Organic Syntheses

Discussion Addendum for:

Preparation of a Carbazole-Based Macrocycle Via Precipitation-Driven Alkyne Metathesis

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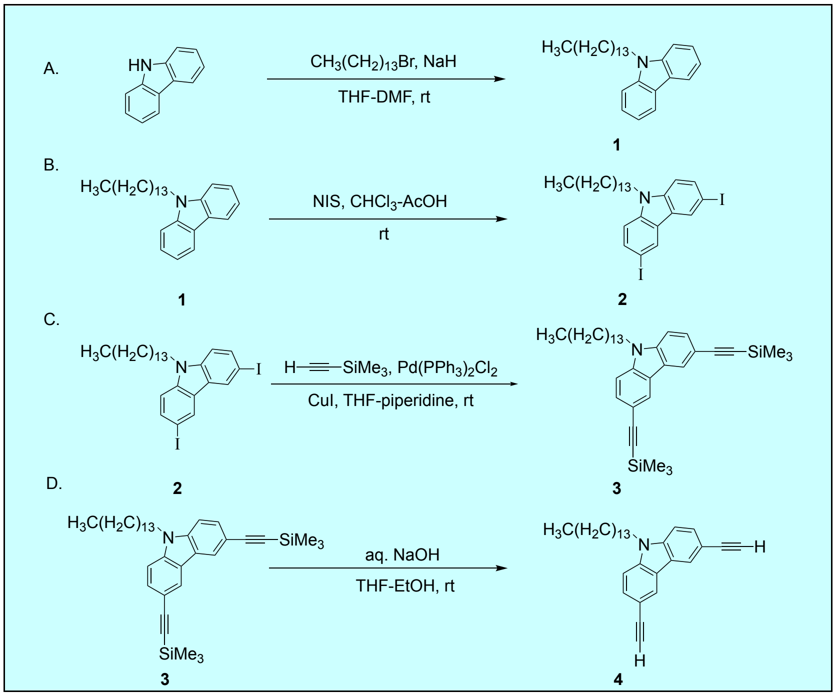
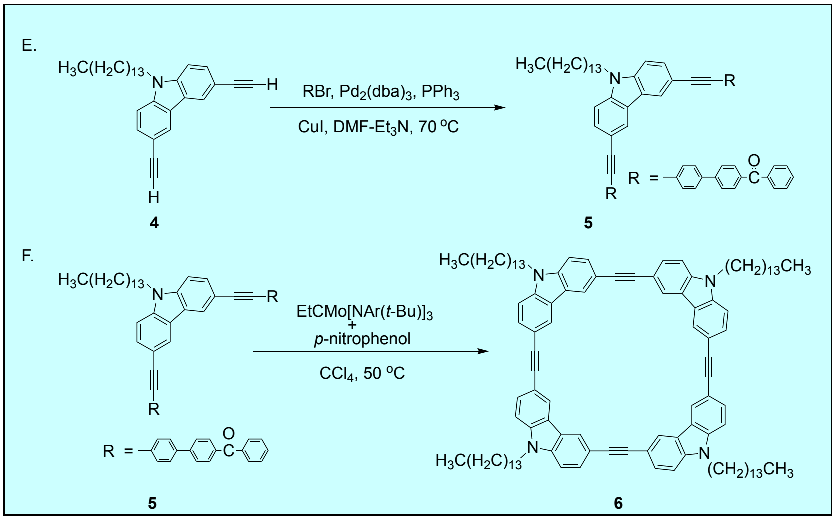
Original Article: Zhang, W.; Cho, H.M.; Moore, J.S. Org. Synth. **2007**, *84, 177-191*



Org. Synth. **2018**, *95*, 231-239
DOI: 10.15227/orgsyn.95.0231



Within the last two decades, the development of efficient alkyne metathesis catalytic systems has allowed for the application of this methodology in both organic synthesis and materials chemistry.[2–6] The utility of alkyne metathesis dynamic covalent chemistry (DC$_V$C) for the preparation of complex molecular architectures has resulted in the use of this method for the synthesis of discrete, shape persistent molecular structures.[3]

The inherent reversibility of alkyne metathesis means that undesired byproducts must be continually removed in order to drive the reaction forward to a desired product.[4,5] Classically, this may be achieved through the use of propynylated substrates that produce 2-butyne as a reaction byproduct (Figure 1A).[5,7] This volatile product may then be removed *via* continually subjecting the reaction mixture to high vacuum.[5,7] While this method can efficiently facilitate conversion to the desired product, the use of vacuum-driven metathesis conditions can lead to a number of drawbacks.[4] In order to minimize solvent loss, high-boiling solvents such as toluene or chlorobenzenes are often used, or solvent must be periodically added.[4] The efficiency of this method also decreases dramatically as the scale of the reaction is increased, greatly limiting the utility of vacuum-driven metathesis on large scale.[7]

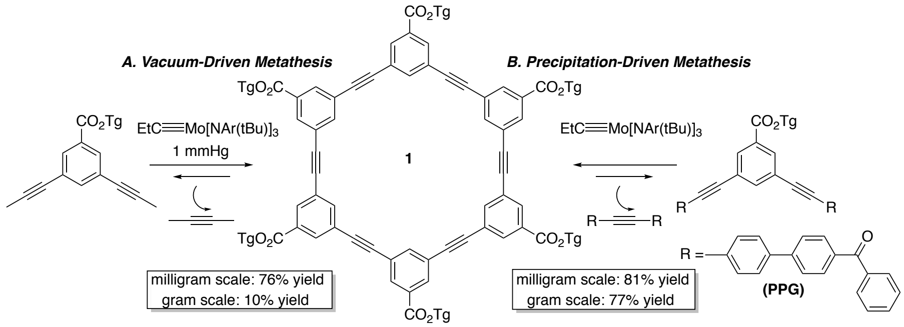


Figure 1. Comparison of vacuum and precipitation-driven alkyne metathesis

In order to address these limitations, we developed a *precipitation-driven* alkyne metathesis system (Figure 1B).[7,8] This strategy relies on the incorporation of a *precipitating group* (PPG) into the desired reaction precursor (Figure 1B).[7,8] Upon metathesis, the resulting diaryl acetylene byproduct precipitates from the reaction mixture thus driving the reaction equilibrium toward product formation.[7] The advantage of this method is that it is highly effective for the large-scale synthesis of a variety of macrocycles (i.e. **1**) *via* alkyne-metathesis that would afford low yields under classical vacuum-driven methods.[7,8]

In the years since we reported this method, the precipitating group strategy has been employed in both our own work and that of others.[3] In addition to our original report where we prepared a variety of phenylene ethynylene macrocycles, we have also reported the synthesis of cyclic trimer **2** *via* precipitation-driven alkyne metathesis (Figure 2).[7–9]

Upon mixing macrocycles **2** and **3** under metathesis conditions, tetrameric macrocycle **4** could be identified by mass spectrum analysis, demonstrating that arylene ethynylene macrocycles are dynamic under these conditions.[9] Our own group and others have further demonstrated the utility of precipitation-driven alkyne metathesis in the development of a variety of robust alkyne metathesis catalysts.[6,10–14] In order to simplify purification and catalyst lifetimes we have demonstrated that both solid silica-supported and polyhedral oligomeric silsesquioxane (POSS) ligands are highly active and selective catalysts for a variety of substrates, including those which rely on the use of the precipitation strategy.[13,14] Zhang and coworkers have also pioneered the use of multidentate triphenol ligands that also show high catalytic activity and functional group tolerance and can be extended to the use of our precipitation driven method in high yields and short reaction times.[10–12,15]

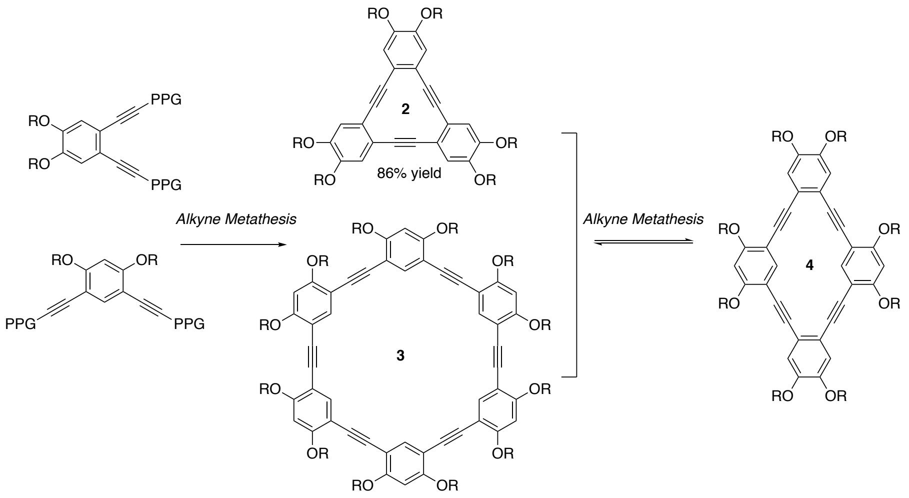
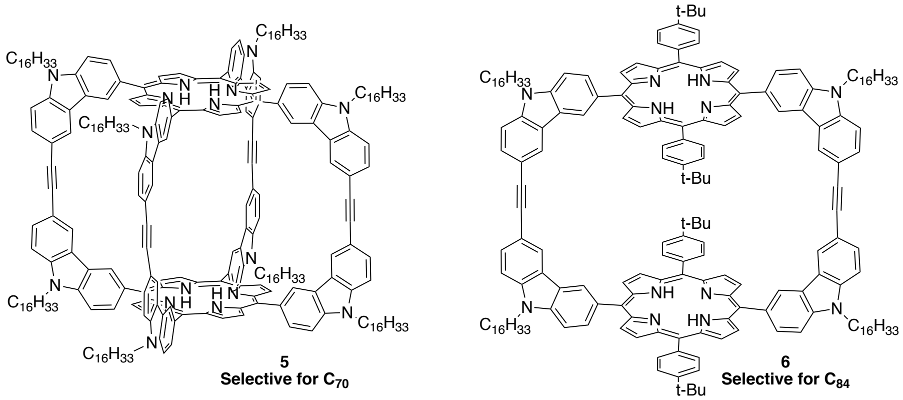


Figure 2. Dynamic trimeric and hexameric macrocycles *via* precipitation-driven metathesis

The utility of precipitation-driven alkyne metathesis is particularly noteworthy for the synthesis of complex molecular cages.[16–20] Zhang and coworkers have made use of this methodology for the preparation of a number of molecular cages (Figure 3). Cage **5** was prepared in 56% yield *via* precipitation driven metathesis from a rigid porphyrin precursor.[17] Notably, this shape-persistent molecular prism shows high binding affinity for both C_{60} and C_{70} fullerenes, with the binding constant for encapsulation of C_{70} being three orders of magnitude greater than that for C_{60}.

Following this report, Zhang and coworkers prepared bisporphyrin macrocycle **6** in 60% yield through precipitation alkyne metathesis.[19] Fullerene binding studies demonstrated that this macrocycle shows the highest affinity for C_{84}. These results demonstrate the ability to prepare a number of structures with variable properties that can be accessed through efficient precipitation-driven metathesis.[19] In addition to facilitating efficient metathesis, the use of the precipitating group moiety can improve the purification of complex substrates.[16,20] Zhang and coworkers have demonstrated this in the synthesis of both carbazole[20] and porphyrin[16] -

based precursors. In both examples, the inclusion of the precipitating group was found to improve purification owing to its increased polarity over other alkyne substitutions. These results demonstrate the additional utility of this strategy as a handle for improved purification of metathesis precursors.



5
Selective for C_{70}

6
Selective for C_{84}

Figure 3. Molecular cages prepared by Zhang and coworkers using precipitation-driven metathesis

While precipitation driven alkyne metathesis is broadly applicable and has been widely used for many different substrates, this method requires additional synthetic overhead to include the precipitating moiety.[4,7] Additionally, the high molecular weight of the precipitating group results in poor atom economy for the overall reaction.[4] Methyl-capped alkynes produce volatile 2-butyne as a side product, which has classically been removed *via* vacuum to drive the reaction.[7] In 2010, Fürstner and coworkers reported that 5Å molecular sieves efficiently sequester 2-butyne with comparable yields as precipitation and vacuum-driven procedures.[21]

Molecular sieves have successfully been used to drive alkyne metathesis on a variety of different substrates, and can be used for large-scale synthesis in comparable yields to precipitation-based methods as demonstrated in the synthesis of carbazole macrocycle **7** (Figure 4).[8,21] We have also demonstrated that carbazole macrocycle **7** may be prepared *via* a depolymerization/macrocyclization route from polymeric carbazole precursors.[22]

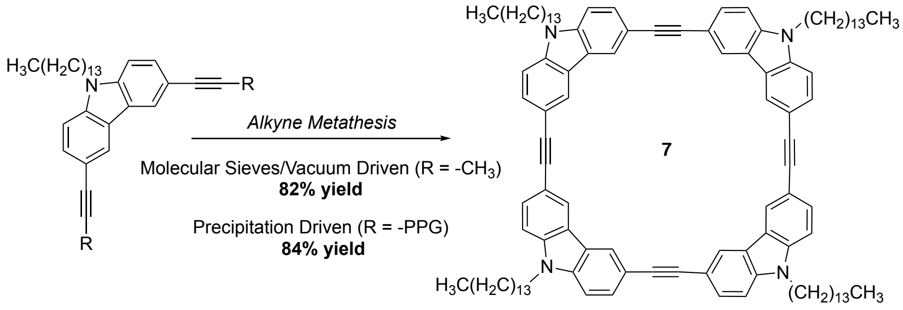


Figure 4. Comparison of molecular sieves and vacuum/precipitation driven methods

The use of molecular sieves in alkyne metathesis is an effective and general method that has been widely applied in both natural product and materials synthesis.[3,4] In recent years we have heavily relied on this method for the synthesis of a number of complex molecular architectures (Figure 5).[23–26] In 2016 we reported the preparation of kinetically trapped tetrahedral cages (**8**) *via* alkyne metathesis from methyl-capped tritopic precursors using molecular sieves to sequester 2-butyne.[25] This reaction proceeds through initial formation of oligomeric intermediates that 'self-correct' to the tetrahedral cage product. The use of propynylated substrates is particularly advantageous in terms of solubility for both precursors and reaction products, especially for reactions that proceed through initial formation of oligomeric intermediates along the pathway to a discrete product. We have also demonstrated the cyclooligomerization of bifunctional precursors to prepare cycloparaphenyleneacetylene precursors (**9**). Both of these processes proceed in near quantitative yields through the use of molecular sieves and can be performed on gram scales with similar efficiency.[26] Commercial grade 5Å powdered molecular sieves are used for these reactions, and must be thoroughly dried in a vacuum oven prior to use. We typically employ a ratio of 800 mg to 1 g of molecular sieves per millimole of propynyl groups, and recommend stirring the mixture vigorously to ensure distribution of powdered sieves.[25,26]

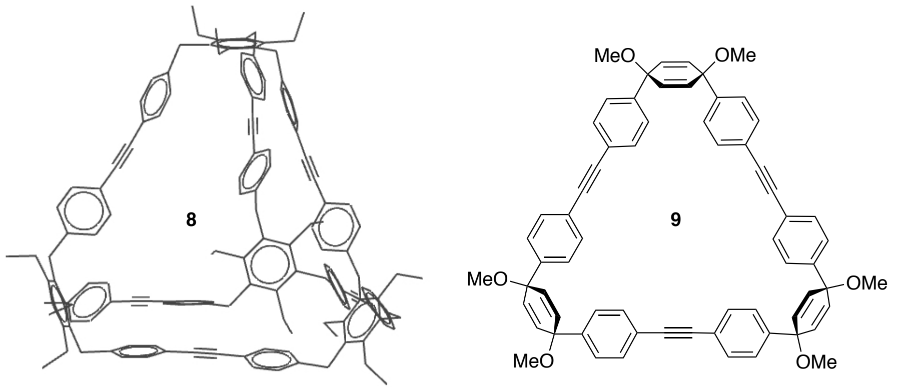


Figure 5. Tetrahedral cages and cyclooligomers prepared via alkyne metathesis using molecular sieves

The use of a precipitating group or a molecular sieves approach largely depends on both the synthetic overhead and structural characteristics of the system in question. The use of a precipitating-group strategy can be advantageous in terms of both scalability and purification of complex reaction precursors.[8,16] The use of this moiety also results in poor atom economy and can complicate solubility of reaction precursors. The use of methyl-capped precursors in conjunction with molecular sieves is an attractive and scalable method with high efficiency.[4,25] Installation of propyne groups is synthetically simple and significantly more atom economical. Overall, while both precipitation and molecular sieve strategies are viable methods that furnish very comparable yields and scalability across a wide range of precursors, the efficiency and synthetic ease of using a molecular-sieves driven approach make this method the most general for driving alkyne metathesis reactions.[4,7]

References

1. Department of Chemistry, University of Illinois at Urbana-Champaign, Urbana, IL, 61820. email: jsmoore@illinois.edu. This work was supported by the National Science Foundation, CHE Division under Grant Number 16-10328.
2. Fürstner, A. *Alkyne Metathesis*; 2014; Vol. 5.

3. Jin, Y.; Wang, Q.; Taynton, P.; Zhang, W. *Acc. Chem. Res.* **2014**, *47* (5), 1575–1586.
4. Fürstner, A. *Angew. Chem. Int. Ed.* **2013**, *52* (10), 2794–2819.
5. Fürstner, A. *Handb. Metathesis Second Ed.* **2015**, *2–3*, 445–501.
6. Gross, D. E.; Zang, L.; Moore, J. S. *Pure Appl. Chem.* **2012**, *84* (4), 869–878.
7. Zhang, W.; Moore, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 12796.
8. Zhang, W.; Cho, H.M.; Moore, J.S. *Org. Synth.* **2007**, *84, 177–191*
9. Zhang, W.; Brombosz, S. M.; Mendoza, J. L.; Moore, J. S. *J. Org. Chem.* **2005**, *70* (24), 10198–10201.
10. Jyothish, K.; Zhang, W. *Angew. Chem. Int. Ed.* **2011**, *50* (15), 3435–3438.
11. Yang, H.; Liu, Z.; Zhang, W. *Adv. Synth. Catal.* **2013**, *355* (5), 885–890.
12. Du, Y.; Yang, H.; Zhu, C.; Ortiz, M.; Okochi, K. D.; Shoemaker, R.; Jin, Y.; Zhang, W. *Chem. Eur. J.* **2016**, *22* (23), 7959–7963.
13. Cho, H. M.; Weissman, H.; Moore, J. S. *J. Org. Chem.* **2008**, *73* (5), 4256–4258.
14. Hyeon, M. C.; Weissman, H.; Wilson, S. R.; Moore, J. S. *J. Am. Chem. Soc.* **2006**, *128* (46), 14742–14743.
15. Jyothish, K.; Wang, Q.; Zhang, W. *Adv. Synth. Catal.* **2012**, *354* (11–12), 2073–2078.
16. Yu, C.; Long, H.; Jin, Y.; Zhang, W. *Org. Lett.* **2016**, *18* (12), 2946–2949.
17. Zhang, C.; Wang, Q.; Long, H.; Zhang, W. *J. Am. Chem. Soc.* **2011**, *133* (51), 20995–21001.
18. Wang, Q.; Yu, C.; Zhang, C.; Long, H.; Azarnoush, S.; Jin, Y.; Zhang, W. *Chem. Sci.* **2016**, *7* (5), 3370–3376.
19. Zhang, C.; Long, H.; Zhang, W. *Chem. Commun.* **2012**, *48* (49), 6172.
20. Wang, Q.; Yu, C.; Long, H.; Du, Y.; Jin, Y.; Zhang, W. *Angew. Chem. Int. Ed.* **2015**, *54* (26), 7550–7554.
21. Heppekausen, J.; Stade, R.; Goddard, R.; Fürstner, A. *J. Am. Chem. Soc.* **2010**, *132* (32), 11045–11057.
22. Gross, D.; Moore, J. *Macromolecules* **2011**, 3685–3687.
23. Moneypenny, T. P.; Liu, H.; Yang, A.; Robertson, I. D.; Moore, J. S. *J. Polym. Sci. Part A Polym. Chem.* **2017**, 1–14.
24. Moneypenny, T. P.; Walter, N. P.; Cai, Z.; Miao, Y.-R.; Gray, D. L.; Hinman, J. J.; Lee, S.; Zhang, Y.; Moore, J. S. *J. Am. Chem. Soc.* **2017**, 3259–3264.
25. Lee, S.; Yang, A.; Moneypenny, T. P.; Moore, J. S. *J. Am. Chem. Soc.* **2016**, *138* (7), 2182–2185.
26. Lee, S.; Chénard, E.; Gray, D. L.; Moore, J. S. *J. Am. Chem. Soc.* **2016**, *138* (42), 13814–13817.

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