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Efficient Macrocyclization Achieved via Conformational Control Using Intermolecular Noncovalent π-Cation/Arene Interactions

Philippe Bolduc, Alexandre Jacques, and Shawn K. Collins*

Université de Montréal, Département de Chimie, C.P. 6128 Station Downtown, Montréal, Québec, H3C 3J7, Canada

Received July 8, 2010; E-mail: shawn.collins@umontreal.ca

Abstract: Quinolinium salt **3** is an effective additive that acts as a conformation control element (CCE) to promote macrocyclization to form rigid cyclophanes via olefin metathesis or Glaser−Hay coupling, which do not cyclize in the absence of the additive. The additives are easily synthesized and highly modifiable and have solubility profiles which allow for simple recovery via filtration.

Macrocycles are prevalent in numerous fields of chemistry and are key structural motifs in natural products,[1] pharmaceuticals,[2] materials science,[3] and supramolecular chemistry.[4] Rigidified or strained macrocycles are of particular interest as their shape persistent structures can be exploited in medicinal chemistry[2] and for well-defined carbon-based materials.[5] However, the desired strain or rigidity in the resulting macrocycle can render macrocyclization problematic unless some form of conformational control is exerted over the precursors. This is exemplified in the synthesis of cyclophane-containing natural products that possess inflexible aromatic cores, where increased dilution does not enable cyclizations.[6]

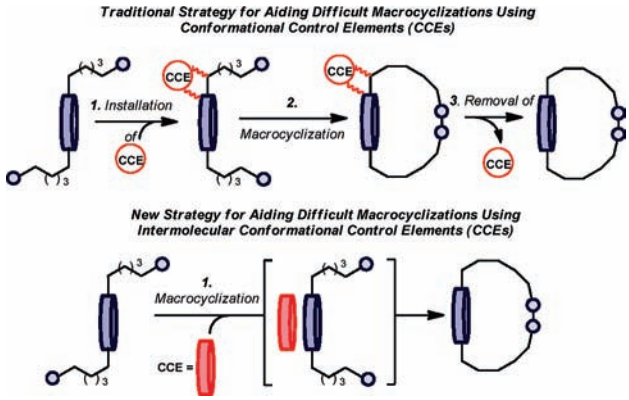
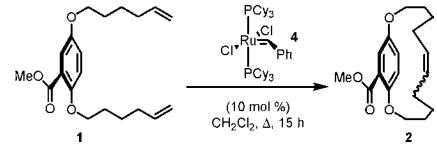


Figure 1. Strategies for achieving conformation control in acyclic precursors prior to macrocyclization.

The traditional strategy to enforce conformational control involves installing a substituent on the macrocyclization precursor (Figure 1). The substituent can be placed next to the aromatic core[3] or, alternatively, attached onto the aromatic moiety.[7] In either case, these conformational control elements (CCEs) help orient the acyclic precursors in a conformation that is conducive to ring closure. Although macrocyclization can be achieved using these methods, a disadvantage is that a number of synthetic steps may be required to install and/or remove the CCE (an additional two or more steps). An alternative strategy would be to control the conformation of the macrocyclic precursor via an intermolecular noncovalent interaction with an inexpensive, readily available additive that can be easily separated through simple workup procedures. Herein we report that difficult macrocyclizations can be achieved through the use of quinolinium cations as intermolecular CCEs.[8]

In searching for potential CCEs that would interact with molecules through noncovalent interactions with arenes,[9] our attention was drawn to biological systems, where cation/arene interactions are well documented to enforce a conformational bias.[10] We decided to investigate using π-cations as CCEs in the macrocyclization of [12]paracyclophanes, as these systems are found in natural product structures and had already been demonstrated as challenging and difficult macrocyclizations.[7]

Table 1. Optimization of Conformational Control Element (CCE)



entry	CCE additive	CCE substituent	X^-	yield (%)[a]
1	None	None	None	0
2			I^-	31
3			PF_6^-	41
4			NTf_2^-	18
5		R^1 = F, R^2 =H,	BF_4^-	20
6		R^1 = CN, R^2 =H,	PF_6^-	20
7		R^1 = H, R^2 =CN,	PF_6^-	20
8		R^1 = H, R^2 =NMe_2,	PF_6^-	20
9		R^1 = Bn,	PF_6^-	30
10		R^1 = 4-NO_2Bn,	PF_6^-	30
11	*N*-Me-isoquinolinium		PF_6^-	25
12	*N*-Me-benzo[h]quinolinium		PF_6^-	30
13		**3** R^1 = H,	PF_6^-	45
14		R^1 = CN,	PF_6^-	45

[a] Isolated yields after chromatography.

Thus, we began our investigations with the macrocyclization of ester **1** via olefin metathesis. Upon treating ester **1** under standard macrocyclization conditions (Table 1, entry 1), only linear dimers and higher oligomers were observed.[11] Upon repeating the macrocyclization with the addition of the *N*-Me-pyridinium iodide, the desired macrocycle **2** was isolated in 31% yield. Further increases in yield were observed upon changing the counterion to PF_6^- (40% yield).[12] Further substitution of the pyridine nucleus was also not beneficial, as the inclusion of electron-withdrawing groups (entries 4, 5, and 6), electron-donating groups (entry 7), or *N*-substitution (entries 8 and 9) did not result in an increase in the isolated yield of **2**. Finally, we investigated increasing the size of the CCE. Both *N*-Me-benzo[*h*]quinolinium and isoquinolinium PF_6^- were unsuccessful at increasing the yield of **2**. However, both the quinolinium **3** and its 3-cyano analog afforded a 45% yield of **2**. Upon identifying **3** as an optimal CCE for olefin metathesis-mediated macrocyclizations, we next probed its substrate scope (Table 2).

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Importantly, we first determined the ester functionality of **1** was not necessary and that additional substituents were tolerated, as the [12]paracyclophanes **5** and **6** were isolated in 50% and 45% yield respectively. Larger macrocycles such as the [13]paracyclophanes **8** as well as [14]paracyclophane **9** were isolated in good yields. Similarly, [12]metacyclophanes **7** and **10** could also be isolated in good yields (61% and 45% respectively). All paracyclophanes shown in Table 2 are not observed when macrocyclizations are carried out in the absence of additive, except **9**, which is formed in 50% yield.

Table 2. Macrocyclizations via Metathesis Employing **3** as a CCE

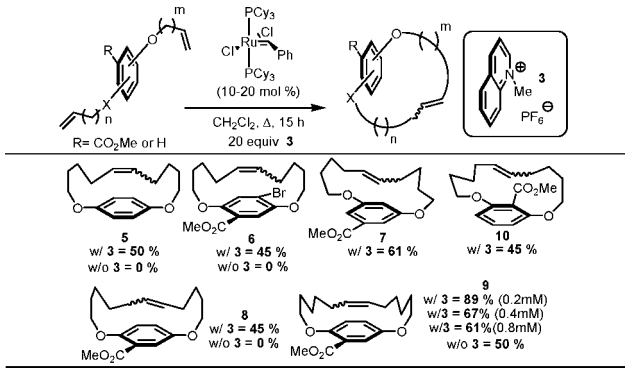
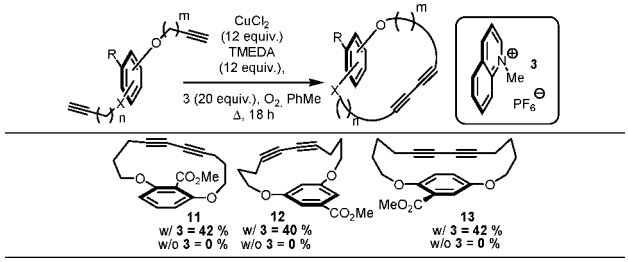


Table 3. Glaser−Hay Macrocyclizations Employing **3** as a CCE



To demonstrate the generality of the quinolinium based CCEs, Glaser−Hay couplings were also investigated (Table 3). Three diyne-containing macrocycles were also prepared using **3** as a CCE. Macrocyclization under standard conditions afforded the corresponding metacyclophanes **11** and **12** in 42% and 40% yields respectively. The paracyclophane **13** was also prepared in 42% yield. Note that all macrocyclization products shown above are not observed when carried out in the absence of the additive. The results also demonstrate the ability of the CCEs to promote conformational control even under elevated temperatures and in the presence of a competing π-rich solvent like toluene.

The quinolinium additives are easily recyclable;[13] following cyclization, the reaction mixture is concentrated and the addition of Et_2O or ethyl acetate causes the precipitation of the additive as a white solid that is easily collected via filtration (>95% recovered) and can be reused in subsequent macrocyclizations.[14] Furthermore, the CCEs can improve the yields of macrocyclizations that normally function without the need for conformational control, even at higher concentrations (Table 2).[15] Macrocyclization afforded the macrocycle **9** in 50% yield in the absence of additive ([M] = 2×10^{-4}). At identical concentrations, the addition of **3** as a CCE greatly improved the isolated yield, affording the macrocycle in 89% isolated yield. As such, we increased the concentration 2-fold and observed an isolated yield of 67% for **9**. Following increasing the concentration 4-fold, the isolated yield of the macrocycle was 61%. These observations demonstrate the potential applicability of the cationic CCEs to improve general macrocyclizations by allowing the reactions to be conducted at much higher concentrations.

The mechanism by which **3** interacts with the macrocyclization substrates merits some discussion. There is precedent in the literature both experimentally[8b] and theoretically[8c] to support a face-to-face pyridinium/arene interaction, although recent theoretical studies have shown that T-shaped conformations are also energetically possible.[8d]

In summary, the quinolinium salt **3** is an effective additive that acts as a CCE to promote macrocyclization to form rigid cyclophanes via olefin metathesis or Glaser−Hay coupling, which do not cyclize in the absence of the additive. The additives are easily synthesized and highly modifiable, have solubility profiles which allow for recovery via filtration, and have demonstrated the ability to enforce conformational control to promote macrocyclization at higher concentrations and temperatures. Further study is directed toward determining the exact mechanism by which **3** promotes macrocyclization and examining applications in asymmetric and natural product synthesis.

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Supporting Information Available: Experimental procedures 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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(11) More reactive catalysts resulted in ring opening of the desired macrocycle. Thus, **4** was required at higher catalyst loadings to ensure 100% conversion.
(12) When reduced amounts of **3** are used, the yields decrease (10 equiv of **3** = 27%, 1 equiv of **3** = 25%). Increasing the amount of additive also did not improve the reaction (50 equiv of **3** = 22%). Possible explanations for these effects are under investigation.
(13) See Supporting Information for details.
(14) The additives are hygroscopic and are placed in an oven (>100°C) overnight before use. Quinolinium **3** has been reused in the macrocyclization of **1** without any drop in yields.
(15) For an example of scaling a macrocyclization reaction to industrially relevant scales, see: (a) Farina, V.; Shu, C.; Zeng, X.; Wei, X.; Han, Z.; Yee, N. K.; Senanayake, C. H. *Org. Process Res. Dev.* **2009**, *13*, 250–254. (b) Tsantrizos, Y. S.; Ferland, J.-M.; McClory, A.; Poirier, M.; Farina, V.; Yee, N. K.; Wang, X.-j.; Haddad, N.; Wei, X.; Xu, J.; Zhang, L. *J. Organomet. Chem.* **2006**, *691*, 5163–5171.

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