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In Situ Conformational Fixation of the Amide Bond Enables General Access to Medium-Sized Lactams via Ring-Closing Metathesis

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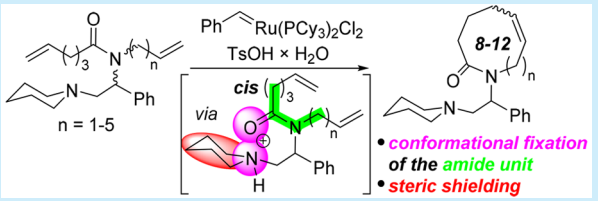
Supporting Information

ABSTRACT: In this work, a novel phenethylamine-derived protecting group is introduced, which is able to significantly enhance the Grubbs I-catalyzed formation of 9- to 12-membered lactams through charge-induced conformational fixation under acidic conditions. As the new approach is particularly valuable for 10- and 11-membered ring systems, for which no related precedence was available so far, the overall strategy now offers general access to medium-sized lactams via ring closing metathesis. Cleavage of the protecting group can be achieved through a mild sequence combining *N*-oxidation and Cope elimination or alternatively under standard hydrogenation conditions.

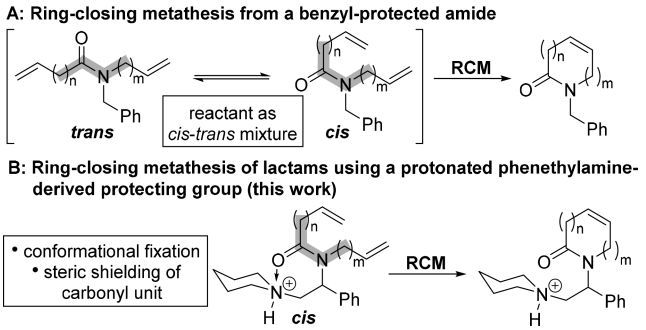


Metathesis reactions in general and ring-closing metathesis (RCM) in particular belong to the most important transformations in modern chemistry,[1] which was also prominently pointed out by the award of the Nobel Prize in 2005.[2] The large diversity of catalysts that is available today enables a broad variety of applications under manifold reaction conditions.[1d,e,g,3] Along with these valuable achievements, a broad range of carbo- and heterocyclic ring systems[4] were made accessible by ring-closing metathesis, and it opened attractive synthetic routes to numerous natural products[5] as well as compounds with applications in medicinal chemistry[6] including various cyclic peptides.[7]

However, significant difficulties still arise when ring-closing metathesis is applied in the preparation of medium-sized ring systems.[8] This is due to enthalpic (ring strain in the product) and entropic (probability of suitable conformations in the reaction course) factors, and as a result, the yield of dimers and oligomers often largely prevails over that of the desired cyclic compound. Besides working under high dilution, a common countermeasure against such side reactions is structural modifications to improve the conformational preorganization of the reactant with regard to the desired C−C bond formation.[9] Regarding cyclizations of amides and esters to medium-sized lactams and lactones, such transformations may additionally suffer from the formation of stable substrate−catalyst chelate complexes.[1c,10] Although this effect can be partially overcome by the addition of a cocatalyst or by sterically shielding the metal-coordinating centers,[7d,11] these countermeasures often impose significant limitations on the reaction scope.[11a]

Against this general background and the particular challenges associated with the synthesis of lactams using ring-closing metathesis, we reasoned that a carefully chosen protecting group on the nitrogen atom of the amide not only might be able to enhance the intended cyclization by preorganization but could also suppress the complexation of the catalyst, in which the carbonyl unit is involved. Typically, and not relying on covalent conformational restraints[8,12] or particular substituent effects on the alkenyl chains,[5b,7d,e,13] medium sized lactams are prepared from amides bearing a benzyl protecting group on the nitrogen atom[14,15] (Scheme 1A).

Scheme 1. Ring-Closing Metathesis for the Synthesis of Medium-Sized 8- to 12-Membered Lactams



The presence of the benzyl group is thereby essential, as the related secondary amide would almost fully adopt the unfavorable *trans* conformation.[13a,14] In the presence of the benzyl group, an approximately 1:1-mixture of the *cis* and *trans* rotamer is usually formed, from which ring closing metathesis can proceed but still with the above-mentioned limitations, which are largely due to ring size.[14]

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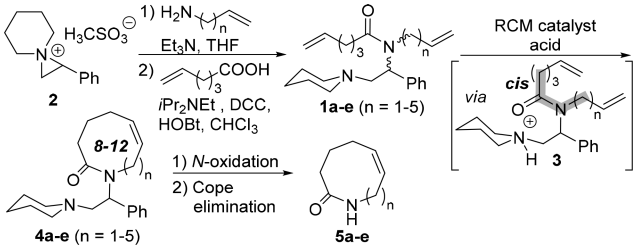
With this work, we now introduce a phenethylamine-derived protecting group, which not only can enhance cyclization by preorganization but also is likely to suppress complexation of the catalyst through the presence of the positive charge (Scheme 1B). The effect of preorganization does thereby rely on the conformational fixation of amides induced by proximate positive charges.[16]

Within the intended strategy (Scheme 2), the acyclic amide **1** is assembled starting from aziridinium methanesulfonate **2**,

Scheme 2. Intended Synthetic Strategy for Medium-Sized Lactams 5

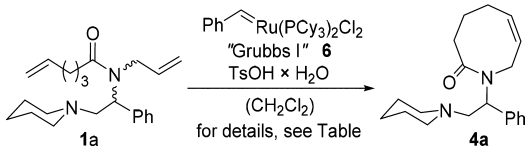


which can itself be prepared on large scale over only two steps from styrene oxide (see Supporting Information (SI) for details).[17] In this way, the synthesis of the metathesis precursor **1** does not require more steps as if **2** would be replaced by conventional benzyl chloride or benzaldehyde (via reductive amination) (cf. Scheme 1A). Ring-closing metathesis under acidic conditions should then benefit from conformational fixation and carbonyl shielding (via **3**), so that the cyclic product **4** is obtained.[16] For the cleavage of the phenethylamine-derived protecting group to give lactam **5**, we reasoned that an *N*-oxidation/Cope elimination sequence[18,19] might be an attractive option, as such pathway would leave the double bond in the lactam unit intact, which is typically not the case when benzylic groups are cleaved by catalytic hydrogenation.[20]

In preliminary studies, the conformational fixation of the five lactam precursors **1a**–**e** was validated by ^{1}H NMR under the addition of trifluoroacetic acid (see SI for details). As dichloromethane is often reported as the solvent of choice for RCM reactions and gave satisfying results in the NMR study (*cis*/*trans* ratios >95:5), the reactions aimed at the optimization of the RCM step were carried out in this solvent. In the course of the early optimization, trifluoroacetic acid was replaced by *p*-toluenesulfonic acid (TsOH).[21] The Grubbs I catalyst **6** was chosen due to its cost-effectiveness and to allow comparison with earlier attempts to prepare medium-sized lactams by RCM. Moreover, Grubbs II-type catalysts have been reported to cause partial double bond isomerization in syntheses of lactams.[13a] Selected results from the variations regarding the amount of catalyst and the reaction time are summarized in Table 1.

An experiment using 10 mol % Grubbs I catalyst **6** and 1 equiv of TsOH provided **4a** in a yield of 32%, but only 20% of **1a** could be recovered (entry 1). By reducing the amount of solvent to 50 mL and prolonging the reaction time to 48 h, the yield of **4a** could be increased to 40% (entry 2). A breakthrough regarding the recovery of **1a** was then achieved by doubling the amount of TsOH (entry 3), thereby showing that a higher acid concentration can protect unconverted **1a** from decomposition. The addition of a second batch of **6** (5 mol %) under prolongation of the reaction time did at first not improve the overall result (entry 4), but when the first interval

Table 1. Preoptimization of Reaction Conditions for the 8-Membered Lactam 4a[a]



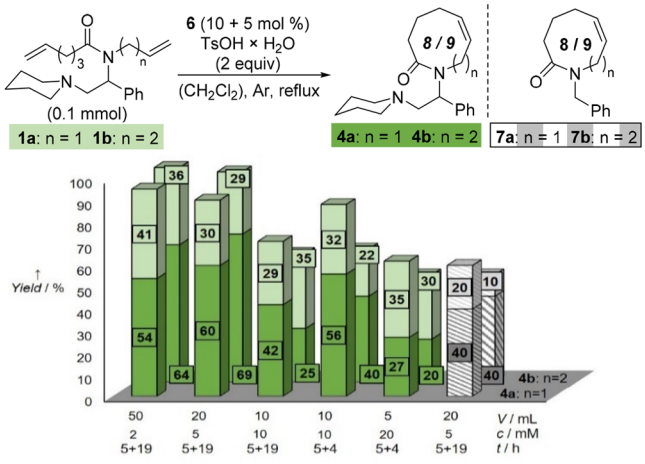
entry	Grubbs I (mol %)	TsOH (equiv)	CH_2Cl_2 (mL)	time (h)	yield **4a** [**1a**][b] (%)
1	10	1	150	24	32 [20]
2	10	1	50	48	40 [10]
3	10	2	50	24	28 [51]
4[d]	10 + 5	2	50	20+ 25	23 [54]
5[d]	10 + 5	2	50	5+ 19	54 [41]
6[d]	10 + 5	2	50	19+ 5	15 [53]

[a]For detailed reaction conditions, see SI. [b]Reaction course was monitored by TLC and HPLC-MS. [c]Yields determined by ^{1}H NMR using dimethyl terephthalate as internal standard. [d]Additional **6** (5 mol %) was added after the first time interval.

was shortened to 5 h, satisfactory yields of 54% for **4a** and 41% for **1a** were obtained (entry 5). A control experiment under identical conditions, in which the time intervals of 5 and 19 h were switched, demonstrated the importance of a relatively short first interval (entry 6).

As the cyclization precursors **1a**–**e** for ring sizes 8 to 12 can be expected to behave differently under the metathesis conditions determined so far (Table 1), we studied the single reactions in more detail. One particular question was how far the concentration could be increased through the use of the new protecting group inducing conformational fixation. The results obtained for the 8- and 9-membered ring systems are summarized in Scheme 3.

Scheme 3. Synthesis of 8- and 9-Membered Lactams 4a and 4b



For both ring sizes, the best yields were obtained at a 5 mM concentration (0.1 mmol **1a**/**b** in 20 mL) at a total reaction time of 24 h (5 h + 19 h). While the concentration could not be further increased for the 9-membered system (**1b** → **4b**, *n* = 2) without significant losses in yield, a good result was also be achieved for **1a** → **4a** (56%) at 10 mM and at a shortened reaction time of 9 h (5 h + 4 h). To evaluate the performance of the new protecting group in comparison to the classical

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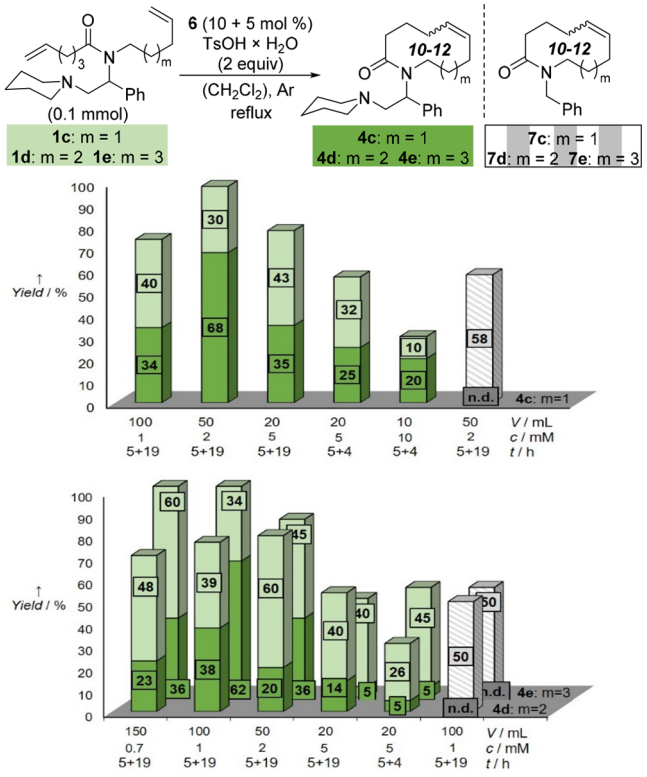
benzyl group, the reference lactams **7a** and **7b** were prepared under the best yield conditions, but under the omission of TsOH. In these experiments, **7a** and **7b** were produced in significantly lower yields than **4a** and **4b**, and much less uncyclized starting material could be recovered. The maximum RCM yields that can be found in literature for lactams closely comparable to **7** are 74−80% for the 8-membered ring (with no starting material recovered) and 59% for the 9-membered system along with 25% of starting material.[14] This data shows that the new protecting group does not yet have a clear benefit over benzyl for 8-membered lactams but that the so far best literature result could be exceeded for the 9-membered system.

Encouraged by this finding, we next turned to lactams with ring sizes in the range of 10 to 12 (Scheme 4). Remarkably, not

Scheme 4. Synthesis of 10- to 12-Membered Lactams 4c−e

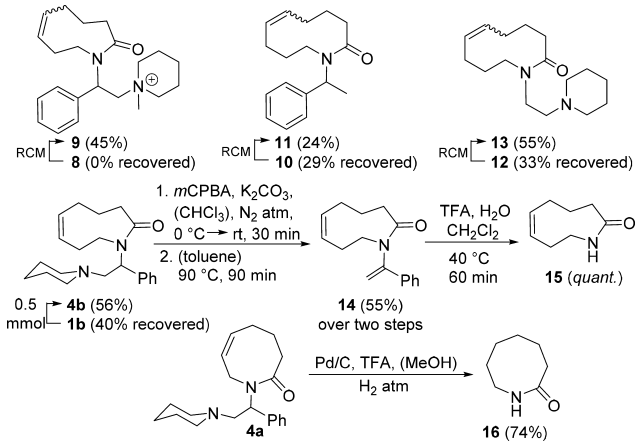


a single example for the successful synthesis of 10- and 11-membered lactams by RCM can be found in the literature so far, if covalent fixation and side-chain substitution are excluded.[22] The synthesis of the 10-membered lactam **4c** (*m* = 1) proceeded best at a 2 mM concentration after 24 h reaction time, but shortening the reaction time to 9 h at 5 mM did not give a satisfactory result. The high value of the conformational fixation of amide **1c** under the acidic reaction conditions became obvious when the cyclization was attempted with the corresponding benzyl-protected amide to give lactam **7c**. At 2 mM concentration and after 24 h reaction time, **7c** could not even be detected in traces in the product mixture.

Regarding the results for lactams **4d** and **4e** with ring sizes of 11 and 12 (*m* = 2, 3), these cyclic systems appear the most challenging to prepare, as the so far highest dilution of 1 mM had to be applied to achieve the maximum yields of 38% for **4d** and 62% for **4e** after 24 h. Shortening the reaction time to 9 h at the higher concentration of 5 mM, as it had before been successful for the 8-membered system (Scheme 3, *n* = 1), did again not increase the outcome. Similar to what was observed for ring size 10, the reference reactions to the benzyl-protected lactams **7d** and **7e** were unable to provide even trace amounts of the desired products at 1 mM concentration. Regarding the literature, maximum yields of 44−53% were just recently reported for the preparation of 12-membered benzyl-protected lactams comparable to **7e**, but with no remaining starting material.[23,24] Moreover, the related reactions were carried out in the presence of the more expensive second generation Hoveyda Grubbs catalyst, so that the new strategy is beneficial in two ways.

Structural variations on the protecting group (Scheme 5) showed that quaternary ammonium salts such as **8** are less well

Scheme 5. Variations of the Protecting Group and Cleavage Group through *N*-Oxidation and Cope Elimination or Catalytic Hydrogenation



suited precursors since a lower yield for **9** (45%) and a lower reactant recovery (0%) were observed than in the standard procedure leading to **4b** from **1b** (69% yield, 29% recovery, cf. Scheme 3). A comparison of the truncated derivatives **10** and **12** revealed that the charge effect is more important than steric interactions as a minor drop in yield and reactant recovery occurred for **12** → **13** compared to the related standard protocol converting **1c** to **4c** (68% yield, 30% recovery, cf. Scheme 4).

In the final stage, we studied the removal of the novel phenethylamine-derived protecting group (Scheme 5). Prior to this, the 9-membered lactam **4b** was prepared on a larger 0.5 mmol scale applying the optimized conditions shown in Scheme 3. The drop in yield from 68% to 54% thereby seems to be due to a slowed reaction, as a high combined yield (96%) of recovered amide **1b** and lactam **4b** could still be determined. Selective *N*-oxidation in the presence of the C−C double bond could be achieved for **4b** by using *meta*-chloroperoxybenzoic acid (*m*CPBA) in the presence of potassium carbonate.[25] After changing the solvent to toluene, Cope elimination under mild conditions (90 °C) provided vinyl amine **14** (55% over 2 steps, not optimized), which was finally cleaved with trifluoroacetic acid to give the unsaturated lactam **15** in quantitative yield. Hydrogenation of lactam **4a** led to removal of the protecting group and the double bond to give **16** in 74% yield.

In conclusion, we herein present the first generally applicable RCM approach to medium-sized lactams, which is based on a novel, readily available phenethylamine-derived protecting

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group. By exploiting the conformational fixation of the amide bond under acidic conditions, 8- to 12-membered lactams were successfully prepared with a favorable degree of recovery of the starting material for each ring size. Compared to previous syntheses, this new strategy offers advantages for 9- and 12-membered ring systems, and it turned out as highly valuable for the synthesis of 10- and 11-membered lactams, for which no related literature precedent exists so far. Through an *N*-oxidation/Cope elimination sequence, the phenethylamine-derived protecting group can be cleaved under mild conditions and with full preservation of the C−C double bond.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03320.

Experimental details and ^{1}H and ^{13}C NMR-spectra of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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