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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Inhibitory Effect of Ethylene in Ene–Yne Metathesis: The Case for Ruthenacyclobutane Resting States

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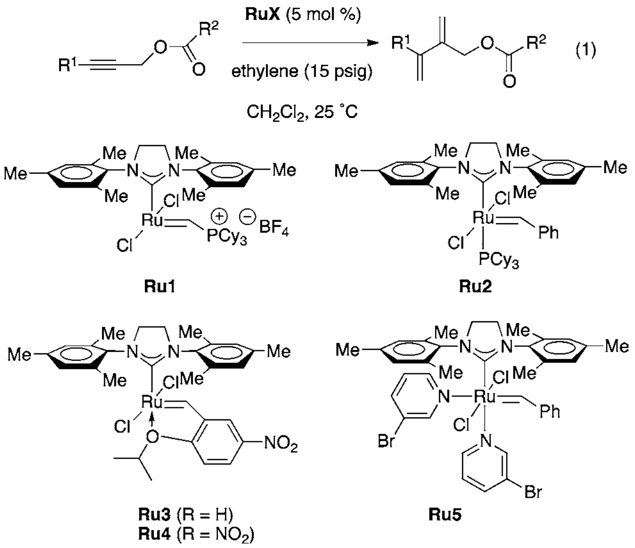
Supporting Information

ABSTRACT: Reaction kinetics and mechanistic studies for ethylene–internal alkyne metathesis promoted by the phosphine-free initiator **Ru1** (Piers's catalyst) is described. The kinetic order of reactants and catalyst was determined. The effect of ethylene was studied at different solution concentrations using ethylene gas mixtures applied at constant pressure. Unlike earlier studies with the second-generation Grubbs complex, ethylene was found to show an inverse first-order rate dependence. Under catalytic conditions, a ruthenacyclobutane intermediate was observed by proton NMR spectroscopy at low temperature. Combined with the kinetic study, these data suggest a catalytic cycle involving a reactive $L_nRu{=}CH_2$ species in equilibrium with ethylene to form a ruthenacyclobutane, a catalyst resting state. Rates were determined for a variety of internal alkynes of varying substitution. Also, at low ethylene pressures, preparative syntheses of several 2,3-disubstituted 1,3-butadienes were achieved. Using the kinetic method, several phosphine-free inhibitors were examined for their ability to promote ethylene–alkyne metathesis and to guide selection of the optimal catalyst.

Scheme 1. Ethylene–Alkyne Metathesis



Alkene and ene–yne metathesis have become synthetically important catalytic reactions, owing their success to the functional group tolerant Grubbs's precatalysts. Recently, phosphine-free initiators have been increasingly used, especially in demanding applications.[1,2] With these new initiators, the rate-determining step of catalysis and resting states are not known. Ethylene has played a prominent role in ring-closing enyne metathesis applications. Ethylene has two major effects: it assists vinyl carbene turnover,[3] giving productive enyne metathesis, and it helps inhibit alkyne oligomerization,[4] a major side reaction. Higher ethylene pressure gives faster cross-ene–yne metathesis (EYM) with the first-generation Grubbs complex.[5] With newer catalysts such as **Ru1** (Scheme 1), does ethylene kinetically accelerate intermolecular EYM? We predicted that the lack of phosphine in these catalytic reactions could alter the catalyst "resting states", which might define a new role for ethylene. In this Communication, we describe a new ethylene effect: inhibition of a cross-metathesis by excess ethylene. The detailed kinetics of a cross-EYM using **Ru1** are reported, showing that the resting state is a ruthenacyclobutane, observed under catalytic conditions of EYM. Contrasting rate data are provided for some commonly used Grubbs catalysts, suggesting that the kinetic profiling of catalysts may be a useful aid for catalyst selection.

In metathesis chemistry, ethylene has great significance, and synthetic applications employing "more reactive" phosphine-free initiators such as **Ru3** have increased in recent years.[1,2] In alkene metathesis, ethylene is a byproduct that influences equilibrium, but more importantly it can lead to catalyst decomposition via a $L_nRu{=}CH_2$ species. Ethylene was used to generate ruthenacyclobutane intermediates in seminal studies by Piers et al.[6] and by Grubbs et al.[7] Those studies showed that ruthenacyclobutanes are intermediates in alkene metathesis. However, the intermediacy or agency of a ruthenacyclobutane has never been established in catalytic EYM. Ethylene is widely used in EYM, but its kinetic role is understood only in the context of phosphine-containing catalysts.[3,8] Ethylene helps ring-closing metathesis of terminal alkynes ("Mori's conditions"), leading to higher product yields.[9] The functional role of ethylene has been difficult to understand because of its multifaceted nature: it stabilizes carbene intermediates,[6,7,9] assists the rate of turnover,[3] and inhibits competing processes.[4] Ethylene has also been used to promote stereoselective cross-metathesis[10] and to help difficult cross-EYM.[11] The trend toward the use of phosphine-free inhibitors allows more forcing conditions,[1,2] but it may alter the catalytic landscape by changing the rate-determining step of the

Received: August 16, 2013
Published: November 5, 2013

dx.doi.org/10.1021/ja4085012 | J. Am. Chem. Soc. 2013, 135, 16777−16780

cycle. The use of phosphine-free initiators such as **Ru1** to promote the ethylene–alkyne cross-metathesis provided a means to evaluate the confluence of these ideas in EYM.

To study the effect of ethylene with phosphine-free ruthenium carbene initiators, an in situ method was used to monitor change in the alkyne reactant concentration. Internal alkyne disappearance followed first-order kinetics. Decrease in [alkyne] was followed by in situ FT-IR, monitoring the change in absorptions at 1155 cm^{-1} (C–O bond) and 1755 cm^{-1} (C=O bond). The loss of alkyne correlated with the appearance of the expected 1,3-diene product, as corroborated by ^1H NMR. For instance, aliquots were taken at various time points and analyzed by ^1H NMR, measuring the integral values of 1,3-diene compared to alkyne reactant. Typical conditions began with 25 mM 1,4-diacetoxy-2-butyne (**1a**), 1 mM **Ru1**, and 15 psig of ethylene held in a heavy-walled glass vessel with the bath temperature actively regulated at 25 °C. Equilibrium of ethylene concentration was established by obtaining a steady absorption at 960 cm^{-1}, a strong C–H overtone unique to ethylene. Mass transfer from the gas phase, under stirring and with a positive pressure, maintains a constant ethylene concentration through the duration of the EYM. During the EYM, the absorption at 960 cm^{-1} did not drop significantly (±5%), indicating that the rate of ethylene mass transfer was comparable to that of the EYM. In Figure 1, the first-order plot of ln [alkyne] vs time is shown, yielding the k_{obs} value.[12]

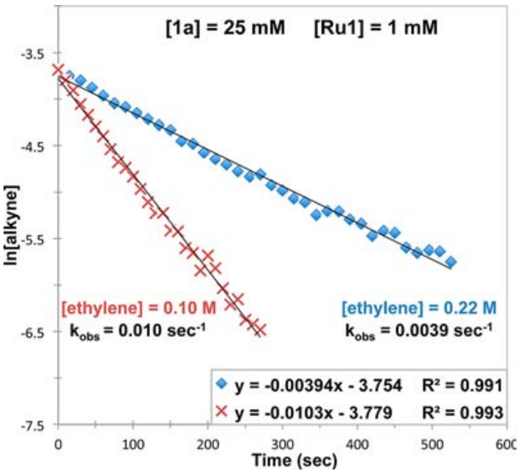


Figure 1. Plot of ln [alkyne] vs time at two ethylene concentrations at constant pressure.

Surprisingly, the rate of ethylene–alkyne metathesis was found to be slower at higher solution concentration of ethylene. To change ethylene concentration but to maintain the same pressure, the ethylene was diluted in argon. Using the gas mixture at 15 psig with varying mole fraction of ethylene produced a known solution concentration of ethylene.[13] Slower rate at higher ethylene concentration can be seen by comparison of the k_{obs} values determined from the logarithmic plot in Figure 1. At 0.22 M ethylene, k_{obs} = 0.0039 s^{-1}, whereas at 0.10 M ethylene, k_{obs} = 0.010 s^{-1}. Though these graphs show that ethylene is inhibiting the ethylene–alkyne metathesis, a more detailed analysis of k_{obs} vs ethylene concentration was needed to establish kinetic order in ethylene reactant.

Kinetic orders in ethylene and the Piers catalyst **Ru1** were established by measuring rates using different concentrations of the species under question with other concentrations held constant (Figure 2). As ethylene was diluted, the reaction rate was found to increase. After k_{obs} values were obtained at three different ethylene concentrations, a plot of ln(k_{obs}) vs ln [ethylene] produced a line with a slope of −1. Similarly, the precatalyst concentration [**Ru1**] was varied from 0.3 to 5 mM to obtain k_{obs} values. A similar double logarithmic plot yielded first-order dependence in [**Ru1**]. Overall, the rate law is rate = $k[\text{alkyne}]^1[\text{Ru1}]^1[\text{ethylene}]^{-1}$, where k is the experimentally determined apparent first-order rate constant.

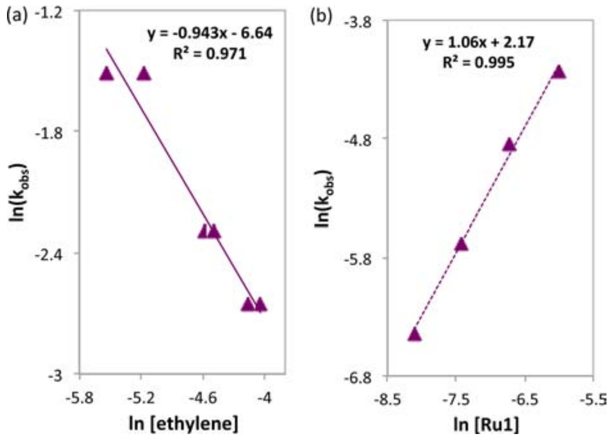
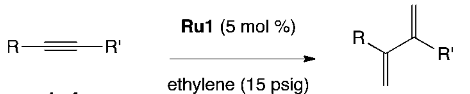


Figure 2. Plots showing kinetic order in ethylene and **Ru1**: (a) ln(k_{obs}) vs ln [ethylene] and (b) ln(k_{obs}) vs ln [**Ru1**]. The plotting equation used is ln(k_{obs}) = n ln [species] + ln(c).

The effect of alkyne substitution on reaction rate was studied for a group of internal alkynes. Using the rate method and standard kinetic conditions, apparent first-order rate constants for a variety of internal alkynes were readily obtained and compared (Table 1).

Importantly, for each of these alkynes, the same rate law is obeyed.[14] The apparent first-order rate constant k could be obtained from the expression $k_{obs} = k[\text{Ru1}]^1[\text{ethylene}]^{-1}$ at given

Table 1. Rate Constants and Yields of 2,3-Disubstituted 1,3-Butadienes[a]



1a-f 2a-f

Entry[a]	Alkyne	R	R'	k / s^{-1}	Diene	% Yield[b]
1	**1a**	CH_2OAc	CH_2OAc	1.27 ± 0.14	**2a**	91
2	**1b**	CH_3	CH_2OBz	1.20 ± 0.16	**2b**	89
3	**1c**	n-C_3H_7	n-C_3H_7	0.53 ± 0.05	**2c**	79
4	**1d**	i-Pr	CH_2OBz	0.69 ± 0.08	**2d**	97
5	**1e**	CH_2OTBS	CH_2OTBS	0.42 ± 0.05	**2e**	86
6	**1f**	H	$CH(OBz)CH_3$	1.66 ± 0.19	**2f**	85
7	**1g**	Ph	CH_2OBz	N. R.	-	-
8	**1h**	H	CH_2OBz	N. R.	-	-

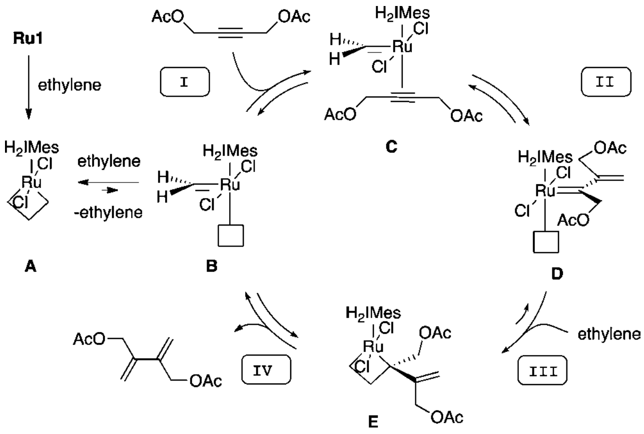
[a] Standard conditions: 5 mol % **Ru1**, alkyne (0.1 M), ethylene (15 psig) in CH_2Cl_2, for **1** h at rt; quenched with KO_2CCH_2NC in MeOH. [b] Isolated yields. N. R. = no reaction.

values of **Ru1** and ethylene. Replacement of one propargylic acetate gave alkyne **1b** that reacted at the same rate (entry 2) as the parent internal alkyne **1a** (entry 1). With linear alkyl substituents on the alkyne, as in **1c**, the rate constant is 2.4 times slower than with **1a** (entry 3). Similarly, secondary propargylic substitution on one site reduces the rate (entry 4), as do bulky *tert*-butyldimethylsilyl ethers (entry 5). Even though ethylene inhibited the reaction rate, preparatively useful yields of 2,3-disubstituted 1,3-butadienes were obtained (last column in Table 1). To make a comparison between internal and terminal alkynes, terminal alkyne **1f** was studied (entry 6). Alkyne **1f** was found to obey the same rate law and reacted at a comparable rate as the parent alkyne **1a**. Earlier studies using the Grubbs catalyst **Ru2** had shown zero-order ethylene dependence and first-order alkyne dependence.[8] To the best of our knowledge, these data provide the first direct kinetic comparison of a terminal alkyne with an internal alkyne. Interestingly, under the standard conditions (4 mol % **Ru1**), alkynes **1g,h** were found to be unreactive.[15]

Inhibition of reaction rate at higher ethylene concentrations suggested that a ruthenacyclobutane may be the catalyst resting state. ^{1}H NMR experiments in CD_2Cl_2 conducted at −40 °C identified the ruthenacyclobutane **A** (see Scheme 2) before, during, and after ethylene metathesis of **1a**. After a solution of **Ru1** was pressurized with ethylene (balloon pressure), complete conversion to **A** was observed.[16] Because the metathesis proved slow at −40 °C, warming was necessary. Upon recooling to −40 °C, the ruthenacyclobutane was again observed at both 15% and 100% conversion. To the best of our knowledge, this is the first direct observation of a ruthenacyclobutane under catalytic EYM conditions.

The proposed mechanism based on the kinetic data and mechanistic study described above is shown in Scheme 2. The rate-determining step involves the alkyne reacting with the highly reactive 14-electron ruthenium methylidene **B** (step I). The lack of Cy_3P allows intermediate **B** to partition between alkene (ethylene) binding and alkyne binding. Ethylene binding leads to **A**, an intermediate that undergoes reversible, degenerate alkene metathesis.[6c,7a] Alkyne binding ushers **B** into the catalytic cycle. In this EYM, ethylene is involved at two places: in the catalytic cycle after the rate-determining step (at step III) and at the entry point to the EYM catalytic cycle. Inhibition by ethylene is due to competitive binding to the reactive intermediate **B**, leading to resting state **A**. The inverse dependence on ethylene provides kinetic support for the existence of **A**, which is favored in its equilibrium with **B** and ethylene due to the high solution concentration of ethylene vs alkyne. As a resting state, **A** can reversibly lead back to catalysis (via **B**) or undergo slow decomposition.[6a] In contrast, phosphine-containing catalyst **Ru2** produces a phosphine-bound resting state derived from vinyl carbene **D**.[8] Using catalyst **Ru1**, there is no such resting state. The absence of phosphine-bound resting states is a key difference from our earlier mechanistic studies with **Ru2**.

Scheme 2. Proposed Mechanism and Resting State



The rate studies were extended to other ruthenium carbene precatalysts, especially phosphine-free initiators.[17] Catalyst optimization in EYM typically focuses on product yields, rather than rates of conversion. Kinetic profiling of catalysts for EYM is rare.[18] Using the method of initial rates, a direct rate comparison could be made for a group of commonly used ruthenium carbene complexes (Figure 3 and Table 2).[13] Precatalyst **Ru1** gave the fastest overall rate (entry 1). The Hoveyda−Grubbs family of catalysts is widely used and highly effective for both alkene and EYM applications. Hoveyda catalyst **Ru3**[17b,c] showed a brief induction period and an initial rate slower than that of complex **Ru1** (entry 2). The Grela catalyst **Ru4**[17d] is a highly active initiator in alkene metathesis, showing a rate comparable to that of **Ru1** (entry 3). Interestingly, the Grubbs pyridine solvate **Ru5**,[17e] known to be one of the fastest initiators for alkene metathesis, was found to promote a slower EYM than the other

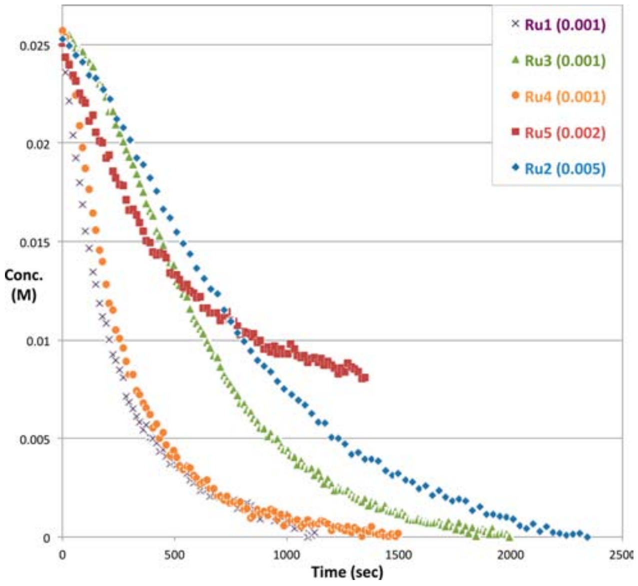


Figure 3. Comparison of commonly used catalysts in ethylene−alkyne cross-metathesis. Reaction conditions are listed in Table 2. The rate of alkyne disappearance was found to show first-order dependence. The order in ethylene was not determined for each of these catalysts.

Table 2. Relative Rates of Ethylene−1a Metathesis by Various Phosphine-Free Initiators

Entry[a]	RuX (concn/M)	Initial rate/M s^{-1}[b]	Rel. rate
1	**Ru1** (0.001)	1.40×10^{-4}	30
2	**Ru3** (0.001)	2.96×10^{-5}	6
3	**Ru4** (0.001)	1.16×10^{-4}	24
4	**Ru5** (0.002)	1.84×10^{-5}	4
5	**Ru2** (0.005)	4.74×10^{-6}	1

[a]Reaction conditions: 1−5 mM **RuX**, 220 mM ethylene (14 psig), CH_2Cl_2, 25 °C. [b]Normalized for concentration of **RuX**, since the reaction rate is first-order dependent on **Ru1**.[19]

phosphine-free initiators (entry 4). Furthermore, this reaction failed to go to full conversion, suggesting that catalyst decomposition had occurred. As a point of comparison, the second-generation Grubbs complex **Ru2**[17a] gave an initial rate comparable to that of **Ru5** when used at a much higher catalyst loading (20 mol %). **Ru2** was about 30 times slower than **Ru1**, but both reactions went to completion. Based on alkene initiation profiles, **Ru1**, **Ru4**, and **Ru5** should be the best catalysts.[19] For catalytic EYM, a low steady-state concentration of carbene **B** is needed to sustain catalysis; if it builds up too rapidly, bimolecular decomposition[20] may subvert productive catalysis. Further studies on catalyst decomposition under phosphine-free conditions are needed, and are ongoing in our laboratories. With so many precatalysts commercially available, and many easily prepared, kinetic profiling should help with catalyst selection in specific metathesis applications where phosphine-free initiators are desirable.

In conclusion, an inverse effect of ethylene on the rate of ethylene−alkyne metathesis was found. The kinetic and mechanistic studies identify a ruthenacyclobutane resting state in EYM promoted by catalyst **Ru1**. These studies offer insight into a catalytic cycle devoid of the traditional phosphine-bound carbene resting states, with a corresponding change in the rate-determining step. This study provides a rate comparison for a variety of internal alkynes, which was contrasted with a terminal alkyne. Though kinetically inhibited, ethylene−alkyne metathesis could be brought to completion, resulting in practical syntheses of 2,3-disubstituted 1,3-butadienes. Last, the kinetic method was extended to other phosphine-free catalysts, providing a simple method to kinetically profile catalysts to assist in catalyst selection for EYM applications. Further studies in kinetic profiling as a means for rational ruthenium carbene catalyst selection are currently underway in our laboratories.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank the NSF (CHE-1012839 to S.T.D. and J.B.K.) for continuing support of mechanistic studies of ene-yne metathesis. We thank David J. Fortman (Canisius College) for technical assistance preparing alkynes and Justin Griffiths (SUNY Buffalo) for assistance with VT NMR experiments. We are also grateful to Materia for a generous gift of Grubbs' complexes and to Wes Walker (Mettler-Toledo) for assistance with the React IR.

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(12) The method of initial rates and linear regression of ln [alkyne] vs time gave similar values for k_{obs}; however, the reported k_{obs} values were obtained from the ln plots (e.g., Figure 1) because of the greater number of data points.

(13) See Supporting Information for full details.

(14) This was determined by measuring k_{obs} at two different reactant or catalyst concentrations to verify rate dependence. For each alkyne substrate, this required at least six kinetic runs.

(15) For **1g**, 100% alkyne remained after the standard conditions. For **1h**, ∼30% consumption was obtained, but there was only ∼10% 1,3-diene, which was contaminated with other byproducts. See Supporting Information.

(16) Piers and Romero's conversion (ref 6a) took longer because they used only 2.2 equiv of ethylene. In the present study, we use >20-fold excess.

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