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Exploiting Non-Covalent Interactions in Synthesis: Macrocyclization Employing Amide-Based Auxiliaries

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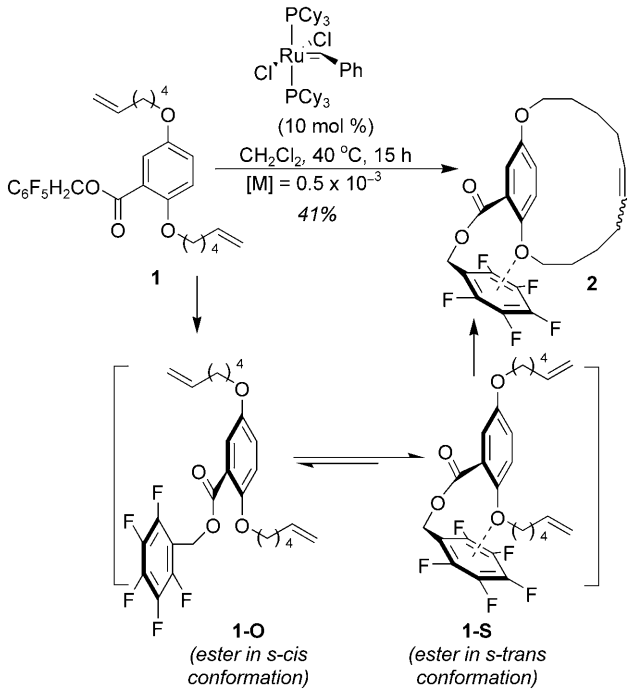
Abstract: Efficient macrocyclic olefin and en-yne metathesis can be conducted employing benzyl ester auxiliaries that engage in quadrupolar interactions. The use of amide linkers in place of esters results in higher overall yields. Computational studies suggest that amide auxiliaries stabilize conformers conducive to macrocyclization over 22 times more efficiently than an ester linkage. Molecular modelling studies also suggest a preference for engaging in quadrupolar interaction for the amide auxiliaries, in contrast to the lone-pair (lp):π interactions predicted for ester-based auxiliaries.

Keywords: cyclophanes; macrocyclization; natural product synthesis; olefin metathesis; quadrupolar interactions

The number of isolated biologically active macrocyclic natural products continues to expand, reinforcing the importance of developing new synthetic methods for macrocyclic compounds. Macrocyclization *via* olefin metathesis has evolved into one of the most efficient synthetic methods available to construct macrocycles.[1] However, in some cases the predisposition of the substrate towards macrocyclization can be difficult to overcome. This has been observed in the synthesis of macrolide natural products[2] as well as macrocyclic peptides.[3] In such cases, the availability of methodologies to enable macrocyclization becomes increasingly important. Recently our group disclosed that the formation of strained paracyclophane structures was possible using ester-based auxiliaries.[4] We have demonstrated that these auxiliaries are effective in forming strained ring systems either by ring-closing olefin or ring-closing en-yne metathesis.[5] The auxiliaries can contain perfluorophenyl or bis-3,5-trifluoromethylphenyl groups which can engage in either lone-pair (lp):π[5] or π:π interactions[6] with the aromatic group of the substrate. These non-covalent interactions result in stabilizing conformations of the substrate that are conducive to ring closing. For example, molecular modelling investigations have suggested that the ester **1** can adopt an "open" conformation **1-O**, whereby the auxiliary is extended and not involved in any non-covalent interactions with the central benzene ring. This conformer would exist in equilibrium favoring **1-S**, in which the perfluorophenyl ring is folded inwards and engages in a lone-pair:π interaction with oxygens connected to the central benzene ring (Scheme 1). As a result of the lone-pair:π interaction, **1-S** is favored by $-0.20\ \text{kcal mol}^{-1}$ over **1-O**. It is remarkable that such small differences in energy can be responsible for the "gearing" of **1** towards productive macrocyclization.

In examining the structure of conformer **1-S**, we noticed two conformational characteristics that could contribute against the stabilization of such conformers. The first conformational element of the auxiliary examined was the ester's conformation, which was of the *s-trans* type. The second conformational element was that the carbonyl moiety is rotated out of conjugation with the phenyl ring. Therefore, we reasoned that further energy stabilization of conformers such as **1-S** might be achieved through replacing the ester-based auxiliary with an amide-based auxiliary, in an effort to further favor an *s-trans* conformation and electronically stabilize the auxiliary. These studies would also indicate whether the use of perfluorophenyl-based auxiliaries could be applied to the synthesis of cyclic peptides, where an amide linker would likely be employed. Herein, we report the investigation of amide-based auxiliaries for macrocyclization using both chemical synthesis and molecular modelling in parallel.



Scheme 1. Macrocyclization to form [12]paracyclophanes mediated by a pentafluorobenzyl ester auxiliary.

We decided to investigate the use of amide-based auxiliaries for macrocyclization through molecular modelling using a model system similar to that used in our previous studies.[5] Previous reports of the stacking interactions of perfluoroarenes and other arenes in the solid state point towards a preference for a face-to-face orientation.[7,8] However, our previous molecular modelling studies using a DFT geometric and energy analysis[9] suggested that a conformer exhibiting an oxygen lone pair:arene (lp:π) interaction[10,11] was responsible for the gearing of the system towards macrocyclization.

DFT calculations showed that the conformer **1-S** was favored by -0.20 kcal mol^{-1} compared to the conformer **1-O**. As noted above, the auxiliary does not overlap efficiently with the arene core, instead opting to sit over the pendant oxygen atoms in these systems (Figure 1). The analysis of the analogous amide **3** was performed in the following manner. Starting with the conformers obtained for **1-S** from AM1 calculations, the oxygen atom was exchanged for a NH group to give **3**. Subsequently, **3** was refined using AM1 level of theory in which only the torsion angles about the amide functionality were allowed to vary. The resulting conformers was then further refined *via* a DFT geometric and energy analysis. We again observed

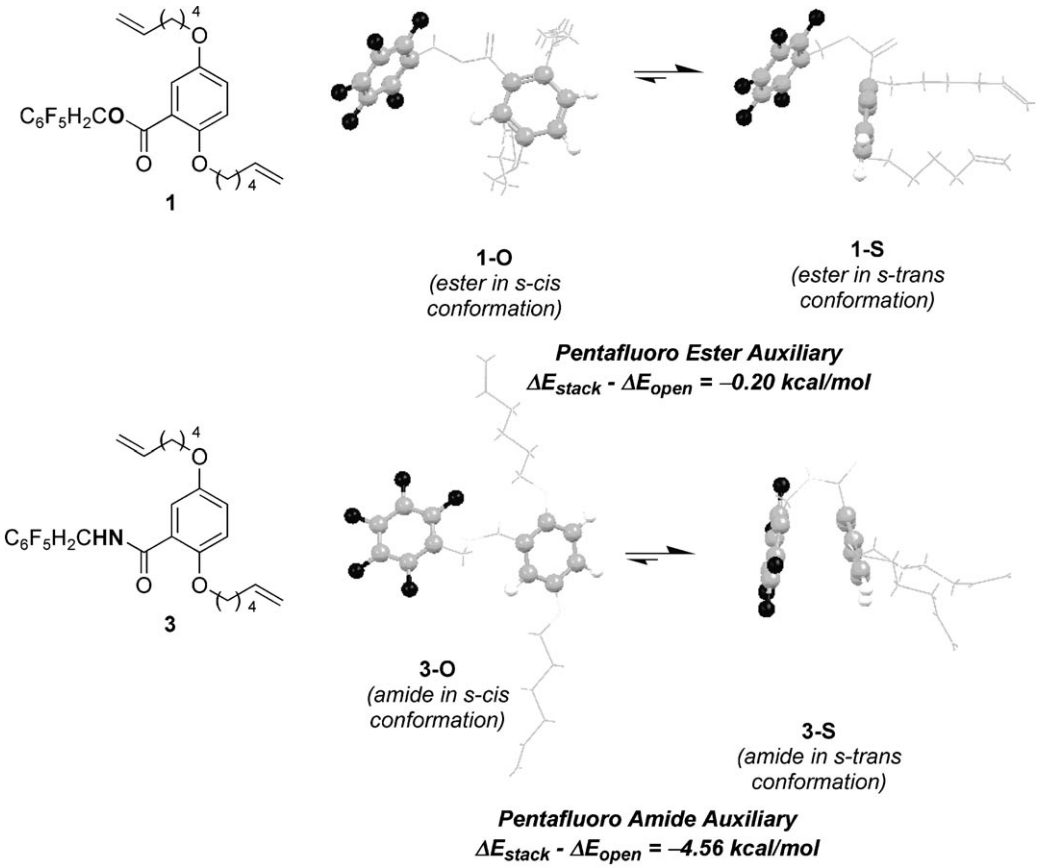


Figure 1. Molecular modelling of **1** and **3** to compare pentafluorobenzyl ester and amide auxiliaries.

two distinct conformations, in which the "stacked" conformer **3-S** was preferred over the "open" conformer **3-O** by $-4.56\ kcal\,mol^{-1}$ (Figure 1). These calculations suggest that both stacked conformers **1-S** and **3-S** are preferred compared to their respective open conformers. The calculations suggest, however, that the amide auxiliary stabilizes its respective stacked conformer (**3-S**) over 22 times more efficiently than the corresponding ester (**1-S**). This suggests that the conformer **3-S** is highly likely to predominate in solution and could result in higher yields in macrocyclization processes.

Interestingly, the molecular modelling calculations also suggest that the amide auxiliary would result in **3-S** engaging in π–π quadrupolar interactions and not lp–π interactions as was calculated for the ester conformer **1-S**. Figure 2 depicts the two different non-covalent interactions calculated for **1-S** and **3-S**. The switch in non-covalent interactions could be due to the added rigidity in **3-S** afforded by the amide auxiliary.

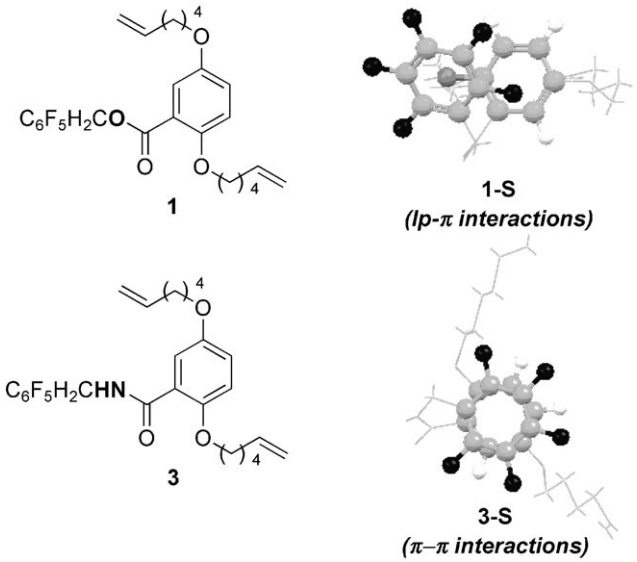
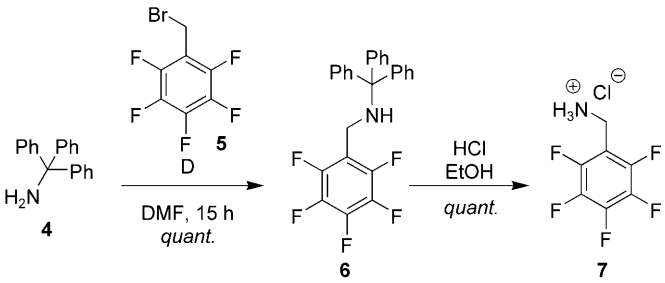


Figure 2. Calculations suggest that **1-S** and **3-S** are stabilized by different non-covalent interactions.

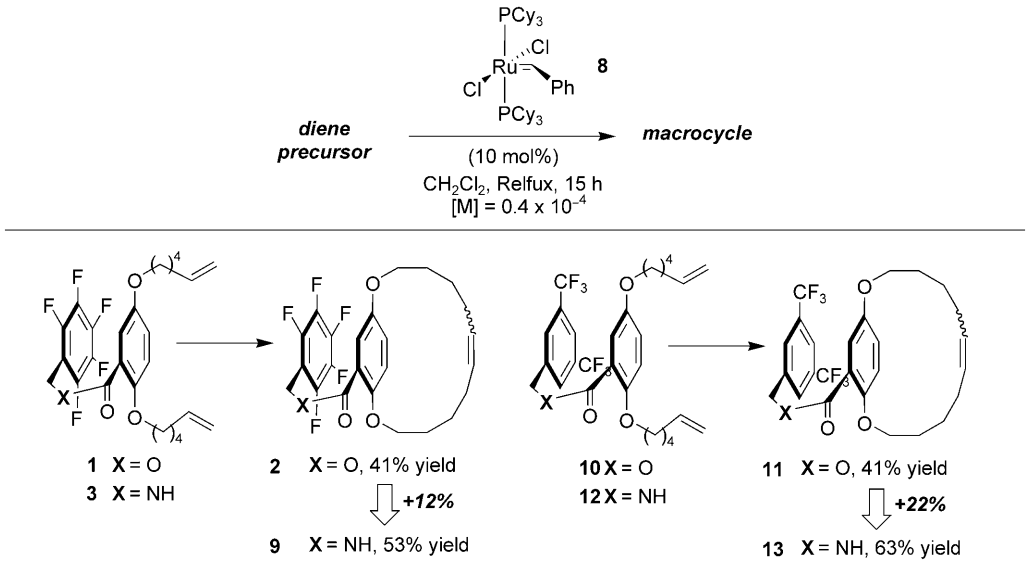
We next decided to evaluate the amide-based auxiliaries based on both 2,3,4,5,6-pentafluorobenzyl and 3,5-bis(trifluoromethyl)benzyl groups.[12] Synthesis of the respective amides (such as **3**) would most likely require access to both 1,3-bistrifluoromethylbenzylamine, or 2,3,4,5,6-pentafluorophenylbenzylamine. The former is commercially available,[13] and the latter has been previously prepared.[14] However, pentafluorophenylbenzylamine has been observed to polymerize on standing and is volatile. As such, we developed a new protocol to access **7** starting from 2,3,4,5,6-pentafluorobenzyl bromide, **5** (Scheme 2). The displacement of bromide from **5** with tritylamine lead to amine **6** is quantitative yield. The trityl protecting group could be removed under acidic conditions and the corresponding HCl salt isolated *via* filtration. The HCl salt of **7** was observed to be bench-stable for many months. The hydrochloride salt **7** was used in the synthesis of various amide precursors for their evaluation in macrocyclization.[15]



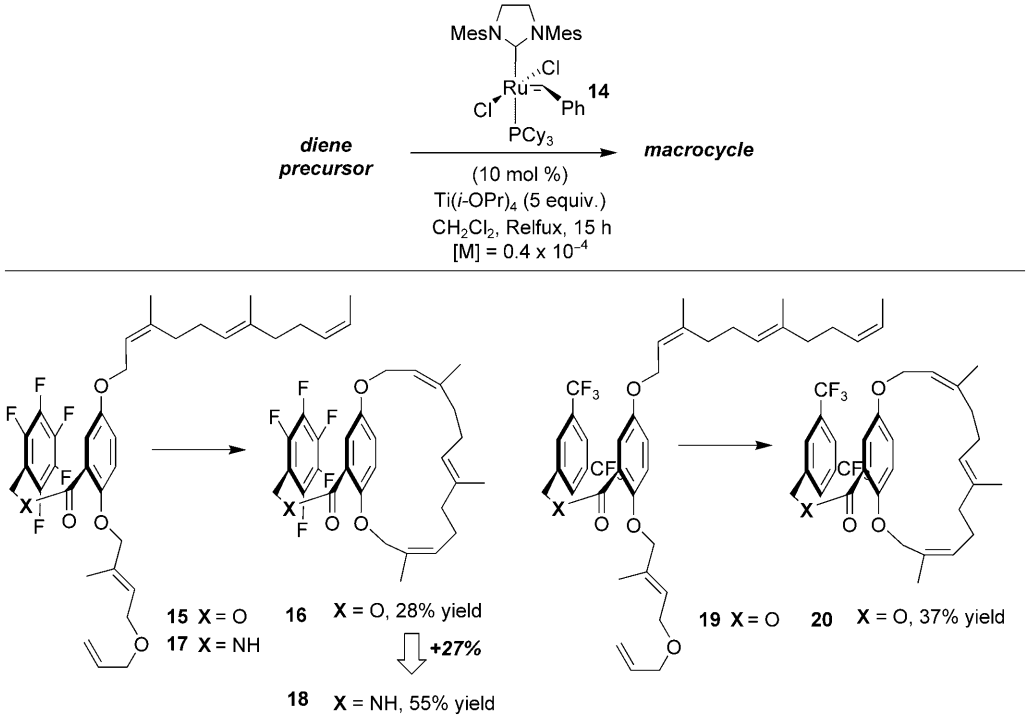
Scheme 2. Synthesis of 2,3,4,5,6-pentafluorobenzylamine hydrochloride **7**.

The amide-based auxiliaries were first evaluated in olefin metathesis macrocyclizations; esters **1**,**10** and **15** and amides **3**, **12** and **17** were each subjected to identical macrocyclization conditions (Scheme 3). The ester **1** was found to afford the macrocycle **2** in 41% isolated yield.[4a] When the cyclization of amide **3** was performed, in which the ester linkage was replaced with an amide linkage, the corresponding macrocycle **9** was obtained in an improved yield of 53%, representing an increase of 12%. Increases in the isolated yield was also found with 3,5-bis(trifluoromethyl)benzyl auxiliaries. The 3,5-bis(trifluoromethyl)benzyl ester **10** afforded the [12]paracyclophane **11** in 41% yield upon macrocyclization. However, the corresponding amide **12** cyclized to give **13** in 63% yield – an increase of 22%!

The comparison of amides *versus* esters was also conducted with more challenging substrates, such as ester **15**, and **19** and amide **17** (Scheme 4). Macrocyclization of these substrates is made possible by exploiting a relay ring-closing metathesis strategy.[16] Thus, the metathesis catalyst reacts with the terminal olefin and undergoes an intramolecular ring-closing event and then subsequently undergoes macrocyclization. Treatement of **15** with Grubbs 2nd generation catalyst **14** forms a trisubstituted olefin and affords macrocycle **16** with a rigidified [14]paracyclophane skeleton due to the presence of three stereodefined olefins. The isolated yield of the macrocycles **16** and **20** using the ester-based auxiliaries was 28% and 37%, respectively. Gratifyingly, switching to a pentafluorobenzylamide auxiliary nearly doubled the isolated yield of the macrocyclic product and the macrocyclization of **17** afforded the macrocyclic amide **18** in 55% yield. The synthesis of macrocycles **16**, **18** and **20** is noteworthy as the carbon skeleton of the macrocy-



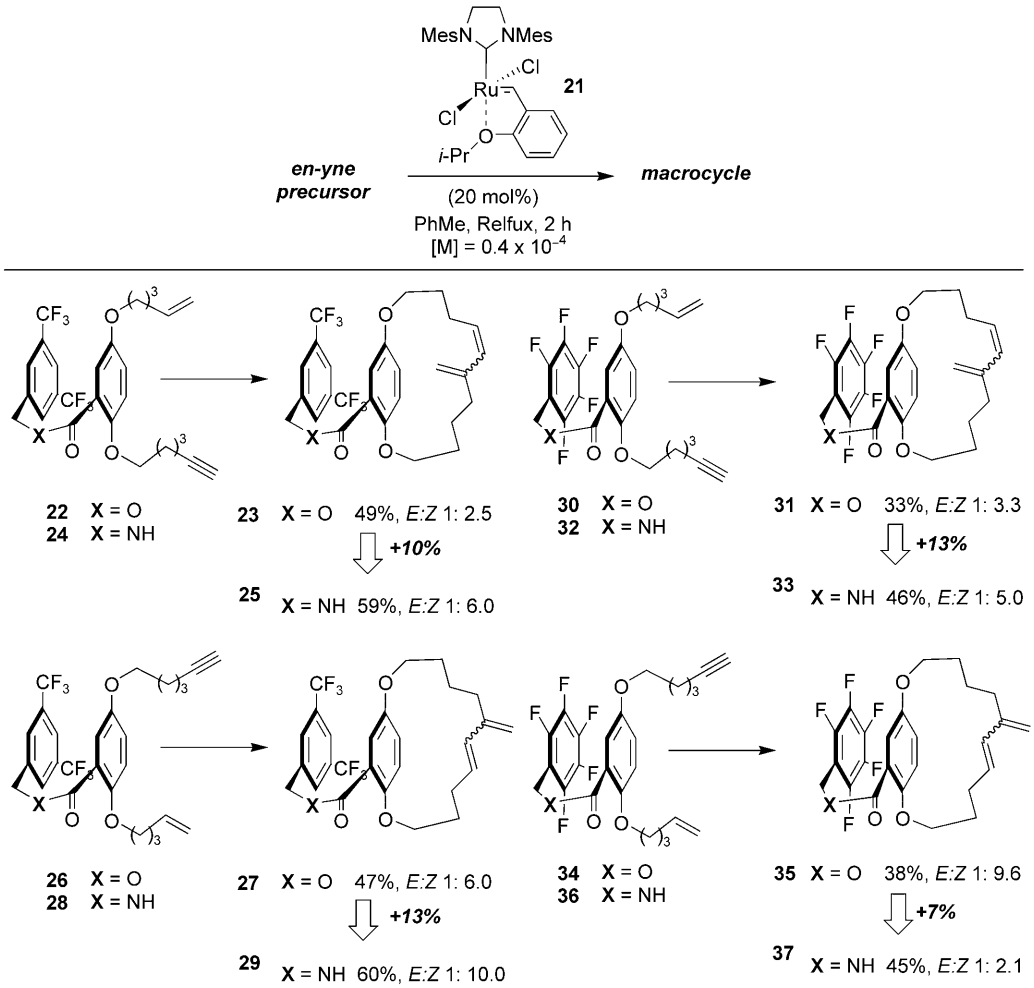
Scheme 3. Evaluation of new amide auxiliaries in macrocyclic olefin metathesis.



Scheme 4. Evaluation of new amide auxiliaries in challenging macrocyclizations.

cle is identical to that observed in the longithorone family of natural products.[17]

Amide-based auxiliaries bearing both a 2,3,4,5,6-pentafluorobenzyl and a bis-3,5-(trifluoromethyl)benzyl group were also evaluated in macrocyclizations using en-yne metathesis substrates (Scheme 5).[18] When the amide **24** underwent macrocyclization with Grubbs–Hoveyda catalyst **21**, the [12]paracyclophane **25** was isolated in 59% yield following purification by silica gel chromatography.[19] The yield of **25** was approximately 10% higher than the analogous cyclization of ester **22** to give the same core macrocycle **23** (49%).[5] In addition, the *E*:*Z* ratio of the products was improved, with the *Z*-isomer still predominating (1:6.0 *E*:*Z* for **25**). The same improved yields and *E*:*Z* ratios were observed during cyclizations of ester **26** and amide **28**. While the ester **26** afforded the macrocyclic diene **27** in 47% yield (*E*:*Z* 1:6.0), the corresponding amide **28** afforded the analogous macrocyclic amide **29** in an increased yield of 60% (*E*:*Z* 1:10).



Scheme 5. Evaluation of amide-based auxiliaries in macrocyclic en-yne metathesis.

Similar results were obtained using 2,3,4,5,6-pentafluorobenzyl auxiliary series. The ester **30** afforded the cyclophane **31** in 33% yield, however, treatment of the corresponding amide **32** with the same catalyst **21** afforded a 46% yield of the macrocycle **33**. Not only was the isolated yield increased by 13%, but the *E*:*Z* ratio of the amide **33** was slightly improved compared to the analogous ester **31** (1: 5.0 *vs.* 1: 3.3 *E*:*Z*). The ester **34**, in which the alkynyl and alkenyl sidechains have been reversed with respect to ester **30**, was also compared in macrocyclizations with the amide **36**. A modest 7% increase in the isolated yield of macrocyclic amide **37** *versus* the macrocyclic ester **35** was observed.

The improved macrocyclizations *via* olefin or en-yne metathesis are likely a result of the improved preference for conformers such as **3-S**, where non-covalent interactions between the auxiliary and aromatic core enable a conformation conducive to cyclization. In addition, the improved yields of products may be due to the fact that the amide auxiliaries enable quadrupolar π–π interactions over lp–π interactions. While it is difficult to make a direct comparison of the energies of these interactions, some computational investigations have studied the interactions of hexafluorobenzene with water (3.77 kcal mol^{-1})[10a,11a] and benzene (~4–5 kcal mol^{-1}),[20] suggesting that the latter may be stronger and hence more effective for gearing the conformation of molecules. In the cases of en-yne metathesis, an increase in the preference for the *Z*-isomer was observed. Although molecular modelling studies suggest a thermodynamic preference for the *Z*-isomers,[5] there is no clear cut explanation, it is clear that each auxiliary exerts an influence during the formation of the macrocycle. It is reasonable to assume that the increased rigidity afforded by the amides may restrict the various degrees of freedom of the sidechains in the macrocyclization precursors, perhaps influencing the preference for the *Z*-isomer.

In summary, the substitution of an ester linker for an amide linker results in higher overall yields and better *E*:*Z* ratios in macrocyclic olefin and en-yne metathesis. Macrocyclizations employing olefin metathesis were improved by 12–27% in terms of isolated

yields, while macrocyclizations employing en-yne metathesis were improved by 7–13%. Improved macrocyclizations were observed with both the 2,3,4,5,6-pentafluorobenzyl and bis-3,5-(trifluoromethyl)benzyl series and each auxiliary type gave similar increases. Calculations suggest that conformer **3-S** is highly favored over **3-O**, which may be responsible for the efficient macrocyclization. The molecular modelling studies also suggest that quadrupolar interactions may be responsible for the gearing of the amide auxiliaries, in contrast to the lp–π interactions predicted for **1-S**. Despite the large energetic stabilization provided the amide linkage in **3-S** compared to the ester linkage in **1-S**, further increases in yields are likely to be obtained only by exploiting stronger non-covalent interactions, such as pyridinium (cation)–π interactions. Of note is the molecular modelling calculations that suggest the selective preference for π–π interactions with the amide auxiliaries. These results bode well for further application of these auxiliaries in macrocyclization of more complex and densely functionalized substrates containing numerous heteroatoms. Of interest would be the application of these auxiliaries in the synthesis of bioactive macrocyclic peptides. Further development of these new auxiliaries through the preparation of chiral versions and investigations in atroposelective macrocyclization is also being studied in our laboratories.

Experimental Section

Representative experimental procedures for macrocyclic olefin and en-yne metathesis reactions are described below. Complete experimental details can be found in the Supporting Information.

General Procedure for Olefin Metathesis Macrocyclization

To a flame-dried, three-neck, round-bottom flask equipped with a reflux condenser under nitrogen, the appropriate metathesis catalyst (10 mol%) and anhydrous CH_2Cl_2 (volume is determined by the amount needed to afford a final concentration of $[M]=0.4\times10^{-4}$ M after complete addition of the precursor solution) were added. The solution was heated to reflux and treated dropwise with a solution of the precursor dissolved in CH_2Cl_2 (50 mL) over 1 h using a syringe pump or an addition funnel. The reaction was allowed to stir at reflux for 10–14 h and was monitored by TLC (hexanes/ethyl acetate, 10/1). The reaction mixture was quenched with ethyl vinyl ether (5 mL), evaporated to about 1 mL, and purified by silica gel flash chromatography (hexanes/ethyl acetate, 20/1) to afford the desired macrocycles in the indicated yields

General Experimental Procedure for En-Yne Metathesis Macrocyclization

A flame-dried, 500-mL, three-neck, round-bottom flask, equipped with a magnetic stirrer, reflux condenser, and isobar addition funnel or a syringe pump system was charged with Grubbs–Hoveyda 2nd generation catalyst (20 mol%) and anhydrous toluene (volume is determined by the amount needed to afford a final concentration of $[M]=0.4\times10^{-4}$ M after complete addition of the precursor solution). The catalyst solution was then placed at reflux 110 °C (toluene). The metathesis precursor in solution (approximately 50 mL) was placed in the addition funnel or the syringe pump system and added over 1 h. After addition, the solution was allowed to stir at reflux for 1 additional hour to ensure complete conversion. The reaction mixture was concentrated under vacuum, dry-packed and purified by flash column silica chromatography (hexanes/ethyl acetate, 20/1) to afford the desired 1,3-diene paracyclophanes.

Supporting Information

Experimental procedures and characterization data for all new compounds are available as Supporting Information.

Acknowledgements

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[12] We also attempted to prepare tertiary amide-based auxiliaries for macrocyclization. However, the synthesis of the corresponding amides from *N*-ethyl-2,3,4,5,6-pentafluorobenzylamine was problematic. Typical peptide couplings (EDC, DCC, HOBt) as well as various reactions involving acyl chlorides failed to afford the desired tertiary amides.

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[18] Although the model systems in our molecular modelling study contain two olefinic sidechains, we believe it is reasonable to assume that similar energetic values would be obtained for en-yne substrates. This based upon the fact that the substitution of an alkyne for a alkene is a minor structural change unlikely to alter the solution state conformations in a significant manner.

[19] The [12]paracyclophane isolated is the *endo*-product resulting from en-yne metathesis. The corresponding *exo*-product is never observed, as it results in the formation of a [11]paracyclophane that is too rigid to form *via* olefin metathesis.

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