Ruthenium-catalyzed tandem enyne metathesis/hydrovinylation†

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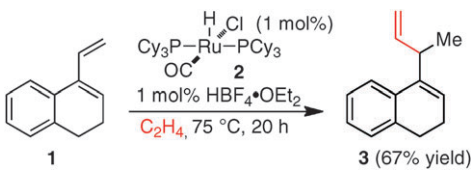
***In situ* modification of Grubbs' first-generation metathesis catalyst allows for a tandem enyne metathesis/hydrovinylation that is complementary to the regioselectivity of known ruthenium-catalyzed hydrovinylations.**

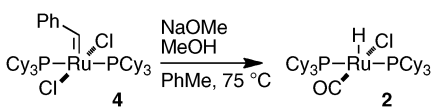
Olefin metathesis is a versatile carbon–carbon double bond-forming reaction that has been used widely in the preparation of complex organic compounds.[1] Tandem, concurrent, domino, or cascade processes that convert the alkene created through metathesis into other useful functionalities can provide even greater increases in molecular complexity with minimal added cost or waste.[2] While there are several examples of ruthenium-catalyzed tandem processes involving an olefin metathesis followed by hydrogenation,[3] isomerization,[4] or oxidation,[5] there are relatively few cases in which the subsequent metal-catalyzed reaction creates additional carbon–carbon bonds. Two examples include a tandem ring-closing olefin metathesis/Kharasch addition[6] and an enyne metathesis/cyclopropanation.[7] Both processes generate new carbon–carbon bonds through unique ruthenium-catalyzed mechanisms in a single reaction vessel. Considering the importance of streamlining synthetic sequences, we report herein a new tandem process that combines ruthenium-catalyzed enyne ring-closing metathesis with ruthenium-catalyzed 1,3-diene hydrovinylation.[8]

Yi and coworkers published several examples of hydrovinylations of 1,3-dienes using ruthenium hydride **2** as an effective catalyst (eqn (1)).[9]



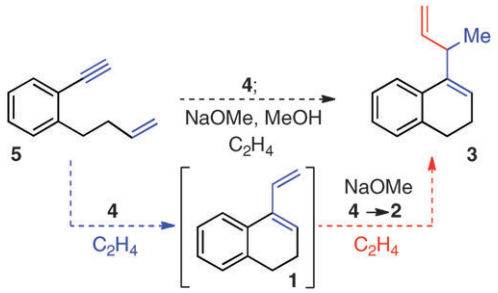
(1)

Considering that hydride **2** can be generated from Grubbs' olefin metathesis catalyst **4** (eqn (2)),[10] it should be



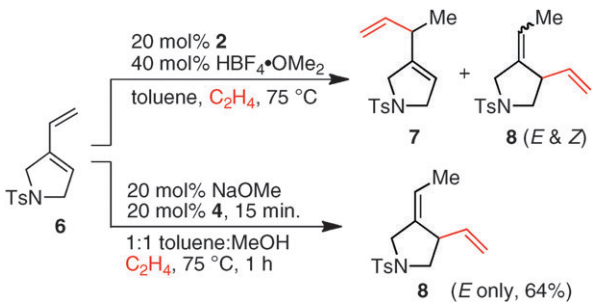
(2)

possible toeffect an enyne metathesis[11] with Grubbs' catalyst **4**, followed by a hydrovinylation of the resulting 1,3-diene **1** upon appropriate *in situ* modification of the ruthenium complex, as illustrated in eqn (3).



(3)

Initial studies towards realizing this tandem process focused on developing the hydrovinylation step. Unfortunately, control reactions with diene **6** showed poor selectivity using Yi's conditions.[9] Catalyst **2** in the presence of $HBF_4{\cdot}OMe_2$ led to the formation of multiple products, including the expected 1,2-hydrovinylation product **7** and both olefin isomers of the 1,4-hydrovinylation product **8**. In retrospect, this was not surprising, since Yi had reported similar results for dienes not conjugated with another π-system.[9] On the other hand, when diene **6** and ethylene were warmed in the presence of alkylidene **4** that had been treated with NaOMe in MeOH/toluene, the 1,4-hydrovinylation product **8** was formed exclusively as a single olefin isomer (eqn (4)).[12] Not only did this observation bode well for developing a "single-flask" olefin metathesis/hydrovinylation sequence, the unique regioselectivity complemented existing ruthenium-catalyzed hydrovinylations.[8]



(4)

The results for the tandem enyne metathesis/hydrovinylation sequence are summarized in Table 1. Readily accessible acyclic enynes that were known to undergo facile ring-closing metatheses were employed in this study.[11] Entry 1 illustrates the conversion of enyne **9** to 1,4-diene **8**. The overall efficiency and selectivity of the tandem sequence is comparable to the hydrovinylation reaction described in eqn (4).

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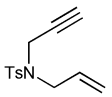
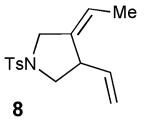
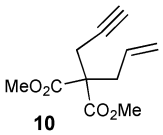
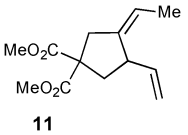
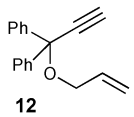
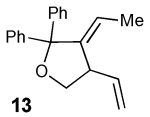
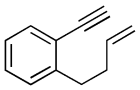
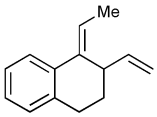
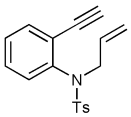
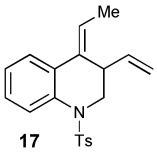
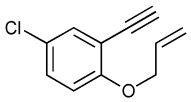
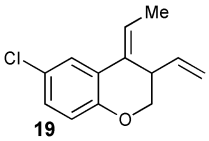
† Electronic supplementary information (ESI) available: Experimental procedure for enyne metathesis–hydrovinylation and characterization data for **8**, **11**, **13**, **15**, **16**, **17**, and **19**. See DOI: 10.1039/c0cc00008f

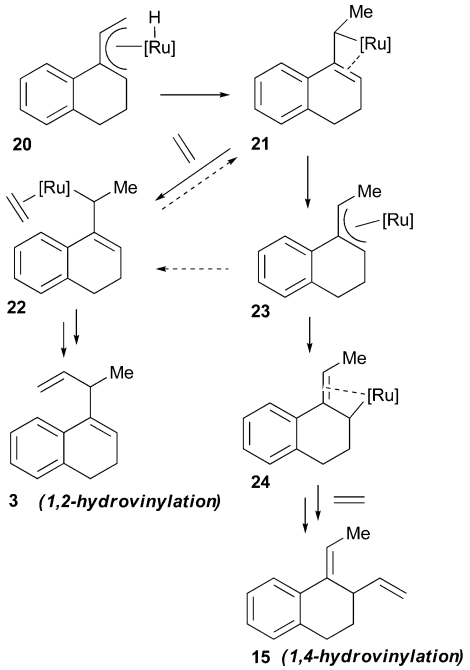
Table 1 Tandem, enyne metathesis/1,4-hydrovinylation

Entry	Enyne[a]	Product	Yield[13]
(1)	 **9**	 **8**	56%[b]
(2)	 **10**	 **11**	57%[c]
(3)	 **12**	 **13**	64%[d]
(4)	 **14**	 **15**	71%[e]
(5)	 **16**	 **17**	67%[e]
(6)	 **18**	 **19**	49%[e]

[a] Enyne metatheses were performed with 20 mol% **4** under 1 atm ethylene in toluene (0.20 M enyne) at 75 °C, followed by treatment with NaOMe (20 mol%, 0.04 M in MeOH for 10 min prior to hydrovinylation. [b] Hydrovinylation was run for 80 min. [c] Hydrovinylation was run for 180 min. [d] Hydrovinylation was run for 5.5 h. [e] Hydrovinylation was run for 90 min.

In general, the highest yields for the tandem process were obtained for enynes with a quaternary or sp^2-hybridized carbon adjacent to the alkyne. Under these conditions, enyne **12**, for example, is transformed to the expected 1,4-hydrovinylation product **13** in 74% isolated yield (64% yield based on 87% purity as indicated by GC analysis, entry 3). Similarly, aromatic enynes (*i.e.*, **14**, **16**, and **18**) are converted predominantly to 1,4-dienes (**15**, **17**, and **19** respectively) in 49–71% yields.[13] Some of the lower yields in these examples are likely due to the instability of the products upon work-up.[14] Albeit with elevated catalyst loading, the "single-flask" conversion of enyne **14** to diene **15** proceeded in higher overall yield than that reported for the stepwise sequence that leads to diene **3**.[9,11] While 1,4-adducts have been observed in cobalt-catalyzed hydrovinylations of 1,3-dienes,[12] to the best of our knowledge, 1,4-hydrovinylation of these type of dienes has not been reported previously.

It is possible to rationalize the selectivity of the hydrovinylation by considering the ruthenium intermediates proposed

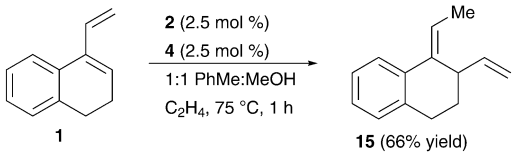


Scheme 1 Mechanism for 1,2- and 1,4-selective hydrovinylations.

by Yi and coworkers (Scheme 1).[9] The *E*-stereoselectivity could be established by initial coordination of ruthenium to the s-*cis*-diene (**20**), a conformation more favorable in substrates **12**, **14**, **16**, and **18**. Insertion of the terminal olefin into the ruthenium-hydride bond (**2**) could then provide σ-allyl species **21** that, upon coordination of ethylene, can form σ-allyl complex **22**, which leads to the 1,2-hydrovinylation product **3**. Alternatively, complex **21** can isomerize to σ-allyl complex **24** *via* π-allyl **23**, which then leads to the 1,4-hydrovinylation product **15**. Given the higher dilution of our reaction, the absence of HBF_4,[15] and the presence of a Lewis-basic co-solvent (MeOH), it is possible ethylene coordination to form intermediate **22** could be retarded, allowing for isomerization of the allyl intermediates (*i.e.*, **21** → **23** → **24**) prior to insertion of ethylene into the corresponding ruthenium–carbon σ-bond.

With this in mind, we examined if the conditions required to convert Grubbs' alkylidene **4** to complex **2** *in situ* accounted for the 1,4-hydrovinylation selectivity observed in our tandem process. Control reactions using ruthenium hydride **2** at higher dilutions in the presence of MeOH resulted in an extremely sluggish 1,4-hydrovinylation of diene **1** (2% conversion to **15** after 24 h). Formation of diene **3** was not observed, indicating that the presence of methanol may account for the selectivity, but not the reactivity of this system. Since NMR studies indicated that the conversion of alkylidene **4** to hydride **2** is incomplete on the time scale of the tandem sequence (*ca.* 50% conversion in 10 min.), a mixed catalyst system of **2** and **4** (2.5 mol % each) in methanol/toluene was then examined. In this case, the hydrovinylation of diene **1** resulted in complete consumption of starting material, generating **15** after 1 h (eqn (5)), matching both the reactivity and selectivity of the tandem process, even at reduced catalyst loadings.

Given these observations, a more complex mechanism than that outlined in Scheme 1 is likely involved.



(5)

In summary, we have developed a single-vessel, ruthenium-catalyzed, enyne metathesis/hydrovinylation sequence. Unlike other ruthenium-catalyzed hydrovinylations, this transformation proceeds stereoselectively with overall 1,4-addition of ethylene across the 1,3-dienes. Further studies into the selectivity, scope, and mechanism of this process, as well as applications to natural product synthesis, are currently underway.

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13 1,4-Hydrovinylation yields reported are based on isolated yields corrected for product purity as determined by GC analyses.

14 When multiple attempts using silica gel chromatography were used to improve product purity, increased levels of minor byproducts were observed by NMR and recovery of the desired 1,4-hydrovinylation products suffered significantly.

15 HBF_4 likely promotes the dissociation of PCy_3 (see ref. 8).

