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Communication

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Tandem Nucleophilic Addition / Oxy-2-azonia-Cope Rearrangement for the Formation of Homoallylic Amides and Lactams: Total Synthesis and Structural Verification of Motuporamine G

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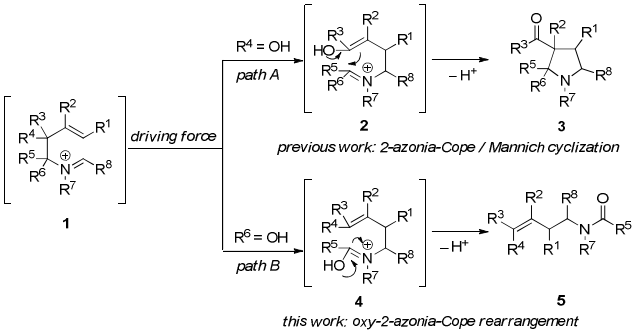
Supporting Information Placeholder

ABSTRACT: In the presence of a Lewis acid, β,γ-unsaturated ketones and oximes or imines undergo nucleophilic addition to produce zwitterion intermediates, followed by oxy-2-azonia-Cope rearrangements to give homoallylic amides. In the case of 2-vinylcycloalkanones, the process results in ring-enlargement, providing a novel route to 9- to 16-membered lactams. The preparative significance of this protocol was evidenced by a short synthesis of macrocyclic alkaloid Motuporamine G. The stereochemistry defining step of this oxy-azonia-Cope rearrangement was further studied computationally. Despite a high energy preequilibrium in the formation of zwitterionic intermediates, the [3,3]-sigmatropic step is the rate and product determining step. Chair-like transition states (TS) are generally preferred over boat-like TS.

Amides are ubiquitous motifs in natural products, pharmaceuticals and materials.[1] The widespread occurrence of amides often makes us overlook that amide formation under neutral conditions and without generation of waste is a contemporary challenge in organic synthesis. In 2005 the American Chemical Society Green Chemistry Institute (comprising members from leading global pharmaceutical corporations) voted 'amides formation avoiding poor atom economy reagents' is the top priority research area in organic chemistry.[2] Diversified or improved methods for the synthesis of amide functionality are in great demand.[3]

2-Azonia-Cope rearrangements constitute highly efficient means to construct carbon-carbon bonds under mild conditions.[4] The inherent problem of the method is the reversibility of the process. There have been four major approches to drive 2-azonia-Cope rearrangements to completion: (1) by aryl conjugation of the iminium ion;[4,5] (2) by trapping the imminium ion in a subsequent nucleophile induced ene-iminium cyclization;[6] (3) by selectively cleaving the iminium ion of one sigmatropic isomer[7-9] (4) by a tandem Mannich cyclization process. This fourth method is the particularly well established 2-azonia-Cope/Mannich cyclization process which was first introduced by Overman *et al*. (Scheme 1, path A). The reaction has been used as the key step in a number of alkaloid total syntheses.[10] Herein, we describe a new method to overcome the problem of reversibility: an oxy-2-azonia-Cope rearrangement of cross-addition product **4** into homoallylic amides **5** (Scheme 1, path B).

Scheme 1. The 2-azonia-Cope Rearrangement and its Novel Extension to an Oxy-2-azonia Cope Rearrangement Reaction

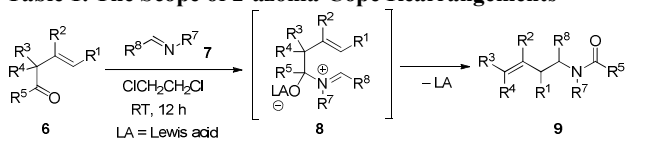


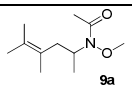
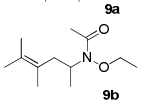
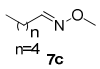
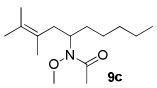
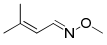
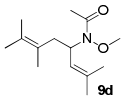
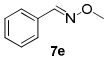
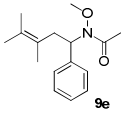
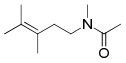
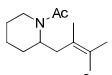
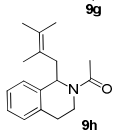
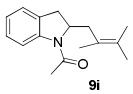
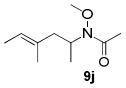
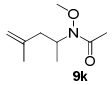
Recently, we discovered a novel cross-dimerization of a β,γ-unsaturated carbonyl compound with another aldehyde to produce homoallylic esters in an atom-economical way.[11] The proposed well-organized intermediates occurring in this oxy-oxonia-Cope rearrangement enable high degrees of diastereoselectivities and transfer of chirality. It has been successfully applied to a new synthesis of macrocyclic musks.[11b] In continuation of our studies of atom-economical rearrangement chemistry, we decided to examine the oxy-2-azonia-Cope rearrangement in the context of the synthesis of odorants[12] and natural products. Macrolactams and related azacycles are attractive targets which are often encountered in biologically active natural products,[13,14] and especially in drug candidates such as bioisosteres of macrolides.[15] However, direct cyclization approaches to the synthesis of macrolactams are often limited by entropic reasons, applications wich require high dilution techniques and the lack of functional diversity.[16]

Our design of the oxy-2-azonia-Cope concept is based on the assumption that intermediate **8** can be formed through a nucleophilic addition of an imine derivative to the carbonyl group of **6**, activated by a rather oxophilic Lewis acid (Table 1). Initial experiments revealed that oxy-azonia-Cope rearrangements can indeed be performed by conversion of β,γ-unsaturated ketone **6a** with oxime ether **7a** and a Lewis acid such as $SnCl_4$ (Table 1, entry 1). The expected homoallylic

amide **9a** was obtained in excellent yield in the presence of 1.0 equivalent of $SnCl_4$ at room temperature during 24h. The reaction also works with catalytic amounts of Lewis acid (20% eq. $SnCl_4$), only a much longer reaction time, more than 6 days, was required to reach quantitative conversion.[17] We therefore decided to use stoichometric amounts of Lewis acids in the following investigations.

Table 1. The Scope of 2-azonia-Cope Rearrangements[a]



entry	substrate **6**	substrate **7**	Lewis acid (1.0 eq.)	Product **9**	Yield (%)[b]
1	 **6a**	 **7a**	$SnCl_4$	 **9a**	97
2	**6a**	 **7b**	$SnCl_4$	 **9b**	89
3	**6a**	 n=4 **7c**	$SnCl_4$	 **9c**	94
4	**6a**	 **7d**	$SnCl_4$	 **9d**	67
5	**6a**	 **7e**	$SnCl_4$	 **9e**	39
6	**6a**	 **7f**	$EtAlCl_2$	 **9f**	92[c]
7	**6a**	 **7g**	$EtAlCl_2$	 **9g**	29[c]
8	**6a**	 **7h**	$EtAlCl_2$	 **9h**	83[c]
9	6a	 **7i**	$EtAlCl_2$	 **9i**	58[c]
10	 **6b**	**7a**	$SnCl_4$	 **9j**	84
11	 **6c**	**7a**	$SnCl_4$	 **9k**	93

[a]Experimental conditions: 1,2-dichloroethane solution (50ml) of **6** (10 mmol), imine **7** (12mmol) and Lewis acid (10 mmol) were stirred under argon atmosphere for 24 hours at room temperature. [b]Isolated yield after chromatography or Kugelrohr distillation. [c]When 1.0eq of $SnCl_4$ was used, the conversion is less than 20% detected by GC analysis.

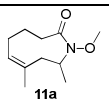
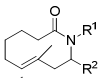
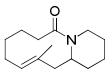
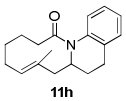
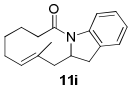
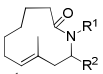
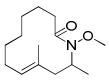
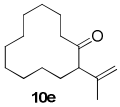
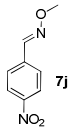
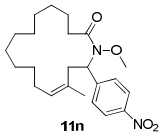
Encouraged by the efficiency of this concept, we employed β,γ-unsaturated ketones **6a-c** to define the scope of this novel rearrangement with regard to the tolerated diversity of imine substrates (Table 1). Oxime ethers and imine derivatives **7** smoothly underwent the desired transformation to give homoallylic amides **9b-k** in moderate to excellent yields. The reactions with oxime ethers were run in the presence of 1.0 equivalent of $SnCl_4$ at room temperature (entries 1-5, 10, 11). Lower yields were obtained with oxime ethers of decreased nucleophilicity, such as those derived from α,β-unsaturated and aromatic aldehydes (entries 4,5). Comparatively electron rich imines **7f-i** were beneficially converted using 1.0 equivalent of more oxophilic $EtAlCl_2$ (entries 6-9). Notably, precursor **7f**, the trimeric form of N-methylenemethanamine, was cleaved in situ to generate the desired rearrangement product **9f** in excellent yield (entry 6). Reactions with cyclic imines such as **7g** and **7h** resulted in acetyl protected piperidines **9g** and **9h** (entry 7, 8). Interestingly, 1*H*-indole reacted via its tautomeric 3*H*-indole[18] with **6a** to give indoline acetamide **9i** (entry 9). Rearrangement reactions of β,γ-unsaturated ketones carrying α protons such as **6b**,**c** were also investigated. Both substrates were converted into amides **9j** and **9k** in excellent yields (entries 10, 11). Importantly, the double bond in product **9j** is exclusively *E*-configured (entry 10). Over-all, with regard to substrate diversity, the scope of the oxy-azonia-Cope rearrangement was found to be surprisingly broad.

In an attempt to design a new synthetic access to macrolactams, we now investigated the oxy-azonia-Cope reaction of 2-vinylcycloalkanones **10**: by simply linking R^3 together with R^5 (Scheme 1) in substrate **6** by a carbon chain of a given length. After nucleophilic addition of imine **7**, the resulting zwitterionic intermediates of type **8** were expected to undergo spontaneous rearrangements to afford the corresponding ring-expanded lactams **11** (Table 2).[17,19] Depending on the ring-size of 2-vinylcycloalkanones **10**, the products are medium-ring or macrocyclic homoallylic lactams. In comparison to classical macrocyclic lactam formations, which require activated carboxylic acid derivatives in high dilution,[20] the described lactam formation is rather a [n+4] ring enlargement and offers a new opportunity for the rapid assembly of complex macrolactams. As illustrated in Table 2, cyclic 5-8 and 12-membered substrates **10a-e** and various oxime ethers and imines **7a-j** were smoothly converted to the desired homoallylic macrolactams. 9-Membered lactam **11a** was exclusively obtained with *Z*-configuration (entry 1). The 10-, 11-, and 12-membered lactam products were formed with prevailing *E*-configuration (entries 2-13), while the double bond in the 16-membered rings (entry 14) was constructed less stereoselectively. Notably, cyclic imines such as **7g**, **7h** and indole **7i** were also applicable and resulted in bicyclic and tricyclic lactam products of higher structural complexity (entries 7-9). The structures and double bond configurations of these lactams were unequivocally determined by NMR analysis and confirmed in several cases by X-ray analysis.[17]

To demonstrate the preparative benfit, the new protocol was further utilized to synthesize motuporamine G (Scheme 2), a natural alkaloid isolated from the marine sponge *Xestospongia exigua* by Andersen et al.[21] The reaction of compound **12** and imine **13** with $EtAlCl_2$ gave 13-membered lactam **14** in excellent yield.[22] Three additional simple standard transformations, *i.e.* hydrogenation of **14**, conversion to **15** followed by reduction of both amide groups, completed this short total synthesis of *rac*-**16**. In the crude extract of the sponge, Motuporamines A, B, and C and the mixture of motuporamine G, H, and I were found to be primarily responsible for anti-invasion activity against cancer cells.[21b] However, as motuporamines G, H, and I were all obtained in very small quantities, the exact location of the methyl branch within the macrocyclic ring of Motuporamine G, I and H had only been tentatively assigned. By means of comparison of the NMR data of compound **16** with the corresponding data reported for authentic samples

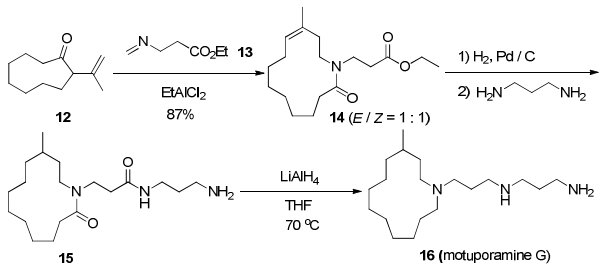
of motuporamines G, H and I,[21b] we can confirm that the constitution of **16** is identical with that of motuporamine G.

Table 2. Oxy-2-azonia-Cope [n+4] Ring Enlargement to Macro Lactams[a]

entry	substrate **10**	substrate **7**	Lewis acid (1.0 eq.)	Product **11**	Yield (%)[b] [E/Z]
1	 **10a**	**7a**	$SnCl_4$	 **11a**	35 [<1:99]
2	 **10b**	**7a**	$SnCl_4$	 **11b**: R^1 = MeO-,R^2 = Me	84 [>99:1]
3	**10b**	**7b**	$SnCl_4$	**11c**: R^1 = EtO-, R^2 = Me	80 [>99:1]
4	**10b**	**7c**	$SnCl_4$	**11d**: R^1 = MeO-, R^2 = n-pentyl	59 [98:2]
5	**10b**	**7e**	$SnCl_4$	**11e**: R^1 = MeO-, R^2 = Ph	70 [>99:1]
6	**10b**	**7f**	$EtAlCl_2$	**11f**: R^1 = Me, R^2 = H	96[c] [>99:1]
7	**10b**	**7g**	$EtAlCl_2$	 **11g**	69[c] [>99:1]
8	**10b**	**7h**	$EtAlCl_2$	 **11h**	92[c] [>99:1]
9	**10b**	**7i**	$EtAlCl_2$	 **11i**	77[c] [>99:1]
10	 **10c**	**7a**	$SnCl_4$	 **11j**: R^1 = MeO-, R^2 = Me	90 [>99:1]
11	**10c**	**7b**	$SnCl_4$	**11k**: R^1 = EtO-, R^2 = Me	73 [>99:1]
12	**10c**	**7f**	$SnCl_4$	**11l**: R^1 = Me, R^2 = H	59 [>99:1]
13	 **10d**	**7a**	$SnCl_4$	 **11m**	89 [95:5]
14	 **10e**	 **7j**	$EtAlCl_2$	 **11n**	35[c] [25:75]

[a]Experimental conditions: 1,2-dichloroethane solution (50ml) of **10** (10 mmol), imine **7** (12mmol) and Lewis acid (10 mmol) were stirred under argon atmosphere for 24 hours at room temperature. [b]Isolated yield after chromatography or Kugelrohr distillation. [c]When 1.0eq of $SnCl_4$ was used, the conversion is less than 20% detected by GC analysis.

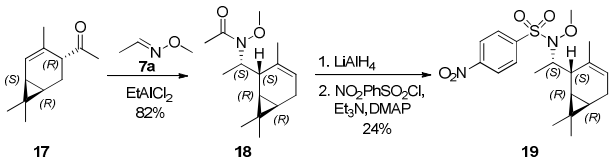
Scheme 2. Application of an Oxy-azonia-Cope Rearrangemment to the Total Synthesis of Motuporamine G



12 14 (*E* / *Z* = 1 : 1) 15 16 (motuporamine G)

To gain deeper insight into the stereochemistry-defining step of the oxy-2-azonia Cope rearrangement, the reaction of acetyl carene **17** with oxime ether **2** in the presence of the Lewis acid (LA) $AlEtCl_2$ (Scheme 3) was investigated experimentally as well as computationally, using Density Functional Theory.[23,24]

Scheme 3. Chirality Transfer Study of Oxy-2-azonia-Cope Rearrangement of Acetyl Carene 17 and Oxime 7a



17 **18** **19**

The transformation of **17** to **18** was calculated to proceed *via* the mechanism illustrated in Figure 1. After initial addition of the oxime ether to Lewis acid activated **17**, the zwitterionic intermediate **Int-17** is formed. A concerted, asynchronous Cope rearrangement subsequently takes place as the rate-determining step to give **18**. The reaction was calculated to be relatively facile and exergonic ($\Delta\Delta G^{\ddagger}$ = 16.6 kcal/mol and ΔG_{rxn}= –11.5 kcal/mol at M06-2X level of theory, see Figure 1). As such, the reaction mirrors the reactivity of our recently investigated oxonia-Cope transformation,[11a,25] and the the Cope rearrangement constitutes the selectivity determining step.

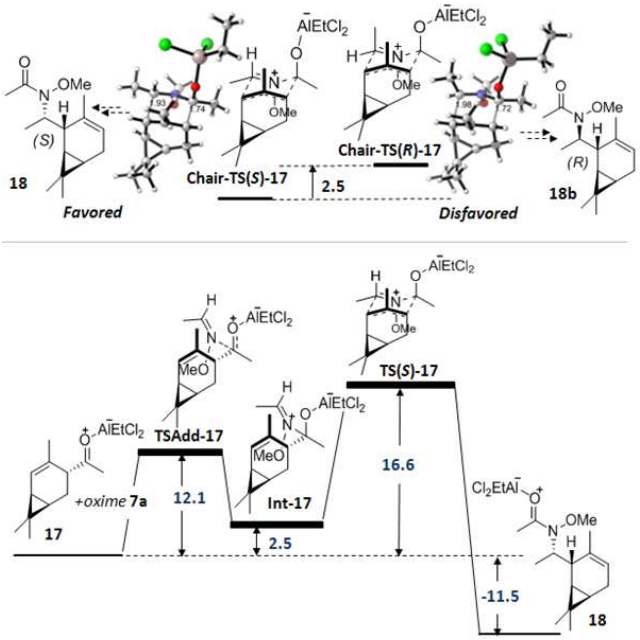


Figure 1. Selectivity ($\Delta\Delta G^{\ddagger}$) in favor of **18** (top) and free energy reaction profile leading to product **18** with $AlEtCl_2$ as Lewis acid (bottom); calculated at CPCM(DCE) M062X/6-31+G(d,p)//B3LYP/6-31G(d) with SDD (for Al). Standard state was converted to 1M.[21]

The chair-like transition state (**TS(*S*)-17**) is calculated to be significantly favored in the oxy-2-azonia Cope rearrangement, consistent with the experimental finding of *S*-stereochemistry in the product.[17] The next higher-energy TS ($\Delta\Delta G^{\ddagger}$ = 2.5 kcal/mol), *i.e.* **TS(*R*)-17**, would lead to **18b -** the product of opposite stereochemistry with respect to the forming C-N bond (Figure 2). This selectivity trend is found to be largely

method- and also Lewis-acid-independent (see SI for further information).[24, 25]

In summary, we have found a novel, atom economical way for the preparation of homoallylic tertiary amides and macrolactams via a tandem nucleophilic addition / oxy-2-azonia-Cope rearrangement mediated by a Lewis acid. The transformation proceeds at room temperature. Most of the transformations proceed with high *E*/*Z* selectivity. The synthetic potential of the present protocol was illustrated by total synthesis and structure verification of the motuporamine G. In addition, a chirality transfer study and computational analysis disclosed a highly-ordered transition state of this transformation.

ASSOCIATED CONTENT

Supporting Information
Experimental procedures, compound characterization, compilation of computational and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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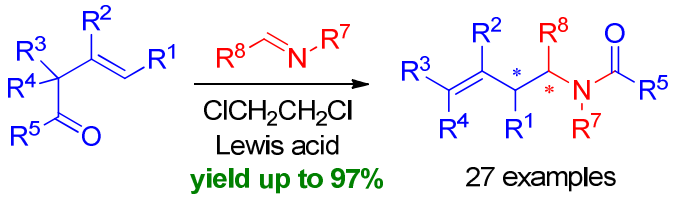
(25) Calculations on the 2-oxonia Cope rearrangement also suggest a chair-like TS to be favored. The predicted selectivity in the 2-oxonia Cope reaction was $\Delta\Delta G^{\ddagger} = 3.5$-$4.8$ kcal/mol (depending of level of theory), see ref. 11a.


R2
R3
R1
R4
R5
O
R8
N
R7
ClCH2CH2Cl
Lewis acid
yield up to 97%
R2
R8
O
R3
*
*
N
R5
R4
R1
R7
27 examples