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Geminal Alkene–Alkyne Cross Metathesis Using a Relay Strategy

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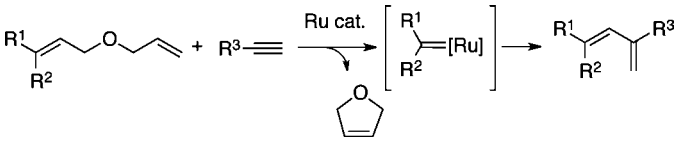
ABSTRACT



Ru cat. = Grubbs' catalysts

A relay strategy was employed to achieve an intermolecular ene–yne metathesis between 1,1-disubstituted alkenes and alkynes. The relay serves to activate an unreactive alkene which will not participate in ene-yne metathesis. The new relay cross ene–yne metathesis gives rise to 1,1, 3-trisubstituted-1,3-dienes previously inaccessible by direct ene–yne metathesis methods.

Ene–yne metathesis has become a useful method for carbon–carbon bond formation, used increasingly in complex molecule synthesis and with atom economy.[1] Mechanistic studies have shown that cross ene–yne metathesis requires a reactive alkene, capable of initiating with the ruthenium carbene catalyst. One of the most significant limitations in the alkene reactant is that posed by geminal disubstitution. Geminally substituted, or 1, 1-disubstituted, alkenes fail to react with alkynes in ene–yne cross metathesis. In this report, we have used the relay metathesis strategy[2] to achieve metathesis reactivity of geminally substituted alkenes in order to promote intermolecular ene–yne cross metathesis (Scheme 1a). This work is a unique application of relay metathesis which serves to expand the breadth of this important concept to include intermolecular reactions.

The relay metathesis strategy has not been used to overcome a substrate limitation in ene–yne metathesis. Relay metathesis was developed by Hoye and co-workers[2] as a means to differentiate the ends of a dienyne (Scheme 1c). In this case, a relay is used to initiate the cascade, thereby favoring the formation of one bicyclic product over another. In intramolecular (i.e., ring-closing) cases, relay metathesis has emerged as a powerful technology. For instance, in total synthesis applications of ring-closing metathesis (RCM) the relay strategy has been used to direct initation to a particular site.[2b,c] Applications in cross metathesis are limited.[3,4] We wanted to use relay metathesis to overcome poorly reactive alkenes for use in cross ene–yne metathesis.

(1) Enyne reviews: (a) Poulsen, C. S.; Madsen, R. *Synthesis* **2003**, 1–18. (b) Mori, M. Ene-Yne Metathesis. In *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, 2003; Vol. 2, pp 176–204. (c) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317–1382. (d) Diver, S. T. *Sci. Synth.* **2009**, *46*, 97–146. (e) Ring-closing enyne metathesis: Villar, H.; Frings, M.; Bolm, C. *Chem. Soc. Rev.* **2007**, *36*, 55–66.

(2) (a) Hoye, T. R.; Jeffrey, C. S.; Tennakoon, M. A.; Wang, J.; Zhao, H. *J. Am. Chem. Soc.* **2004**, *126*, 10210–10211. (b) Hoye, T. R.; Jeon, J.; Kopel, L. C.; Ryba, T. D.; Tennakoon, M. A.; Wang, Y. *Angew. Chem., Int. Ed.* **2010**, *49*, 6151–6155. (c) Hoye, T. R.; Jeon, J. In *Metathesis in Natural Product Synthesis*; Wiley-VCH Verlag GmbH & Co. KGaA: 2010; p 261.

(3) Relay RCM has been elegantly used in mechanistic studies involving metallotropic shift, which was subsequently followed by a cross alkene metathesis; see: Cho, E. J.; Lee, D. *Org. Lett.* **2008**, *10*, 257–259.

(4) In one case, we observed a relay closure and cross ene–yne metathesis in the same step: Clark, J. R.; French, J. M.; Diver, S. T. *J. Org. Chem.* **2012**, *77*, 1599–1604.

(5) There is only one example that we are aware of: (a) Watanabe, K.; Minato, H.; Murata, M.; Oishi, T. *Heterocycles* **2007**, *72*, 207–212. Using strain: (b) Clark, D. A.; Basile, B. S.; Karnofel, W. S.; Diver, S. T. *Org. Lett.* **2008**, *10*, 4927–4929.

(6) Geminal alkenes will give ring-closing (i.e., intramolecular) enyne metathesis with the right choice of catalyst; see: (a) Michrowska, A.; Bujok, R.; Harutyunyan, S.; Sashuk, V.; Dolgonos, G.; Grela, K. *J. Am. Chem. Soc.* **2004**, *126*, 9318–9325. (b) Boeda, F.; Clavier, H.; Nolan, S. P. *Chem. Commun.* **2008**, 2726–2740. For macrocyclization enyne metathesis benefits from relay assistance, see: (c) Zakarian, J. E.; El-Azizi, Y.; Collins, S. K. *Org. Lett.* **2008**, *10*, 2927–2930.

(7) The Grubbs model for cross alkene metathesis predicts poor initiation reactivity of geminal alkenes; see: Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.

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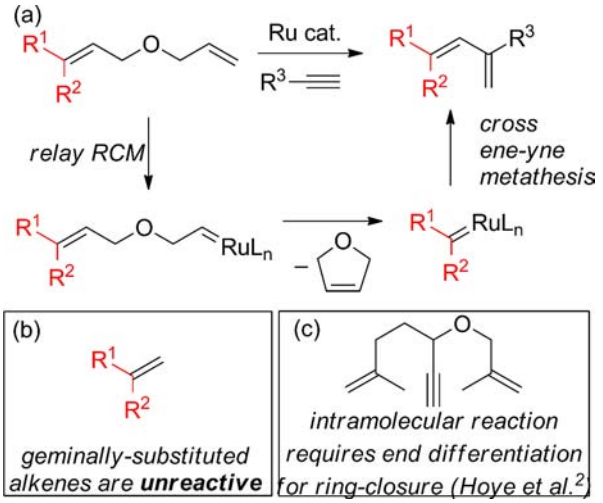
Scheme 1. The Relay Approach in Cross Ene–Yne Metathesis for Unreactive Geminally Substituted Alkenes

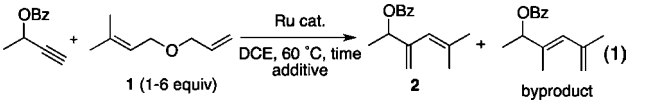


Geminally-substituted alkenes fail to give cross ene–yne metathesis.[5–7] The mechanism of ene–yne metathesis[8] requires that the alkene react with the Grubbs catalyst to form an alkylidene. If the alkylidene cannot form, then the catalytic ene–yne metathesis cannot proceed. The relay metathesis offers a potential solution if it can be used to direct carbene formation to an unreactive site and avert the formation of side products.[9]

The relay cross ene–yne metathesis was evaluated using different conditions in an effort to identify the optimum reaction conditions (eq 1). A significant concern was the number of equivalents of the relay substrate—too much could lead to cross ene–yne metathesis before RCM.[10] The optimization of reaction conditions is summarized in Table 1. As a starting point, it was discovered that the Hoveyda–Grubbs catalyst (**Ru1**) gave the relay ring-closing metathesis/cross ene–yne metathesis product in reasonable yield. Due to its volatility, the dihydrofuran was not observed after isocyanide quenching[11] and evaporative removal of volatiles. At higher temperatures, a byproduct was formed in significant amounts (eq 1). Increasing **1** had a negligible effect on yield. In entry 3, the Grubbs catalyst **Ru2** gave similar results as those obtained with **Ru1**. A decrease in catalyst loading and increase in alkene equivalents gave a reaction at rt, although it did not go to completion after a period of 1 h (entry 4). Shorter reaction times were favored because greater catalyst decomposition was expected after prolonged heating. The byproduct is thought to arise from a ruthenium hydride species generated *in situ* by catalyst decomposition.[12] Since fewer equivalents of **1** resulted in byproduct formation, we sought to accelerate the cross metathesis by using 2 equiv of **1** and to suppress the byproduct by use of 1,4-benzoquinone (BQ) as an additive. The use of BQ suppressed byproduct formation and was used to vouchsafe the 1,3-diene formed by the tandem relay ring-closing/cross ene–yne metathesis. Comparison of entries 5 and 6 show that inclusion of benzoquinone has a slightly beneficial effect on chemical yield. A further increase in the amount of BQ did not improve the yield (entry 7) nor did tetrachlorobenzoquinone (entry 8). The conditions in entry 5 were adopted as the standard conditions. Additional catalysts were screened, but none were found to be superior to the Hoveyda–Grubbs catalyst when considering the short reaction time.

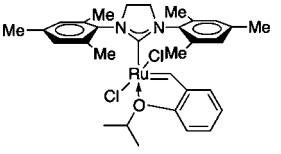
The relay-triggered delivery of geminal alkylidenes was found to be useful for a range of alkynes (Table 2). Using the optimized conditions found in Table 1, the cross ene–yne metathesis proceeded in good yield as evident from the crude ^{1}H NMR taken right after isocyanide quenching. In the first entry, the produced diene was formed in 83% yield and trapped by subsequent cycloaddition

Table 1. Optimization of the Relay Cross Ene–Yne Metathesis

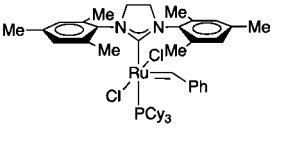


entry	Ru (mol %)	equiv **1**	time (h)	additive	yield **2**[a]	by-product
1	**Ru1** (10)	1	1	none	52%	20%
2[b]	**Ru1** (10)	1.5	1	none	48%	9%
3	**Ru2** (10)	1.5	1	none	48%	18%
4[c]	**Ru1** (5)	6	1	none	73%	0%
5	**Ru1** (7.5)	2	0.5	BQ (10 mol %)	83%	0%
6	**Ru1** (7.5)	2	0.5	none	73%	0%
7	**Ru1** (7.5)	2	0.5	BQ (25 mol %)	75%	0%
8	**Ru1** (7.5)	2	0.5	Cl_4BQ (10 mol %)	76%	0%

[a] NMR yield determined by integration vs mesitylene internal standard. [b] Entry 2 was run in toluene. [c] Entry 4 had 10% unreacted alkyne.



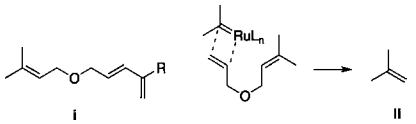
Ru1 (*Hoveyda-Grubbs*)



Ru2 (*Grubbs gen-2*)

(8) Galan, B. R.; Giessert, A. J.; Keister, J. B.; Diver, S. T. *J. Am. Chem. Soc.* **2005**, *127*, 5762–5763.

(9) Potential side reactions include cross ene–yne metathesis prior to relay ring-closing metathesis (giving **i**), poor cross selectivity (alkene vs alkyne, giving **ii**), and competing alkene isomerization.



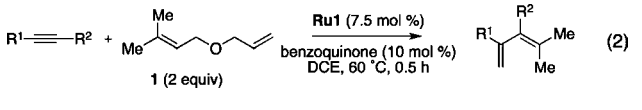
(10) Concentration was also optimized.

(11) Isocyanide quenching of metathesis reactions: Galan, B. R.; Kalbarczyk, K. P.; Szczepankiewicz, S.; Keister, J. B.; Diver, S. T. *Org. Lett.* **2007**, *9*, 1203–1206.

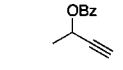
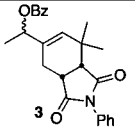
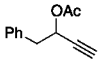
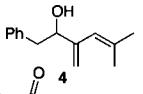
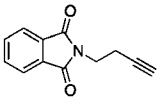
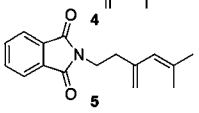
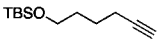
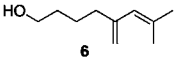
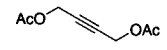
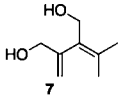
(12) Hong, S. H.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 17160–17161.

with *N*-phenylmaleimide. Due to the hydrophobic nature of the products, their separation from unreacted excess **1** was sometimes difficult. In those cases, a subsequent deprotection step was used to liberate the alcohol, which aided the purification step. In these cases (entries 2, 4, 5), the isolated yield is provided over two steps. The NMR yield taken after the metathesis step provides a good indication of the effectiveness of the metathesis. Branched and linear terminal alkynes performed equally well in the cross metathesis (entries 1–4). In one case, the reaction of an internal alkyne gave a lower yield in the metathesis step; the diene product was characterized after saponification of the acetates to aid purification from excess **1**.

Table 2. Alkyne Scope Study



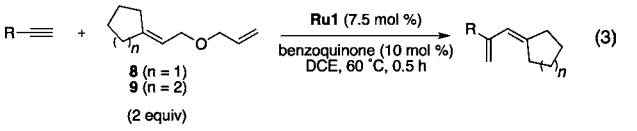
(2)

entry	alkyne	yield (NMR)[a]	isolated product	yield (isol)
1		83%	 **3**	72%[b]
2		81%	 **4**	67%[c]
3		80%	 **5**	66%
4		96%	 **6**	66%[c]
5		69%	 **7**	43%[c]

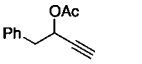
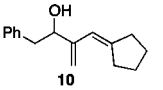
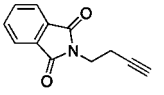
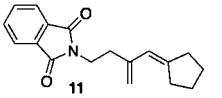
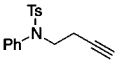
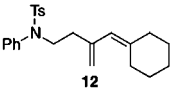
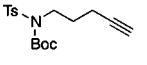
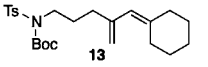
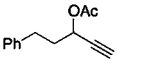
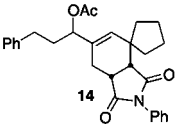
[a] NMR yield determined after the relay cross metathesis. [b] Isolated yield after Diels–Alder cycloaddition with *N*-phenylmaleimide ($PhCH_3$, 80 °C, 72 h). [c] Isolated yield after two steps.

Next, we considered relay cross metathesis as a vehicle to transfer cycloalkylidenes to external alkynes (Table 3). To activate these alkenes, an appended exocyclic allyl ether was required. Substrates **8** and **9** were easily prepared from the corresponding cycloalkanones by a Horner–Emmons–Wadsworth/reduction/allylation sequence which proceeded uneventfully. In the event, relay cross metathesis worked efficiently for a range of terminal alkynes (eq 3). Cyclopentylidenes were transferred by ene–yne metathesis to branched and unbranched alkynes (entries 1, 2) under the standard conditions found in Table 1, with 10 mol % benzoquinone present. Transfer of the cyclohexylidene proved more difficult (entries 3, 4). Presumably the increased steric hindrance imposed by the endocyclic allylic hydrogens (see **A**) impedes the ring closure step, decreasing the overall effectiveness of the tandem process. With the last example, the product was trapped through an *in situ* thermal Diels–Alder reaction giving cycloadduct **14**.

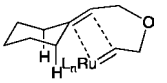
Table 3. Cycloalkylidene Transfer by Relay Cross Ene–Yne Metathesis



(3)

entry	alkyne	yield (NMR)[a]	isolated product	yield (isol)
1		81%	 **10**	51%[b]
2		72%	 **11**	62%
3		57%	 **12**	46%
4		50%	 **13**	43%[b]
5		75%	 **14**	52%[c]

[a] NMR yield after the relay metathesis step. [b] Isolated yield after two steps. [c] Isolated yield after two steps including Diels–Alder cycloaddition ($PhCH_3$, 80 °C, 36 h).

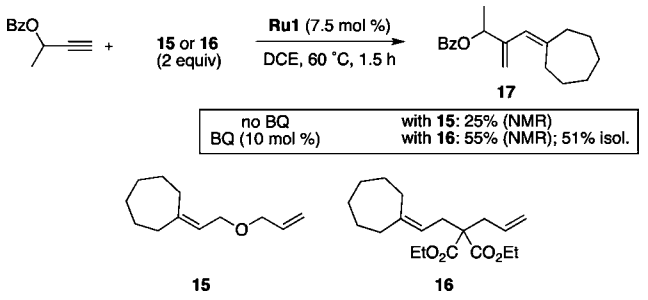


A

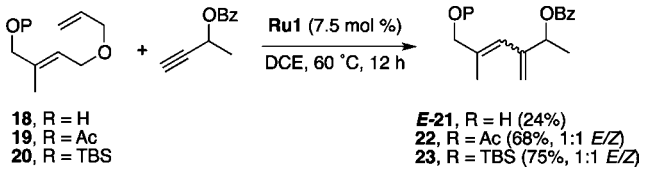
Following the cycloalkylidene transfers of Table 3, the attempted transfer of a cycloheptylidene led to use of an alternate relay (Scheme 2). Hoye had studied various relay tethers in his relay ring-closing metathesis reaction, mostly employing ethers and malonates.[2] These were mainly selected based on synthetic convenience, although Hoye has noted distinction of the malonate relay tether.[13] In our attempted cycloheptylidene transfers, the ether-containing tether **15** did not perform well; only 22% of the desired product was obtained (Scheme 2). The major reaction pathway was that of cross ene–yne metathesis, without the preemptive relay ring closure. This clearly suggested that the relay was not efficient enough. The malonate linker **16** was thus prepared and gave a much better yield of **17**. Benzoquinone was included and gave a slight improvement in chemical yield. The results were comparable to that obtained in the more difficult cycloalkylidene transfers of Table 3. A strain-driven cyclobutylidene transfer has been previously reported.[5b]

(13) Attributed to better ejection of the bound cycloalkene after the relay ring closure; see: Hoye, T. R.; Jeon, J.; Tennakoon, M. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 2141–2143.

Scheme 2. Cycloheptylidene Transfer



Scheme 3. Relay Transfer of Unsymmetrical Alkylidenes



Unsymmetrical geminal alkenes fitted with a relay tether also give cross ene−yne metathesis. These relay-activated alkenes were considered to be more difficult due to their potential to form geometrical isomers. This system was also used to probe allylic substituent effects in the geminal alkylidene transfer. In cross metathesis applications, the allylic substituent has a pronounced effect on reactivity.[14] For instance, allylic alcohols are thought to accelerate initiation of cross metathesis,[14a−c] whereas TBS ethers in the same position tend to retard reaction.[14d] Would steric and electronic factors impact the effectiveness of the relay cross ene−yne metathesis, when brought to bear on these proximal functional groups? Relay alcohol **18** was prepared by a four-step synthetic sequence and isolated as the *E*-isomer shown. The relay cross ene−yne metathesis proceeded in low yield, giving *E*-**21** in 24% isolated yield (Scheme 3). Including BQ did not significantly improve the reaction (data not shown). In the case of the acetate **19**, the chemical yield was significantly improved, and **22** was obtained as a 1:1 *E*/*Z* mixture. Use of the TBS ether could have impeded the relay ring closure; however it gave the best yield compared to the relay cross metathesis of **18** and **19**. For the allylic silyl ether **20**, steric bulk was not sufficient to influence the stereoselectivity of the cross ene−yne metathesis. Further substitution at the allylic center may be needed to obtain stereoselective alkylidene transfers.

In conclusion, the relay metathesis strategy has been used to promote cross ene−yne metathesis involving unreactive geminal alkene substrates. The relay provides a gain of alkene reactivity in an alkene substrate that normally lacks sufficient reactivity for cross metathesis. This reactivity gain expands the scope of the intermolecular ene-yne metathesis and elaborates the synthetic potential of the relay metathesis concept. Simple 1,1-disubstituted alkylidenes and cycloalkylidenes can be transferred using simple relay tethers that are easy to synthesize. Functional group effects were observed in the alkene undergoing intermolecular transfer. In some cases, higher temperatures resulted in positional isomerization of the 1,3-diene, but this could be minimized using benzoquinone as an additive.

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

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