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Ring Synthesis by Stereoselective, Methylene-Free Enyne Cross Metathesis

Amol A. Kulkarni and Steven T. Diver*

Department of Chemistry, University at Buffalo, The State University of New York, Buffalo, New York 14260-3000

Received April 21, 2004; E-mail: diver@buffalo.edu

Conjugated dienes are versatile building blocks for complex molecule synthesis and are readily functionalized (e.g., through cycloaddition). Enyne metathesis is a powerful catalytic reaction for *acyclic* diene synthesis,[1] but cyclodiene synthesis through tandem metathetical transformation is expected to display the principal shortcoming of cross enyne metathesis: low stereoselectivity (ca. 1:1 *E*/*Z* ratios). In this communication, we disclose a solution to the selectivity problem through the use of methylene-free metathesis conditions. This development has resulted in an efficient and stereoselective synthesis of 1,3-cyclohexadienes (Scheme 1).

Ring synthesis by cross metathesis is a potentially powerful reaction. The conjoining of a four-carbon subunit with a two carbon alkyne subunit bears analogy to ring synthesis achieved through 4 + 2 cycloaddition. Yet unlike cycloaddition, the intermolecular tandem reaction must attain stereoselective *cis*-$\Delta^{3,4}$ alkene bond synthesis (to be followed by a nonsynchronized alkene ring-closing metathesis). At the outset of this work, it was unclear whether internal alkenes would participate in this reaction and what effect internal alkenes would have on stereoselectivity. The Grubbs ruthenium carbene complex **2**[2] initiates with internal alkenes, making the latter accessible reactants for enyne metathesis. Since there is no CH_2 source to generate [Ru] = CH_2, we use the term "methylene-free" to differentiate the catalytic process of Scheme 1 from most enyne metatheses which use 1-alkene reactants. This simple and atom economical method offers a practical, one-step synthesis of 1,3-cyclohexadienes.

Slow addition of the reactants was considered necessary to suppress competing alkene ring-opening metathesis polymerization (ROMP). The analogous reaction between cyclobutene and alkynes fails because of rapid, exothermic ROMP of the strained cycloalkene.[3] A similar (though less favorable) ROMP pathway of **1** was expected to compete with the enyne ring synthesis of Scheme 1. Direct mixing of **1** and **3** (1 equiv each) required continued, portionwise addition of catalyst to attain low conversion to diene **4A**. This suggested catalyst deactivation.[4] Similarly, slow addition of **1** and alkyne to precatalyst **2** gave no observable reaction. However, with excess **1** present in the reaction, catalyst spiking (2.5 mol %) resulted in complete alkyne conversion. This suggested that **1** plays a role in protecting the catalytic intermediates from decomposition pathways and that excess **1** may be necessary to obtain low (5 mol %) catalyst loadings.

The methylene-free ring synthesis using 1,5-cyclooctadiene (COD) **1** and alkyne **3** was examined under high dilution conditions (Table 1). With 1 to 2 equiv of COD, high catalyst loading was needed for complete conversion (entries 1,2). With COD in excess, direct mixing required 15 mol % of **2** to consume alkyne, independent of reaction temperature (entries 3 and 4). Slow addition of alkyne with excess COD seemed optimal for conversion, and we speculated that excess COD could be used to stabilize the carbene intermediates to attain low (5 mol %) catalyst loading. Delivery of an additional 2 equiv of COD, along with the alkyne being added, achieved low catalyst loadings (entries 5−7).[5] With complete conversions and high NMR yield (89% against internal standard), reactions were repeated on 1 mmol scale (right column, entries 6 and 7).

Scheme 1. Ring Synthesis by Methylene-Free Enyne Metathesis

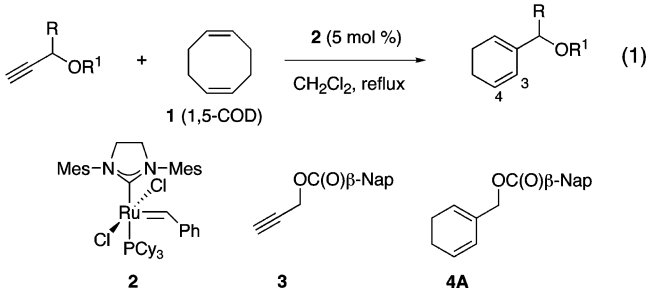

Table 1. Optimization of Alkyne **3**-COD Cross Metathesis[a]

entry	COD (equiv)	temp	cat. (load)	addition time/h	yield (%)
1	1	reflux	**2** (20 mol %)	4	38
2	2	reflux	**2** (12.5 mol %)	4	49
3[b]	2	reflux	**2** (15 mol %)	direct	42
4[b]	2	rt	**2** (15 mol %)	direct	39
5[c]	2 + 2[d]	rt	**2** (5 mol %)	4	74
6[c]	2 + 2[d]	reflux	**2** (5 mol %)	4	76 (69)[e]
7[e]	2 + 2[d]	rt	**2** (5 mol %)	4	89 (64)[e]

[a] Conditions: Alkyne was added over the indicated time period to COD (1 to 2 equiv, 20-40 mM) in 10 mL of CH_2Cl_2 with 5 mol % catalyst at the indicated temperature. Additional catalyst was added if conversion stalled. [b] [Alkyne] = 20 mM, [COD] = 40 mM, mixed directly. [c] Total [1,5-COD] = 200 mM. [d] Syringe pump addition of second portion of COD over indicated time. [e] 1 mmol scale.

A variety of 2-substituted 1,3-cyclohexadienes were synthesized in one step from terminal alkynes in good yields (Table 2). Alkynes with propargylic functionality (entries 1−3) and propargylic substitution (entries 4, 5) were among the best substrates. The presence of homopropargylic heteroatoms was tolerated (entries 6−8), but the dienes were obtained in lower yields compared to entries 1−5.[6] A remote ester posed no difficulties despite the potential for metal coordination through the carbonyl oxygen (entry 8), but oxygen coordination is suggested in entry 9. The methylene-free ring synthesis is more sensitive to coordinating functionality in the alkyne as compared to other cross enyne metathesis.[1a,7]

The reversibility of ROMP and the search for additional methylene-free conditions led us to consider *polymeric* sources of the four-carbon subunit. We were also intrigued to learn whether the alkyne would trigger alkene depolymerization. Polybutadiene[8] is a cheap, widely available polymer, and it reacted with alkynes under the same conditions used with the low-strain cycloolefin COD. The intermediate dienes could be isolated or intercepted by cycloaddition (Scheme 2). The intermediate cyclohexadiene **4A** was isolated in 64% yield, identical to that obtained with 1,5-COD (entry 7, Table 1). A multicomponent coupling is demonstrated in the direct thermal 4 + 2 cycloaddition of the crude dienes **4A** and **6B**

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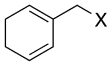
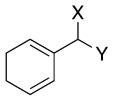
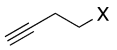
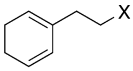
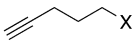
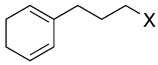
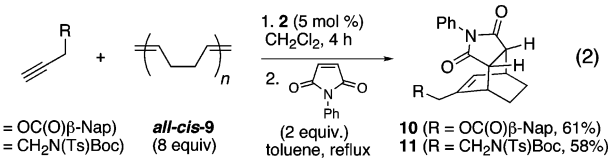
Table 2. Cyclohexadiene Ring Synthesis[a]

entry	alkyne	X	Y	yield (%, NMR)	yield (%)
					
1		OBz	-	**4B,** 83	71
2		OTBDPS	-	**4C** 62	51
3		OCH_2Ph	-	**D**	59
					
4		CH_3	OBz	**5A**	74
5		CH_2Ph	OAc	**5B**	66
					
6[b]		OC(O)β-Nap-		**6A**, 50	41
7		N(Ts)Boc	-	**6B**, 77	62
8		CO_2Et	-	**6C**, 72	68
					
9[b,c]		ONap	-	**7A**	42
10		Cl	-	**7B**	48

[a] Conditions: A solution of alkyne (1 equiv) and 1,5-COD (2 equiv) was added to a solution of **2** (5 mol %) and 1,5-COD (2 equiv) in refluxing CH_2Cl_2 over a period of 4 h. Bz = C(O)Ph. [b] Incomplete conversion. [c] 10 mol % **2** used.

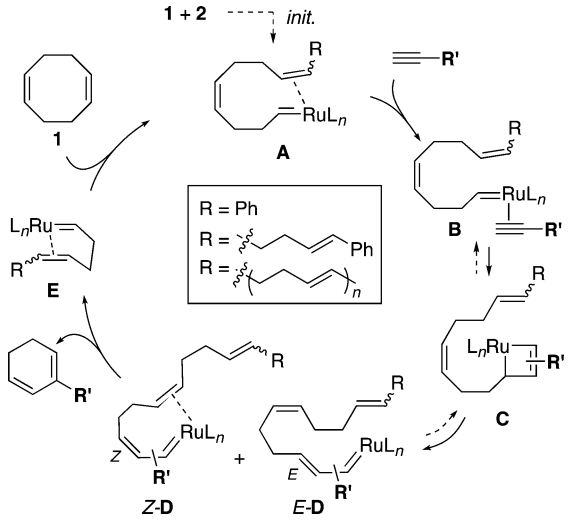
Scheme 2. Alkyne-Polybutadiene Cross-Metathesis/Cycloaddition



with *N*-phenylmaleimide, providing the corresponding cycloadducts **10**, **11** in good overall yield (Scheme 2).

The mechanism of the methylene-free ring synthesis is proposed in Scheme 3. The alkylidene **A** will contain pendant alkenes of varying lengths depending on its genesis (initiation of **2** with COD

Scheme 3. Proposed Mechanism



or with polybutadiene; alkylidene from oligiomerization of COD). Alkyne binding, metallacyclobutene formation, and electrocyclic opening will afford the *E*- and *Z*-vinyl carbenes **D**. The *Z*-isomer can undergo ring-closing metathesis to release diene and truncated alkylidene **E**. The apparent *Z*-selectivity is unique to the methylene-free reaction conditions: 1,5-hexadiene gives a 1:1 mixture of products[9] derived from *Z*-**D** and *E*-**D**, since 1-alkene coordination leads to rapid CH_2 transfer and catalyst turnover (kinetic control). In the methylene-free reaction, the selectivity may result from selective ring-opening of **C** or reversible electrocyclization of *E*-**D**.

Each explanation for selectivity is consistent with the stabilizing role of COD and the sensitivity of the ring synthesis to coordinating functionality within the alkyne. The turnover of vinylcarbenes is believed to be the slow step of enyne metathesis,[1g] and presumably the turnover step (**D** to **E**) is slower for an internal alkene. With intrinsically slower olefin coordination and turnover, the carbenes **D** are vulnerable. For instance, equilibration requires *E*-**D** to persist, and yet *E*-**D** is susceptible to chelation from functionality within the alkyne. When COD concentration is low, η^2-coordination of the vinyl group may also compete with catalysis.[10]

In conclusion, a simple and effective 1,3-cyclohexadiene ring synthesis has been achieved through use of methylene-free tandem metathesis. The modest *Z*-selectivity may be due to a *Z*-selective ring-opening or equilibration permitted by the methylene-free conditions. Further mechanistic studies and whether the *Z*-selectivity can be extended to other tandem cross-metatheses are ongoing investigations.

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Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Reviews: (a) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317−1348. (b) Mori, M. "Ene-yne Metathesis" in *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, Germany **2003**, *2*, 176−204. (c) Poulsen, C. S.; Madsen, R. *Synthesis* **2003**, 1−18. (d) Mori, M. *Top. Organomet. Chem.* **1998**, *1*, 133−154. Early papers using ruthenium carbenes: (e) Kinoshita, A.; Mori, M. *Synlett* **1994**, 1020−1022. (f) Kim, S.-H.; Bowden, N.; Grubbs, R. H. *J. Am. Chem. Soc.* **1994**, *116*, 10801−10802. (g) Stragies, R.; Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, 36, 2518−2520. (h) Kinoshita, A.; Sakakibara, N.; Mori, M. *J. Am. Chem. Soc.* **1997**, *119*, 12388−12389.

(2) (a) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956. (b) Trnka, T. M.; Morgan, J. P.; Sanford, M. S.; Wilhelm, T. E.; Scholl, M.; Choi, T.-L.; Ding, S.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 2546−2558. Hoveyda−Blechert class: (c) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168−8179. (d) Gessler, S.; Randl, S.; Blechert, S. *Tetrahedron Lett.* **2000**, *41*, 9973−9976.

(3) Snapper used high dilution in ROM-CM of cyclobutenes in alkene metathesis: Randall, M. L.; Tallarico, J. A.; Snapper, M. L. *J. Am. Chem. Soc.* **1995**, *117*, 9610−9611.

(4) In contrast, low loadings (high monomer/catalyst ratios) are used for COD polymerization. (a) Bielawski, C. W.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2000**, *39*, 2903−2906. (b) Morgan, J. P.; Morrill, C.; Grubbs, R. H. *Org. Lett.* **2002**, *4*, 67−70. (c) Bielawski, C. W.; Benitez, D.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 8424−8425. (d) *Olefin Metathesis and Metathesis Polymerization*; Ivin, K. J., Mol, I. C., Eds.; Academic Press: New York, 1996.

(5) Benzene proved to be a poor solvent, and low conversions were obtained.

(6) Homopropargyl benzyl ether goes to 50% conversion after addition of 15 mol % catalyst; the TBDPS ether gives complete conversion but only 33% yield by ^{1}H NMR.

(7) Coordinating functionality in the alkyne has been overcome in intramolecular and most intermolecular enyne metatheses using the second generation Grubbs' precatalysts. In the cases of Table 2, slower turnover with internal alkene may exacerbate coordination effects from the alkyne.

(8) Polybutadiene, all-*cis*-**9**, $n = 37000-55000$ ($M_w = 2-3 \times 10^6$) is available commercially. The terminii of the polymer chains contain free CH_2 groups in ca. 0.001−0.0015%. The reaction is statistically 99.999% "methylene-free" using polymer **9**, suggesting that very little reaction takes place from the terminii.

(9) Smulik, J. A.; Diver, S. T. *Tetrahedron Lett.* **2001**, *42*, 171−174.

(10) Trnka, T. M.; Day, M. W.; Grubbs, R. H. *Organometallics* **2001**, *20*, 3845−3847.

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