Styrene-Alkyne Cross Ene-Yne Metathesis: Catalyst Screening and Optimization for Unbranched Terminal Alkyne Substrates

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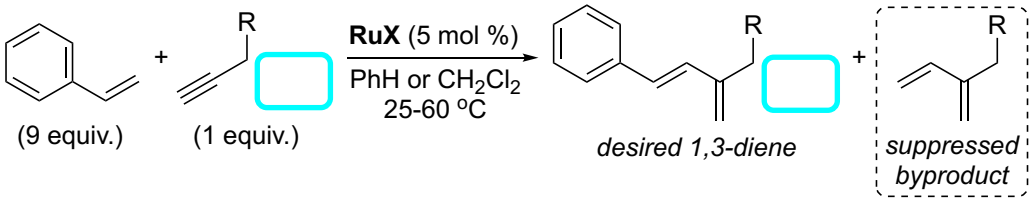

ABSTRACT

Cross metathesis between styrenes and unbranched terminal alkynes is reported. Styrene cross metathesis with terminal alkynes that lack branching at the propargylic position are unknown. In general, unbranched terminal alkynes have been problematic in cross metathesis due to competing alkyne oligomerization. A catalyst screen was performed for a variety of Grubbs catalysts to optimize the yield of the desired 1,3-diene product. This catalyst screen identified two ruthenium carbene complexes that have been rarely used for cross metathesis applications. Additionally, a side product arising from a competing alkene metathesis was minimized by choice of catalyst and through reaction optimization.

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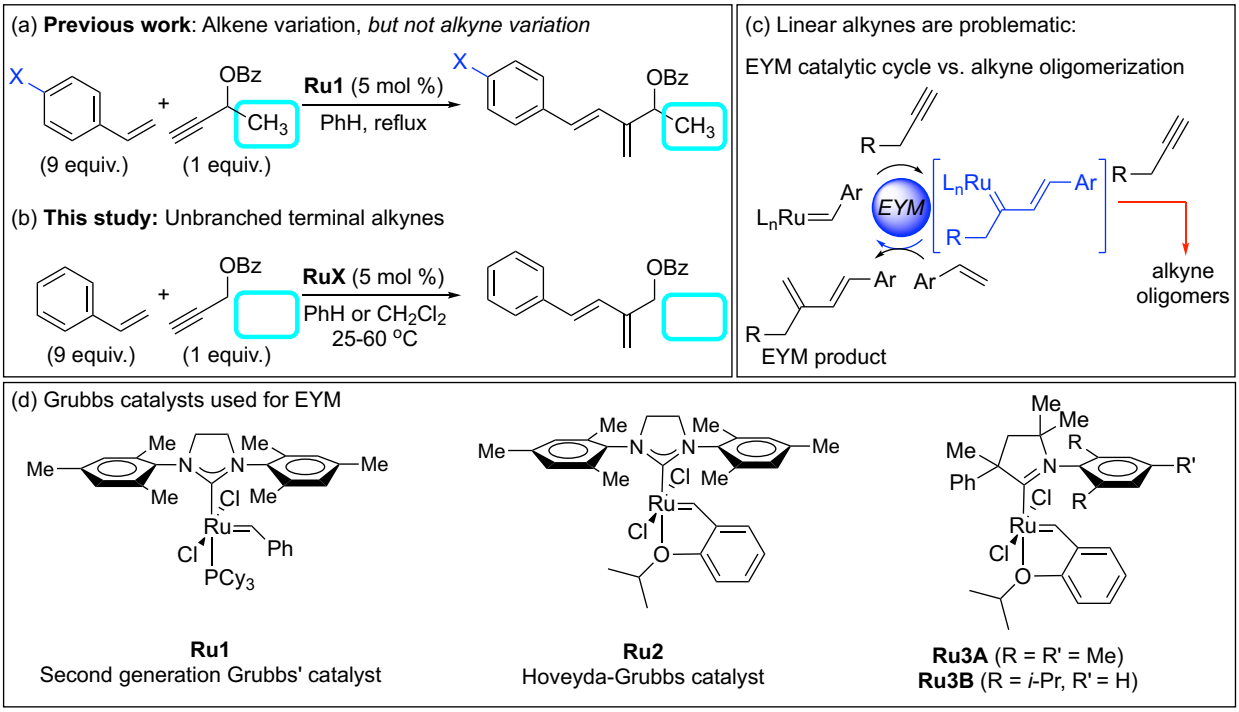
1. Introduction

Ene-yne metathesis offers a rapid synthesis of 1,3-dienes from simple alkynes and 1-alkenes.[1] Conjugated dienes undergo a variety of addition reactions allowing for the assembly of six-membered rings[2] and for the introduction of heteroatoms.[3] In the very best cases, the intramolecular reaction can be brought about with nearly equimolar amounts of alkyne and alkene, achieving atom economy.[4] However, most ene-yne metathesis (EYM) require an excess of the alkene and the alkene is typically a reactive alkene, ideally a type 1 alkene.[5] These characteristics allow for an efficient EYM catalytic cycle by avoiding side reactions that can lead to catalyst decomposition. As an alkene reactant, styrene is a more challenging alkene because of its electronic delocalization. Our earlier report utilized 9 equivalents of styrene with an α-branched terminal alkyne (2-benzoyloxy-3-butyne) in refluxing benzene (Scheme 1a).[6] Presently, we desired phenyl-substituted 1,3-dienes that could be made by cross EYM between styrenes and non-branched terminal alkynes as shown in Scheme 1b. The Grubbs catalysts **Ru1** and **Ru2** are most commonly used for ene-yne metathesis (Scheme 1d).[1b, 1c, 7] Only recently have CAAC-based catalysts (Grubbs-Bertrand catalysts)[8] such as **Ru3A** been found to deliver better yields in ene-yne metathesis for less reactive reactants.[4b] In this report, we describe a catalyst screening study[9] that optimized the reaction of Scheme 1b into a synthetically-useful one. These optimized conditions were applied to several unbranched terminal alkynes. We also found that a by-product, the 2-substituted butadiene, could be minimized through choice of Grubbs catalyst and reaction set up, which makes the reaction more selective and higher yielding.



Scheme 1. Styrene-alkyne cross metathesis, competing alkyne polymerization and the common Grubbs catalysts used

Unbranched terminal alkynes have been problematic in cross ene-yne metathesis especially when coupled with less reactive alkenes. Terminal alkynes undergo competitive alkyne polymerization with the more reactive second generation Grubbs catalysts, and similar side reactions such as alkyne cyclodimerization[10] and cyclotrimerization[11] have been observed. Early mechanistic work using the tricyclohexylphosphine-containing Grubbs catalyst **Ru1** showed that branched alkynes react faster than their unbranched analogs.[12] More recent mechanistic work using the Hoveyda-Grubbs complex **Ru2** also showed shortcomings for the linear alkyne propargyl benzoate, even at high concentrations of reactive alkene (1-4M 1-hexene).[13] In the synthesis of amphidinolide P, we found that alkyne polymerization could be minimized at lower reaction temperature, improving the mass recovery and yield of the expected 1,3-diene product.[14] If the yields can be improved in EYM cases involving less reactive alkenes through the use of new catalysts, then it is possible that similar gains in reactivity

might be attained for other delocalized or electron-poor alkenes, thus increasing yields and extending the scope of this cross metathesis.

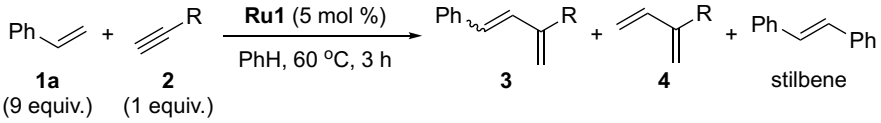
Alkyne oligomerization/polymerization is a competitive reaction of the ruthenium vinyl carbene intermediate. The vinyl carbene is at a nexus point joining the productive EYM catalytic cycle with the alkyne polymerization side reaction (Scheme 1c). Katz and coworkers described alkyne insertion of metal carbenes as a mechanistic explanation for alkyne polymerization.[15] As shown in early kinetic studies, high alkene equivalents or high alkene concentrations accelerate the slow step in the ene-yne metathesis catalytic cycle.[12] Reactive, electron-rich alkenes and a rapid EYM help to outcompete the alkyne insertion side reaction by keeping the vinyl carbene propagating forward in the ene-yne metathesis catalytic cycle.[13] Conversion of the vinyl carbene into the 1,3-diene product is an irreversible step.[16] But less reactive alkenes, such as electronically-delocalized or electron-deficient alkenes, allow the side reaction to be competitive. The nature of the alkyne reactant is also important: less hindered and electron-rich terminal alkynes are most reactive towards alkyne insertion. For synthetic applications, alkyne polymerization can be elusive in that it does not form a tractable product. In previous studies, we have found that poor mass balance in the recovered alkyne and the 1,3-diene product indicated alkyne oligomerization/polymerization.[14a]

With unbranched terminal alkynes being more problematic substrates than their branched analogs, we hypothesized that catalyst attributes could be matched with the less hindered nature of this alkyne reactant to differentially accelerate ene-yne metathesis or thwart vinyl carbene polymerization. In either case, this would provide improved yields of the desired styrene-alkyne cross metathesis products (Scheme 1b). To our knowledge, most synthetic applications of ene-yne metatheses utilize the conventional catalysts **Ru1** or **Ru2** and catalyst screening for problematic EYM is rare (especially as compared to alkene metathesis).[17] Also, a greater diversity of Grubbs catalysts are now commercially-available and the use of specific, task-based metathesis catalysts for particular applications is now widely accepted.

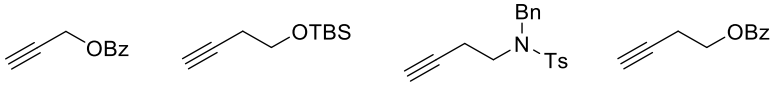
2. Results and Discussion

Cross metathesis between styrene and unbranched terminal alkynes gave poor yields of the desired 4-phenyl-substituted-1,3-diene **3** under the standard conditions given in the original report.[6] Several terminal alkynes that are unbranched at the propargylic position were examined in their cross metathesis with an excess of styrene (**2a-2d** in Table 1). For instance, propargyl benzoate **2a** gave full conversion, but gave only a 60% yield of the 1,3-diene **3aa** (entry 1). For comparison, the methyl-branched analog of **2a** gave 95% isolated yield under the same conditions using **Ru1**. Other unbranched alkynes **2b, 2c** with more remote heteroatoms gave incomplete alkyne conversions at the standard 3 h reaction time, and gave 42-43% product yields, showing that another pathway was consuming the alkyne (entries 2,3). The homopropargyl benzoate **2d** gave full alkyne conversion but a 65% yield of **3ad**, similar to that observed for alkyne **2a**. In all of these reactions, alkene self-metathesis of the styrene also occurred to variable extents, producing stilbene.

Table 1. Styrene cross metathesis with terminal, unbranched alkynes.



Entry	**2**	Conv. (%)[a,b]	**3** (%)	*E/Z* Ratio	**4** (%)[b]	stilbene (%)[b,c]
1	**2a**	100	**3aa**, 60%	5 : 1	7	69
2	**2b**	87	**3ab**, 43%	2 : 1	0	2
3	**2c**	70	**3ac**, 42%	3.4 : 1	0	0
4	**2d**	100	**3ad**, 65%	3 : 1	0	5

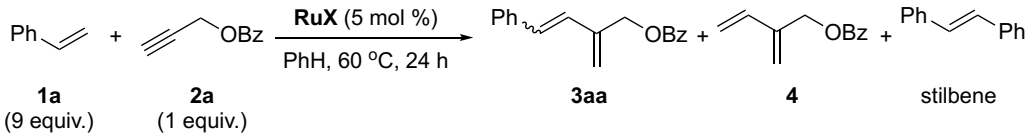


2a **2b** **2c** **2d**

[a] Conversion of **2**. [b] Conversion, E/Z ratio and ^{1}H NMR yields were determined based on integration of the appropriate resonances vs. mesitylene or dioxane as an internal standard. [c] NMR yield assuming full conversion of 9 equivalents of styrene to 4.5 equivalents of stilbene.

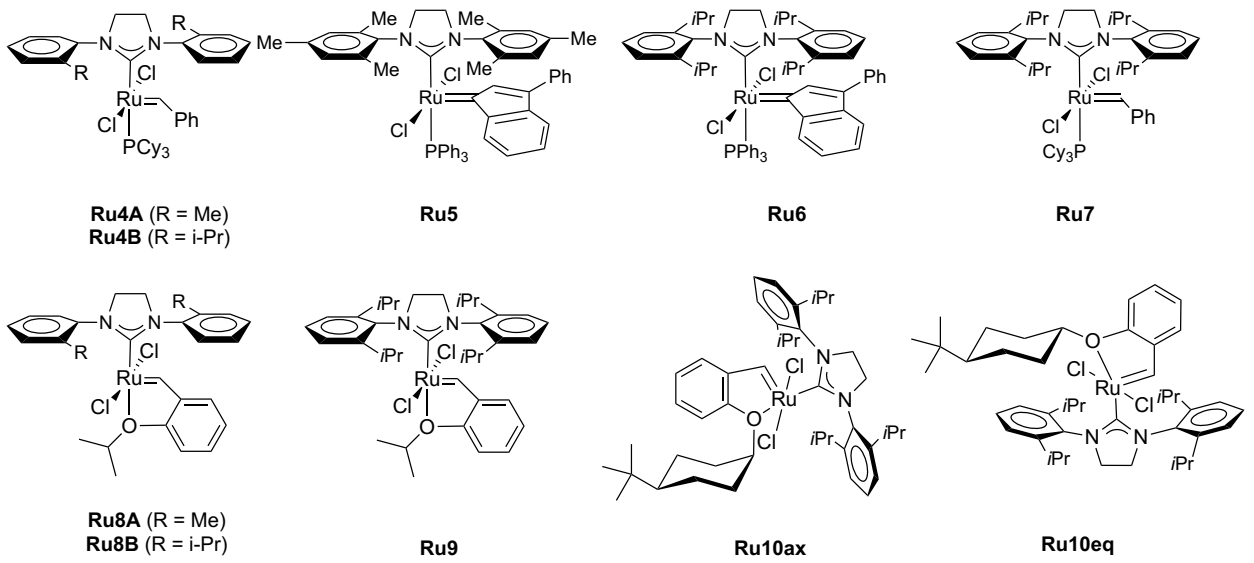
Because of the poor performance of these unbranched alkynes, a catalyst screen was performed as shown in Table 2. The catalyst screen was performed in a nitrogen-filled glovebox in loosely capped vials, heated for a standard time period. The catalyst structures are provided in Scheme 3. The yield of the desired product **3aa** was determined against an internal standard, along with the butadiene coproduct **4** and the alkene metathesis product, stilbene. The commonly used catalysts **Ru1-Ru3A** (entries 1-3) gave complete conversion of alkyne, but afforded ca. 60% yields of **3aa** along with ~5% butadiene **4**. These catalysts were all competent for alkene metathesis, producing a similarly high yield of stilbene. The hindered **Ru3B** did not produce products; the ^{1}H NMR of the catalyst looked clean but no further attempts to purify or re-run this entry were done. **Ru4A** gave poor yield and did not show alkene metathesis, which suggested catalyst decomposition (entry 5). Increasing ortho steric demand in **Ru4B** gave one of the highest yields of **3aa** (entry 6). Less stilbene in this entry hinted at EYM selectivity. The indenylidenes **Ru5** and **Ru6** showed an increase in yield as steric demand of the NHC was increased from H_2IMes to H_2IPr (SIPr) as seen in entries 7-8. Next, **Ru7** also with high steric demand, was found to give a moderate yield, but a high E/Z selectivity and only a trace amount of the butadiene **4** was observed (entry 9). **Ru8A** is the Hoveyda chelate analog of **Ru4A** and it offered better yield of **3aa**, but full conversion of the alkyne was not observed (entry 10). In the same series of mono ortho-substituted phenyl NHCs, **Ru8B** (R = isopropyl), a Hoveyda chelate analog of **Ru4B**, gave the highest yield of **3aa** and only trace amounts of **4** (entry 11). **Ru9**, a Hoveyda chelate of **Ru7**, gave full conversion of the alkyne and comparable yield, but the *E*/*Z* ratio was halved. However, it still offered one of the higher *E*/*Z* selectivities in comparison to other catalysts. Last, we had previously synthesized faster initiators **Ru10** bearing bulky SIPr ligands[18] and found good yield of **3aa** but high amounts of **4** (entries 13-14). Overall, bulky SIPr and mono isopropyl substituted NHC ligands gave the best performance. With this set of Ru catalysts, a wide range of initiation rates were covered,[19] but any superior performance by faster initiators would only be detected at shorter reaction times or lower temperatures.

Table 2. Catalyst screen for propargyl benzoate



Entry	**RuX**	Conv. (%)[a,b]	**3aa** (%)[b]	*E*/*Z* Ratio	**4** (%)[b]	stilbene (%)[b,c]
1	**Ru1**	100	60	5/1	7	69
2	**Ru2**	100	58	5/1	5	73
3	**Ru3A**	100	56	3.3/1	5	54
4	**Ru3B**	63	0	-	0	0
5	**Ru4A**	81	33	2/1	0	< 1
6	**Ru4B**	100	72	1.7/1	7	33
7	**Ru5**	100	49	4/1	10	64
8	**Ru6**	100	59	1.5/1	8	53
9	**Ru7**	100	55	10/1	2	64
10	**Ru8A**	92	48	2/1	2	2
11	**Ru8B**	100	73	2/1	3	64
12	**Ru9**	100	52	4.7/1	3	74
13	**Ru10ax**	100	58	2.5/1	10	64
14	**Ru10eq**	100	45	3.5/1	8	64

[a] Conversion of **2**. [b] Conversion and NMR yields were based on integration vs. mesitylene or dioxane as an internal standard. [c] NMR yield assuming full conversion of 9 equivalents of styrene to 4.5 equivalents of stilbene.

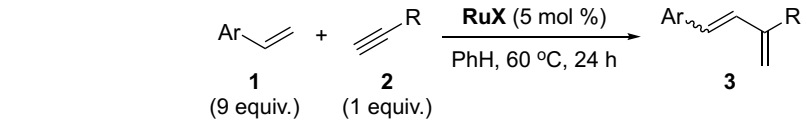


Scheme 3. Additional Grubbs Catalysts Evaluated in the Catalyst Screen

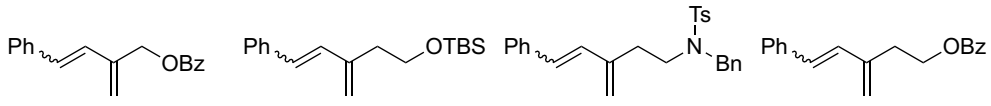
From Table 2, the best catalysts were selected on the basis of the highest yield of 1,3-diene and the least amount of butadiene co-product. Based on these criteria, **Ru4B**, **Ru7**, and **Ru8B** were the best catalysts. The mono ortho-isopropylphenyl-substituted catalysts **Ru4B** and **Ru8B** gave the highest overall yields of **3aa**. From these, **Ru8B** was slightly more selective since it gave less butadiene byproduct, and considered slightly better than **Ru4B**. The hindered bis orthoisopropylphenyl-substituted catalyst **Ru7** was the next most selective, giving a 55% yield of **3aa** and only 2% of butadiene **4**. The other SIPr-based catalysts (entries 8, 13-14) all gave a similar result, albeit with greater amounts of butadiene **4**.

With a few of our best catalysts identified, we proceeded to examine the synthetic utility of this cross ene-yne metathesis between styrenes and unbranched terminal alkynes (Table 3). We determined **Ru7** and **Ru8B** as our catalysts of choice for this survey. Metathesis of **1a** (styrene) with **2a** catalyzed by **Ru7**, our highly *E*-selective catalyst, furnished **3aa** in moderate yield, obtained solely as the *E*-isomer. Alternatively, **Ru8B** was found to give an increased yield of **3aa**, but with reduced selectivity (1.6:1 *E*/*Z* ratio of **3aa**). Previously, **2b** gave incomplete conversion and low yield of **3ab** via **Ru1**, but use of **Ru7** gave predominantly the *E*-isomer of **3ab** in 79% yield. Metathesis to **3ac** was also possible with **Ru1**, and **Ru7** was found to give only slightly improved yield. Alkynes with longer alkyl chains gave the expected products **3ad** and **3ae** in good yields, but 1-octyne gave **3af** in lower yield. Next, we examined variation in the styrene. To our surprise, **3ba** formed in a low 27% yield with **Ru7**. This suggested alkyne polymerization since the alkyne was fully consumed and the diene **3ba** was obtained in low yield. Use of **Ru8** suppressed significant polymerization of **2a** and furnished **3ba** in 68% yield. Last, substituted styrenes could be used as alkene substrates, giving products **3bd**, **3ce** and **3db** derived from *p*-methylstyrene, *p*-methoxystyrene and *p*-bromostyrene, respectively.

Table 3. Substrate scope using Grubbs catalysts **Ru7** and **Ru8B**



1 (9 equiv.) **2** (1 equiv.) **3**

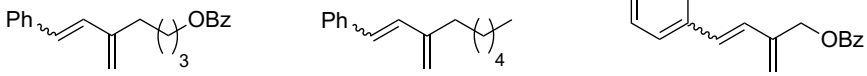


3aa
Ru7: 64%, *E*-only
Ru8B: 86%, 1.6:1 *E*/*Z*[a]

3ab
Ru7: 79%, 19:1 *E*/*Z*

3ac
Ru7: 54%, 2.4:1 *E*/*Z*

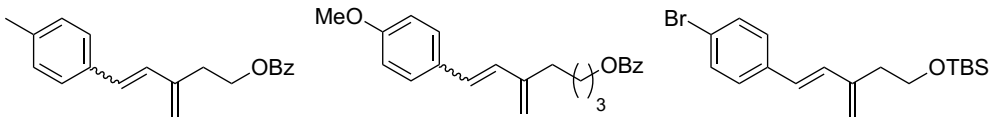
3ad
Ru7: 72%, 2.6:1 *E*/*Z*



3ae
Ru7: 69%, 2:1 *E*/*Z*

3af
Ru7: 49%, 2.4:1 *E*/*Z*

3ba
Ru7: 27%, 7:1 *E*/*Z*
Ru8B: 68%, 2.2:1 *E*/*Z*[b]



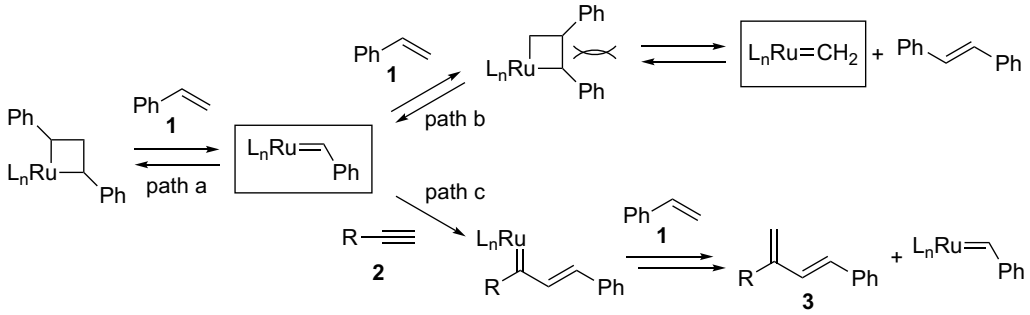
3bd
Ru7: 76%, 2.7:1 *E*/*Z*

3ce
Ru8B: 77%, 2.6:1 *E*/*Z*

3db
Ru8B: 55%, *E*-only

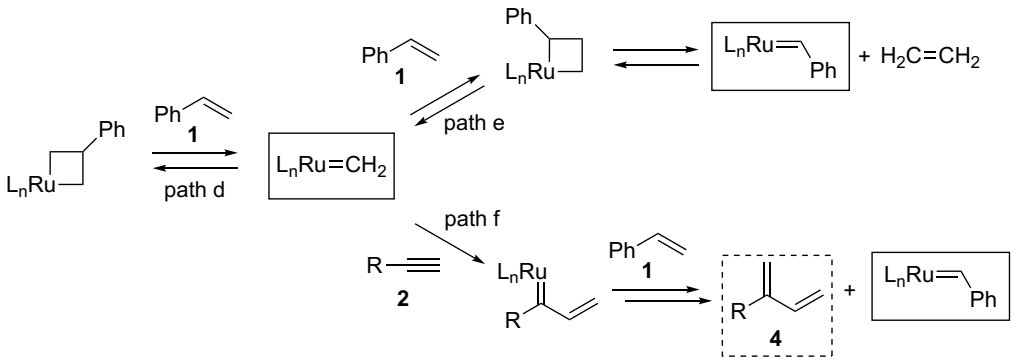
[a] Run for 15 min. [b] Run for 1 h.

Since the butadiene side product **4** arises from ethylene, we were interested to find if the rate of ene-yne metathesis could be optimized so that alkene self-metathesis would be less competitive and generate less ethylene (Scheme 4). The relevant reactive intermediate is [Ru]=CHPh, which is formed by initiation with styrene. A Ru benzylidene can react with styrene in three possible metathesis pathways. In path a, degenerate benzylidene exchange with styrene is non-productive and does not affect the partitioning of the [Ru]=CHPh through alkene and ene-yne metathesis. In path b, alkene metathesis of styrene produces stilbene, which forms [Ru]=CH_2. This pathway competes with the desired alkyne insertion, path c. The partitioning of the [Ru]=CHPh intermediate amounts to a competition between alkene metathesis and ene-yne metathesis.



Scheme 4. The generation of ruthenium methylidene

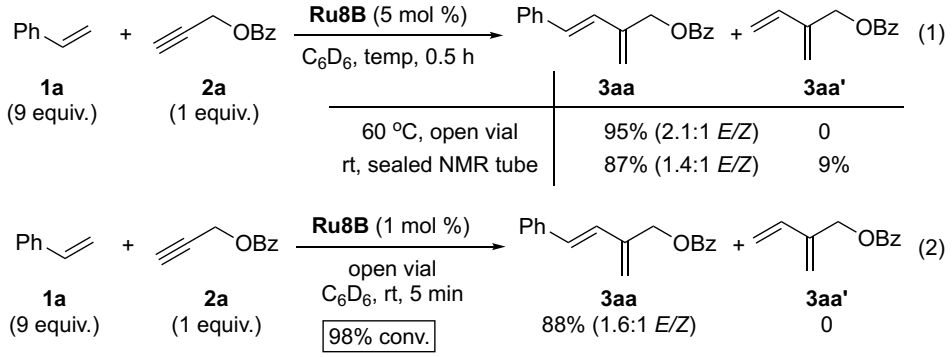
Once formed, Ru=CH_2 can react via three possible metathesis pathways (Scheme 5). In path d, degenerate exchange with styrene would re-form the same intermediate, but the reaction with styrene with alternate regiochemistry in path e would generate ethylene and form the Ru=CHPh. Competing with styrene reactions would be the alkyne insertion via path f, which forms the 2-substituted-1,3-butadiene **4**. The presence of ethylene indicates the presence of the Ru=CH_2 intermediate, and as ethylene is formed, butadiene can form by alkyne insertion.



Scheme 5. A ruthenium methylidene intermediate leads to butadiene by-product

In a majority of entries in Table 2, a significant amount of stilbene was formed from the self-metathesis of styrene, and in many cases a small amount of butadiene co-product had still formed. Yet the observation of significant yields of stilbene did not always correlate with higher yields of the butadiene by-product. We were curious about the timeframe of ene-yne metathesis compared to the timeframe of alkene metathesis and set about examining this in greater detail.

To prepare for kinetic studies with **Ru8B**, we probed the reaction rate and found that the reaction was exceedingly fast with this initiator (Scheme 6). At 60 ˚C in an open vial in the glovebox, the reaction was complete at the 0.5 h timepoint. As a Hoveyda-Grubbs precatalyst, **Ru8B** is a faster initiator, so this observation is not too surprising; yet in the previous paper, only **Ru1** was used at 80 ˚C in benzene and no catalyst comparisons have been made.[6] Additionally, there are few papers that note improvements in ene-yne metathesis yield or efficiency with faster initiators. Plenio et al. studied initiation rates of a wide range of Hoveyda-Grubbs catalysts with different alkenes,[19a] though to our knowledge, no initiation rate data is available in the literature for catalyst **Ru8B**. Importantly, the ene-yne metathesis conducted in an open vial did not show any butadiene coproduct. When the same reaction was performed at RT in a sealed NMR tube, the EYM was nearly complete with 87% **3aa** and now 9% of butadiene **4** was detected. The sealed NMR tube trapped ethylene that formed from styrene self-alkene metathesis, which led to the appearance of **4**. Still, the reactions proved too fast for ^{1}H NMR monitoring. In an open vial system, the catalyst loading was reduced to 1 mol % and the temperature kept at RT. Even in this last case, in 5 min, the reaction gave a high 88% **3aa** yield and none of the butadiene by-product. The catalyst **Ru8B** gave a very fast ene-yne metathesis and as long as the reaction vessel was left open, none of the undesired butadiene side product formed.



Scheme 6. Initial attempts to probe reaction rates using Grubbs catalyst **Ru8B**.

With the Hoveyda-type catalyst **Ru8B** delivering ene-yne metathesis products too fast for rate profiling, we turned to the phosphine-containing analog, **Ru4B**. Generally, the phosphine analogs initiate more slowly than the Hoveyda-Grubbs catalysts bearing a chelating benzylidene.[20] Monitoring the reaction conducted in an open vial in a nitrogen-filled glovebox, the unreacted alkyne, diene products and stilbene could be tracked by analyzing aliquots via ^{1}H NMR spectroscopy. In Figure 1, it is evident that ene-yne metathesis has mostly occurred once stilbene forms (74% **3aa** vs. 4% stilbene at 115

min). In this example, none of the butadiene coproduct was observed, which can be attributed to the open system and the delayed onset of alkene metathesis.

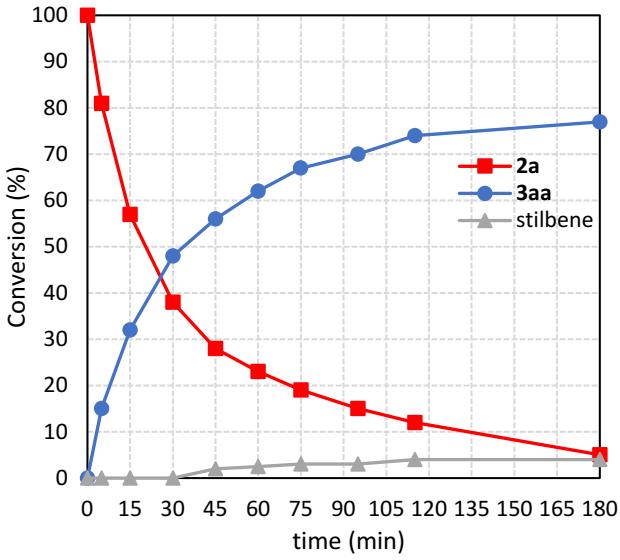


Fig. 1. Reaction composition during ene-yne metathesis. Conditions: **1a** (9 equiv.), **2a** (1 equiv.), **Ru4B** (2 mol %), C_6D_6 (ca. 0.08M), rt, time; open vial in a nitrogen filled glovebox.

When the same reaction was tracked in a closed system, a higher yield of the desired diene was seen and a greater amount of butadiene was observed (Figure 2). Interestingly, the yield of **3aa** was higher in the closed system ~90% (vs. ~70% product in the open system). The retention of ethylene may have provided a salvage pathway for the vinyl carbene to convert to 1,3-diene product (Scheme 7a). The formation of the butadiene byproduct closely matched the rate of formation of stilbene, indicating that as alkene metathesis took place, the byproduct formed. This shows that ethylene is very effectively captured by the alkyne to form the byproduct **4**, even as very little stilbene has formed. Additionally, Figure 2 shows that diene formation by ene-yne metathesis is much faster than stilbene formation due to alkene metathesis, despite the ninefold higher concentration of styrene.

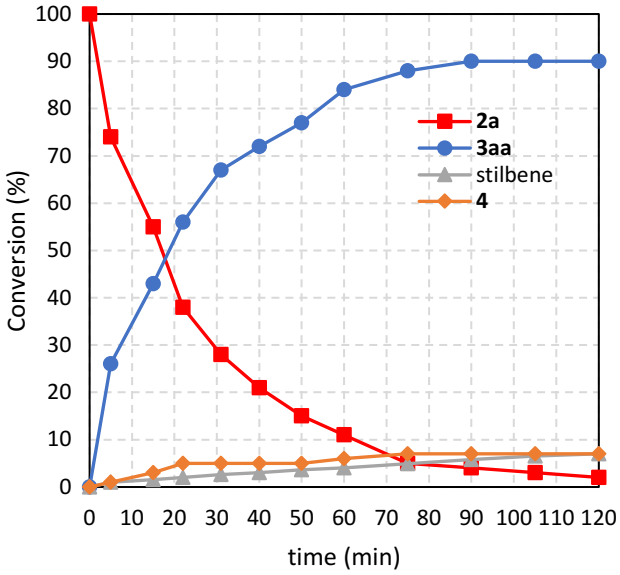
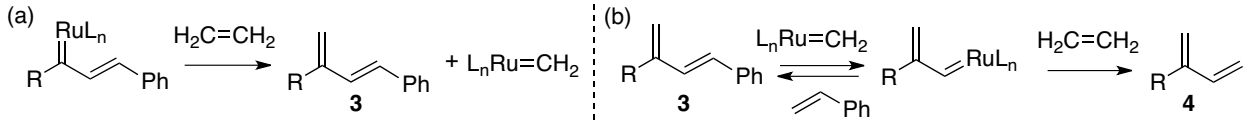
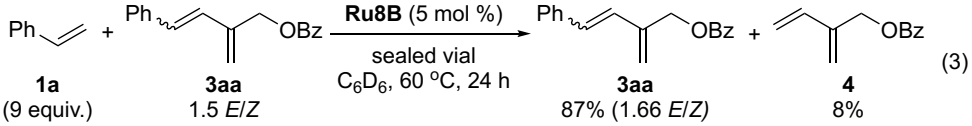


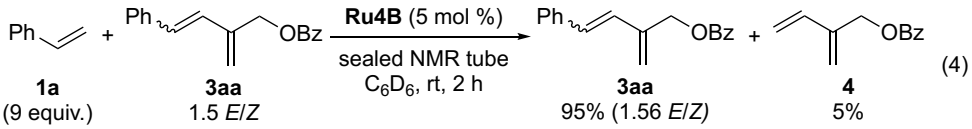
Fig. 2. Reaction composition during ene-yne metathesis. Conditions: **1a** (9 equiv.), **2a** (1 equiv.), **Ru4B** (3 mol %), C_6D_6 (ca. 0.08M), rt, time; sealed screw cap NMR tube.



Scheme 7. (a) Ethylene turnover of a vinyl carbene and (b) possible secondary metathesis by $L_nRu=CH_2$.

Finally, we examined whether a secondary metathesis could explain the formation of the butadiene product. Secondary metathesis has been observed previously for 1-substituted-1,3-dienes.[21] For ethylene, secondary metathesis is shown in Scheme 7b. Since the rate plots above showed a slower rate of alkene self-metathesis, we considered that as alkene metathesis occurred, the reactive $Ru=CH_2$ species might cleave the 1-phenyl substituted-1,3-diene **3** to form the butadiene **4**. First, a E/Z mixture of **3aa** was exposed to excess styrene with **Ru8B** under mock reaction conditions in a sealed vial (Scheme 8, eq 3). After 24 h, 8% butadiene **4** was observed and the E/Z ratio upgraded slightly in the E-isomer, consistent with greater secondary metathesis of the Z-isomer. In a second run using **Ru4B**, the butadiene was detected at shorter reaction times under milder conditions (eq 4). Together these experiments show that the catalysts used in this study are capable of secondary metathesis. Previously, Lee and Snapper found that 2-substituted butadienes (ethylene-alkyne metathesis products) could be converted into cross products with 1-alkenes for stereoselective 1,3-diene formation.[22] Ethenolysis has been extensively studied for the conversion of higher olefins by alkene metathesis.[23, 8b] However, to the best of our knowledge, ethylene being formed from competing alkene metathesis has not been shown to cleave a 1,3-diene during ene-yne metathesis. To minimize this undesired process, short reaction times at room temperature in open vials (open to a nitrogen atmosphere) offer the best selectivity for unbranched terminal alkynes undergoing cross metathesis with styrene.





Scheme 8. 1,3-Diene product stability: evidence for secondary metathesis

3. Conclusion

In conclusion, the styrene cross metathesis with unbranched terminal alkynes was optimized through catalyst screening and reaction set up. As an electronically-delocalized alkene, styrene is less reactive than 1-alkenes (such as 1-hexene) in ene-yne metathesis and higher equivalents were needed for high conversions to the desired 1-phenyl-1,3-dienes. Unbranched terminal alkynes are vulnerable to competing alkyne oligomerization. Through the catalyst screen, Grubbs catalysts with high steric demand were found to give the best yields and were used for the synthesis of a variety of terminal alkynes that proved low yielding under the standard conditions. Reaction profiling showed that the ene-yne metathesis occurred much faster than the production of stilbene. The generation of stilbene generates a ruthenium methylidene intermediate which can lead to an unwanted byproduct arising from the net addition of ethylene across the alkyne. Though potentially detrimental to selectivity, as long as ethylene is allowed to escape from the reaction vessel, the 2-substituted-1,3-butadiene could be completely suppressed. Last, a secondary metathesis cleavage of the desired substituted 1,3-dienes was found when ethylene remained trapped in the reaction vessel, which also led to the byproduct.

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5. References

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