Substituent-enhanced Intermolecular Catalytic Ene-yne Metathesis for Efficient 1,3-Diene Synthesis

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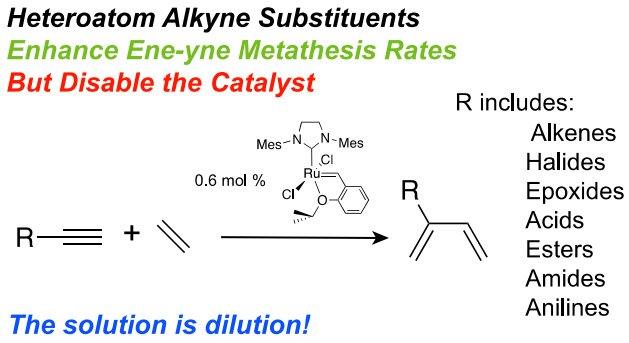
ABSTRACT. The appropriate reaction conditions for ruthenium-catalyzed ene-yne metathesis are substantially affected by the substituents and functional groups on the terminal alkyne reactant. We have identified that two distinct methods, utilizing a single precatalyst IMes(Cl)$_2$Ru(=CHC$_6$H$_4$O*i*Pr) (**1**; IMes = 1,3-dimesitylimidazol-2-ylidene), are needed to achieve high turnover numbers and good yields in ene-yne metathesis reactions of heteroatom-free or functionalized terminal alkynes and ethylene. The wide-ranging yields of 1,3-dienes from ene-yne metathesis of a series of terminal alkynes under a single set of benchmark conditions, namely 3 mol % **1**, toluene, 75 °C, at 20 bar C_2H_4, identified groups of highly, moderately, or poorly performing alkynes. Studies of the effects of reaction conditions on yields, turnover numbers, and effective rates in reactions of alkynes from these groups lead to distinct optimized approaches for efficacious syntheses. Quantitative yields are obtained using 0.6 mol % **1**, one fifth of a benchmark loading, in preparative scale experiments under conventional conditions, in which the highly efficient alkyne and **1** are mixed, followed by pressurization with ethylene. In

contrast, the metered addition method, in which a moderately or poorly performing alkyne and a solution of **1** are slowly and separately added to an ethylene-pressurized reaction vessel, can improve turnover numbers up to 1500% to access 2-substituted-1,3-diene containing carboxylic acids, carbonyls, amines, epoxides, or halides in a single step. Moreover, increased effective rates of reactions for functionalized alkynes under dilute conditions, and comparisons with heteroatom-free alkyne conversions, suggests that the former react more rapidly than the latter in ene-yne metathesis, but their transformations are also more sensitive to catalyst deactivation.

keywords: ene-yne metathesis, Hoveyda-Grubbs catalyst, 1,3-dienes, terminal alkynes, metered addition

Graphic for Table of Contents:



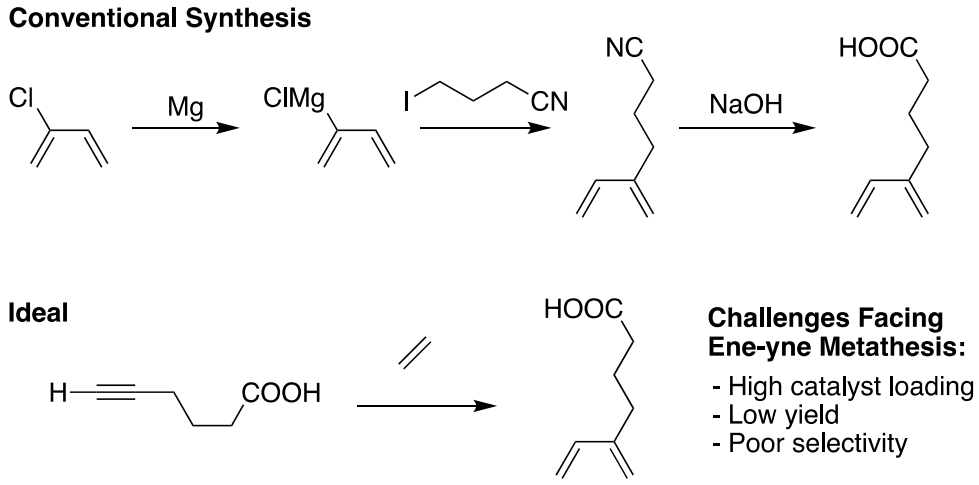
Introduction

The versatile reactivity of 1,3-dienes in cycloadditions, hydrosilylation, hydroamination, and hydroalkoxylation,[1-5] as well as addition-polymerizations[6-10] enables important chemical and materials syntheses.[11] Unfortunately, classical preparations of 1,3-dienes can be problematic, often requiring large excesses of reagents, involving hazardous reactants, and generating large quantities of byproducts. For example, reductions of 1,4-dihaloalkenes to give 1,3-dienes require super-stochiometric quantities of zinc, while chloroprene, synthesized via acetylene process, is limited by considerable safety concerns. Conventional syntheses are sufficiently limiting that Kumada-type cross coupling of enol phosphates and vinyl Grignard reagents, producing magnesium phosphate salt by-products, appears promising as a recently advanced approach,[12, 13] especially given myriad challenges facing intermolecular ene-yne metathesis.

As a mild and atom-economical catalytic reaction to create new C–C bonds by combination of alkenes and alkynes,[14] ene-yne metathesis could potentially provide 1,3-dienes at preparative scale from readily available reactants (see the representative example in Scheme 1). Moreover, intramolecular ene-yne metathesis reactions, catalyzed by ruthenium carbenes, efficiently give cyclic 1,3-dienes with high turnover numbers (TON = moles product/moles catalyst) and turnover frequencies, good stereo- and regio-selectivity for the desired product, and tolerance of Si–O, ester, halide, carboxylic acid, ether and amine functional groups present in the reactants.[15-18] Contrasting these catalytic cyclizations, intermolecular ene-yne metathesis is underdeveloped in the context of sustainable syntheses of dienes. High catalyst loading (2.5-10 mol %), often required to overcome low yields and catalyst decomposition, leads to low TON and inefficient use of the precious ruthenium catalyst, limiting larger scale preparations.[19-25] The requirement of high catalyst loading may be exacerbated by reactive moieties such as peroxides,[26] resulting in

seemingly poorer tolerance of some functional groups.[27] In addition, complications from alkene metathesis and alkyne polymerization side reactions, and limited control over regioselectivity have impeded the broad application of intermolecular ene-yne metathesis in synthetic applications.[28]

Scheme 1. Representative example of proposed synthesis of 1,3-dienes via intermolecular ene-yne metathesis reactions compared to its conventional synthesis



Nonetheless, the success of the intramolecular variant, the synthetically useful nature of metathesis reactions,[29] along with a driving need for sustainable, versatile diene synthesis have motivated studies to advance intermolecular ene-yne metathesis.[20, 21, 30-34] Kinetics provide considerably guidance. For example, zero-order dependence on terminal alkyne concentration (rate $\propto$ $[HCCR]^0$; R = CH(Me)OBz) and first-order dependence on internal alkyne concentration (rate $\propto$ $[HCCR']^1$; R = CH_2OAc) reveals that these two species react via inequivalent mechanisms in reactions catalyzed by $IMesCl_2Ru(=CHC_6H_4O$*i*Pr) (**1**; IMes = 1,3-dimesitylimidazol-2-ylidene).[31] Thus, preparative scale experiments should be guided by the

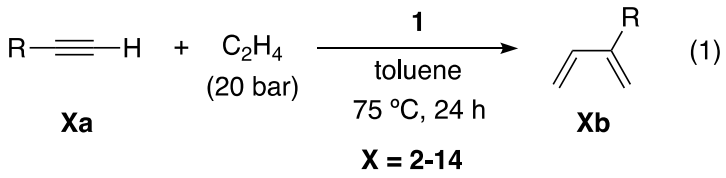
principle that terminal alkyne concentrations should not influence the performance of the catalyst. In addition, relative rates of reaction of the precatalyst and either ethylene[35] or alkyne, as a function of substitution and reaction conditions, could dramatically affect the catalyst activation process. Moreover, studies of the decomposition of the catalysts aid in identifying concentration dependences and the effects of specific functional groups.[27, 36 37, 38] However, many of the rules governing the performance of many ene-yne reactions are not yet established, and anticipating behavior a priori is difficult, as exemplified by the acceleration of some transformations by ethylene, the simplest alkene, whereas other ene-yne metathesis reactions are inhibited by ethylene.[39-41]

We sought to identify catalytic conditions for ene-yne metathesis that would be effective on a preparative scale, as well as frame the effects of reaction conditions in the context of proposed ene-yne metathesis mechanisms to provide useful general guidance for the synthesis of 2-functionalized butadienes from terminal alkynes and ethylene. In this study, we investigate Ru-catalyzed ene-yne metathesis reactions of a series of terminal alkynes with ethylene to establish general strategies leading to high TON and high yield. TON is used as the metric for catalyst efficiency (we note that efficiency is typically defined as the ratio of output to input), used here as the amount of product formed to the amount of catalyst in the reactor after a specified time. Yield characterizes the efficiency of the alkyne itself in preparations of 2-butadienes. The reaction models from mechanistic studies described above, as well as examples of ene-yene metathesis of functional alkynes with high catalyst loading,[21, 22, 30] guided our initial choices of reaction conditions, but we quickly discovered unique responses of several alkynes. Nonetheless, a few conditions such as temperature, reactant concentrations, and addition procedures have outsized influence on catalytic performance leading to dramatically improved yields, TON after

fixed times, and functional group tolerance. Using a qualitative analysis of these observations from many alkynes, as well as considering the established mechanistic data for catalyst activation and deactivation, we have proposed molecular-based interpretations of the catalytic behavior. Using a single pre-catalyst, the method giving highly efficient ene-yne metathesis of ethylene and heteroatom-free alkynes is remarkably ineffective for functionalized alkynes, whereas optimal conditions for conversion of the latter alkynes give poor TON and poor yields for the former. Initial choices of conditions for previously untested alkynes may be guided by these empirical observations. The observed reactivity trends also lead to conclusions about the effects of functional groups on rates of ene-yne metathesis reactions.

Results

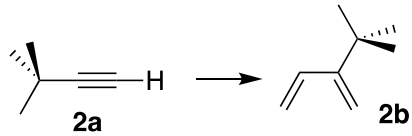
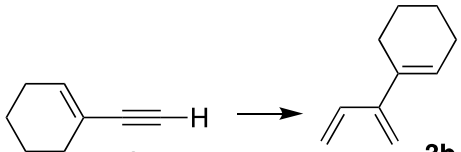
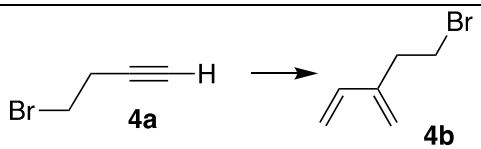
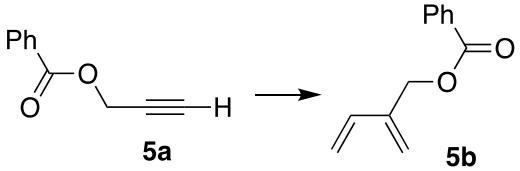
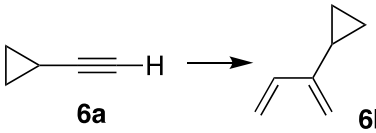
*Benchmarking performance of **1** in ene-yne metathesis.* The most studied catalysts for ene-yne metathesis are based on ruthenium carbenes.[15] We chose to employ the second generation Hoveyda-Grubbs catalyst **1** to avoid the competing, inhibitory coordination of phosphine ligands, even though fewer studies utilize the **1** in ene-yne metathesis reactions compared to other ruthenium carbene catalysts[42] and nitro-substituted analogues of **1** show higher reactivity in ring-closing ene-yne metathesis.[43] Quantitative baseline screening experiments in a multi-well reactor system (Figure S1-S2) involved an array of 12 alkynes (0.25 M) mixed with 3 mol % **1** (0.0075 M) in toluene (4 mL), pressurized with ethylene (20 bar), and heated at 75 °C for 24 h (eq 1).

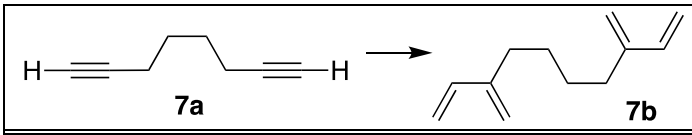
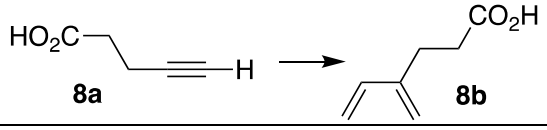
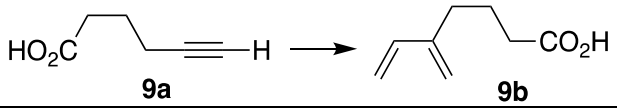
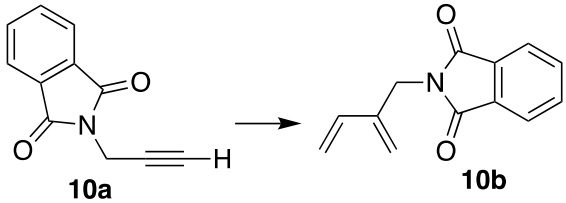
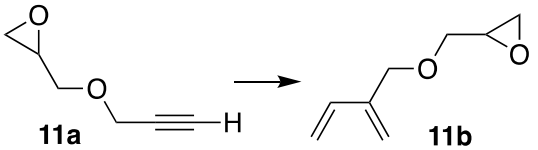
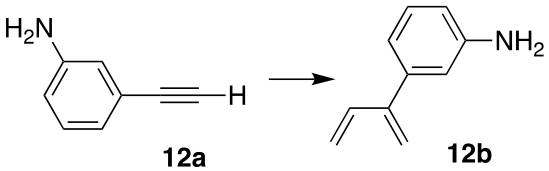
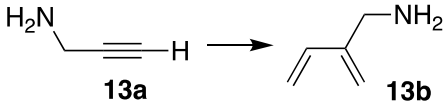


(1)

The yields, which range from quantitative down to 0%, and TON highlight the finicky nature of these transformations (Table 1). For example, the significant variations in yields, even for reactants with similar functional groups (e.g., 3,3-dimethyl-1-butyne vs. 1-hexyne, or 4-pentynoic acid vs. 5-hexynoic acid), reveal the great substrate-dependent sensitivity of the catalysis that is not captured in studies on a single model substrate. From these experiments, the alkynes were grouped into highly-efficient (>75%), moderately-efficient (75–25%), and poorly-efficient classes (<25%) for the next phase of study, using much lower catalyst loading (0.6 mol %).

Table 1. Ene-yne metathesis of alkynes and ethylene grouped according to butadiene yield

Alkyne[a]	Yield (%)[b]	TON[b]
Highly efficient alkynes		
 **2a** **2b**	>99	33
 **3a** **3b**	82	27
 **4a** **4b**	76	25
Moderately efficient alkynes		
 **5a** **5b**	59	20
 **6a** **6b**	44	15

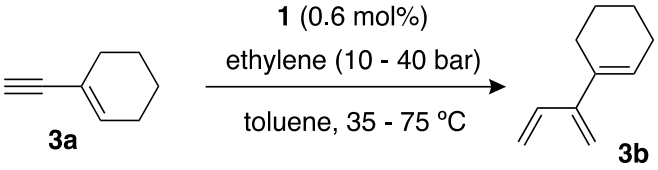
 **7a** **7b**	26	9 [c]
Poorly performing alkynes		
 **8a** **8b**	21	7
 **9a** **9b**	5	2
 **10a** **10b**	1	0
 **11a** **11b**	n.d.[c]	n.d. [c]
 **12a** **12b**	n.d. [c]	n.d. [c]
 **13a** **13b**	n.d. [c]	n.d. [c]

[a] Reaction conditions: 1 mmol alkyne, 3 mol % **1**, toluene (4 mL), C_2H_4 (20 bar), 75 °C, 325 rpm vortex mixing, 24 h in a multiwell reactor (array of 8 mL vials). [b] Yield and TON determined by GC-MS. [c]0.5 mmol dialkyne used, with 0.03 mmol **1** (3 mol % relative to alkyne, TON is defined by the number of ene-yne metathesis steps). [c] not detected

Highly efficient alkynes. Intermolecular ene-yne metathesis of the bulky and heteroatom-free alkyne **2a** and ethylene is the most straightforward of the conversions. At a catalyst loading of 0.6 mol % **1**, reaction of **2a** and ethylene either at 35 °C and 40 bar of ethylene or at 75 °C and 10 bar of ethylene pressures reproducibly gives butadiene **2b** in high yield (90 to >99%) and TON (150 to 167, the maximum possible at 0.6 mol % **1**). That is, this transformation and its catalytic intermediates are insensitive to a wide range of reaction conditions, and this

transformation could not provide additional insight to guide improvements. In contrast, conversions of the other high- or moderate-yielding alkynes in Table 1 are sensitive to the temperature, ethylene pressure, concentration, and rate of catalyst and/or alkyne addition.

Although ene-yne metathesis of **3a** and ethylene is efficiently catalyzed by 0.6 mol % **1** under 5.1 mmol-scale batch conditions (eq 2), the TON of 138 is below the ideal value of 167 at this catalyst loading (Table 2, entry 1).



(2)

Based on the assumption that high alkyne and ruthenium concentrations accelerate catalyst deactivation, addition of alkyne and the ruthenium pre-catalyst to an ethylene-pressurized, pre-heated reactor using a syringe-pump was investigated (identified in this paper as *metered-addition* in contrast with *conventional* conditions, in which catalyst and alkyne are mixed followed by addition of ethylene and heating). Metered-addition decreases the contact time of pre-catalyst and alkyne prior to initiation of the reaction and decreases the concentration of active ruthenium in the reactor (assuming short lifetime for the active catalyst). Instead, this metered-addition approach leads to lower TONs for ene-yne metathesis of **3a** and ethylene over 100 mins (40 min of addition and 60 min after complete mixing of catalyst and reactant) compared to conventional conditions (90 mins of complete mixing). Although equivalent concentrations of reactants over the reaction times, needed for a perfect direct comparison of these two conditions, are not possible, an experiment with an even slower metered-addition of catalyst and alkyne (0.1 $mL \cdot min^{-1}$; 200 min of addition, 60 min after complete mixing of catalyst and reactant) gives poorer yield than faster metered addition (0.5 $mL \cdot min^{-1}$). That is, this conversion does not benefit from metered addition. Finally, higher yields of the triene product

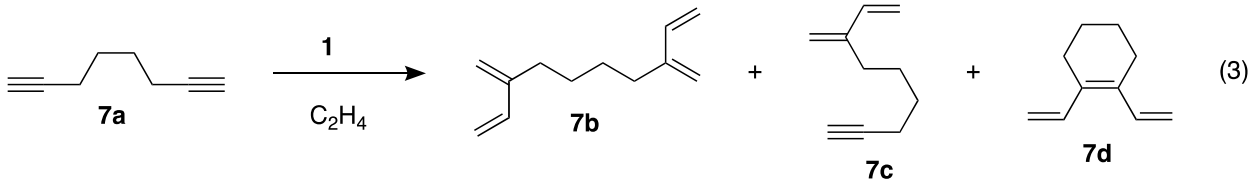
and higher TON are obtained with lower ethylene pressure in metered addition reactions. In fact, the highest yield (97%) and the highest TON (162) are obtained at lower ethylene pressure (10 bar) and higher temperature with conventional conditions.

Table 2. Ene-yne metathesis of 1-ethynylcyclohexene (**3a**) and ethylene

Entry	Temperature	Ethylene Pressure	Conditions	Yield	TON
1	75 °C	40 bar	conventional [a]	83%	138
2	75 °C	40 bar	metered addition [b]	48%	80
3	75 °C	20 bar	metered addition [b]	63%	105
4	75 °C	10 bar	metered addition [b]	83%	138
5[c]	75 °C	10 bar	conventional [a]	97%	162

[a] *Conventional conditions*: 1-ethynylcyclohex-1-ene and 0.6 mol % **1** are dissolved in toluene (20 mL). Reactor is pressurized with C_2H_4 and heated for 90 min. [b] *Metered Addition:* Reactor containing toluene (20 mL) is pressurized with C_2H_4. 1-ethynylcyclohex-1-ene and 0.6 mol % **1** dissolved in toluene are added at 0.5 mL/min and allowed to react for 60 min.

Moderately effective alkynes. The reaction of 1,7-octadiyne **7a** and ethylene could provide the desirable bis(diene) product (**7b**) from two sequential ene-yne metathesis steps or form side products, depending on rates of cyclization versus reaction with ethylene. Under the baseline conditions, mixtures of **7b**, diene-alkyne (**7c**), and a cyclized triene (**7d**) are obtained (eq 3). The mono-diene **7c** was initially assumed to be an intermediate that could form either **7b** or **7d** as final products, with selectivity affected by temperature, ethylene pressure, or concentration of catalyst precursor **1** and/or **7a**, with behavior following that of **2a** or **3a**.



(3)

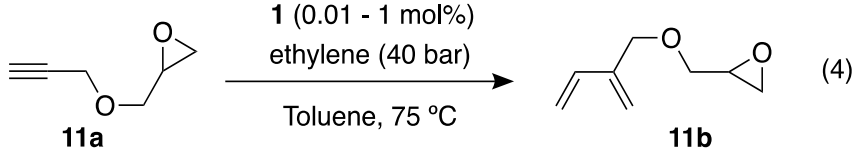
The lower ethylene pressure conditions developed for **3a** also give higher conversion of **7a** (74%, corresponding to 196 individual ene-yne metathesis steps) than obtained from the baseline study (26%); however, selectivity for **7b** is poor (Table 3). A few of the typical reaction parameters, including lower temperature, longer reaction times, or more concentrated reaction mixtures do not provide satisfactory selectivity for **7b**. In contrast to the behavior of **3a**, higher ethylene pressure (40 bar) increases the conversion of **7a** (>95%) and the yield of **7b**. The side product **7d**, however, is formed with equivalent selectivity under low and high ethylene pressures, ruling out the initial mechanistic hypothesis that **7c** is a common intermediate on the paths to **7b** and **7d**. Instead, metered addition of **7a** and **1** (0.1 mL/min over 110 min) to the ethylene-pressurized and pre-heated reactor provides **7b** and **7c** in a 1:1 ratio, albeit with moderate alkyne conversion (58%), whereas **7d** was not detected. Efficient (166 TON), high yielding and selective synthesis of the bis(diene) product (>95%) is accomplished with longer reaction time. In summary, higher ethylene pressure and temperature provide higher conversion of **7a** and higher yield of **7b**, while low concentrations of **7a** and catalyst **1** give higher selectivity for **7b** and **7c** compared to **7d**.

Table 3. Ene-yne metathesis of **7a** and ethylene, catalyzed by **1**

Temp.	Ethylene pressure	Conditions	Total Time	**7a** Conversion	**7b**	**7c**	**7d**
75	10 bar	conventional [a]	90 min	74%	31%	41%	28%
35	10 bar	conventional [a]	90 min	42%	19%	57%	24%
35	10 bar	conventional [a]	190 min	50%	22%	54%	24%
35	40 bar	conventional [a]	190 min	>95%	62%	12%	26%
35	40 bar	metered addition [b]	190 min	58%	52%	47%	n.d. [c]
35 [d]	40 bar	metered addition [b]	380 min	>95%	>95%	n.d.	n.d.

[a] *Conventional conditions*:1,7-Octadiyne and **1** are dissolved in toluene (20 mL), C_2H_4 is added, and the reactor is heated for 90 min. [b] *Metered addition:* Reactor containing toluene (20 mL) and C_2H_4 is heated to reaction temperature, then toluene solutions of 1,7-octadiyne and **1** are added at 0.1 mL/min. [c] not detected by GC. [d] optimized condition.

Poor yielding alkynes. Intermolecular ene-yne metathesis of glycidal propargyl ether **11a** and ethylene (eq 4) employed metered addition of catalyst **1** to overcome the undetectably low conversion under the baseline conditions in Table 1.



(4)

Investigations using metered catalyst addition reveal that high catalyst TON comes at the expense of yield. Experiments with lower total amount of catalyst afford higher efficiency, for example, 1 or 0.01 mol % **1** afford TON of 98 and 370, respectively; however, the former provides >98% yield whereas the latter affords only 3.7% yield. Investigation of a range of concentrations of **1** and **11a** reveal that highest TON is obtained with the lowest concentrations of *both* **11a** and **1** (Table 4). Although these catalytically efficient conditions are not practical for

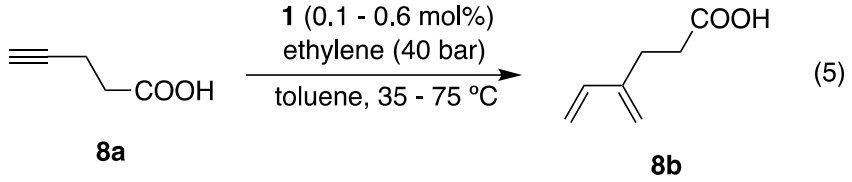
synthesis because catalytic yield and theoretical yields are low, the results suggest that lower concentrations accessed through metered addition and/or dilute reaction conditions could provide both high TON and high yield. For example, metered addition of **1** improves both TON and yield two-fold, and metered addition of both **1** and **11a** gives a three-fold improvement. Slower metered addition of **1** and **11a**, as well as slightly higher loading provides a reasonable compromise of optimal yield and TON. This idea proves useful for ene-yne metathesis of ethylene with **11a** as well as the other poor-yielding functionalized alkynes.

Table 4. Ene-yne metathesis of glycidal propargyl ether (**11a**) and ethylene

[**11a**]$_0$ (M)	[**1**]$_0$ (mM) (mol%)	Method[a]	% Yield[b]	TON
0.37	3.7 (1)	A	>98 (4.46 mmol); 66%[c]	98
0.37	0.037 (0.01)	A	3.7 (0.16 mmol)	370
0.37	0.37 (0.1)	B	7.4 (0.33 mmol)	74
0.37	0.37 (0.1)	A	14 (0.62 mmol)	140
0.37	0.37 (0.1)	C	23 (1.03 mmol)	230
0.42	2.52 (0.6)	D	83 (4.15 mmol)	138

[a]Reaction Conditions: **A**: The reactor was charged with **11a** (12 mL) solution, then the reactor was sealed, pressurized with ethylene (40 bar) and heated (75 °C). Catalyst **1** (as a solution in toluene, 12 mL) was added into the pressurized reactor at a rate of 0.5 mL/min over 24 min, and the mixture was stirred for 60 min. **B**: *Conventional conditions*. The reactor was charged with **11a** (12 mL in toluene) and **1** (12 mL in toluene). The reactor was sealed, pressurized with ethylene (40 bar), and heated to 75 °C for 124 min. **C:** Toluene (2 mL) was added to the (empty) reactor, which was sealed, pressurized with ethylene (40 bar) and heated to 75 °C. Solutions of **11a** (11 mL) and **1** (11 mL) were each added at a rate of 0.5 mL/min over 22 min to the reactor. **D:** The reactor was pressurized with ethylene (40 bar) and heated to 75 °C. **11a** (12 mL in toluene) and **1** (12 mL in toluene) were added at a rate of 0.1 mL/min over 110 min. [b] GC yield. [c] Isolated yield.

These metered addition methods are also critical for conversions of pentynoic acid **8a** (eq 5), improving the TON from 7 to 78.



(5)

Unfortunately, the yields are poor at ca. 8%. Lower temperature and slower metered addition of **1** and **8a** (0.1 mL/min) give a small increase in yield and TON (Table 5). Remarkably, a positive non-linear response to increased catalyst loading from 0.1 to 0.3 mol % gives higher yield (74%) and increased TON (250), and full conversion and the maximum potential TON are obtained with 0.6 mol % **1**. Further diluted reaction mixtures, by adding toluene (20 mL) to the reactor prior to initiating the catalysis, give quantitative conversion at 0.3 mol % catalyst, corresponding to a TON of 333 and 99% yield.

Table 5. Ene-yne metathesis of pentynoic acid (**8a**) and ethylene[a]

Temperature	mol %	Addition Rate (mL/min.)	Addition Time (min.)	% Yield[c]	TON
75 °C	0.1	0.5	22	7.8	78
35 °C	0.1	0.5	22	10	100
35 °C	0.1	0.1	110	17	170
35 °C	0.3	0.1	110	74	250
35 °C	0.6	0.1	110	>99 (78.3)[d]	167
35 °C[b]	0.3	0.1	110	>99% (72.3)[d]	333

[a]Pentynoic acid (0.5 g) and 0.1 mol % **1**, added concurrently to a preheated and C_2H_4-pressurized reactor; theoretical [product] = 0.21 M, theoretical yield = 5.1 mmol. [b] Reactor

contained 20 mL toluene prior to pressurizing with ethylene. [c]Determined by GC-MS. [d]Isolated yield.

The optimization of reaction conditions for the ene-yne metathesis affords up to a 10-fold reduction in catalyst loading, compared to the original conditions in Table 1, while providing quantitative yields (illustrated in Figure 1). In three examples with a single pre-catalyst, the reactions are improved from no detectable products to providing the diene product on preparative scale. This increase in catalyst efficiency (Table S5) is evaluated by taking the difference in TON between optimized and the baseline in Table 1 (improved TON) that ranges from 40 to >300 or as percentage.

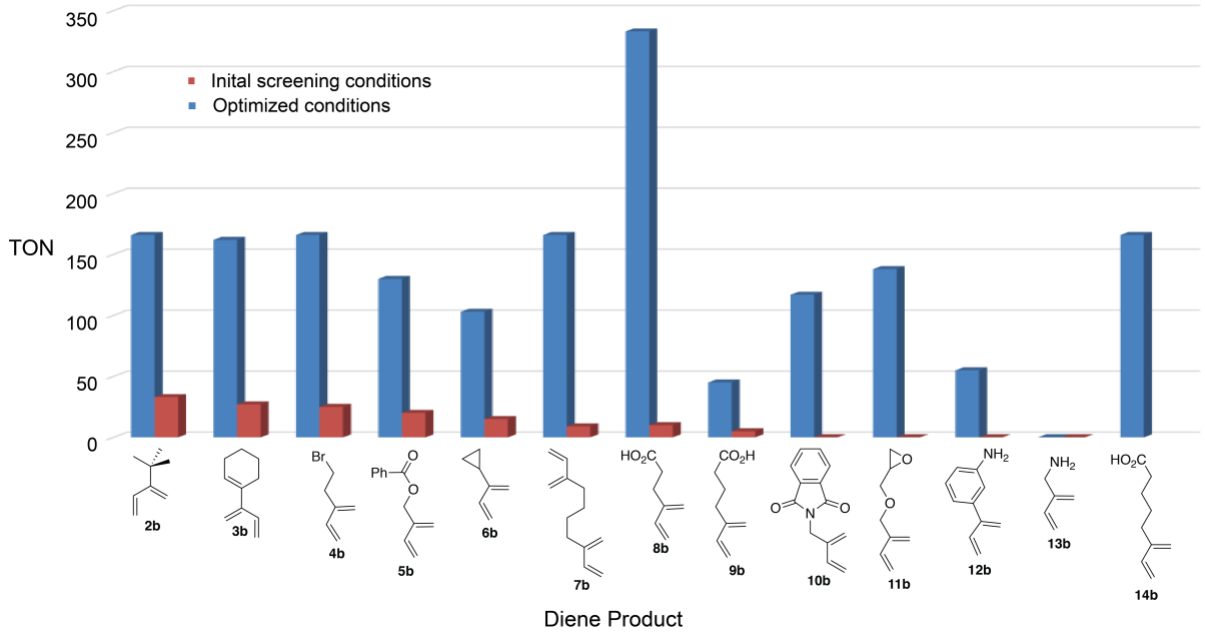
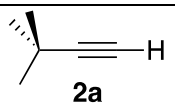
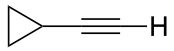
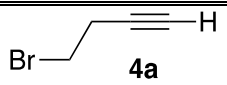
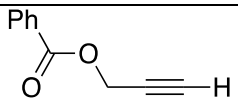
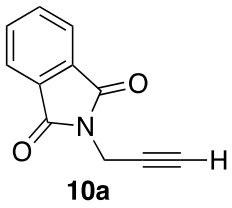


Figure 1. TON with optimized ene-yne metathesis conditions versus initial screening conditions for 13 terminal alkynes and ethylene.

Discussion

Higher catalytic TON, rates, and yields are accessed in ene-yne metathesis reactions of a wide range of terminal alkynes by matching the alkyne substrate to appropriate reaction conditions (Table 6). Importantly, two methods emerge. In *conventional conditions*, catalyst and alkyne are premixed in the unconditioned reactor, which is subsequently heated to elevated temperatures (75 ºC) and ethylene is introduced at a moderate 10 bar. In *metered addition*, the reactor is preconditioned at 35 °C with ethylene at 40 bar and solvent, and then the alkyne and catalyst are added slowly, separately, and concurrently. Conventional conditions are effective for conversion of *tert*-butyl-substituted **2a**, cyclohexenyl-substituted **3a**, and cyclopropyl-containing **6a**. In contrast, the optimal performance of **1** in conversions of alkynyl acid **8a** and epoxide **11a,** halide-containing **4a**, heptynoic acid (**14a**), benzoate **5a**, and phthalimide **10a** generally benefit from metered addition. The conversions of the latter group of alkynes are much poorer under conventional conditions. For example, yield of **4a** is 75% poorer under conventional conditions than metered addition. Likewise, the yields obtained using the former group of alkynes in ene-yne metathesis are poorer under metered addition.

Table 6. Substrate-specific conditions for improved ene-yne metathesis

		Conventional conditions		***Metered Addition***	
	Addition method	Ethylene added to alkyne and catalyst		Alkyne and catalyst added to ethylene-pressurized reactor	
	Pressure	10 bar		40 bar	
	Temperature	75 ºC		35 ºC	
Alkyne		Yield (%)	TON	Yield (%)	TON
 **2a**		**96**	**160**	90	150
 **6a**		**62**	**103**	43	71.7
 **4a**		23	38.3	**>99**	**>166**
 **5a**		6	10	**78**	**130**
 **10a**		12	20	**32**	**53.3**

Likely, steric hinderance of encumbered alkynes leading to slower ene-yne metathesis[32] is not responsible for the observed method-dependent catalytic performance. Although increased rates at the higher concentrations of conventional conditions could be most noticeable for the conversion of hindered alkynes, the most sterically bulky substrate **2a** reacts similarly and quantitatively using either method. That is, the presumed slower rate for the bulky alkyne does

not necessitate conventional reaction conditions for high turnovers. Moreover, some less hindered alkynes, such cyclohexenyl alkyne **3a** and cyclopropylalkyne **6a** provided higher yields under conventional conditions, whereas other unhindered alkynes such as 5-bromopentyne **4a** and benzoate **5a**, afford dienes in higher yield under metered addition conditions.

Ethylene is postulated to inhibit ene-yne metathesis reactions by formation of non-productive ruthenacyclobutane species,[42] which presumably would be favored at higher effective ethylene concentrations. Alternatively, ethylene reacts with the benzylidene pre-catalyst as well as the postulated ruthenium vinylalkylidene catalytic intermediate, presumably faster at higher ethylene pressures. These processes depend on the form of the active catalyst, which likely varies based on the individual alkyne substrate. Thus, the effects of ethylene concentration will likely vary depending on the alkyne. Conventional conditions (run at higher temperature and low ethylene pressure) lead to a smaller effective concentration of ethylene. On the other hand, metered addition leads to a larger excess of ethylene. (As a caveat to evaluating the effects of ethylene pressure by comparison of conventional and metered addition, the conclusions must be tempered because of other changes in catalyst and alkyne concentration and temperature.) Cyclohexene-yl alkyne **3a** gives lower yields at higher ethylene pressures, with otherwise identical reaction conditions. This effect of ethylene pressure on the reaction of **3a** is observed for both conventional conditions and metered addition. In contrast, bromo-alkyne **4a**, propargyl benzoate **5a**, and phthalimido alkyne **10a** give excellent yields of diene products under metered addition conditions.

The cascade conversion of diyne **7a** provides an interesting opportunity to investigate the effects of ethylene pressure, in that the diene-alkyne **7c** intermediate could react via an intramolecular cyclization to give the triene **7d**, or with ethylene to give the targeted bis-diene

7b. One might expect that the yield of **7b** would increase with higher ethylene pressure, which would require increased conversion of **7a** to **7c**. Conversion of **7a** and the ratio of **7b**:**7c** both increase at higher ethylene pressures, as predicted.

One also might expect that the subsequent reaction of intermediate **7c** to give **7b** or **7d** would favor **7b** at higher ethylene pressure. Unexpectedly, the ratio of (**7b** + **7c**):**7d** is not affected by ethylene pressure, suggesting that the free diene-alkyne intermediate **7c** leads only to **7b**, and not to **7d**. Higher conversion with higher ethylene pressure indicates that the rate controlling steps are affected by ethylene pressure, while the chemo selectivity is barely affected by ethylene pressure; thus, these two aspects of the transformation are separate. Instead, metered addition increases selectivity for **7b**. As discussed next, most functional-group containing alkynes also afford products in higher yields under metered addition. Thus, we suggest that the pendent alkyne in this dialkyne substrate behaves as a functional group on the pathway to **7b**.

Two general trends distinguish ene-yne metathesis reactions of functionalized alkynes from simpler alkynes. First, premixing functionalized alkyne and pre-catalyst gives the lowest catalyst performance, metered addition of either functional alkyne or pre-catalyst is always better than premixed conditions, and metered addition of both catalyst and alkyne leads to the highest catalyst efficiency. Alkyne conversions that benefit most from metered addition are those that contain heteroatomic or coordinating functional groups (e.g., carbonyl groups, epoxides, halides, and amines). These results suggest that the functional groups on these alkynes limit the activation of the pre-catalyst, presumably involving the coordination chemistry of the ruthenium complex.

Second, higher yields and TONs are achieved with slower metered addition than faster addition. An expected effect of metered addition conditions is that the ene-yne metathesis

reactions would have lower apparent rates resulting from the inhibiting effects of the higher ethylene concentration, lower catalyst concentration (over at least part of the experiment), and potentially lower alkyne concentrations (even if the rate has a zero-order dependence on alkyne, it is required as a limiting reactant for turnovers to occur). This expectation proved to be false through several observations. First, and most telling, the catalytic reactions *all* benefit from dilution, both under conventional conditions or through metered addition, and with both classes of alkyne consistently improving catalytic turnovers under otherwise identical reaction conditions and times (see Figure 2, and Table S3 for concentration studies of **11a**). Second, although heteroatom-free alkynes give fewer turnovers under metered addition compared to conventional conditions at equivalent reaction times, the estimated turnover frequency (eTOF) is higher with metered addition; here, eTOF is defined as turnover numbers per reaction time, normalized to account for the changing catalyst concentration, at partial conversion. The functionalized alkynes exhibit larger increases in TON and eTOF in comparison to conventional conditions, again in contrast to the expectations of deleterious kinetic effects from metered addition. These large increases are partly attributed to increased active catalyst lifetime, with catalyst decomposition via bimolecular pathways[42] being more sensitive to concentration effects than the catalytic reaction itself, as well as the more effective catalyst activation noted above. In addition, the low effective alkyne concentration of metered addition can limit alkyne oligomerization reactions.[44]

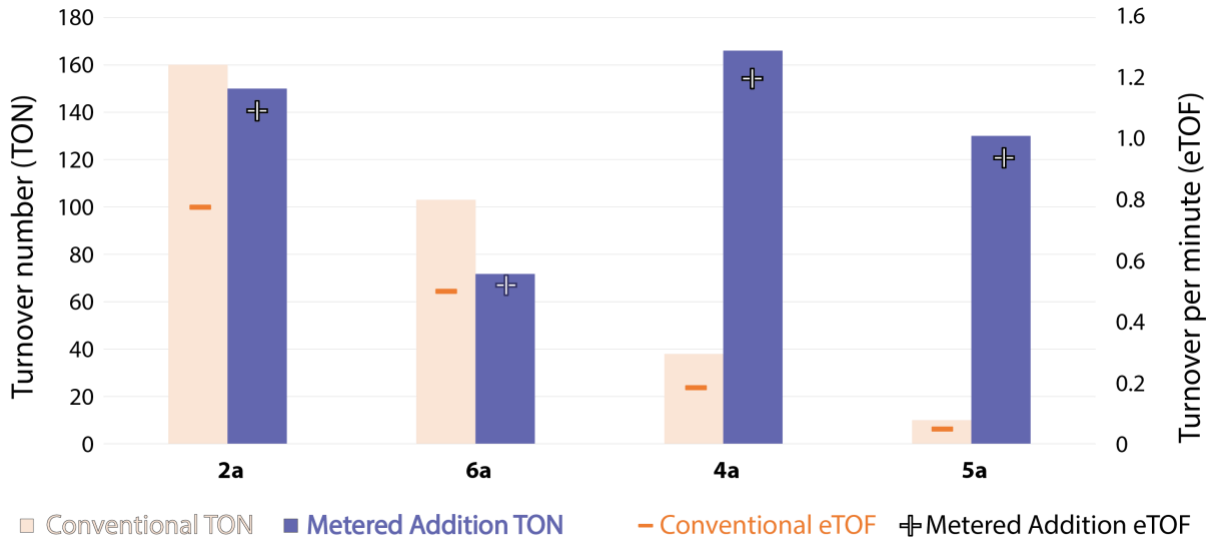
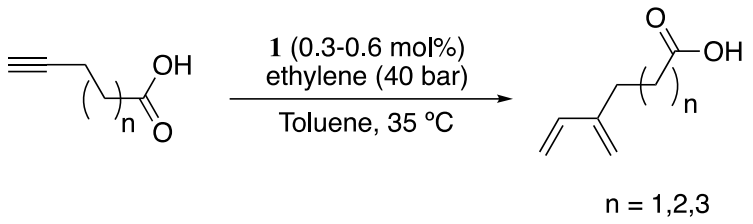


Figure 2. Average TON/min (eTOF) is higher using metered addition. Estimated turnover frequency (eTOF) is defined as turnover numbers per reaction time, normalized to account for the changing catalyst concentration, at partial conversion.

The enhanced rate of ene-yne metathesis for functionalized alkynes could also involve their coordination to ruthenium, for example to displace ethylene from the ruthenacyclobutane (presumed) off-cycle catalytic resting state and facilitate formation of the ruthenacyclobutene intermediate. The largest improvement in turnover numbers and yields from the initial benchmark conditions to metered addition conditions are observed for the alkynes with more strongly coordinating functional groups (i.e., the carboxylic acids and amines improved much more than esters or halides). That is, our analysis suggests that the groups on the alkyne inhibit conversion via precatalyst deactivation and increase rates by coordination to the active species or resting state. Second, the hydrocarbon chain length separating carboxylic acid and alkyne functionalities dramatically impact the yield and TON (pentynoic acid > heptynoic acid >> hexynoic acid; Table 7). This stark difference in reactivity provides further support for

coordination of the functional group, and suggests the phenomenon is, at least in part, intramolecular. For example, these results suggest that the functional groups, at least in some cases, provide a benefit by enhancing the reaction rate.

Table 7. Chain length effects on ene-yne metathesis yield under metered addition



n	**1** (mol %)	Yield (%)
1	0.3	>99
2	0.6	27
3	0.3	74

Conclusions

Synthesis of a series of 2-substituted-1,3-dienes containing a wide range of moieties is accomplished with ene-yne cross metathesis. Appropriate matching of reaction conditions and terminal alkyne leads to large improvements of yield and TON with the second generation Hoveyda-Grubbs precatalyst. This matching of conditions and comparisons of yield and TON response to reaction conditions lead to mechanistic insights with important reactivity implications, including increased rates in the presence of coordinating groups. That conclusion is

counter to initial expectations, since functional groups such as phthalimides, epoxides, and carboxylic acids inhibit ene-yne metathesis in our baseline experiments.

A 400% improvement in catalyst TON was achieved through the optimization of the reaction conditions for *t*BuCCH, the best performing alkyne from our initial screening studies, even in experiments increased to preparative scale. TON improvements exceeding 4,000% from our screening conditions were achieved with alkynes that performed poorly in the initial screen. Catalyst loadings, approximately an order of magnitude lower than those typically employed in synthetic applications of ene-yne cross metathesis reactions, provide good to excellent yields of 1,3-dienes. This work also presents the first published account of ruthenium carbene catalyzed ene-yne cross metathesis with unprotected carboxylic acids and primary amines in the substrates.

Two general conclusions come from these investigations. First, lowering the concentration of catalyst and alkyne in the reaction, by dilution, metered addition, or both (or with lower amounts of catalyst) improves turnover numbers and often increases rate of the catalysis. Because rates are presumed (and in some cases shown)[32] to be directly proportional to ruthenium concentration, this observation likely relates to the amount of active catalyst available. Thus, pre-catalyst activation and catalyst deactivation processes dominate apparent catalyst performance. In this regard, many of the other ruthenium metathesis catalysts may show further improved performance in ene-yne metathesis for specific alkynes.[45] The results of our study imply, however, that careful optimization of conditions would still likely be needed for effective use of new catalysts. Second, the beneficial effect of lower concentration is much greater in the presence of functional-group containing alkynes than hydrocarbon-substituted alkynes. The pre-catalyst activation, activated catalytic species, and catalyst decomposition are manipulated through reaction conditions to markedly improve catalytic performance; however, identifying

relative importance of each of these distinct aspects, which are unique to each alkyne, will require further investigation involving detailed mechanistic (kinetic and modeling) experiments.

ASSOCIATED CONTENT

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Supporting Information.

The following files are available free of charge.

Experimental methods, tables containing additional optimization data, and catalytic products (PDF)

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