

1,5-Enyne Metathesis

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Ring-closing metathesis (RCM) has emerged as a powerful synthetic tool for the synthesis of medium and large cycles.¹ However, it is generally considered that three- and four-membered cycles cannot be formed by RCM. Indeed, such strained cycles may be reopened by the carbene catalyst, the driving force being the relief of ring strain (Scheme 1, equation a). Indeed, cyclobutenes have been used in ring-opening metathesis polymerization (ROMP),² in ring-opening metathesis/cross-metathesis (ROM/CM) reactions,³ in ring-opening metathesis/ring-closing metathesis (ROM/RCM) on cyclobutene-ene and cyclobutene-yne substrates,⁴ and in asymmetric (ROM/RCM) sequences.^{5a} Starting from cyclopropenes, an elegant asymmetric ring-opening/cross-metathesis (AROM/CM) reaction has also recently been described.^{5b} Gold and platinum 1,5-enyne cycloisomerizations have recently been widely described,⁶ but to the best of our knowledge, the 1,5-enyne metathesis has not yet been reported.^{7,8} Nevertheless, we anticipated that the enyne metathesis of 1,5-enynes **1** might give the corresponding substituted cyclobutene derivative **2**.^{9,10} Indeed, in such cyclobutene rings, we surmised that the reactivity of the internal double bond of **2** might be impeded by a preferential coordination of the terminal double bond (Scheme 1, equation b).^{11a}

Initially, the reactivity of enyne **1a** ($R^1 = \text{Ph}$, $R^2 = \text{H}$, $R^3 = n\text{-Bu}$) was explored. Whereas, in the presence of Grubbs I **G-I** catalyst, no cyclized compound could be observed in refluxing dichloromethane, the use of Grubbs II catalyst **G-II** led to the formation of the expected cyclobutene in 20–25% yield (Table 1, entry 2). The use of somewhat diluted conditions ($c = 0.03 \text{ M}$) was found to be essential to prevent the formation of dimerization byproducts resulting from double bond cross-metathesis. Moving to the Grubbs–Hoveyda II **GH-II** catalyst, the cyclobutene **2a** is obtained in 35% yield (Table 1, entry 3). As previously observed in other studies,¹² the use of microwave irradiations proved beneficial, and we were pleased to observe the formation of the desired cyclobutene **2a** in 58% yield (Table 1, entry 5). The reaction is rather clean (see GC spectra of the crude product in the Supporting Information): along with the expected cyclobutenes **2a**, only a small amount of the CM dimer (5%) and starting material **1a** (10–15%) is isolated, but any effort to complete the reaction resulted in lower isolated yields. Efforts to decrease the amount of **GH-II** catalyst were also unsuccessful (Table 1, entry 6), leading to a substantial yield decrease. The reason why such an amount of catalyst is necessary is still unclear. If catalyst decomposition can be suspected, only the 2-isopropoxy styrene could be detected by GC (see GC spectra in the Supporting Information), but none of the recently described decomposition byproducts could be identified by NMR or GC analyses.^{11b,c} Reactions under an ethylene atmosphere (1 atm) have also been carried out in both classical and microwave heating conditions (Table 1, entries 4 and 7), but in both cases, extensive byproduct formation has been observed (see GC spectra in the Supporting Information). The use of PtCl_2 was also investigated, but no reaction could be observed (Table 1,

Scheme 1.

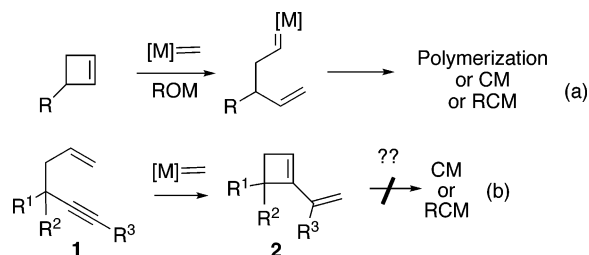


Table 1. Optimization of Reaction Conditions

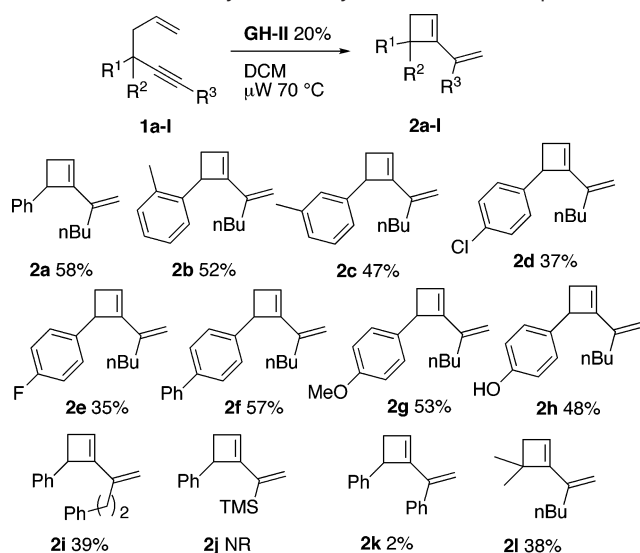
	catalyst	T (°C)	yield (%)
1	G-I , 20%	reflux	NR
2	G-II , 20%	reflux	20–25
3	GH-II , 20%	reflux	35
4	GH-II , 20% ethylene, 1 atm	reflux	22
5	GH-II , 20%	μW , 70 °C	58
6	GH-II , 10%	μW , 70 °C	44
7	GH-II , 20% ethylene, 1 atm	μW , 70 °C	20
8	PtCl_2	toluene, 80 °C	NR

entry 8). Gold-catalyzed reactions on these 1,5-enyne substrates have been previously described to give bicyclo[3.1.0]hexenes.¹³

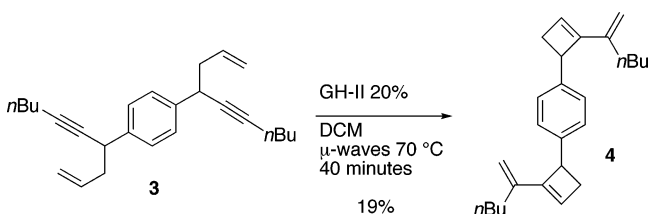
Starting from these initial experiments, we set out to define the scope of the reaction. The 1,5-enyne substrates **1a–l** were synthesized using our recently published Au(III)-cat propargylic substitutions, starting from propargylic alcohols and allyltrimethylsilane.^{13b} On the propargylic side (R^1 , R^2), various aromatic substituents were well-tolerated, leading to the cyclobutenes in 35–57% yields (Scheme 2, **2a–h**). On the alkynyl part (R^3), the methodology seems, however, limited to alkyl substituents (Scheme 2, **2i**): no reaction could be observed with a TMS substituent (Scheme 2, **2j**), and a very low yield was obtained with a phenyl substituent (Scheme 2, **2k**). Finally, a substrate bearing a quaternary carbon at the propargylic position ($R^1 = R^2 = \text{Me}$, $R^3 = n\text{-Bu}$) was also cyclized, leading to the cyclobutene in a modest 38% yield (Scheme 2, **2l**). The moderate yields observed in these reactions can be explained in part by recovered starting material (10–15%) and CM dimerization byproducts (5–10%) and also by difficulties encountered in the purification of such highly nonpolar ($\text{rf} = 0.6\text{--}0.8$ in pentane) and sensitive highly strained molecules in the presence of other nonpolar unidentified degradation byproducts. A double cyclization on a *para*-disubstituted phenyl derivative **3** was finally attempted, leading to the bis-cyclobutene **4** in a modest 19% yield (Scheme 3).

The 1,5-enyne metathesis provides a 1,3-diene unit which can be further used in Diels–Alder reactions. Indeed, in the presence

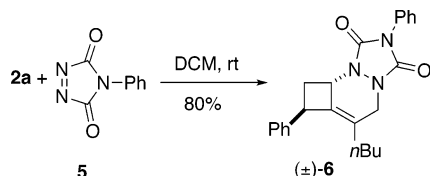
Scheme 2. GH-II-Catalyzed 1,5-Enyne Metathesis: Scope



Scheme 3. A Double 1,5-Enyne RCM



Scheme 4.



of the Cookson's reagent (4-phenyl-4,5-dihydro-3H-1,2,4-triazole-3,5-dione, **5**),¹⁴ cyclobutene **2a** reacts at room temperature, to give the tricyclic compound **6** in 80% yield and as a single diastereomer (Scheme 4). An *anti* configuration was assigned, based on NOESY experiments (see Supporting Information).

In conclusion, we have shown that Grubbs-type catalysts are able to promote enyne metathesis on 1,5-enyne substrates, thus opening a convenient new entry to functionalized cyclobutenes. Further investigations on this reaction and functionalization of the cyclobutenes are ongoing and will be reported on due course.

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Supporting Information Available: Experimental details and characterization for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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