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A Stereoselective Enyne Cross Metathesis

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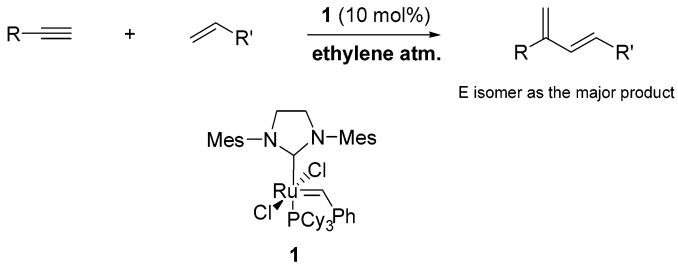
ABSTRACT



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Intermolecular enyne metathesis reaction of alkynes with olefins catalyzed by second-generation Grubbs catalyst (1) proceeded stereoselectively under ethylene atmosphere to produce 1,3-disubstituted butadienes with *E* stereochemistry.

With the development of new metathesis catalysts by Schrock and Grubbs,[1] olefin metathesis has attracted much attention from the synthetic organic chemistry community and numerous synthetic strategies based on metathesis have been developed. On the other hand, enyne metathesis,[2] which is catalyzed by the same catalysts, has not been developed as much, although the reaction produces 1,3-diene, a useful synthon for various cycloadditions.[3,4] Since the first reported enyne metathesis,[5] most research efforts have focused on the ring-closing enyne metathesis, which not only provides cycloalkenes with a conjugated terminal olefin for further manipulation[6] but also allows tandem metathesis processes for the formation of polycyclic compounds.[2a] The major shortcoming of the metathesis reaction has been that intermolecular metathesis reaction has rarely been used in the enyne metathesis reaction mainly due to the formation of a mixture of olefin isomers.[7] This lack of stereoselectivity

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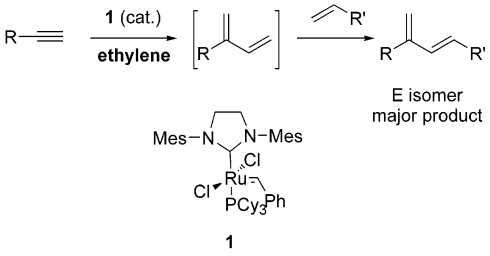
diminishes the value of this facile methodology for the preparation of substituted dienes, otherwise useful in organic synthesis.

Herein, we would like to report the development of a stereoselective enyne cross metathesis using second-generation Grubbs catalyst (**1**).[8] Our strategy for stereoselective enyne cross metathesis is based on Mori's pioneering work on the role of ethylene gas in the enyne metathesis reaction,[9] where ethylene served not only as a substrate for the reaction, but also to maintain the reactivity of the catalyst. We envisioned that if we added ethylene to the enyne cross-metathesis reaction, ethylene will react first with the alkyne to form the monosubstituted diene and the diene will subsequently react with the terminal olefin to form the disubstituted diene (Scheme 1). Even though diene−ene cross

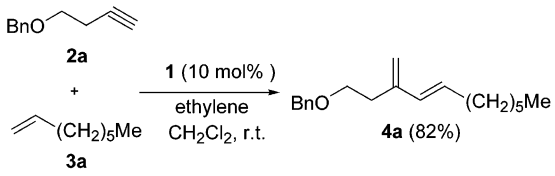
Scheme 1. Strategy for Stereoselective Enyne Cross Metathesis



metathesis has not been reported, this idea was deemed plausible since the intramolecular diene−ene metathesis reaction has been used in organic synthesis.[10] The monosubstituted diene intermediate was expected to provide enough bias to form the *E* stereoisomer selectively during the metathesis reaction.

We tested the idea with an initial experiment using benzyl butynyl ether (**2a**) and 1-octene (**3a**). A mixture of **2a**, and **3a** (10 equiv) with **1** (10 mol %)[11] in dichloromethane was stirred for 24 h under ethylene atmosphere to afford cross-metathesis product **4a** with only *E* stereochemistry in 82% yield (Scheme 2). The ^{1}H NMR spectrum of the reaction

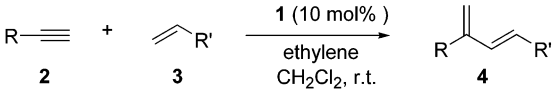
Scheme 2. Enyne Cross Metathesis under Ethylene Atmosphere



mixture before purification showed no indication of the *Z* isomer.

We then expanded the enyne cross-metathesis reaction to other alkynes and alkenes. The results are summarized in Table 1.[12] Alkynes **2a**−**d** were reacted with alkenes **3a**−**d** to give cross-metathesis products **4a**−**n** in good yields, all with *E* stereochemistry as determined by ^{1}H NMR.

Table 1. Enyne Cross-Metathesis Reaction



entry	alkyne	alkene	diene	yield[a] (*E*/*Z*)[b,c]
1	**2a** R = $BnO(CH_2)_2$	**3a** R′ = $(CH_2)_5Me$	**4a**	82% (100/0)
2	**2a**	**3b** R′ = ^{n}Pr	**4b**	88% (100/0)
3	**2a**	**3c** R′ = C_2H_4Br	**4c**	74% (>20/1)
4	**2a**	**3d** R′ = $C_2H_4O_2CEt$	**4d**	57% (>20/1)
5	**2b** R = $TsO(CH_2)_2$	**3a**	**4e**	71% (100/0)
6	**2b**	**3b**	**4f**	83% (100/0)
7	**2b**	**3c**	**4g**	64% (>20/1)
8	**2b**	**3d**	**4h**	59% (>20/1)
9	**2c** R = $TBDPSOCH_2$	**3a**	**4i**	68% (100/0)
10	**2c**	**3c**	**4j**	60% (>20/1)
11	**2c**	**3d**	**4k**	62% (>20/1)
12	**2d** R=$AcO(CH_2)_3$	**3a**	**4l**	82% (100/0)
13	**2d**	**3b**	**4m**	55% (100/0)
14	**2d**	**3c**	**4n**	67% (>20/1)

[a] Isolate yield after 24 h. [b] *E*/*Z* ratio was determined by ^{1}H NMR. [c] In all cases, ~30% of the remaining olefin was converted into the corresponding dimer.

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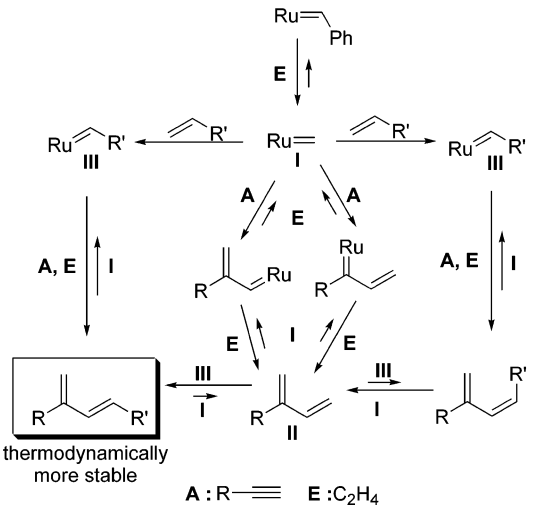
Scheme 3. Plausible Reaction Mechanism for *E* Stereoselectivity



A plausible reaction mechanism is shown in Scheme 3. The metathesis catalyst **1** was converted to the active ruthenium carbene complex (**I**), which in turn could react either with alkyne to give 1,3-diene (**II**) or with alkene to give another ruthenium complex (**III**). The 1,3-diene could then react with ruthenium complex (**III**) to afford enyne cross-metathesis product exclusively with *E* stereochemistry as we have anticipated. However, we could not rule out another pathway, where ruthenium complex (**III**) reacted with alkyne to give enyne cross-metathesis product as a mixture of *E* and *Z* isomers, and the *Z* isomer could have been equilibrated to the thermodynamically more stable *E* isomer via 1,3-diene (**II**) through reversible diene−ene cross-metathesis reaction in the presence of ethylene.

To possibly distinguish between the two pathways, we prepared monosubstituted diene **5** and an *E*/*Z* mixture of **4a**. The metathesis reaction between **5** and 1-octene produced **4i** exclusively with the *E* stereoisomer in 88% yield. Treatment of the *E*/*Z* mixture of **4a** with catalyst **1** under ethylene atmosphere isomerized effectively the mixture to the *E* isomer exclusively along with the formation of **II** (R = $BnOC_2H_4$) (Scheme 4). While either pathway could not be ruled out, these results support a thermodynamically driven isomerization to provide a stereoselective synthesis of 1,3-dienes where the formation of intermediate **II** was the key to the stereoselectivity.

The stereoselectivity of diene formation eroded in cases of olefins with heteroatom substitution at the allylic position as the reaction pathway could be electronically, coordinatively, or sterically biased by the allylic substitution[13] (Table 2). **3f** and **3g** produced enyne cross-metathesis products with moderate selectivity for *E* isomers in 40−50% yields and **3e** produced dienes in good yield but with no selectivity except for a silylacetylene (entry 9). Complete selectivity for the *E* stereoisomer of diene from triphenylsilylacetylene was observed even in the absence of ethylene. Blechert

Scheme 4

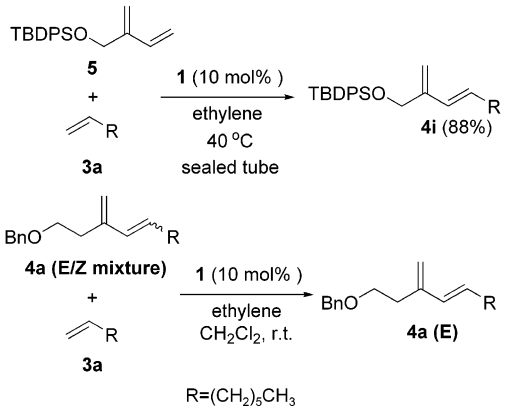
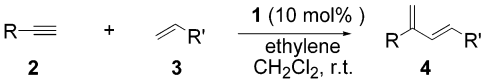


Table 2. Enyne Cross-Metathesis Reaction



entry	alkyne	alkene	diene	yield[a] (*E*/*Z*)[b]
1	**2c**	**3e** R′ = CH_2SiMe_3	**4o**	79% (1.3/1)
2	**2c**	**3f** R′ = CH_2O^nBu	**4p**	44% (3/1)
3	**2c**	**3g** R′ = CH_2OAc	**4q**	49% (6.5/1)
4	**2b**	**3e**	**4r**	84% (1.4/1)
5	**2b**	**3f**	**4s**	42% (3/1)
6	**2b**	**3g**	**4t**	48% (9/1)
7	**2a**	**3e**	**4u**	79% (1.3/1)
8	**2d**	**3e**	**4v**	86% (1.6/1)
9	**2e** R = Ph_3Si	**3e**	**4w**	89% (100:0)[c]

[a] Isolate yield after 24 h. [b] *E*/*Z* ratio was determined by ^{1}H NMR. [c] Only the *E* isomer was obtained even without ethylene in 75% yield.

(11) The amount of olefins and the catalyst had to be maintained to that level to drive the cross-metathesis reaction to completion and to minimize the formation of **II**.

(12) **General Procedure.** Alkyne (0.1 mmol) and olefin (1.0 mmol, 10 equivalent) were dissolved in CH_2Cl_2 (0.2 mL). Second-generation Grubbs catalyst was added to the reaction mixture at room temperature and the resulting reaction mixture was stirred for 24 h at room temperature under ethylene atmosphere (through balloon attachment) and concentrated under reduced pressure. Then the residue was purified by flash column chromatography on silica gel to afford the desired product.

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reported a similar observation with trimethylsilylacetylene where the cross-metathesis reaction of **3e** with TMS-acetylene produced the diene selectively ($E/Z = 6/1$).[8i] The complete stereoselectivity (entry 9) appeared to be due to unfavorable steric interaction of the triphenylsilyl group in the *Z* stereoisomer of diene product.

Allylic alcohol derivatives and allylsilanes seemed to be much less reactive than aliphatic olefins toward dienes as evidenced by the fact that allylsilane **3e** did not react at all with diene **5**.[14] This result reiterated the importance of the diene intermediate **II** in the stereoselectivity of the cross-metathesis reaction.

(14) Treatment of 1,3-diene **5** with allyl trimethylsilane **3e** in CH_2Cl_2 under ethylene atmosphere for 24 h resulted in only the unreacted starting materials. Allyl butyl ether gave a similar result.

In summary, we have developed a stereoselective enyne cross-metathesis reaction by including ethylene in the reaction. This protocol generates 1,3-disubstituted butadienes with *E* stereochemistry for the newly generated 1,2-disubstituted olefins in good yields.

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Supporting Information Available: Experimental procedure for the metathesis reaction and spectral data of cross-metathesis products **4a**−**w**. This material is available free of charge via the Internet at http://pubs.acs.org.

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