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Ruthenium-catalyzed tandem enyne-cross metathesis–cyclopropanation: three-component access to vinyl cyclopropanes

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ABSTRACT

Substituted vinylcyclopropanes are prepared through a ruthenium-catalyzed, tandem three-component coupling between an olefin, alkyne, and diazoester. Grubbs' 2nd generation (NHC) ruthenium complexes in the presence of ethylene effect a stereoselective enyne-cross metathesis between alkynes and olefins to generate 1,3-substituted dienes. The slow introduction of diazoacetates to this reaction mixture then allows for the regioselective cyclopropanation of the resulting diene. When the olefin reaction partner is just ethylene (i.e., R′ = H), the tandem process is less efficient. In this case, the byproducts provide unique insight into possible catalyst decomposition pathways.

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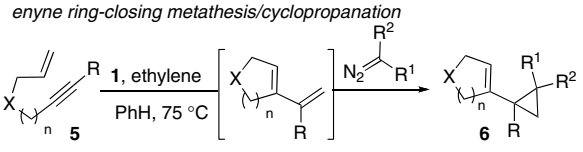
Ruthenium alkylidenes **1**–**4** (Fig. 1) are well recognized and widely used catalysts for olefin metathesis.[1] To extend the synthetic utility of these ruthenium complexes, recent efforts have aimed at developing new, non-metathesis catalytic transformations with these ruthenium complexes.[2,3] When combined with olefin metathesis, these new ruthenium-catalyzed tandem processes allow for the formation of multiple bonds in a single reaction vessel that previously required several steps to accomplish.[4]

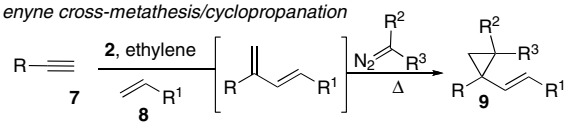
Recently, we reported that alkylidene **1** could effect the cyclopropanation of dienes generated from an enyne ring-closing metathesis by addition of a diazo ester (Eq. 1).[5] Using this procedure, we were able to gain access to cycloalkenyl cyclopropanes directly from enynes. Given the importance of vinyl cyclopropanes as reactive functionalities in variety of transformations,[6] we reasoned that further development of this process was warranted. Herein, we describe a three-component, tandem enyne-cross metathesis/cyclopropanation that allows for the preparation of a diverse array of substituted vinyl cyclopropanes (Eq. 2).

enyne ring-closing metathesis/cyclopropanation



(1)

enyne cross-metathesis/cyclopropanation



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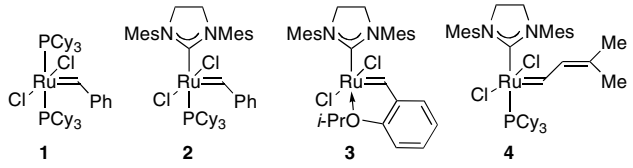

Figure 1. Commercially available ruthenium-based olefin metathesis catalysts.

Several advancements are worth noting in the development of this enyne-cross metathesis/cyclopropanation.[7] For one, enyne-ring-closing has been shown to be successful with ruthenium complex **1**; however, more active catalysts are typically required to perform the enyne-cross metathesis (ECM). In addition, the cross metathesis generally leads to a mixture of *Z*- and *E*-olefin isomers.[8] When the enyne-cross metathesis is run in the presence of catalyst **2** under an atmosphere of ethylene, however, the *E*-selectivity of the newly formed olefin can be improved significantly.[9]

Unfortunately, our initial enyne ring-closing metathesis/cyclopropanation studies indicated that NHC-complex **2** was ineffective as a cyclopropanating agent under the conditions examined (Scheme 1). The added diazoester was rapidly consumed leading to significant quantities of maleate and fumarate,[10] and the resulting diene formed in the enyne ring-closing metathesis at times underwent a secondary cross metathesis to generate triene **11**. We assumed that alkylidene **2** (or derivative thereof) was capable of cyclopropanating; however, the rapid dimerization of the diazoester interfered with the desired mode of reactivity.

As shown in Scheme 2, when the NHC-alkyli dene **4** was used in an enyne-cross metathesis between aromatic acetylene **7a** and octane, diene **12** was generated stereoselectively.[11] By keeping the concentration of the diazoacetate to a minimum, the desired

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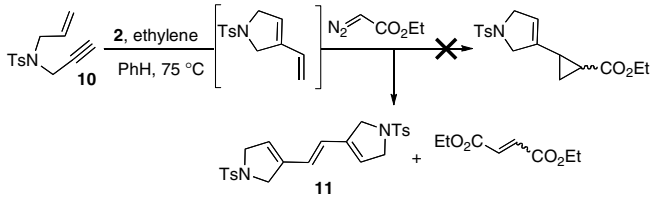
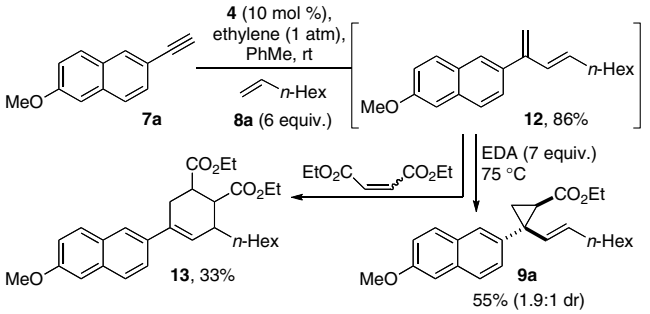


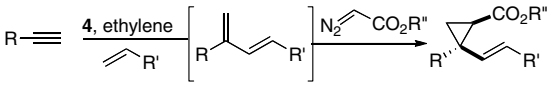
Scheme 1. Previous cyclopropanation results with alkylidene **2**.

diene cyclopropanation could compete effectively with the diazoester dimerization. Slow addition of ethyl diazoacetate to this reaction mixture at elevated temperatures converted diene **12** to a vinyl cyclopropane **9a** as a 1.9:1 mixture of diastereomers in 55% isolated yield. While this is the first NHC ruthenium complex that led to cyclopropanated products, significant quantities of diethyl maleate and fumarate byproducts were also generated. Unfortunately, these dienophilic side products reduced the yield of **9a** by consuming diene **12** through a competitive Diels–Alder reaction (→**13**).[12]



Scheme 2. Preliminary ECM/cyclopropanation results.

Table 1
Tandem ECM/cyclopropanation



Entry	Alkyne	Olefin	Product	Yield (%) (*E*:*Z*)
1	Ph— **7b**	*n*-Hex **8a**	CO$_2$Et, Ph, *n*-Hex **9a**	55–66 (1.7:1)
2	MeO **7a**	**8a**	CO$_2$Et, MeO, *n*-Hex **9b**	53–63 (1.9:1)
3	F$_3$C **7c**	**8a**	CO$_2$Et, F$_3$C, *n*-Hex **9c**	<5
4	**7a**	OTBS (8) **8b**	CO$_2$Et, MeO, OTBS (8) **9d**	55 (1.9:1)
5	**7b**	OBn (6) **8c**	CO$_2$Et, Ph, OBn (6) **9e**	46 (1.5:1)
6	**7b**	**8a**	CO$_2$*t*-Bu, Ph, *n*-Hex **9f**	66–76 (1.9:1)
7	**7b**	**8a**	MeO$_2$C, CO$_2$Me, Ph, *n*-Hex **9g**	25
8	*n*-Bu— **7d**	Ph **8d**	CO$_2$Et, *n*-Bu, Ph **9h**	45–50 (1:1)

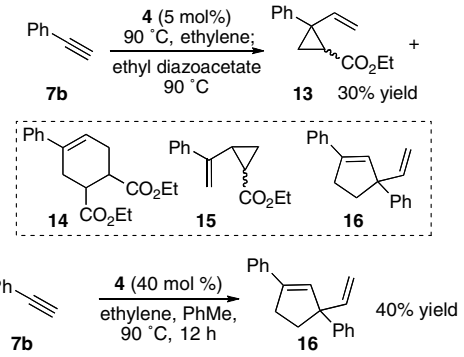
Our efforts to delineate the scope of this three-component coupling process are summarized in Table 1. The tandem ECM/cyclopropanation sequence works for a range of aromatic and aliphatic reaction partners, although some steric and electronic limitations were observed. The cyclopropanation takes place exclusively at the more sterically accessible 1,1-disubstituted olefin over the 1,2-disubstituted olefin. In addition, while electron rich and neutral aromatic acetylenes can be used successfully (entries 1 and 2), the electron poor *p*-trifluoromethyl substituted phenyl acetylene **7c** affords mainly the diene intermediate, with only trace amounts of the desired cyclopropanated product (entry 3). The TBS and benzyl protected alcohols **8b** and **8c** were also shown to be amenable to these conditions (entries 4 and 5). For nearly all of these substrates, there is a slight preference for the trans-substituted cyclopropyl isomer.[13]

Using *t*-butyl diazoacetate led to a slight increase in yields with little change in stereoselectivity (entry 1 vs entry 6). In this case, the additional steric hindrance of the bis-*t*-butyl maleate or fumarate byproduct may slow down the Diels–Alder reaction. Conversely, the use of a diazo dimethyl malonate provided a lower yield of the tandem product **9g**. We reasoned that the highly electron-deficient byproduct resulting from dimerization of the diazo precursor led to greater consumption of the diene intermediate (entry 7).[14] Aliphatic acetylenes can also be used along with aromatic olefins to give vinyl cyclopropanes in approximately 50% overall yield (entry 8). In this case, the cyclopropanation step is less stereoselective, perhaps due to the small steric difference between the aliphatic chain and the vinyl group. In addition, if the excess styrene is not converted to stilbene by warming the reaction with a N_2 purge before the slow addition of the diazoester, significant quantities of the cyclopropanated styrene are also obtained.

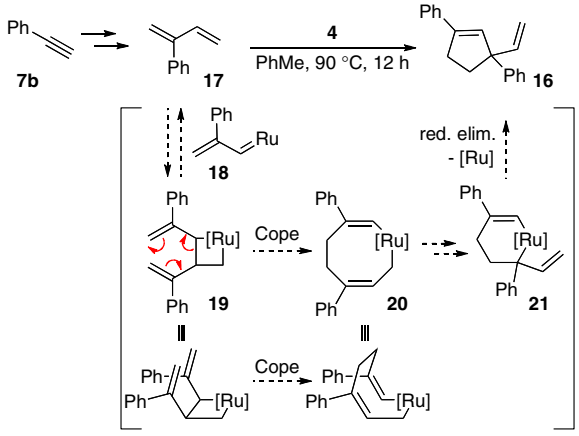
When the enyne-cross metathesis/cyclopropanation was run between aromatic alkynes and ethylene, the yield of the desired vinyl cyclopropanated product was low.[8i] Scheme 3 illustrates some of the products observed in this transformation. In addition to the *E*- and *Z*-cyclopropanated diastereomers (**13**) and the Diels–Alder cycloadducts **14**, notable amounts of the regioisomeric vinylcyclopropyl diastereomers **15** were also obtained. This is not surprising, given the less hindered nature of the corresponding diene. Less clear, however, was the origin of vinyl cyclopentene **16**, which was isolated in approximately 5% yield.

Subsequent studies indicated that the addition of diazoacetate was not necessary for the formation of vinyl cyclopentene **16**. Furthermore, when the catalyst loading was increased to 40 mol % there was a corresponding increase in the yield of vinyl cyclopentene **16** (40%). Also noteworthy was the loss of olefin metathesis activity that corresponded to the generation of **16**. Given these observations, we suspect that the formation of **16** may be part of a catalyst decomposition pathway unique to diene metatheses.[15] Scheme 4 suggests a mechanism that accounts for the formation of **16** at the expense of metathesis active ruthenium alkylidene **4**.

In this alkylidene decomposition pathway, diene **17**, generated in the enyne-cross metathesis, reacts with vinyl alkylidene **18** to produce divinyl metallacyclobutane **19**. This intermediate could undergo a retro-[2+2] to form the triene secondary cross metathesis product (i.e., **11**, Scheme 1) and the corresponding ruthenium methylidene; however, a more facile [3,3]-sigmatropic rearrangement (Cope rearrangement) could occur to provide intermediate **20**. In this case, the Cope rearrangement is favored because the phenyl substituents on diene **19** position the vinyl groups in a bis-*endo* conformation that facilitates the strain-releasing ring expansion. The resulting metallocyclooctadiene **20** can then isomerize to the corresponding metallocyclohexene **21**, which can then undergo a reductive elimination to generate vinyl cyclopentene **16** and a non-metathesis active ruthenium complex. In general, this decomposition pathway may represent one of the challenges in developing a general diene–diene cross metathesis as a useful method for preparing trienes.



Scheme 3. Products arising from enyne-cross metathesis/cyclopropanations between aromatic alkynes and ethylene.



Scheme 4. Possible mechanism for the decomposition of metathesis catalyst **4** and the formation of vinyl cyclopentene **16**.

In summary, ruthenium-catalyzed tandem olefin metathesis/cyclopropanations have been expanded to include enyne-cross metatheses as a route to functionalized vinyl cyclopropanes. The net result of this advancement is a three-component, one-pot preparation of vinyl cyclopropanes from alkynes, alkenes, and diazoacetates. Further investigations into the reaction mechanism as well as catalyst decomposition pathways are underway.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures and data on new compounds are available (PDF)) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.07.119.

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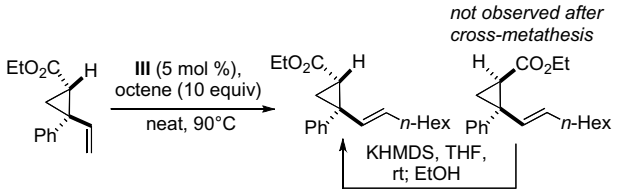
13. Diastereomer identity was determined by ^1H NMR comparison to a known vinyl cyclopropane: Doyle, M. P.; Dorow, R. L.; Buhro, W. E.; Griffin, J. H.; Tamblyn, W. H.; Trudell, M. L. *Organometallics* **1984**, *3*, 44–52. In addition, cross metathesis of the known cis-isomer and octene led to the anticipated cis-product **9a**. When similar tests were made with the trans isomer, no cross metathesis products were observed. However, subjecting the major cyclopropanation diastereomer (trans) to epimerization conditions facilitated partial conversion to the anticipated minor compound (cis).



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