JOC Note

Equilibrium Control in Enyne Metathesis: Crossover Studies and the Kinetic Reactivity of (*E*,*Z*)-1,3-Disubstituted-1,3-Dienes

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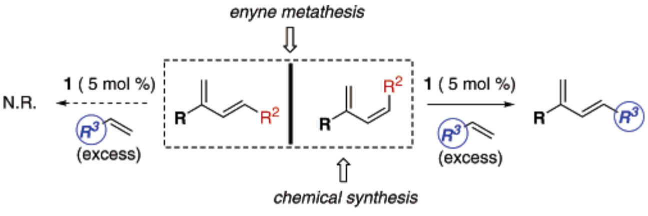
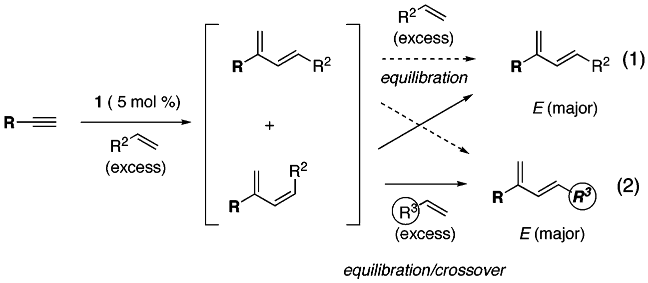


1 = (dihydroIMes)(Cy_3P)Cl_2Ru=CHPh, Grubbs' second generation carbene

The stereoselectivity of diene bond formation in the ruthenium−carbene mediated intermolecular enyne metathesis was studied. Initial reaction between an alkyne and 1-hexene gave mixtures of *E*- and *Z*-isomers in the newly formed 1,3-diene. However, over time the mixtures equilibrated to form mostly the diene of the *E*-configuration. To evaluate individual reactivity of the *E*- and *Z*-dienes, they were independently synthesized. The *E*-diene was found to be kinetically-stable under nominal metathesis conditions while the *Z*-diene isomerized to the *E*-isomer. The *Z*-isomeric dienes were found to react with other alkenes to produce a new diene of *E*-configuration. A secondary metathesis mechanism involving ruthenium alkylidene intermediates was invoked to explain the dynamic stereochemistry observed in this study.

Enyne metathesis has proven efficient for the formation of 1,3-dienes.[1] Yet as powerful as the cross enyne metathesis is as a carbon−carbon bond-forming reaction, its usefulness is limited by lack of selectivity (typically about 1:1).[2] Even with the more reactive second generation Grubbs' carbene **1**, mixtures of stereoisomers are typically obtained in cross metathesis[1a,3] and there are comparatively few examples that exhibit high *E*-selectivity.[4] Most cases exhibiting high *E*-selectivity make use of the second generation Grubbs ruthenium carbene catalyst **1** and aliphatic 1-alkenes (eq 1). Some of the literature variation in *E*/*Z* stereoselectivity might be explained by equilibration (e.g., the *E*-isomers were being formed in certain cases due to thermodynamic control). We hypothesized that the produced dienes might continue to react since precatalyst **1** is known to react with internal alkenes[5] and because dienes will participate in cross alkene metathesis.[6] In this report, the stereoselectivity of enyne metathesis was examined using the second generation Grubbs carbene **1**. The fast metathesis produced initial mixtures of *E*- and *Z*-isomers, which was followed by a dynamic process leading to the most stable *E*-diene in certain cases (Scheme 1).

SCHEME 1. Equilibration of Stereoisomeric Mixtures with Alkene Crossover



1 = (dihydroIMes)(Cy_3P)Cl_2Ru=CHPh, Grubbs' second generation carbene

The reactivity of diene intermediates is a central question in an equilibration mechanism, and yet is not immediately answerable from prior work in enyne metathesis. In the equilibration process, excess $R^2-CH=CH_2$ will react with the dienes to eventually form mostly *E*-diene product (eq 1). Equilibration might be achieved if the reaction was under thermodynamic control since the *E*-dienes are more stable than the Z-dienes. However, equilibration may also be achieved if the *Z*-diene intermediate of Scheme 1 was kinetically-reactive and the *E*-diene was kinetically-stable. In this study, reactivity of the dienes shown as intermediates in Scheme 1 was directly evaluated by chemical synthesis and crossover experiments. In the crossover paradigm, the *Z*-intermediate should react with $R^3-CH=CH_2$ to give crossover product (eq 2). If the *E*-isomer was kinetically reactive, it too should produce crossover product. Since equilibration requires reaction of a metal carbene, the efficiency of this process may depend on the reactivity of the alkylidene derived from the alkene reactant.

Direct kinetic monitoring of a cross metathesis showed equilibration of a kinetic mixture of dienes. The reaction of propargylic alkyne **2** and 1-hexene (eq 3) initially forms a mixture of *E*/*Z*-isomers (Figure 1). The progress of the enyne metathesis was followed by ^1H NMR spectroscopy.

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[1] (a) Diver, S. T.; Giessert A. J. *Chem. Rev.* **2004**, *104*, 1317−1382. (b) Poulsen, C. S.; Madsen, R. *Synthesis* **2003**, 1−18. (c) Mori, M. *Top. Organomet. Chem.* **1998**, *1*, 133−154.

[2] (a) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2037−2056. (b) Smulik, J. A.; Diver, S. T. *Tetrahedron Lett.* **2001**, *42*, 171−174.

[3] In particular, enol ethers give isomeric mixtures: (a) Giessert, A. J.; Brazis, N. J.; Diver, S. T. *Org. Lett.* **2003**, *5*, 3819−3822. (b) Giessert, A. J.; Snyder, L.; Markham, J.; Diver, S. T. *Org. Lett.* **2003**, *5*, 1793−1796.

[4] (a) Lee, H.-Y.; Kim, B. G.; Snapper, M. L. *Org. Lett.* **2003**, *5*, 1855−1858. (b) Diver, S. T.; Giessert, A. J. *Synthesis* **2004**, 466−471. (c) Lee, H.-Y.; Kim, H. Y.; Tae, H.; Kim, B. G.; Lee, J. *Org. Lett.* **2003**, *5*, 3439−3442.

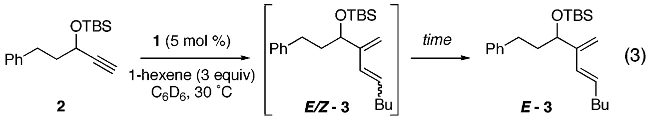
[5] For a full account of alkene reactivity in alkene metathesis, see: Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360−11370.

[6] For a recent example, see: Wang, X.; Porco, J. A. *J. Am. Chem. Soc.* **2003**, *125*, 6040−6041.

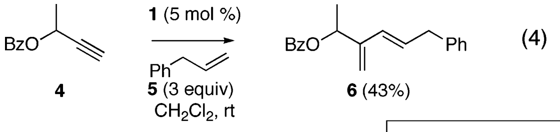
10.1021/jo0482209 CCC: $30.25

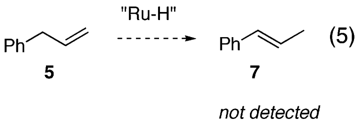
After 50 min, the ratio was found to be 55/41 *E*/*Z*, with 4% unreacted alkyne. The *E*/*Z* mixture was present until all the alkyne was consumed, at which time the diene mixture isomerized to form predominantly the *E*-diene product *E*-**3**.[7] An inspection of the data for the isomeric dienes between 200 and 700 min shows a rate of diminution of the *Z*-isomer that is about equal to the growth rate of the *E*-isomer. This rate was considerably slower than the intermolecular metathesis, but occurred in the time scale under which normal cross metatheses are usually performed. We considered that the observed isomerization could result from a secondary metathesis between diene and excess 1-alkene.

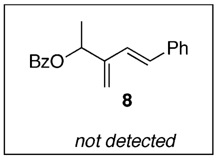
Intermediate ruthenium hydrides were not observed in the precatalysts nor were they detected in the reaction mixtures. Isomerization of *Z*-**3** in Figure 1 might be due to a ruthenium hydride species. It is known that ruthenium hydrides are capable of catalytic olefin isomerization.[8] Examination of precatalyst **1** by ^{1}H NMR showed the absence of ruthenium hydride species, and ^{31}P NMR showed only the resonance of **1**. Also, during the course of the reaction of eq 3, no metal hydride species were observed by ^{1}H NMR. Grubbs recently showed that a ruthenium hydride complex can form by decomposition of $L_nRu{=}CH_2$, and isomerizes a terminal alkene into an internal alkene.[9] However, neither the characteristic hydride peak for this complex (δ −8.6) nor the ^{31}P peak for $CH_3PPh_3^+$ (δ 34.5) were detected in the reaction, or after the in situ isomerization had occurred.



Since it is possible that hydride species were formed below the detection limits of NMR spectroscopy, a further experiment with an isomerization-prone reactant was performed. In this paradigm, undetected quantities of ruthenium hydride should result in terminal alkene isomerization, converting the alkene reactant allyl benzene **5** to β-methyl styrene **7** (eq 5). In fact, the metathesis of eq 4 is a demanding test because terminal alkenes bind more effectively to metal hydrides in general, and in the present case, isomerization would produce conjugated styrene **7**, providing a thermodynamic trap. The metathesis of eq 4 produced diene **6** in 43% yield as the *E*-isomer.[10] Significantly, the intermediate *E*/*Z* mixture could be detected at early timepoints in the reaction, with no β-methylstyrene detected by GC. On the basis of the lack of alkene isomerization in the alkene reactant and the fact that the methylene-truncated product **8** was not found, the observed isomerization of the diene mixture to *E*-**6** is most likely not due to a ruthenium hydride species.







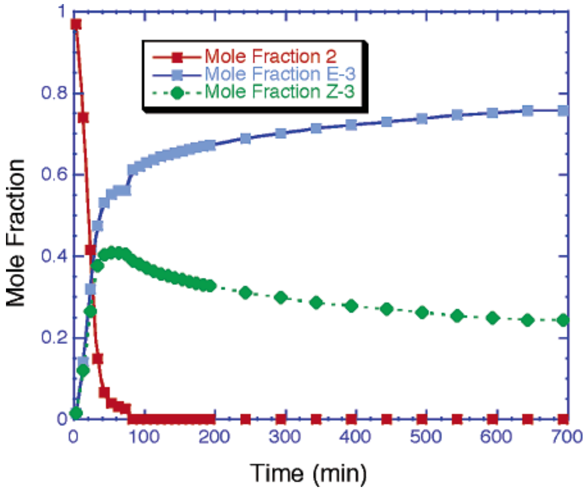


FIGURE 1. Alkyne **2** conversion to *E*-**3**.[7]

The kinetic reactivity of the *E* and *Z* dienes **3** under the reaction conditions was next investigated. As a test for secondary metathesis reactivity, crossover experiments were performed. Exposure of *E*-**3** to the reaction conditions of eq 3 with 9 equiv of 1-octene did not result in the production of the crossover product showing that the *E*-isomer is stable to the reaction conditions. The same experiment could not be performed on pure *Z*-**3** since the *Z*-isomer cannot be obtained by enyne cross metathesis. At best, mixtures of *E*/*Z*-isomers can be prepared. Therefore another method for the preparation of *Z*-diene was necessary.

The desired *Z*-dienes were prepared by using the stereoselective Wittig olefination. Bromoallyl acetate **9** underwent Kishi−Nozaki coupling under Taylor's conditions[11] with dihydrocinnamaldehyde, which gave substituted allyl alcohol **10** (Scheme 2). Routine manipulation furnished the desired aldehyde **11** in 53% yield over three steps. With the desired aldehyde in hand, Wittig olefination[12] was used to form the desired dienes *Z*-**3** (>90% *Z*-isomer by ^{1}H NMR of the crude reaction) and *Z*-**12** (>93−95% *Z*-isomer by ^{1}H NMR of the crude reaction).

Access to the stereochemically pure *Z*-dienes permitted investigation of their kinetic stability to the metathesis

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(7) The final mixture is 3:1 *E*/*Z* **3**.

(8) (a) Trnka, T. M.; Morgan, J. P.; Sanford, M. S.; Wilhelm, T. E.; Scholl, M.; Choi, T.-L.; Ding, S.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 2546−2558. (b) Dinger, M. B.; Mol, J. C. *Organometallics* **2003**, *22*, 1089−1095 (c). Sutton, A. E.; Seigal, B. A.; Finnegan, D. F.; Snapper, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 13390−13391. (d) Ulman, M.; Grubbs, R. H. *J. Org. Chem.* **1999**, *64*, 7202−7207.

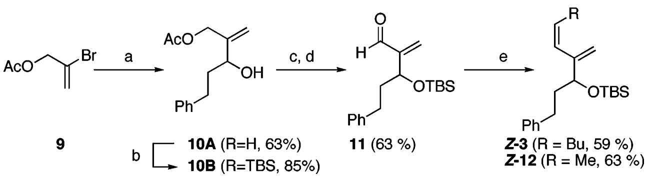
(9) Hong, S. H.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2004**, *126*, 7414−7415.

(10) In this case, only 3 equiv of alkene were used. A minor byproduct was the corresponding butadiene.

(11) Taylor, R. E.; Ciavarri, J. P. *Org. Lett.* **1999**, *1*, 467−469.

(12) (a) Valentine, D. H., Jr.; Hillhouse, J. H. *Synthesis* **2003**, 317−334. (b) Rein, T.; Pedersen, T. M. *Synthesis* **2002**, 579−594. (c) Nicolaou, K. C.; Harter, M. W.; Gunzner, J. L.; Nadin, A. *Liebigs Ann. Recl.* **1997**, 1283−1301. (d) Vedejs, E.; Peterson, M. J. *Adv. Carbanion Chem.* **1996**, *2*, 1−85. (e) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863−927. (f) Schlosser, M. *Top. Stereochem.* **1970**, *5*, 1−30

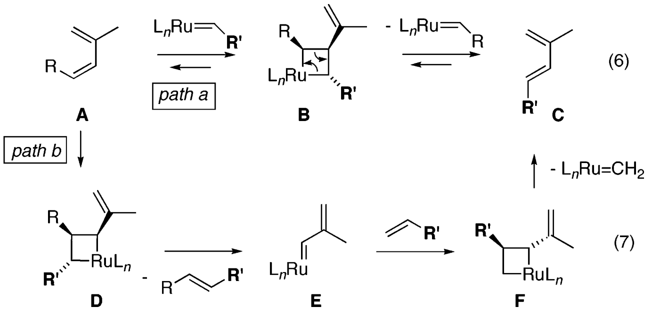
SCHEME 2. Preparation of Z-Dienes Used in This Study^a



^{a} Reagents and conditions: (a) CrCl$_2$, NiCl$_2$, DMF, PhCH$_2$CH$_2$CHO. (b) TBSCl, imidazole, CH$_2$Cl$_2$. (c) K$_2$CO$_3$, MeOH. (d) Swern oxidation. (e) RCHPPh$_3$Br, KHMDS, THF, −78 °C to room temperature.

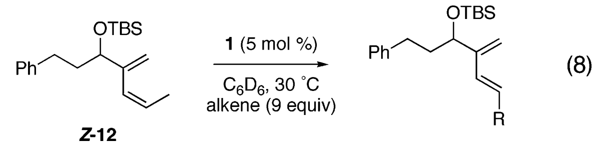
conditions. Exposure of *Z*-**12** to precatalyst **1** resulted in conversion to the *E*-isomer, *E*-**12**. Since evidence of ruthenium hydrides could not be found, the isomerization of *Z*-**12** led us to consider a metathetical mechanism. The two most plausible pathways are outlined in Scheme 3.

SCHEME 3



A metal carbene (R′ = H, alkyl, Ph) can add to the *Z*-alkene **A** by path a, then fragment to the *E*-diene **C**, which should also show crossover when R ≠ R′. The carbene entering eq 6 (L$_n$Ru=CH**R′**) will produce a different carbene on crossover (L$_n$Ru=CHR), and the new carbene will promote further isomerization in the remaining *Z*-diene reactant (e.g., in propagation steps).[13] In path b, the opposite regiochemistry of initial metal carbene cycloaddition (**D** vs **B**) ultimately produces the vinyl carbene **E** (eq 7), which would then give productive cross metathesis with added alkene. The vinyl carbene **E** reacts via metallacyclobutane **F** to give crossover product.[14]

TABLE 1. Crossover Results Obtained with Diene Z-12



entry	alkene^a	conversion	R
1	none	99	Me, *E*-**12**
2	1-hexene	93	Bu, *E*-**3**
3	*cis*-5-decene	80	Bu, *E*-**3**
4	*trans*-5-decene	99	Bu, *E*-**3**
5	ethene (100 psig)^d	61	H, **13**

^{a} Conditions: 0.11−0.24 M *Z*-**12**, 5 mol % of **1**, 9 equiv of alkene (0.99−2.16 M) in C$_6$D$_6$, 30 °C. ^{b} 0.925 M ethene.

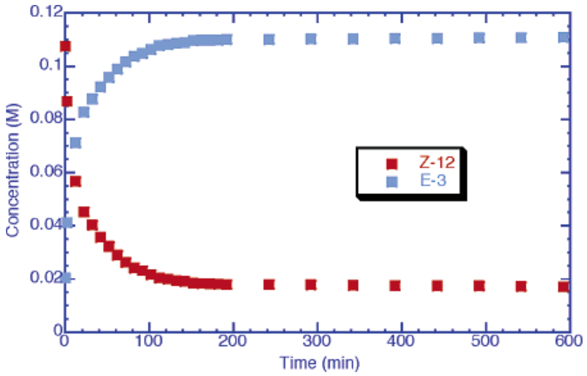


FIGURE 2. Secondary metathesis of 1-hexene with *Z*-**12**, producing crossover isomerization product *E*-**3**.

The proposed metathesis-based isomerization mechanisms of Scheme 3 were tested by crossover experiments with alkenes. The crossover reaction produced the substituted *E*-dienes (eq 8). Diene *Z*-**12** is effectively transformed into the *E*-isomer via exposure to the second generation Grubbs' complex **1**. It was also possible to exchange the 1-methyl group of *Z*-**12** for a butyl group with 1-hexene and 5-decene (Table 1). The comparable conversions obtained for internal alkenes (entries 3 and 4) compared to 1-hexene (entry 2) are notable. In fact, the relative reaction rates for crossover/isomerization are 2.08 for 1-hexene, 2.19 for *cis*-5-decene, and 2.36 for *trans*-decene, indicating that the alkylidenes produced in the latter two cases react as quickly as the metal carbene produced in the reaction with 1-hexene. This argues convincingly that ruthenium pentylidenes are effecting isomerization/crossover in each case, since L$_n$Ru=CH$_2$ cannot be formed in the fast reactions of entries 3 and 4. The effectiveness of the conversion to *E*-**3** is likely a function of carbene longevity; some of the lower conversions in Table 1 are due to catalyst decomposition. In particular, this may explain the low conversion with ethylene (entry 5).[15] Excess allyl trimethylsilane did not react with *Z*-**12** to produce the expected crossover product. The ineffectiveness of allyl trimethylsilane to give crossover product indicates that the derived ruthenium carbene does not react with *Z*-**12**.

Representative crossover of *Z*-**12** with 1-hexene is illustrated in Figure 2. The time course of the secondary metathesis was monitored by ^{1}H NMR in C$_6$D$_6$ at 30 °C, using a 9-fold excess of 1-hexene, identical conditions as those in Figure 1. Most of the reaction has occurred in the first 200 min, similar to the isomerization observed in the 1-hexene cross metathesis of Figure 1. The data show that the *Z*-diene reactant disappears at a rate about equal to the rate of appearance of the *E*-crossover product. This shows that an intermediate is not accumulated during the metathesis isomerization/crossover.

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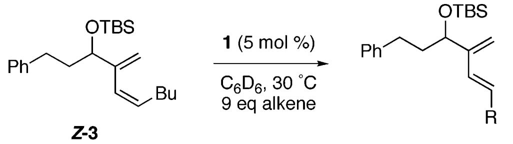
[13] In other words, only the initiation step will provide crossover. The propagating carbene will bear the same R group as the diene reactant and show apparent isomerization as the R group of the *Z*-diene **A** is replaced with the R group to furnish the *E*-diene **C** where R′ = R.

[14] A less likely pathway is the dipolar fragmentation of intermediate ruthenacyclobutanes which would produce open zwitterions, which could collapse after bond rotation.

[15] For an excellent discussion of methylidene reactivity, see: Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543−6554.

TABLE 2. Crossover Results Obtained with Diene *Z*-3



(9)

entry	alkene[a]	conversion	R
1	none	63	Bu, *E*-**3**
2	1-propene	54	Me, *E*-**12**
3	*cis*-2-butene	81	Me, *E*-**12**
4	*trans*-5-butene	75	Me, *E*-**12**
5	ethene (100 psig)[b]	50	H, **13**

[a] Conditions: 0.11−0.24 M *Z*-**3**, 5 mol % of **1**, 9 equiv of alkene (0.99−2.16 M) in C_6D_6, 30 °C. [b] 0.925 M ethene.

The crossover reaction of butyl-substituted diene ***Z*-3** with ethylene, 1-propene, and 2-butenes was similarly explored (eq 9). Crossover of diene *Z*-**3** was slower than that of the lower homolog *Z*-**12** and did not go to completion (Table 2). This is likely due to the difference in steric environment at the terminus of the diene. For example, the isomerization rate by **1** alone (5 mol %) was four times slower than the corresponding isomerization rate of methyl-substituted diene *Z*-**12** in Table 1.[16] Use of 1-propene (entry 2) provided similar results to *cis*-2-butene (entry 3). The reaction was efficient with *trans*-2-butene, providing *E*-**12** (entry 4). Though the reactions did not go to completion, formation of the 2-substituted butadiene **13** was also possible by reaction with ethylene (entry 5). The ethylene crossover proved slower than all the others and proceeded at a rate comparable to the rate of catalysis by **1** alone.

These data are consistent with a metathesis-based isomerization of *Z*-dienes present in the initial mixture of diene products. The isomerization by Grubbs' complex **1** without added alkene is significant. In these cases (entries 1 of Tables 1 and 2), the reaction of complex **1** with the *Z*-diene is an initiation step, which produces the ethylidene, $L_nRu{=}CHMe$, on one turnover. The ethylidene is the propagating carbene that effects isomerization of the remaining *Z*-diene (R′ = Me in path a of Scheme 3). However, during the initiation step, mechanistic path a predicts styryl transfer from complex **1**, and path b predicts the formation of β-methylstyrene. Authentic samples were prepared for GC comparison. Analysis of the **1**-catalyzed isomerization of *Z*-**12** did not show β-methylstyrene (R′ = Ph), but did show the styryl transfer (product of eq 8, R = Ph), providing support for isomerization via eq 6. It is notable that the crossover products are not produced as *E*/*Z* mixtures, but as the *E*-isomers. This may reflect higher intrinsic selectivity of the less reactive Z-diene (viz 1-alkenes) proceeding via stereocontrolled formation of metallacycle **B** (path a, Scheme 3) or reflect higher selectivity of a vinyl carbene intermediate (e.g. **E**, path b, Scheme 3). The vinyl carbene selectivity would be different from that of the more reactive metal carbenes that are encountered in 1-alkene−alkyne cross metathesis, e.g., during the fast initial phase of the cross metathesis shown in Figure 1. A secondary metathetical transformation to exchange alkyl groups followed by a ruthenium hydride isomerization is also unlikely. For the *E*-crossover product to be produced in Figure 2, the isomerization rate must be at least as fast as cross metathesis/crossover such that crossover product *Z*-**3** is never observed. If hydrides were highly reactive, they would have shown isomerization in the metathesis in eq 4.

The best explanation for crossover is the agency of ruthenium alkylidenes not methylidenes. The use of methylidene-free conditions[17] with both *cis*- and *trans*-5-decene (entries 3 and 4, Table 1) gave crossover, proving that alkylidenes are competent to perform the isomerization. This illustrates that the isomerization/crossover is not dependent upon ethylene nor does it require a ruthenium methylidene species. Yet not all 1-alkenes isomerize the *Z*-dienes, despite their potential to produce $L_nRu{=}CH_2$. Butadienes are detected as minor byproducts (less than 10%) in metathesis isomerization/crossover with 1-alkenes, which reveals the presence of $L_nRu{=}CH_2$ (and possibly the formation of ethylene) in a minor pathway. The origin of $L_nRu{=}CH_2$ could be due to either fragmentation of **F** (eq 7) or background homodimerization of 1-alkenes. However, butadienes are less reactive than *Z*-dienes used in the crossover experiments. For instance, isolated butadiene **13** (entry 5, Table 2) gave less than 50% conversion to cross product after 6 h under the conditions of Figure 1. Moreover, the isolation of butadiene as a minor byproduct in the crude reaction shows that they are kinetically-stable under the reaction conditions.

In summary, we have shown that certain *E*-selective enyne cross metatheses produce initial *E*/*Z* mixtures that isomerize over the course of the reaction. Crossover between excess 1-alkenes and the stereochemically-pure *Z*-isomers is consistent with an *E*-selective secondary metathesis (diene−alkene cross metathesis). Internal alkenes react at rates comparable to 1-alkenes and these all react faster than ethylene. The data illustrate the ruthenium alkylidenes are the probable carbene intermediates in the secondary metathesis and can react with the more reactive *Z*-dienes, present in the initial product mixture. This accounts for high *E*-selectivity observed in certain enyne metatheses. Further studies on the mechanism of enyne metathesis are in progress.

Acknowledgment. The authors thank Amol Kulkarni for helpful discussions and Dr. Richard Fisher of Materia, Inc. for providing catalyst support. We gratefully acknowledge the National Cancer Institute (R01CA090603) for financial support of this work.

Supporting Information Available: Experimental procedures and full characterization data for new compounds *Z*-**3**, *E*-**3**, *E*-**6**, **10B**, **10C**, **11**, *E*-**12**, *Z*-**12**, and **13**; conditions used for the rate plots; and detailed procedures for the crossover experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) These isomerizations proceed to higher conversion at elevated temperatures. To allow for a consistent comparison of the data in Tables 1 and 2, we used the same reaction conditions for both isomerization/crossover experiments.

(17) (a) Kulkarni, A. A.; Diver, S. T. *Org. Lett.* **2003**, *5*, 3463−3466. (b) Kulkarni, A. A.; Diver, S. T. *J. Am. Chem. Soc.* **2004**, *126*, 8110−8111.