

Atom Economy in the Metathesis
Cross-Coupling of Alkenes and Alkynes

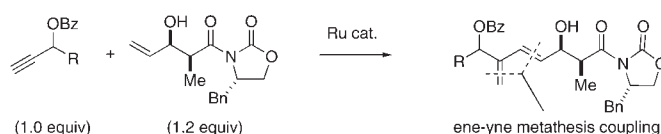
Joseph R. Clark and Steven T. Diver*

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

diver@buffalo.edu

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ABSTRACT

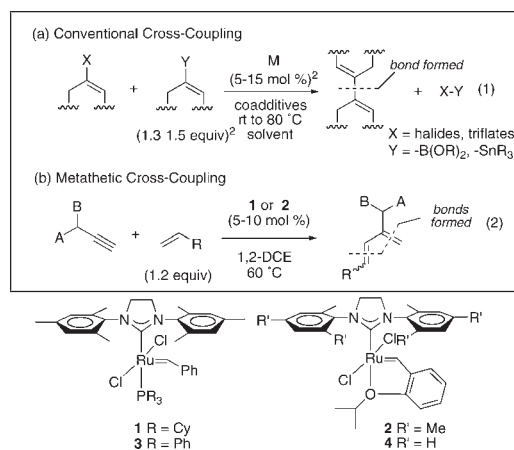


A cross ene-yne metathesis has been achieved at a nearly 1:1 stoichiometry of the unsaturated reactants. This allowed the use of more complex alkene reactants without sacrificing excess alkene reactant. In the alkene, different allylic oxygen protecting groups were explored. Interestingly, alkenes containing the allylic hydroxyl group proved to be the most reactive.

Ene-yne metathesis has the potential to be a practical and efficient carbon–carbon cross-coupling.¹ In general, metal-catalyzed cross-couplings are considered the most powerful and efficient ways to make carbon–carbon bonds. Yet direct cross-couplings require functional groups which activate the substrates, after which they are discarded as byproducts (Scheme 1, eq 1).² Ene-yne metathesis does not require activation by preexisting C–X or C–Y bonds (eq 2). Since there are no activating groups, ene-yne metathesis does not form byproducts. However, the major limitation of ene-yne cross metathesis has been the need to use a *large excess of the alkene reactant*. Mechanistic work with the second generation Grubbs catalyst **1** explains why higher alkene concentrations are beneficial.³ In this Letter, we report a truly atom economical⁴ ene-yne cross metathesis as a practical, metal-catalyzed cross-coupling.

A large excess of alkene reactant and lack of knowledge of substrate reactivity limit ene-yne metathesis as a predictable cross-coupling. Moreover, ene-yne cross metathesis

Scheme 1. Ene-Yne Metathesis: A Cross-Coupling of Unactivated Substrates



kinetic studies have been performed over a limited range of substrates.⁵ With catalyst **1**, the slow step involves the alkene, so alkene concentration is a critical reaction variable. With catalyst **2**, higher alkene concentrations

(1) Recent reviews: (a) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317–1382. (b) Poulsen, C. S.; Madsen, R. *Synthesis* **2003**, 1–18. (c) First ene-yne cross metathesis: Blechert, S.; Stragies, R.; Schuster, M. *Angew. Chem., Int. Ed.* **1997**, *36*, 2518–2520.

(2) A survey of recent synthetic applications of the Suzuki coupling shows that either the vinyl halide or organoborane may be used in 1.3–1.5 molar excess of the limiting reagent. Similarly, between 5 and 15 mol % Pd catalyst is commonly used.

(3) For Grubbs' carbene complex **1**, the rate dependence on [alkene] indicates that it is involved in the slow step in the catalytic cycle.

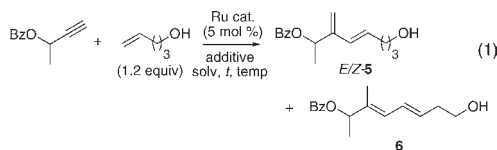
(4) Trost, B. M. *Science* **1991**, *254*, 1471–1477.

(5) Using the second generation Grubbs complex: (a) Galan, B.; Giessert, A. J.; Keister, J. B.; Diver, S. T. *J. Am. Chem. Soc.* **2005**, *127*, 5762–5763. Using the first generation Grubbs complex: (b) Marshall, J. E.; Keister, J. B.; Diver, S. T. *Organometallics* **2011**, *30*, 1319–1321. (c) The kinetics of ene-yne metathesis promoted by phosphine-free carbenes has not, to our knowledge, been studied.

were found to limit a competing pathway that led to catalyst decomposition,⁶ though kinetic studies are lacking with this catalyst.^{5c} By far, the most common alkene reactants are simple 1-alkenes; in these cases large excesses are reasonable. However, the perceived need to use a large excess of the alkene reactant limits the use of ene-yne metathesis with complex substrates. Carbon-carbon coupling achieved by the metathesis could be used as a fragment coupling to join two complex pieces in a total synthesis. The functional group tolerance of the Grubbs catalyst and the catalytic nature of ene-yne metathesis makes alkene-alkyne fragment coupling appealing. However, a notable attempt to use ene-yne cross metathesis as a fragment coupling in a complex molecule synthesis failed despite a screen of reactants and conditions.⁷ This literature example illustrates the need for an improved understanding of the reaction before it can be reliably used in synthesis.⁸ Our study was motivated by the need to better understand critical reaction variables in order to guide the successful use of cross ene-yne metathesis in complex molecule assembly. Ideally, alkyne and alkene would be combined in a 1:1 stoichiometry, minimizing the need to use an excess of a potentially precious alkene.

Screening catalyst and reaction conditions led to optimized reaction conditions with equimolar concentrations of alkyne and alkene reactants (Table 1). A key insight was obtained from previous studies in our group where temperature was found to play a critical role in achieving a rapid intermolecular reaction.⁹ At 60 °C in DCE, complete conversion of alkyne was observed under nominal concentrations of the reactants (0.05–0.08 M alkyne). At these temperatures, an isomerized product **6** was found in 10% yield (entry 1); an extended reaction time resulted in an increased amount of **6** at the expense of the *Z*-isomer, which was not detected at all (entry 2). Using the triphenylphosphine Grubbs complex **3**, very similar results were obtained compared to the case using complex **1** (entry 3 vs 1). Though lower reaction temperatures necessitated longer reaction times for full conversion of alkyne, these conditions successfully eliminated the byproduct in either DCE or toluene (entries 4, 5). At elevated temperature, benzoquinone (BQ) was used as a coadditive. Inclusion of BQ prevented byproduct formation, allowing shorter reaction times at 60 °C (entry 6). Benzoquinone had been used previously by Grubbs to suppress alkene isomerization, a process which was thought to occur due to a ruthenium

Table 1. Screening Results



entry	Ru cat.	additive	solvent	t/h	temp/ °C	E-5	Z-5	6
1	1	-	DCE	0.5	60	65	25	10
2	1	-	DCE	24	70	67	0	28
3	3	-	DCE	0.5	60	59	34	7
4	1	-	DCE	24	25	61	34	nd ^a
5	1	-	PhCH ₃	24	25	64	36	nd
6	1	BQ (10 mol %)	DCE	0.5	60	70	30	nd
7 ^b	4	-	DCE	0.5	60	19	12	nd
8 ^b	4	BQ (10 mol %)	DCE	0.5	60	19	11	nd
9	2	-	DCE	0.5	60	57	28	15
10	2	-	PhH	0.5	60	54	33	13
11	2	BQ (10 mol %)	DCE	0.5	60	65	35	nd

^a 'nd' = not detected by ¹H NMR spectroscopy; BQ = benzoquinone. ^b Incomplete conversion of alkyne was observed.

hydride species formed in situ.¹⁰ Our decision to use BQ as an additive was also based on the known conversion of ruthenium carbenes to ruthenium hydrides in the presence of alcohols.¹¹ Proton NMR monitoring did not detect any upfield proton resonances in the catalyst itself (before the reaction) or in the crude reaction mixture.¹² Continued catalyst screening showed that the bis tolyl Hoveyda-Grubbs carbene **4** was less effective, with incomplete consumption of the alkyne (entries 7, 8). Shorter reaction times and complete conversions were obtained using complex **2** in DCE or benzene solvents, though **6** was still a significant byproduct (entries 9, 10). At higher temperatures, use of the BQ additive limited byproduct formation using catalyst **2** (entry 11). In summary, use of BQ permitted short reaction times with no isomerization to product **6** detected. These conditions were adopted as standard conditions.

A range of alkene-alkyne combinations successfully underwent enyne metathesis cross-coupling (Table 2).¹³ α -Substituted alkynes were generally more reactive than non- α -branched alkynes.¹⁴ 3-Butynyl benzoate reacted with a range of 1-alkenes at nearly equimolar ratios (entries 1–6). If there was no free hydroxyl group in the alkene reactant, then benzoquinone was not used as an

(6) Diver, S. T.; Kulkarni, A. A.; Peppers, B. P.; Clark, D. A. *J. Am. Chem. Soc.* **2007**, *129*, 5832–5833.

(7) Nicolaou, K. C.; Brenzovich, W. E.; Bulger, P. G.; Francis, T. M. *Org. Biomol. Chem.* **2006**, *4*, 2119–2157.

(8) There are a few examples of ene-yne cross metathesis in synthesis, though these are not used as fragment couplings, and the alkene was used in molar excess (2.4–10 equiv): (a) Ko, H. M.; Lee, C. W.; Kwon, H. K.; Chung, H. S.; Choi, S. Y.; Chung, Y. K.; Lee, E. *Angew. Chem., Int. Ed.* **2009**, *48*, 2364–2366. (b) Kim, C. H.; An, H. J.; Shin, W. K.; Yu, W.; Woo, S. K.; Jung, S. K.; Lee, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 8019–8021. (c) Watanabe, K.; Minato, H.; Murata, M.; Oishi, T. *Heterocycles* **2007**, *72*, 207–212. (d) With ethylene: Fürstner, A.; Larionov, O.; Flügge, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 5545–5548. (e) For intramolecular examples, please see ref 1a.

(9) Clark, D. A.; Clark, J. R.; Diver, S. T. *Org. Lett.* **2008**, *10*, 2055–2058.

(10) Hong, S. H.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 17160–17161.

(11) (a) Dinger, M. B.; Mol, J. C. *Organometallics* **2003**, *22*, 1089–1095. (b) 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. (c) Louie, J.; Bielawski, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 11312–11313.

(12) Prepurified catalyst (as in Sutton, A. E.; Seigal, B. A.; Finnegan, D. F.; Snapper, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 13390–13391) gave similar results.

(13) Benzoquinone is included only for alkene reactants bearing free hydroxyl groups, e.g. allylic alcohols.

(14) Our previous rationale for the effect using Grubbs carbene **1** was a phosphine-bound resting state which was destabilized by α -substitution resulting in a higher active catalyst concentration. In the present case without phosphine, there is no tricyclohexylphosphine-bound resting state, so the effect of α -substitution is different with catalyst **2**.

additive. Interestingly, the *E/Z* ratios were dependent on the 1-alkene (cf. entry 3 or 4). A bulky TBS substituent gave lower chemical yields (entry 7), but α -branching in combination with an α acyloxy group proved to be good partners in the coupling (entries 8–10). In each of these cases, the BQ additive was used to suppress isomerization byproduct formation. For alkynes without α -branching the yields were slightly lower (entries 11–13). From these studies, propargylic ester protecting groups emerge as an excellent choice for protection of propargylic hydroxyl groups.

Table 2. Atom Economy in Ene-Yne Metathesis Cross-Coupling

$\text{R}^1\text{—C}\equiv\text{C} + \text{CH}_2\text{=CH-R}^2 \xrightarrow[\text{(1.2 equiv)}]{\text{1 or 2 (10 mol \%), 1,2-DCE, 60 }^\circ\text{C}} \text{R}^1\text{CH=CH-R}^2 \quad (2)$			
entry	product	entry	product
1	7 (79%, <i>E</i> only) ^b	8	14 (86%, <i>E/Z</i> = 1.75:1) ^{c,d}
2	8 (62%, <i>E/Z</i> = 10:1) ^b	9	15, R = Ph (79%, <i>E/Z</i> = 1.5:1.0) ^{c,d}
3	9, R = H (90%, <i>E/Z</i> = 1.8:1) ^{c,d}	10	10 16, R = CH ₂ Ph (79%, <i>E/Z</i> = 1.5:1.0) ^{b,d}
4	10, R = Ac (72%, <i>E</i> only) ^b	11	11 17 (75%, <i>E/Z</i> = 4.5:1.0) ^{c,d}
5	11, R = Ms (68%, <i>E</i> only) ^b	12	12 18 (68%, <i>E/Z</i> = 3:1) ^{c,d}
6	12 12 (60%, <i>E/Z</i> = 1.5:1.0) ^b	13	13 19 (63%, <i>E/Z</i> = 1.5:1.0) ^{c,d}
7	13 13 (50%, <i>E/Z</i> = 1.5:1.0) ^{c,d}		

^a Conditions: 1.0 equiv of alkyne, 1.2 equiv of alkene, **1** or **2** (10 mol %) in 1,2-DCE at the specified temperature for 0.5–2.0 h. Isolated yields are reported. ^b Using Grubbs carbene **1**. ^c Using Hoveyda–Blechert carbene **2**. ^d Using 10 mol % benzoquinone.

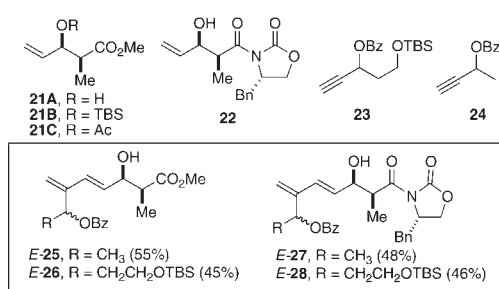
Using the standard conditions from Table 2, alkenes and alkynes of similar complexity were coupled in equimolar amounts. During this study, particular functionality in the allylic position proved detrimental: alkenes **21B** and **21C** failed to react with alkyne **23** under optimized conditions. These protecting groups are not recommended and help explain the poor reactivity observed by Nicolaou et al.⁷ For allylic alcohol derivatives, the free hydroxyl performed the best, most likely due to lesser steric hindrance.¹⁵ As a result, fragment couplings could be carried out in reasonable yields under catalytic conditions. The unprotected *syn*-aldol **21A** gave efficient cross ene-yne metathesis with alkynes **24** and **23** to give the respective dienes *E-25* and *E-26*, each obtained as the pure *E*-isomer. Cross metathesis

(15) (a) Hoye, T. R.; Zhao, H. *Org. Lett.* **1999**, *1*, 1123. (b) Michaelis, S.; Blechert, S. *Org. Lett.* **2005**, *7*, 5513.

coupling of the Evans aldol product **22** with alkyne **24** gave *E-27* in good yield; similarly, coupling with alkyne **23** gave *E-28* in 46% yield. The propargylic benzoate proved to be the best protecting group for propargylic alcohols under these coupling conditions.

Although the yields in Table 2 are generally very good, we investigated whether the conversions could be pushed further. Reaction monitoring by ¹H NMR revealed a very fast cross ene-yne metathesis coupling followed by slow degradation of the alkyne reactant. Most likely, this rapid halt to alkene conversion is a result of catalyst decomposition. To increase the conversion of alkyne, the usual approach would be to increase the alkene concentration to keep the carbene active in the catalytic cycle, and possibly to thwart competing pathways.⁶ Interestingly, efforts to increase the yield by increasing the equivalents of alkenol reactant did not help: Using Grubbs' catalyst **1**, alkyne **24** reacted with 1.2 equiv of **21A** to give *E-25* in 30% yield (¹H NMR versus mesitylene internal standard, benzene, rt, 24 h); with 2.0 equiv of **21A**, the same yield was observed after the same time under identical conditions (Scheme 2). At higher temperatures (1,2-DCE, 60 °C) using Hoveyda–Blechert complex **2**, 70% conversion to *E-25* was obtained after 15 min; with 2 equiv of **21A**, 70% conversion was also obtained after this time and the reaction did not proceed to significantly higher conversion on further reaction monitoring. It is likely that the allylic alcohol offers the best match from a reactivity standpoint, but that ruthenium carbene decomposition is also occurring by a competitive reaction. It should also be noted that the phosphine-free Hoveyda–Blechert carbene **2** may show different alkene rate dependency as compared to Grubbs catalyst **1**; this has not been studied for ene-yne metathesis.^{5c,16,17}

Scheme 2. Cross-Couplings with Functionalized Reactants



The stoichiometric equivalency and efficiency of the cross-coupling permits use of a bifunctional alkene substrate for a two-directional synthesis.¹⁸ Normally this

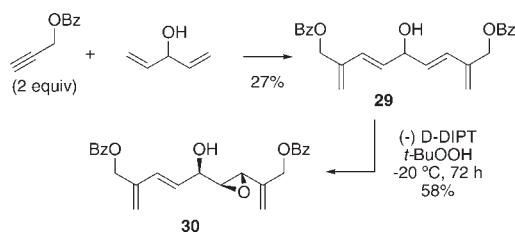
(16) The rate-determining step for *alkene* metathesis depends on alkene concentration for Hoveyda-type catalysts: (a) Gatti, M.; Vieille-Petit, L.; Luan, X.; Mariz, R.; Drinkel, E.; Linden, A.; Dorta, R. *J. Am. Chem. Soc.* **2009**, *131*, 9498–9499. (b) Kuhn, K. M.; Bourg, J.-B.; Chung, C. K.; Virgil, S. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **2009**, *131*, 5313–5320. (c) Vorfalt, T.; Wannowius, K.-J.; Plenio, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 5533–5536.

(17) Efforts to identify the byproduct were unsuccessful.

(18) (a) Schreiber, S. L.; Schreiber, T. S.; Smith, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 1525. (b) Poss, C.; Schreiber, S. L. *Acc. Chem. Res.* **1994**, *27*, 9.

would not be possible since the alkene is used in large excess, preventing double substitution of a diene reactant. Divinyl carbinol was reacted with a 2-fold excess of alkyne, to give the tetraene **29** in 27% isolated yield. The low yield is due to the sensitivity of the tetraene and the result of two modest yielding cross ene-yne metathesis steps (representative yields can be found in Table 2). With tetraene **29** in hand, a site-selective desymmetrization using the Sharpless conditions provided the chiral epoxide **30** in good yield (58% yield, 9:1 dr; 92% ee-chiral HPLC, Scheme 3).

Scheme 3. Double Metathesis Cross-Coupling and Sharpless Desymmetrization



In conclusion, a highly efficient ene-yne metathetical cross-coupling has been achieved. Our studies with more complex alkene reactants revealed shortcomings that explain a previously failed metathesis, and we identified the best combination for an atom-economical cross-coupling. A better picture of substrate reactivity is emerging, and we expect these data to be useful in the planning of complex molecule synthesis where metathesis will be employed as a fragment coupling strategy. Further studies into the catalytic mechanism and applications to total synthesis are ongoing in our laboratories.

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Supporting Information Available. Experimental procedures and characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.