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Functional Group Scope in the Methylene-Free, Tandem Enyne Metathesis

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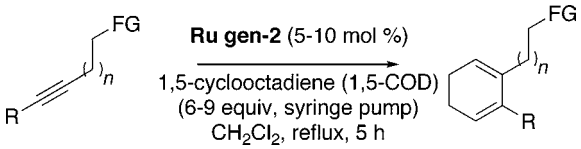
ABSTRACT

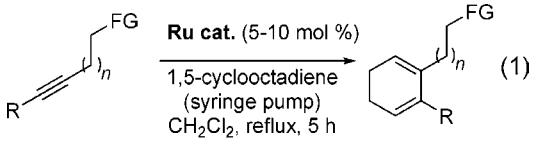


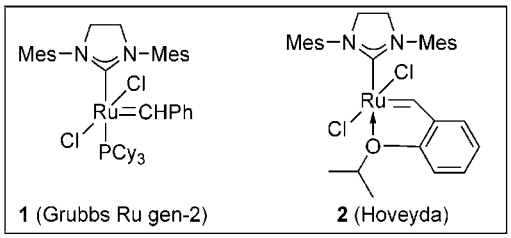
The methylene-free ring synthesis of 1,3-cyclohexadienes has been expanded to include a diverse set of functional group-rich terminal and internal alkynes.

Tandem enyne metathesis[1] between alkynes and dienes provides a useful and efficient ring synthesis.[1d] The tandem reaction (enyne cross metathesis and ring-closing metathesis) is catalyzed by the Grubbs ruthenium carbene complexes. The functional group tolerance of the second generation Grubbs carbene complex **1** and the phosphine-free Hoveyda complex **2**,[2] has significantly emboldened synthetic chemists efforts to utilize metathesis in complex molecule synthesis.[3] We recently developed a tandem metathesis as a method for 1,3-cyclohexadiene synthesis using conditions devoid of CH_2 sources.[4] The 'methylene-free metathesis' is designed to be slow to allow interconversion of isomeric intermediates. As a result, we noted difficulties with certain terminal alkynes. We were interested to discover whether slow turnover conditions compromised functional group tolerance. In this report, we demonstrate that the ring synthesis is successful for functional group-rich alkynes and internal alkynes (Scheme 1).

Despite the tremendous advances in metathesis research,[1−3] there are still problematic cases, especially in molecules where functional group interactions with the carbene are

Scheme 1. Ring Synthesis by Tandem Diene−Yne Metathesis





(1) Recent enyne metathesis reviews: (a) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317−1382. (b) Mori, M. Ene-yne Metathesis. In *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, 2003; Vol. 2, pp 176−204. (c) Poulsen, C. S.; Madsen, R. *Synthesis* **2003**, 1−18. (d) Cross-metathesis between alkyne and diene: Smulik, J. A.; Diver, S. T. *Tetrahedron Lett.* **2001**, *42*, 171−174.

(2) Grubbs' second-generation complex: (a) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956. Hoveyda complex: (b) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168−8179; *J. Am. Chem. Soc.* **2001**, *123*, 3186 [erratum]. (c) Gessler, S.; Randl, S.; Blechert, S. *Tetrahedron Lett.* **2000**, *41*, 9973−9976. (d) Randl, S.; Gessler, S.; Wakamatsu, H.; Blechert, S. *Synlett* **2001**, 430−432.

(3) Metathesis in total synthesis: (a) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490−4527. Development of Grubbs initiators: (b) Love, J. A.; Sanford, M. S.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 10103−10109. (c) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18−29. Alkene metathesis reviews: (d) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900−1923. (e) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012−3043.

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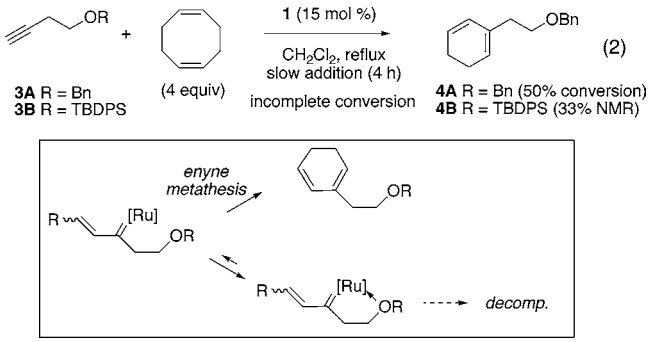
possible.[5] Functional group interactions can slow catalysis through reversible chelation, or they can lead to decomposition. One of the aims of our research is to identify these interactions to aid in planning total synthesis. In our previous methylene-free (MF) ring synthesis, homopropargyl ethers,[4] long known to be difficult substrates in enyne metathesis,[5] gave poor results (Scheme 2, eq 2). Even high catalyst

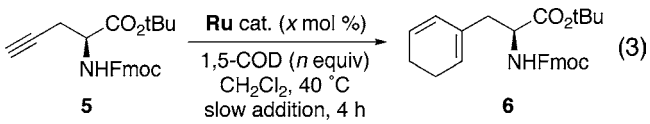
Scheme 2. Problematic Ring Syntheses by Methylene-Free Tandem Dienyne Metathesis (from ref 4)



loadings resulted in incomplete conversions and low chemical yields. From these data, we anticipated that homopropargylic heteroatoms in general would present difficulty. In terms of the enyne metathesis mechanism, the vinyl carbene turnover is typically the slow step,[6] so substrate interactions occurring before this stage could slow catalysis. Chelation by functional groups can retard the reaction rate or possibly direct the carbene toward decomposition.

Several reaction variables were evaluated to improve reaction scope (Table 1). The "methylene-free" metathesis is conducted under slow addition of alkyne to carbene catalyst and excess 1,5-cyclooctadiene (COD).[7] Higher catalyst loading was examined and found to give high conversion to dihydrophenylalanine **6**. The loading could be dropped to 7.5 mol % with increased concentration of COD (entry 2). Fewer equivalents resulted in incomplete conversions at loadings below 10 mol %. The selectivity was high in these cases, as evidenced by the near-quantitative NMR yields of **6** (vs mesitylene internal standard). Longer addition times (8 h) resulted in incomplete conversions (entry 3), possibly due to catalyst decomposition over this period. We employed polybutadiene[8] (PB, 18 equiv) in place of COD using the same number of alkene equivalents as entry 2, which resulted in complete conversion and high isolated yield (entry 4). Polybutadiene and COD can be used interchangeably at similar concentrations. Further reduction in catalyst

Table 1. Optimization Studies Using COD[a]



entry	**Ru** cat.	1,5-COD (equiv)	% yield[b] (NMR)	% **5** (NMR)
1	**1** (10)	6	79.5 (93)	0
2	**1** (7.5)	9	80 (96)	0
3[c]	**1** (7.5)	9	(81)	(15)
4[d]	**1** (7.5)	18[d]	76 (90)	0
5	**1** (5.0)	6	(53)	(26)
6	**1** (5.0)	9	59 (61)	0
7	**2** (10)	6	67 (84)	0
8	**2** (7.5)	6	(39)	(38)
9	**2** (7.5)	9	64 (67)	0
10	**2** (10)	2 + 2	(12)	(47)
11	**2** (10)	4	(23)	(30)

[a] Standard conditions: 0.25 mmol of alkyne was added to *n* equiv of 1,5-cyclooctadiene and the carbene complex in refluxing CH_2Cl_2. After the addition, the reaction was heated for 1 h. [b] Isolated yield. NMR yield against mesitylene internal standard is provided in parentheses. [c] 8 h addition time. [d] *all- cis*-Polybutadiene was used in this run.

loading resulted in incomplete conversion, with 26% unreacted alkyne (entry 5); increased concentration of COD gave complete conversion of alkyne but a moderate chemical yield was obtained (entry 6). In the next series of experiments, the Hoveyda complex **2** was evaluated. At high loading, similar performance was noted as compared to **1** (entry 7 vs entry 1). At lower loading and 6 equiv of COD, incomplete conversion was found (entry 8). In this run, the balance of the mass was recovered alkyne. Increased COD concentration improved conversion, but a moderate yield was obtained (entry 9). In the last two entries, the performance of complex **2** was evaluated under conditions used in our original paper,[4] but with higher catalyst loading (10 mol %). When 2 equiv of COD was added along with the alkyne to 2 equiv of COD and the carbene complex, only 12% NMR yield was obtained, with 47% unreacted alkyne (entry 10). Similar results were obtained in the last entry when 4 equiv of COD was employed, with incomplete conversion and recovered alkyne. In these two cases, only 53−59% alkyne-derived mass can be accounted for in the crude NMR, suggestive of alkyne polymerization and possibly other decomposition pathways that consume alkyne. These two entries also show that increasing catalyst loading by itself is not sufficient to address functional group scope.

In the best circumstances, the carbene **2** performs similarly to carbene **1**. However, the phosphine-free nature of reaction conditions using **2** may explain why the reaction is sensitive to COD concentration.[9] Since there is no phosphine to populate 16-electron carbene resting states, it remains possible that the carbene intermediates decompose. This could occur via chelates or through generic carbene decom-

(4) Kulkarni, A. A.; Diver, S. T. *J. Am. Chem. Soc.* **2004**, *126*, 8110−8111.

(5) Kinoshita, A.; Sakakibara, N.; Mori, M. *Tetrahedron* **1999**, *55*, 8155−8167.

(6) Galan, B. R.; Giessert, A. J.; Keister, J. B.; Diver, S. T. *J. Am. Chem. Soc.* **2005**, *127*, 5762−5763.

(7) Direct mixing of reactants as in entry 2, Table 1, gave only 25% conversion to cyclohexadiene **6**.

(8) Polybutadiene is immediately converted by carbenes **1** or **2** into smaller oligobutadienes. High MW *all-cis*-PB is not soluble in CH_2Cl_2 but quickly "dissolves" when carbene catalyst is added.

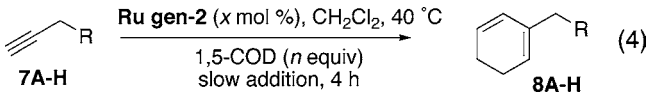
(9) A control experiment was performed using 7.5 mol % of Cy_3P adduct of complex **2** (preparation as ref 2c) under the conditions of entry 9, Table 1. In this case, a higher yield of cyclohexadiene **6** was obtained (89% vs 67% with **2**, determined by NMR; 78% isolated).

position pathways.[10] If this is true, then the role of COD would be protective.[11] With terminal alkynes, higher COD may also help prevent competing pathways such as alkyne polymerization, which is more apparent in the phosphine-free system.

These results compare favorably with the nonstereoselective cross-metathesis/acrylic acid cross-metathesis cleanup procedure.[12] This procedure was developed previously as a temporary solution to the problem of functional group scope. The improved procedure here surpasses the efficiency of the cleanup method. For instance, in entry 2 of Table 1 (above), use of 7.5 mol % of Grubbs' complex **1** gave 80% isolated yield (0.25 mmol scale), whereas the cleanup procedure yielded 36% using the same amount of catalyst **2** (0.5 mmol scale). The doubled chemical yield of **6** is realized because 96% of the alkyne **5** was converted to the 1,3-cyclohexadiene **6**. The advantage of the methylene-free metathesis is a result of improved stereoselectivity.

With optimized conditions employing the four-carbon donor 1,5-COD, we examined terminal alkynes with a variety of functional groups known to perform poorly in cross-metathesis. The results are summarized in Table 2.

Table 2. Functional Group Tolerance in Terminal Alkynes



(4)

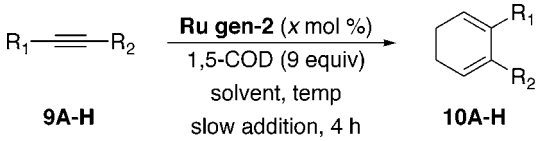
entry	R	**1** (%)	1,5-COD (equiv)	% yield[a] (NMR)
1	**7A**, $CH(CO_2Me)_2$	5.0	6	**8A**, 82 (100)
2[b]	**7B**, $CH(SO_2Ph)_2$	10	9	**8B**, 75 (93)
3	**7C**, CH_2OTBS	7.5	6	**8C**, 72 (87)
4	**7D**, CH_2OBn	7.5	9	**8D**, 70 (85)
5	**7E**, CH_2OTs	5.0	6	**8E**, 72 (79)
6	**7F**, CH_2NHTs	5.0	9	**8F**, 73 (94)
7	**7G**, $(CH_2)_2NHTs$	5.0	9	**8G**, 74 (92)
8[b]	**7H**, $CH(OTBS)(CO_2Me)$	10	9	**8H**, 60 (74)

[a] Isolated yield. [b] Benzene was used as solvent; reaction temperature was 65 °C.

The optimized conditions established in Table 1 were used as the starting point; however, most of the entries were evaluated independently. This procedure helped identify lower loading and when fewer equivalents of COD could be used. A high yield of diene **8A** from dimethyl propargyl malonate was obtained (entry 1). The sulfone proved more difficult, giving incomplete conversion under the same conditions (5 mol % of **1**; CH_2Cl_2, reflux). Higher catalyst loading and higher temperatures were needed to obtain **8B** (entry 2). The homopropargyl silyl ether, a problematic substrate as identified previously, gave high yield at modest loading and 6 equiv of COD (entry 3). The benzyl ether required optimized conditions to give complete conversion and good chemical yield of **8D** (70%, entry 4). The homopropargyl tosylate **7E** underwent ring synthesis efficiently (entry 5); however, the product **8E** was sensitive to elimination and required special care in its handling. Unprotected nitrogen functionality (with a free N−H bond) is rarely employed in cross-metathesis. To circumvent anticipated difficulties with free N-H functionality, Rodriguez introduced nitrogen functionality (as carbamates) after the cross-metathesis step.[13] Under optimized methylene-free conditions, both the homopropargylic sulfonamide **7F** and its higher homologue **7G** underwent ring synthesis in high yield (entries 6,7). The glycolate ester **7H** in entry 8 gave good isolated yield of diene **8H** under high catalyst loading and at higher reaction temperatures.

The synthesis of 2,3-disubstituted 1,3-cyclohexadienes from internal alkynes was accomplished using the optimized procedure (Table 3). The literature has focused on terminal alkynes in enyne metathesis. Unsymmetrical internal alkynes have not been well-studied due to formation of mixtures of unsymmetrical dienes on reaction with 1-alkenes.[14] From the optimization table, it was expected that high loadings of carbene (7.5−10 mol %) would give complete conversion of the internal alkyne reactants, but we examined each alkyne at lower loading (5 mol %). Loading was increased to 10% only if incomplete conversion was observed. Propargylic and homopropargylic ester functionality was well tolerated on the internal alkyne, giving the 2,3-disubstituted diene **10A**,**B** in good yields (entries 1 and 2). The symmetrical ester also

Table 3. Scope of Ring Synthesis for Internal Alkynes[a]



(5)

entry	R_1	R_2	**1** (%)	solvent	yield[b] (%)
1	CH_2CH_3	CH_2OBz	5	CH_2Cl_2	**10A**, 65
2	CH_3	CH_2CH_2OBz	5	CH_2Cl_2	**10B**, 59[c]
3	CH_2OAc	CH_2OAc	5	CH_2Cl_2	**10C**, 63
4	CH_3	CH(OAc)Bn	10	CH_2Cl_2	**10D**, 68
5	CH_3	CH_2CH_2OTBS	10	PhH	**10E**, 53
6	CH_2CH_3	CH_2OBn	10	PhH	**10F**, 49
7	CH_3	$CH_2CH_2N(Ts)Boc$	5	PhH	**10G**, 72
8	CH_3	CO_2Et	10	PhH	**10H**, 61

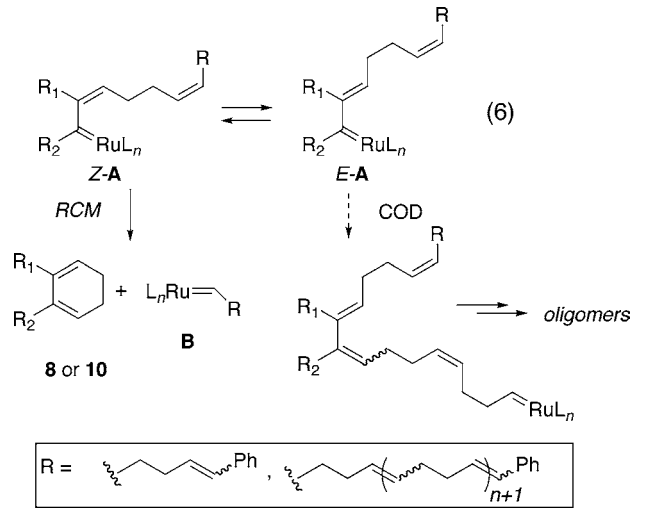
[a] Standard conditions: 0.25 mmol of alkyne was added to 9 equiv of 1,5-cyclooctadiene and the carbene complex in either refluxing CH_2Cl_2 or in benzene at 65 °C. [b] Isolated yield. [c] 62% yield when 18 equiv of polybutadiene and 5 mol % of **1** were used.

(10) Ulman, M.; Grubbs, R. H. *J. Org. Chem.* **1999**, *64*, 7202−7207.
(11) Similar to the original rationale of ethylene effect: Mori, M.; Sakakibara, N.; Kinoshita, A. *J. Org. Chem.* **1998**, *63*, 6082−6083.
(12) Middleton, M. D.; Diver, S. T. *Tetrahedron Lett.* **2005**, *46*, 4039−4043.
(13) Rodriguez-Conesa, S.; Candal, P.; Jimenez, C.; Rodriguez, J. *Tetrahedron Lett.* **2001**, *42*, 6699−6702.
(14) Internal alkynes in cross-enyne metathesis: (a) Giessert, A. J.; Snyder, L.; Markham, J.; Diver, S. T. *Org. Lett.* **2003**, *5*, 1793−1796. (b) Giessert, A. J.; Diver, S. T. *Org. Lett.* **2005**, *7*, 351−354. Recently, Lee et al. demonstrated that silyl alkynes perform well in cross metathesis: (c) Kim, M.; Park, S.; Maifeld, S. V.; Lee, D. *J. Am. Chem. Soc.* **2004**, *126*, 10242−10243.

underwent an efficient ring synthesis at low catalyst loading (entry 3). The effectiveness of polybutadiene was established for internal alkynes by repetition of entry 2 with 18 equiv of PB to give **10B** in 62% yield (footnote c in Table 3). The propargyl-substituted ester proved to be a reactive substrate but required a higher catalyst loading to obtain complete conversion of the alkyne (entry 4). The potentially coordinating homopropargyl silyl ether was evaluated under the optimized conditions, and a good yield of **10E** was obtained (entry 5). Similarly, the propargyl benzyl ether has the potential to chelate to the vinyl carbenes (entry 6). Higher catalyst loading was needed for complete conversion of alkyne, with an isolated yield of 49%. Nitrogen functionality could be introduced onto the disubstituted cyclohexadiene without difficulty (entry 7). Electron-poor alkynes are not commonly used in enyne cross-metathesis.[1a] However, we found that ethyl 2-butynoate gave diene **10H** in good yield at elevated temperature (entry 8).

The mechanism must explain both the isomerization of vinyl carbenes and the effect of COD. First, it is likely that the isomeric vinyl carbene intermediates **A** interconvert under the methylene-free conditions (Scheme 3, eq 6). We suggest

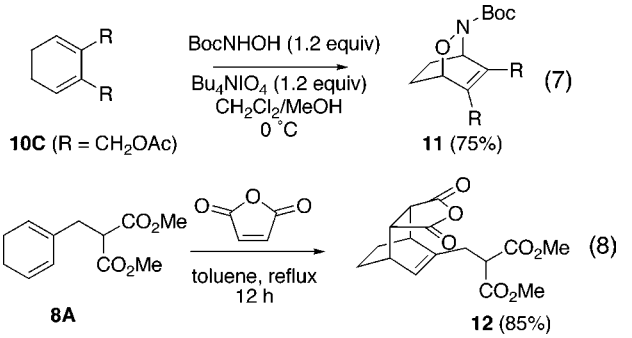
Scheme 3. Proposed Mechanism



that vinyl carbene *Z*-**A** undergoes an intramolecular RCM to give the 1,3-cyclohexadiene and that *E*-**A** slowly isomerizes to *Z*-**A**. We previously suggested this equilibration mechanism[4] to account for the high chemical yields of 1,3-cyclohexadienes in the ring synthesis. This rationale similarly applies to the data presented here since the NMR yields of Table 2 average 90%. Second, the role of COD helps to improve catalyst efficiency and functional group scope. Higher COD concentration would not directly affect the conversion of *Z*-**A** into cyclohexadiene, and its role in the equilibration of eq 6 is not required. We hypothesize that the high COD concentration increases the proportion of active alkylidenes, inhibits chelate formation (and possible decomposition through chelate formation), and inhibits catalyst decomposition. Chelate formation is more prevalent with certain functional groups, especially homopropargylic ethers. COD may be playing additional kinetic roles protecting the catalyst through degenerate alkene coordination complexes. In ring syntheses that gave modest chemical yields (50−60%), the remainder of the alkyne mass is presumably incorporated into COD oligomers, which are removed in the isolation step by a trituration procedure. Higher alkene concentration may keep carbenes in the enyne metathesis manifold and help to overcome chelation, but slow oligomerization of *E*-**A** may significantly compete at even higher alkene concentrations. This would reduce the efficiency of the stereoselective ring synthesis by converting alkyne into oligomers. These proposals need to be further evaluated by synthesis and reactivity studies of isomeric vinyl carbene complexes.

The cyclohexadienes underwent cycloaddition with dienophiles and heterodienophiles in high yields. In situ generation of an acyl nitroso species under oxidative conditions yielded the N−O cycloadduct in 75% yield (Scheme 4, eq 7). Significantly, the oxidative conditions did not cause

Scheme 4. Cycloaddition of Functionalized Cyclohexadienes



aromatization of the cyclohexadiene to any appreciable extent, and no ene reaction products were observed. Similarly, the thermal Diels−Alder cycloaddition of **8A** proceeded in high yield to give cycloadduct **12** (Scheme 4, eq 8).

In conclusion, we have demonstrated functional group tolerance in terminal and internal alkynes under the conditions of stereoselective methylene-free metathesis. This significantly extends the cyclohexadiene synthesis to dienes featuring a wide array of organic functionality. Internal alkynes have sufficient reactivity in the ring synthesis. Further studies are directed toward kinetically evaluating the chelative interactions and identifying the putative vinyl carbene decomposition pathways.

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

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