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Cycloheptadiene Ring Synthesis by Tandem Intermolecular Enyne Metathesis

Amol A. Kulkarni and Steven T. Diver*

Department of Chemistry, University at Buffalo, the State University of New York, Amherst, New York 14260

diver@nsm.buffalo.edu

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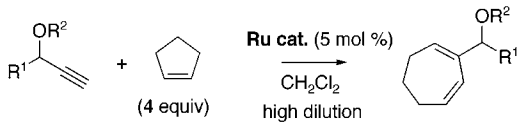
ABSTRACT



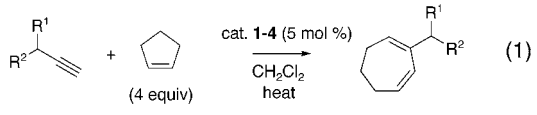
Ru cat. = (dihydroIMes)(Cy_3P)Cl_2Ru=CHPh

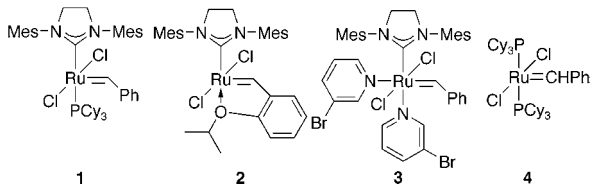
The tandem intermolecular enyne metathesis between 1-alkynes and cyclopentene is reported, providing 2-substituted 1,3-cycloheptadienes. The success of the intermolecular reaction hinges on an appropriate balance between cycloalkene ring strain and reactivity of the alkyne.

Tandem reactions permit the rapid assembly of molecular complexity, ideally through simple carbon−carbon bond-forming reactions. Alkene and enyne metathesis offer a convenient and catalytic means for constructing carbon−carbon bonds.[1] Recently, we reported a tandem metathesis for the construction of 1,3-cyclohexadienes from acyclic precursors, 1-alkynes and 1,5-hexadiene.[2] Such reactions capitalize on a consecutive, in situ ring-closing metathesis that produces the desired ring. In this Communication, we report an atom-economical synthesis of 1,3-cycloheptadienes through intermolecular enyne metathesis of cyclopentene and 1-alkynes (Scheme 1).

It was anticipated from early work with tungsten Fischer carbene catalysts that the reactants of eq 1 would give metathesis polymerization, and the desired ring synthesis was expected to be difficult. Depending on ring strain of the cycloalkene, ring-opening alkene metathesis polymerization (ROMP) should be favorable.[3] Katz discovered enyne metathesis while studying the influence of alkyne modifiers

Scheme 1. Cyclopentene−Alkyne Metathesis





on cycloalkene polymerization, using the aforementioned tungsten Fischer carbene complexes.[4] Katz found that small quantities of alkynes resulted in polymers of increased mean length. For the tandem metathesis of eq 1 to be successful,

(1) Alkene metathesis reviews: (a) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446−452. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450. (c) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012−3043. (d) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18−29. Enyne metathesis reviews: (e) Mori, M. *Top. Organomet. Chem.* **1998**, *1*, 133−154. (f) Poulsen, C. S.; Madsen, R. *Synthesis* **2003**, 1−18.

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

(3) Ivin, K. J., Mol, I. C., Eds. *Olefin Metathesis and Metathesis Polymerization*, 2nd ed. Academic Press: New York, 1996. (b) Ivin, K. J. Cycloalkenes and Bicycloalkenes. In *Ring-Opening Polymerization*; Ivin, K. J., Saegusa, T., Eds.; Elsevier: London, 1984, Chapter 3.

(4) (a) Katz, T. J.; Lee, S. J.; Nair, M.; Savage, E. B. *J. Am. Chem. Soc.* **1980**, *102*, 7940−7942. (b) Katz, T. J.; Sivavec, T. M. *J. Am. Chem. Soc.* **1985**, *107*, 737−738.

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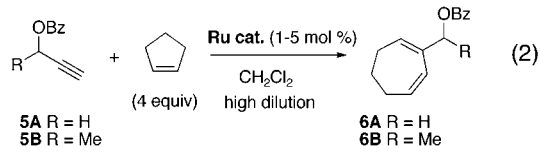
the polymeric pathway must be overcome by alkyne−alkene metathesis. We were interested in learning what substrate parameters would be able to meet these criteria.

Intramolecular, tandem reactions of dienes and alkynes have been used for ring synthesis. In all of the related literature examples, the alkyne and alkene are contained in the same molecule. The Grubbs group demonstrated the utility of tandem enyne metathesis with dienynes, where ring-closing enyne metathesis and another ring-closing alkene metathesis were used to generate bicyclic dienes.[5] Blechert has reported domino metathesis, which results in cyclorearrangement. This process involves cyclopentene ring-opening metathesis followed by ring-closing enyne metathesis.[6] Tandem ring-opening/ring-closing enyne metathesis of *N*-propargyl allyl amides was reported by Mori and Kitamura.[7] It was found that ethylene was needed to suppress ring-opening polymerization, competitive with the intramolecular process. Seven-membered rings and larger were produced in the intramolecular cascade metathesis of Mori and co-workers.[7b] Recently, Banti and North described a ring-opening/double-ring-closing enyne metathesis.[8] Outside of the mechanistic superfamily of carbene-mediated enyne metathesis, it should be noted that the intramolecular reaction of cycloalkenes with alkynes is known from work by Trost using Pd(II)- and Pt(II)-catalyzed enyne bond reorganization.[9]

The intermolecular reaction between cycloalkenes and alkynes is potentially more difficult for several reasons. Foremost, the intermolecular reaction will be more prone to polymerization since alkene ring-opening produces an alkylidene that is not suspended near an alkyne, making alkene homopolymerization (via ROMP) a likely outcome. Second, an intermolecular reaction does not have geometric ring constraint to enforce stereochemistry of the newly formed alkene, and so the newly formed alkene is produced as a mixture of (*E*)- and (*Z*)-isomers. This is a current problem for intermolecular enyne metathesis.

Optimization of the cycloalkene−alkyne metathesis with respect to catalyst and reaction conditions is summarized in Table 1. Direct mixing of reactants and heating in a sealed tube at 110 °C produced the 2-substituted 1,3-cycloheptadiene, albeit in low isolated yield (entry 1). Once the high reaction temperatures were found to be unnecessary for catalyst initiation and sustained catalysis, reactions were carried out in refluxing dichloromethane with better results (entry 2). The significant amount of baseline polymer produced was suppressed by maintaining high dilution through syringe pump addition.[10] Over 12 h addition times, polymer was still present but significantly reduced. Use of fewer equivalents of cyclopentene resulted in incomplete consumption of alkyne, partly due to evaporative loss of cyclopentene.

Table 1. Optimization Studies



entry	alkyne	Ru cat. (in mol %)	temperature	yield (%)[a]
1	**5A**	**1** (5 mol %)	110 °C (sealed tube)	22
2	**5A**	**1** (5 mol %)	reflux	48
3	**5A**	**2** (5 mol %)	reflux	45
4	**5A**	**3** (5 mol %)	reflux	42
5	**5A**	**4** (5 mol %)	reflux	b
6	**5B**	**1** (5 mol %)	reflux	56
7	**5B**	**2** (5 mol %)	reflux	48
8	**5B**	**3** (5 mol %)	reflux	55
9	**5B**	**4** (5 mol %)	reflux	b
10	**5B**	**1** (5 mol %)	reflux	17
11	**5B**	**2** (5 mol %)	room temp	40
12	**5B**	**3** (5 mol %)	room temp	38

[a] Isolated yield, 0.2 mmol scale. [b] No product formed in these rats.

A variety of ruthenium−carbene complexes initiated the cross enyne metathesis. The Hoveyda catalyst **2**[11] initiates the reaction with results comparable to those of the second-generation Grubbs' catalyst **1** (entries 3, 7). Grubbs' pyridine solvate **3**[12] effectively catalyzed the desired transformation (entries 4, 8) but gave lower conversions and yields when conducted at room temperature (entry 12). Since these are very fast initiators for alkene metathesis, we suggest that the refluxing temperature more efficiently converts the intermediate vinylcarbenes to diene products. The first-generation catalyst did not catalyze the cycloheptadiene synthesis (entries 5, 9). From earlier work,[2] we expected the formation of geometrical isomers in a ca. 1:1 ratio. Surprisingly, one major product was obtained.

The scope of the cyclopentene−alkyne cross metathesis is illustrated in Table 2. The reactions were conducted under standard high dilution conditions (syringe pump addition over 12−20 h). In all cases, the cycloheptadiene was obtained as a single product, although trace dimer could be observed (TLC) in isolated runs. The propargyl esters underwent reaction in high yield (entries 1, 2), and propargylic substitution did not diminish the chemical yields (entries 3, 4). The coordinating propargyl benzyl ether **11** and propargyl silyl ether **13** gave good yields (entries 5, 6). Aromatic or aliphatic groups could also be introduced onto the cycloheptadiene ring by suitable choice of alkyne (entries 7, 8). The

(5) (a) Kim, S.-H.; Bowden, N.; Grubbs, R. H. *J. Am. Chem. Soc.* **1994**, *116*, 10801−10802. (b) Kim, S.-H.; Zuercher, W. J.; Bowden, N. B.; Grubbs, R. H. *J. Org. Chem.* **1996**, *61*, 1073−1081.

(6) (a) Ruckert, A.; Eisele, D.; Blechert, S. *Tetrahedron Lett.* **2001**, *42*, 5245−5247. (b) Randl, S.; Lucas, N.; Connon, S. J.; Blechert, S. *Adv. Synth. Catal.* **2002**, *344*, 631−633.

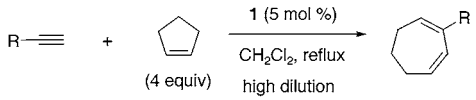
(7) (a) Kitamura, T.; Mori, M. *Org. Lett.* **2001**, *3*, 1161−1163. (b) Mori, M.; Kuzuba, Y.; Kitamura, T.; Sato, Y. *Org. Lett.* **2002**, *4*, 3855−3858.

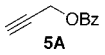
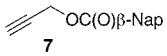
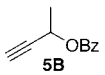
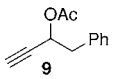
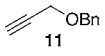
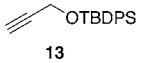
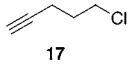
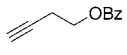
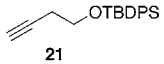
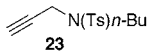
(8) (a) Banti, D.; North, M. *Tetrahedron Lett.* **2002**, *43*, 1561−1564. (b) Banti, D.; North, M. *Adv. Synth. Catal.* **2002**, *344*, 694−704.

(9) (a) Trost, B. M.; Trost, M. K. *Tetrahedron Lett.* **1991**, *32*, 3647−3650. (b) Trost, B. M.; Trost, M. K. *J. Am. Chem. Soc.* **1991**, *113*, 1850−1852. (c) Trost, B. M.; Doherty, G. A. *J. Am. Chem. Soc.* **2000**, *122*, 3801−3810.

(10) Snapper used syringe pump addition to suppress ROMP in order to achieve selective cross alkene metathesis; see: Randall, M. L.; Tallarico, J. A.; Snapper, M. L. *J. Am. Chem. Soc.* **1995**, *117*, 9610−9611.

Table 2. Scope of Cyclopentene−Alkyne Metathesis



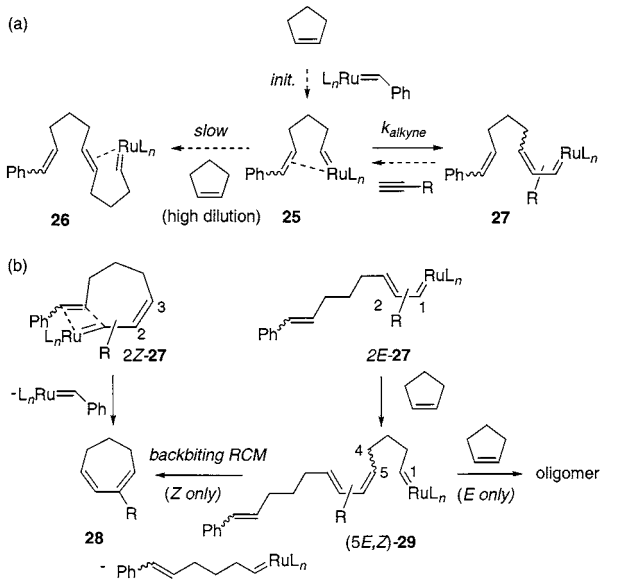
entry	alkyne	1,3 cycloheptadiene	isolated yield (%)
1	 **5A**	**6A** R = CH_2OBz	75[a]
2	 **7**	**8** R = $CH_2OC(O)\beta$-Nap	62
3	 **5B**	**6B** R = $CH(OBz)CH_3$	74[a]
4	 **9**	**10** R = $CH(OAc)CH_2Ph$	62
5	 **11**	**12** R = CH_2OBn	56[a]
6	 **13**	**14** R = $CH_2OTBDPS$	56
7	 **15**	**16** R = Ph	58
8	 **17**	**18** R = $(CH_2)_3Cl$	(70)[b]
9	 **19**	**20** R = $(CH_2)_2OBz$	57
10	 **21**	**22** R = $(CH_2)_2OTBDPS$	53
11	 **23**	**24** R = $CH_2N(Ts)n$-Bu	65

[a] Yield on 2.5 mmol scale. [b] Conversion by NMR.

homopropargylic series gave similar results (entries 9, 10) as did the propargyl tosylamide substrate **23** (entry 11). Given the expectation of a nonstereoselective cross metathesis, the fact that yields exceeded 50% was unexpected. The removal of the ruthenium byproducts was accomplished using DMSO as prescribed by Georg.[13]

A working hypothesis for the mechanism of the cross metathesis is illustrated in Scheme 2. Presumably the reaction is triggered by ring-opening of the cyclopentene. The alkyne must be able to intercept dienylidene **25** before cycloalkene complexation (Scheme 2, panel a), an additional step that is possibly reversible. The high dilution helps suppress cycloalkene homopolymerization. Addition of alkylidene **25** to the alkyne will produce two new stereoisomeric vinyl

Scheme 2. Bifurcation between ROMP and Enyne Metathesis



carbenes **27**. The regiochemistry of this step cannot be deduced from product **28**. The *Z*-isomer (2*Z*)-**27** can undergo ring-closing metathesis with regeneration of the benzylidene initiator (Scheme 2, panel b). Because the (*E*)-isomer (2*E*)-**27** cannot experience ring closure, it is likely to react with cyclopentene, which is present in molar excess. However, reaction with cyclopentene would give a new *E*,*Z*-mixture, (5*E*,*Z*)-**29**. In this instance, the *Z*-isomer is geometrically-poised for backbiting which would release more cycloheptadiene. The *E*-isomer (5*E*)-**29** reacts with cyclopentene to give an oligomer, which explains the remaining mass balance of alkyne.[14]

Previous examples of cross enyne metathesis have utilized 1-alkenes. With 1-alkenes, there is the possibility of generating a reactive methylidene, [Ru] = CH_2, which adds to the alkyne with high regioselectivity.[15a] In the ring synthesis reported here, it is not possible to produce a methylidene, so the reaction must proceed through the intermediacy of ruthenium alkylidenes.[15] This mechanistic possibility has been considered in certain ring-closing metatheses.[15b,c] To the best of our knowledge, this is unprecedented for an intermolecular enyne metathesis.

The ring synthesis appears to be confined to terminal alkynes. With 1,4-diacetoxy-2-butyne, only alkene polymer was observed without significant consumption of the alkyne. Presumably, the internal alkyne reacts intrinsically slower with alkylidene **25**, thereby partitioning into the ROMP pathway (**25** to **26**, Scheme 2, panel a).

(11) (a) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168−8179. (b) Gessler, S.; Randl, S.; Blechert, S. *Tetrahedron Lett.* **2000**, *41*, 9973−9976.

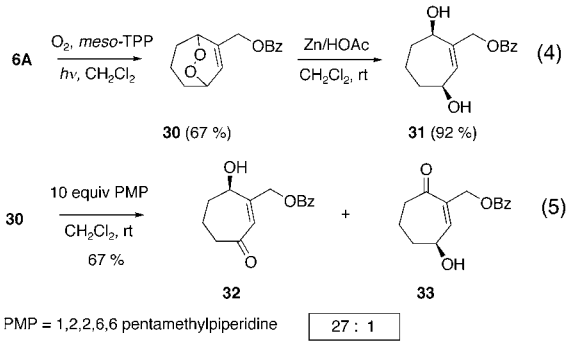
(12) Love, J. A.; Morgan, J. P.; Trnka, T. M.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 4035−4037.

(13) Ahn, Y. M.; Yang, K.; Georg, G. I. *Org. Lett.* **2001**, *3*, 1411−1413.

(14) An extension of the proposed backbiting RCM depicted in Scheme 2, panel b, is that polymerization is unavoidably occurring, even at low cyclopentene concentration. Polymeric alkylidene could then consume alkyne to produce a polymeric vinylcarbene analogous to **27**, which could backbite to give the observed cycloheptadiene.

(15) (a) Stragies, R.; Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed.* **1997**, *36*, 2518−2520. For related mechanistic discussion, see: (b) Hoye, T. R.; Donaldson, S. M.; Vos, T. J. *Org. Lett.* **1999**, *1*, 277−279. (c) Schramm, M. P.; Reddy, D. S.; Kozmin, S. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4274−4277.

Scheme 3. Cycloaddition of 1,3-Cycloheptadienes with Singlet Oxygen

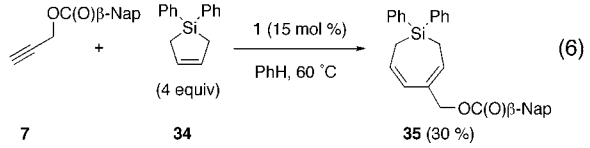


The diene products could be functionalized at the 1- and 4-positions. For example, **6A** gave clean cycloaddition with singlet oxygen to produce the endoperoxide **30**. The peroxide cycloadduct was reductively cleaved (Zn, HOAc) to afford diol **31** (eq 4, Scheme 3). Similarly, regioselective base-induced fragmentation of endoperoxide **30** gave a 27:1 mixture of regioisomeric γ-hydroxy cycloheptenones **32** and **33** (eq 5).

Guided by the crude approximation that intermediately strained cycloalkenes will give the ring products based on their proclivity toward ROMP[16] ("ROMPability"), we investigated whether silole **34** would undergo the enyne metathesis. Heating the silole and alkyne **7** in benzene provided the novel silepin **35** (Scheme 4). This is remarkable since molecular modeling (MMX) of the silepin reveals that the diene is twisted out of conjugation (ca. 90°), suggesting that this enyne metathesis derives less enthalpic driving force than its unconstrained relatives.[17] This single result demonstrates that the ring synthesis is adaptable to other cycloalkenes and may have further utility to access heterocycles.

(16) Ability of a cycloalkene to give ring-opening metathesis polymerization suggests minimally that the cycloalkene will initiate.

Scheme 4. Synthesis of a Novel Silepin



In summary, a classic alkyne-promoted cycloalkene polymerization reaction has been transformed into a useful synthesis of seven-membered rings. Use of the second-generation ruthenium carbenes and high dilution conditions were critical to the ring synthesis. Notable features of the reaction include its mildness and that the products are obtained as single stereoisomers. The success of the intermolecular reaction is thought to be a result of a properly balanced rate of enyne metathesis, which can outcompete alkene (or alkyne-assisted) ring-opening metathesis polymerization. Extension of the reaction to other ring sizes and to cycloalkenes bearing heteroatom substitution is under active study in our group.

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Supporting Information Available: Experimental procedures and full characterization data for new compounds **6**, **8**, **10**, **12**, **14**, **17**, **18**, **20**, **22**, **24**, **30**, **31**, **32**, **35**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL035246Y

(17) Atropisomers of **35** are enantiomers, but when a chiral center is present, the dihedral twist gives rise to diastereomers as seen in the silepin derived from alkyne **5B** (data not shown).