ORGANIC LETTERS

2005
Vol. 7, No. 2
351−354

Cross Enyne Metathesis of *para*-Substituted Styrenes: A Kinetic Study of Enyne Metathesis

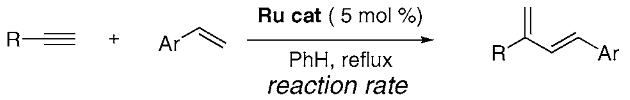
Anthony J. Giessert and Steven T. Diver*

Department of Chemistry, University at Buffalo, The State University of New York, Amherst, New York 14260

diver@nsm.buffalo.edu

Received October 5, 2004; *(Revised Manuscript Received December 1, 2004)*

ABSTRACT



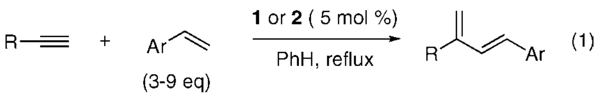
Ar = *p*-NMe_2, *p*-OMe, *p*-Me, *p*-H, *p*-Br, *p*-NO_2
Ru cat = (dihydroIMes)$(Cy_3P)Cl_2Ru{=}CHPh$

The intermolecular enyne metathesis between alkynes and styrene derivatives was developed to study electronic effects in enyne metathesis. A Hammett plot for the overall reaction, catalyst initiation and vinyl carbene turnover was determined with the second generation Grubbs ruthenium carbene catalyst.

Enyne metathesis is a powerful method for the synthesis of 1,3-dienes;[1] however, despite its usefulness, little is known about the mechanism of the reaction. Enyne metathesis makes use of ruthenium carbene catalysts (**1**, **2**)[2] developed by Grubbs[2a,b] for olefin metathesis. Due to the lack of mechanistic studies focused on enyne metathesis, mechanistic parallels have been drawn between olefin and enyne metathesis. Herein, we report the enyne cross metathesis between alkynes and styrenes (Scheme 1). The effectiveness of the synthetic method permitted us to investigate electronic effects in the styrene with a Hammett study.

Styrenes have seen limited application in cross enyne metathesis.[3] In one case, Blechert terminated a tandem ring-rearrangement with a variety of 1-alkenes, including styrene.[3a] However, the generality of the cross metathesis for a range of electronically-differentiated styrenes was not demonstrated. In alkene metathesis, styrene reactivity varies considerably.[4] Styrenes provide a potentially useful mechanistic probe for the sensitivity of enyne metathesis to electronic effects. To the best of our knowledge, styrene has not been used for intermolecular enyne metathesis for the synthesis of acyclic 1,3-dienes.

Scheme 1. Styrene-Alkyne Metathesis



$(Cy_3P)_2Cl_2Ru{=}CHPh$ **1** (Grubbs' first generation)
(dihydroIMes)$(Cy_3P)Cl_2Ru{=}CHPh$ **2** (Grubbs' second generation)
dihydroIMes = 1,3-bis(mesityl)-4,5-dihydroimidazolylidene

Uncertain of the scope and efficiency of the cross-metathesis, metathesis conditions were developed for a series of para-substituted styrenes (Table 1). The required styrenes are either commercially available or can be synthesized by Wittig methylenation of the corresponding benzaldehyde.[5]

---

(1) Recent 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.

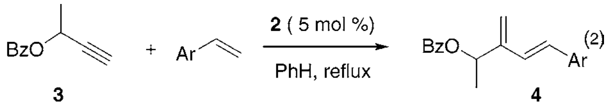
(2) (a) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100−110. (b) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956. (c) Weskamp, T.; Schattenmann, W. C.; Spiegler, M.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **1998**, *37*, 2490−2493.

(3) (a) Imhof, S.; Blechert, S. *Synlett* **2003**, 609−614. (b) Lee, H.-Y.; Kim, H. Y.; Tae, H.; Kim, B. G.; Lee, J. *Org. Lett.* **2003**, *5*, 3439−3442. (c) Banti, D.; North, M. *Adv. Synth. Catal.* **2002**, *344*, 694−704.

(4) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360−11370.

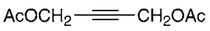
10.1021/ol047533n CCC: $30.25

Table 1. Scope of Alkyne–Styrene Metathesis

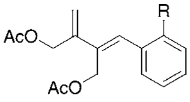


entry[a]	alkyne	alkene	product	yield (%, *E*/*Z*)
1	**3**	styrene	**4a**	99 (5:1)
2	**3**	4-methylstyrene	**4b**	93 (5:1)
3	**3**	2-methylstyrene	**4c**	99 (5:1)
4	**3**	4-dimethylaminostyrene	**4d**	94 (5:1)
5	**3**	4-vinylanisole	**4e**	95 (3:1)
6	**3**	4-bromostyrene	**4f**	94 (5:1)
7	**3**	4-nitrostyrene	**4g**	56 (1:1)
8	**3**	1-vinylnaphthalene	**4h**	93 (5:1)
9	**3**	2-vinylnaphthalene	**4i**	90 (4:1)
10	**5**	styrene	**6a**	86 (>20:1)
11	**5**	2-methylstyrene	**6b**	86 (4:1)

[a] Conditions: alkyne (1.0 equiv), alkene (9.0 equiv), **2** (5 mol %) PhH, reflux.


$AcOCH_2{-}C{\equiv}C{-}CH_2OAc$

5

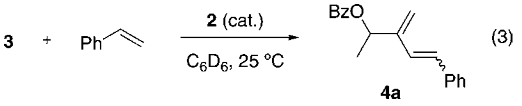


6a (R = H)
6b (R = CH_3)

The reaction worked equally well with substitution at the ortho or para position of styrene (entries 2, 3). Styrenes with electron-donating substituents furnished dienes **4** in good yield (entries 1–5). Electron-withdrawing substituents could be utilized on the phenyl ring (entries 6, 7), and both 1- and 2-vinyl naphthoates as alkene partners (entries 8, 9) gave good yields. Nitrostyrene gave a 1:1 *E*/*Z* diene mixture[6] in moderate yield. Use of symmetrical internal alkyne **5** was also well tolerated, providing good yields of diene (entries 10, 11).[7]

Kinetic order in reactants and catalyst was established by concentration doubling experiments. The reaction of butynyl benzoate **3** and styrene was chosen as the standard reaction. The reaction of **3** and 9 equivalents styrene was examined with the catalyst **2** at 25 °C, monitored for loss of **3** by ^{1}H NMR spectroscopy (thermostatted NMR probe). Doubling the concentration of styrene (entry 2, Table 2) resulted in a doubling of the reaction rate, indicating that the reaction is first order in styrene. Several reaction rates were obtained at different styrene concentrations, and this plot confirmed first-order behavior (see the Supporting Information, Figure S1). When the alkyne concentration was doubled (entry 3, Table 2), there was no change in the rate of reaction. Therefore, the reaction is zero order in alkyne, indicating that the alkyne is not involved in the rate-determining step and therefore excluded from the rate law. Doubling of the catalyst concentration caused the reaction rate to double, indicating that the reaction is first order in catalyst. This agrees with the current assumption that turnover of the vinyl carbene is rate-limiting for the enyne metathesis reaction.[8]

Table 2. Relative Rates of Reaction for Alkyne **3** and Styrene



entry	[alkyne]/M	[alkene]/M	[cat. **2**]/mM	rate^{a,b}/M min^{-1}
1	0.05	0.45	2.5	1.0×10^{-3}
2	0.05	0.90	2.5	2.0×10^{-3}
3	0.10	0.90	2.5	2.0×10^{-3}
4	0.05	0.45	5.0	2.0×10^{-3}

[a] These reactions showed linear disappearance of alkyne concentration versus time. The reported rate is the slope of this line. [b] Average of at least two runs.

To evaluate electronic effects in the styrene, the enyne metathesis was examined by a Hammett study. The overall reaction was monitored for conversion of alkyne **3** to dienes **4** (eq 4)[9] with a variety of styrene derivatives. At 2.5 mM concentration of complex **2**, the disappearance of the alkyne was monitored by ^{1}H NMR with excess styrene. These conditions yielded the rate constants used in the Hammett plot shown in Figure 1.[10] The plot shows scatter over the full range of donating and withdrawing substituents. However, for substituents with $\sigma < 0.3$, there is a linear

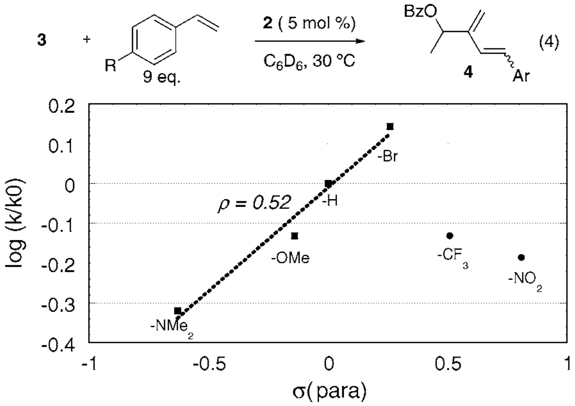


Figure 1. Hammett plot for the reaction of alkyne **3** and *p*-substituted styrenes catalyzed by **2** (5 mol %) at 30 °C. Additional experiments showed that the data points represented as circles are zero-order in these styrenes.

---

(5) (a) Iida, T.; Itaya, T. *Tetrahedron* **1993**, *49*, 10511–10530. (b) Casalnuovo, A. L.; RajanBabu, T. V.; Ayers, T. A.; Warren, T. H. *J. Am. Chem. Soc.* **1994**, *116*, 9869–9882. (c) Balema, V. P.; Wiench, J. W.; Pruski, M.; Pecharsky, V. K. *J. Am. Chem. Soc.* **2002**, *124*, 6244–6245.

(6) Unlike the other entries of Table 1, this reaction is zero order in the styrene and proceeds with a different, and slower, rate-determining step.

(7) Phenylacetylene and 1-octyne provided the expected 1,3-dienes; however, concentration of the crude solutions resulted in polymerization.

(8) (a) Blechert, S.; Stragies, R.; Schuster, M. *Angew. Chem., Int. Ed.* **1997**, *36*, 2518–2520. (b) Giessert, A. J.; Brazis, N. J.; Diver, S. T. *Org. Lett.* **2003**, *5*, 3819–3822.

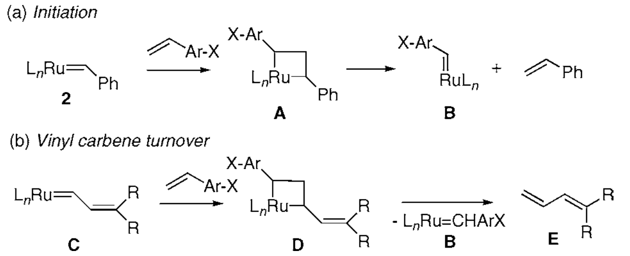
(9) The rate of disappearance of the alkyne was the same as the rate of appearance of product.

(10) The four leftmost data points (–NMe_2, –OMe, –H, –Br) show linear disappearance of [alkyne]; the right two points show linear plots for -ln[alkyne] vs time, indicating zero-order and first-order behavior, respectively, in the two regimes of the plot.

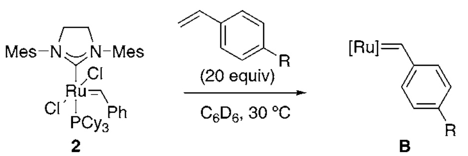
region (left side of Figure 1). In this region, the slope, ρ, is 0.52, indicating rate acceleration by electron-withdrawing substituents on the phenyl ring. This is similar to observations made for arylidene intiation with 2-butene.[11] In the more electron-withdrawing styrene examples, the slope appears negative. A Hammett analysis assumes that all styrenes react by the same mechanism and proceed through the same rate-determining step. Figure 1 indicates that there may be a change in rate-determining step or a significantly reorganized transition state (e.g., change in regiochemistry of cycloaddition). The three rightmost data points in Figure 1 (bromo-, CF_3-, and nitro-) were investigated for reaction order in styrene derivative. Like the enyne metathesis of strryrene, bromostryrene was first order in bromostyrene. However, the reaction rates of trifluoromethylstyrene and nitrostyrene were both found to be *zero order* in the styrene over three different alkene concentrations (0.9−1.5 M alkene, see Figures S2 and S3 in the Supporting Information). On the basis of this distinction, the two rightmost data points in Figure 1 are drawn as circles and excluded from the linear regression.

Since the Hammett plot of Figure 1 characterizes a catalytic process with many elementary steps, we sought to extricate individual steps in enyne metathesis. Understanding these steps will help rationalize the data of Figure 1 and provide a more comprehensive mechanistic picture. Two distinct steps in the catalytic reaction were examined: catalyst initiation (Scheme 2, panel a) and catalyst turnover (Scheme 2, panel b). The initiation step was used to probe regiochemistry, and identify kinetically-formed metal carbenes. The reaction of a vinyl carbene **C** with styrene models the catalyst turnover step, which is both unique to enyne metathesis and thought to be rate-determining.[8] For this to be true, the reaction rate would show a first-order dependence on alkene concentration.

Scheme 2. Important Steps in Enyne Metathesis



Catalyst initiation (eq 5) proceeded with high regioselectivity and gave a linear free energy relationship (Figure 2). Initiation kinetics were obtained by ^{1}H NMR spectroscopy in a thermostatted probe at 30 °C, observing loss of the benzylidene carbene proton. The observed slope of $\rho = 0.06$ was much smaller than that found for the linear region of the overall reaction ($\rho = 0.52$; see Figure 1, above). This step is nearly degenerate (substituted styrene to styrene), which may explain the small substituent effect on reaction rate. Proton NMR confirmed the appearance of the substituted benzylidenes **B** in every case except for *p*-nitrostyrene. The initiation of **2** with *p*-nitrostyrene produced a mixture of ruthenium methylidene $L_nRu{=}CH_2$ **7** and ruthenium *p*-nitrobenzylidene **B**. The high regioselectivity via **A** is consistent with the regiochemistry observed in the transalkylidenation step of alkene metathesis.



(5)

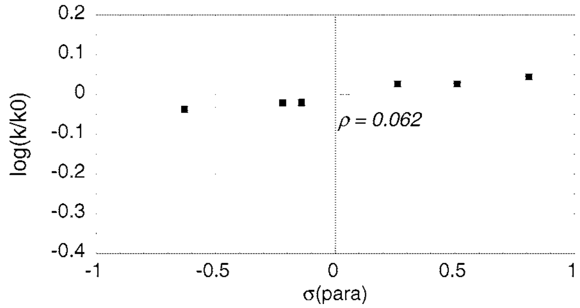


Figure 2. Hammett plot for the initiation of **2** with *p*-substituted styrenes (20 equiv) in C_6D_6 at 30 °C.

The last step in the catalytic cycle, vinyl carbene turnover, proved more sensitive to electronic perturbation in the styrene. To model this step, vinyl carbene **8**[12] was reacted with electronically-differentiated styrenes (eq 6). The concentration doubling experiments of Table 2 show that the reaction is first order in styrene, which is consistent with turnover being the slow step. This step of catalysis shows a bimodal rate plot, with slight acceleration by moderately electron-withdrawing substituents, then a break for the highly electron-withdrawing $-CF_3$ and $-NO_2$ substituents (Figure 3). By studying the vinyl carbene turnover step, regiochemical preference of the carbene is apparent. In all cases, the arylidene **B** was the kinetic product, arising from CH_2 transfer to the carbene carbon (eq 6). This observation is consistent with an "arylidene-first" mechanism (transfer of ArCH to the alkyne).[1a,13] If arylidene transfer had occurred, **7** would have formed directly. After vinyl carbene **8** was consumed, arylidenes **B** were slowly[14] converted to methylidene **7** through secondary olefin metathesis of **B** with excess styrene, a process that was fastest in the *p*-nitrostyrene case. Secondary olefin metathesis resulting in ruthenium methylidene production has been observed by Grubbs in the first

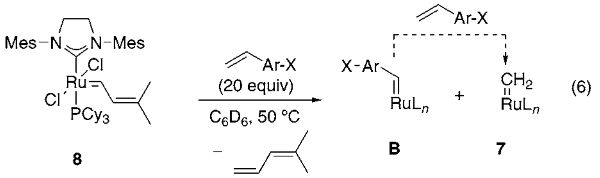
---

(11) Adlhart, C.; Hinderling, C.; Baumann, H.; Chen, P. *J. Am. Chem. Soc.* **2000**, *122*, 8204−8214.

(12) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783−3784.

(13) (a) Hoye, T. R.; Donaldson, S. M.; Vos, T. J. *Org. Lett.* **1999**, *1*, 277−279. (b) Schramm, M. P.; Reddy, D. S.; Kozmin, S. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4274−4277.

(14) The higher temperatures needed to react carbene complex **8** are attributed to a slow phosphine off-rate. In a normal enyne metathesis, carbene **C** is likely formed without a bound phosphine.



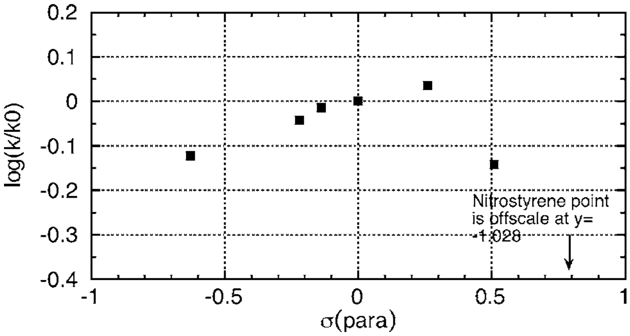
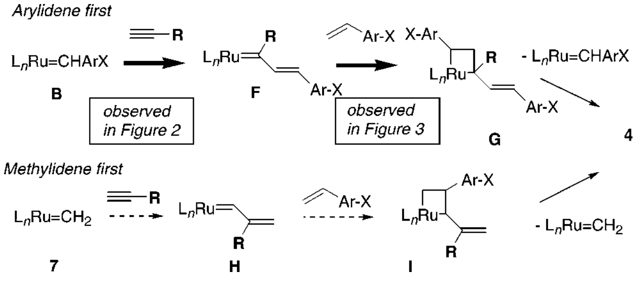


Figure 3. Hammett plot for the initiation of vinyl carbene **8** and various styrene derivatives at 50 °C in C_6D_6.

generation ligand environment.[15] Highly electron-withdrawing substituents slow the modeled vinyl carbene turnover rate significantly. This is a direct probe for electronic effects in the interaction of the styrene with the electron-deficient carbene species. This may also explain the moderate yields in the nitrostryrene metathesis of eq 1 (entry 7, Table 1). Last, reaction of **8** with styrene should produce 2-methyl-2,4-pentadiene as the organic product, which was observed by ^{1}H NMR spectroscopy and established by comparison to an authentic sample.

The styrene cross metathesis is consistent with an arylidene-first mechanism, involving rate-determining turnover of vinyl carbene species **F** (Scheme 3). Kinetic formation of arylidenes **B** (Figure 2) is consistent with their agency as the active carbenes that react with the alkyne to give vinyl carbene **F**. In the modeled vinyl carbene turnover step (eq 6, Figure 3), methylene transfer occurred to the vinyl carbene carbon with concomitant formation of the ruthenium arylidene. This implicates a metallacycle of type **G**. In the “alkylidene-first” mechanism,[13] vinyl carbene **F** would similarly undergo methylene transfer with alkene (or styrene) to give the 1,3-disubstituted dienes (e.g., **4**) of enyne cross metathesis. In the “methylidene-first” mechanism, the vinyl carbene **H** would need to transfer an arylidene (ArCH) group to the carbene carbon from the styrene. The vinyl carbene **8** is similar to carbenes **F**, **H**, and reveals the preferred regiochemistry of these species. Based on this similarity, the direct observation of methylene transfer supports the intermediacy of **F** in enyne cross metathesis. The rate data presented here suggest that turnover of vinyl carbene **8** is rate-limiting for

Scheme 3. Mechanistic Comparisons and Summary



styrenes of $\sigma < 0.3$. The first-order behavior of styrenes of $\sigma < 0.3$ and the regiochemistry of eq 6 is consistent with the vinyl carbene turnover step **F** to **G** to **4** as the rate-limiting step in catalysis for styrenes with $\sigma < 0.3$.[16] Styrenes with moderate electron-withdrawing groups (i.e., *p*-Br) may bind better due to improved back-bonding to the electron-rich metal, similar to the finding of Grubbs and coworkers[17] concerning the increased reactivity of the second generation carbene **2** vs. **1** in alkene metathesis. Interpretation of the break in the Hammett plot of Figure 1 is more complicated since the conditions necessitate catalytic turnover, probably involve several catalytic species (including Ru=CHAr or Ru=CH_2) and may involve competing alkene metathesis. Further kinetic study is needed to isolate these factors.

In summary, a new cross enyne metathesis with substituted styrenes has been reported and used to probe electronic effects in a study of the enyne metathesis mechanism. The data show regioselective methylene group transfer to a vinyl carbene intermediate consistent with an “arylidene-first” mechanism. A break in the Hammett plot for the catalytic reaction is likely due to a change in rate-determining step for the most electron-poor styrenes. Further kinetic investigation of the alkyne reactivity is ongoing in our laboratories.

Acknowledgment. We thank Brandon Galan and Professor Jerry Keister for helpful discussions and Dr. Richard Fisher (Materia, Pasadena, CA) for catalyst support. We acknowledge the NIH (R01CA90603) and the NSF (CHE-092434) for financial support of this work.

Supporting Information Available: Experimental procedures and full characterization data for new compounds **4a**–**i** and **6a**,**b**, methods for the rate determinations, and supplemental plots. This material is available free of charge via the Internet at http://pubs.acs.org.

OL047533N

---

(15) Kinetic formation of alkylidenes relevant to alkene metathesis, see: Zuercher, W. J.; Scholl, M.; Grubbs, R. H. *J. Org. Chem.* **1998**, *63*, 4291–4298.

(16) In these cases (styrenes of $\sigma < 0.3$), electronic effects of the styrene are being probed in the same rate-determining step. Up to the inflection point, electron-withdrawing substituents accelerate the reaction slightly. The kinetic data alone do not differentiate the vinyl carbene turnover steps illustrated in Scheme 3.

(17) (a) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543–6554. (b) Love, J. A.; Sanford, M. S.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 10103–10109.