Dipeptide Mimetics **19** and **20**



10 depicted in Scheme 2. This is due to a substantial amount of olefin isomerization of **19** and aromatization to the corresponding pyridone derivative. These side products were not isolated, but identified by NMR from the crude mixture. A much cleaner conversion was observed with educt **14** to give dipeptide mimetic **20** along with unreacted starting material. Seven-membered heterocycle **20** was obtained as a mixture of two diastereoisomers and is less prone to olefin isomerization than its six-membered analogue **19**.

It should be noted that bicyclic compounds **19** and **20** are ready for structural modification in both parts of the dipeptide mimetic because the internal double bond at the N-terminus and the external double bond at the C-terminus are easily differentiated. Our route thus addresses a major drawback of known syntheses to azabicycloalkane dipeptide mimetics, and a number of these useful compounds with various amino acid side chains at both termini are now accessible.

Different metal-catalyzed protocols for desymmetrization of 7-azabicycloalkenes or their oxa-analogues have been shown to be excellent methods for the construction of valuable chiral synthetic intermediates.[14] In this context, asymmetric tandem metathesis has been achieved with symmetrical norbornenes and oxanorbornenes as educts.[15] A transfer of this reaction to 7-azabicycloalkenes such as **22** and **25** has not been reported so far to the best of our knowledge.[16] However, it would lead to the formation of extremely interesting chiral scaffolds for the synthesis of dipeptide mimetics or natural products.

We chose azabicycloalkene **21** for our first studies because it is easy to synthesize on a large scale and it should give interesting isoindole scaffolds in the final products.

Conversion of **21** to metathesis precursor **22** was performed in a two-step procedure via deprotection of the Boc group with HCl[17] and coupling of vinylacetic acid to the resulting free amine with DCC/HOBt to give **22** (Scheme 4). When bisolefin **22** was submitted to the standard metathesis conditions, the unexpected products were pyridones **23** and **24** in overall 35% yield along with large

(13) It has been reported that precatalysts **7** and **8** generate reactive ruthenium species at an elevated temperature promoting a number of unwanted side reactions: Hong, S. H.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc*. **2004**, *126*, 7414−7415.

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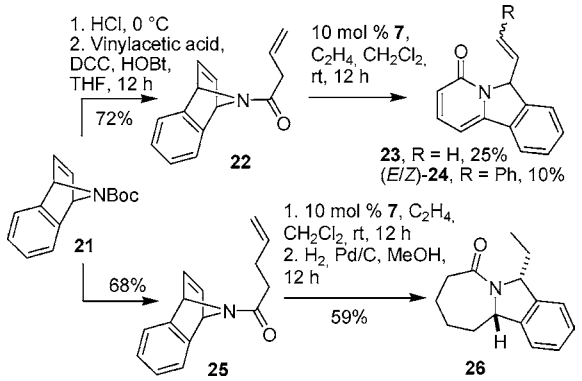
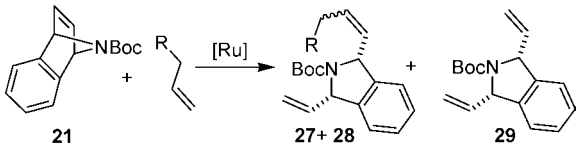
Scheme 4. Acylation of **21** and Subsequent RORCM



Scheme 5. ROCM of Boc-Protected 7-Azabicycloalkene **21**



R	[Ru], mol %	isoindole, [%]	29 [%]
CO_2Me	**7**, 5	**27**, 61	12
CO_2Me	**8**, 3	**27**, 62	9
$SiMe_3$	**8**, 7	**28**, 98	0
$SiMe_3$	**7**, 3	**28**, 100	0
$SiMe_3$	**8**, 3	**28**, 97	0
$SiMe_3$	**8**, 1	**28**, 73	0

amounts of unreacted starting material. This is remarkable because at least a ROCM sequence of azabicycloalkene **21** with ethylene would be expected. With a turnover of only three, the Grubbs catalyst **7** is thus quite ineffective in this metathesis reaction. Although the underlying mechanism leading to the unique product distribution and reactivity for the conversion of **22** to **23** and **24** were not clear, we assumed that either the structure of the educt **22** (location of the exocyclic double bond) or the aromatization was the reason for the low catalytic efficiency.

We tested this hypothesis with metathesis precursor **25**, which was synthesized according to a known protocol for one-pot acylation of azabicycloalkene **21** with pentenoyl chloride.[18] As expected, bisolefin **25** was converted smoothly to the corresponding seven-membered ring system under standard metathesis conditions. This metathesis product was difficult to purify and was therefore hydrogenated to give **26**, which was isolated in pure form after column chromatography.

A suitable workaround for the corresponding six-membered ring systems is a sequence of ring opening and cross metathesis (ROCM) of azabicycloalkene **21** with vinylacetic acid and subsequent intramolecular cyclization. This type of ROCM has been accomplished for another 7-azabicycloalkene scaffold by Rainier and co-workers.[19] Reactions can be performed according to Scheme 5 at room temperature without an ethylene atmosphere to give disubstituted isoindoles **27** and **28** in good to excellent yields. In the reactions with methyl butenoate as the CM partner, a significant amount of an additional isoindole **29** resulting from ROCM of azabicycloalkene **21** and ethylene was observed. The formation of this side product is due to the relatively low reactivity of methyl butenoate in these ROCMs and its homodimerization resulting in small quantities of ethylene in the reaction mixture.

It should be noted that reaction conditions for metatheses of 7-azabicycloalkenes such as **21** are significantly milder (room temperature vs 40 °C) and that catalyst loading can be substantially lower (can be lowered to 1% with still acceptable yields) if compared to the corresponding reactions with 2-azabicycloalkenes (see Schemes 2 and 3).

Cyclization of **27** to the corresponding lactam should be easy to perform, and suitable conditions are reported in the literature for similar substrates.[19]

In conclusion, we presented our initial studies on tandem metatheses of 2- and 7-azabicycloalkenes to give functionalized bicyclic scaffolds useful for the preparation of dipeptide mimetics and various natural products. As a general trend, it has been found that 7-azabicycloalkenes are significantly more reactive than 2-azabicycloalkenes.

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Supporting Information Available: Experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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