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The allenic Alder-ene reaction: constitutional group selectivity and its application to the synthesis of ovalicin

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Abstract—The scope of the novel allenic Alder-ene reaction using Rh(I) and Ir(I) catalysts has been extended to differentially substituted 1,1,3-trisubstituted allenes. This allenyl substitution pattern can give three possible cross-conjugated triene products. The selectivity of this transformation can be controlled by varying reaction temperature, solvent, and catalyst. Progress toward the synthesis of ovalicin using this triene forming protocol is described.

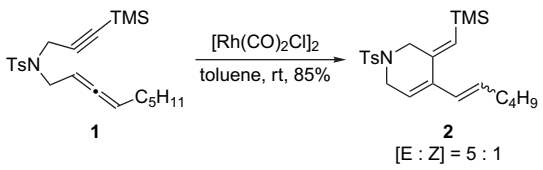
1. Introduction

Transition metal-catalyzed carbon–carbon bond formation is an efficient method to rapidly increase molecular complexity via skeletal reorganization and/or cycloaddition processes.[1] The mild conditions, functional group compatibility, and high regio- and stereoselectivities of these transition metal-catalyzed reactions are just a few reasons for their prominence in natural product synthesis. Transition metal-catalyzed cycloisomerizations such as the formal Alder-ene reaction utilize functionalized enynes or allenynes to access a unique array of cyclic structures.[2] For example, Trost[3] has worked extensively on the intramolecular Alder-ene reaction of 1,6-enynes using palladium or ruthenium to obtain 1,3- or 1,4-dienes, respectively. Ruthenium gives exclusively the 1,4-diene regioisomer while palladium gives regioisomeric ratios dependent on the substrate structure. Trost has also used ruthenium to effect an intermolecular Alder-ene allene–ene coupling to give diene substrates.[4] Buchwald[5] and Takacs[6] formed 1,4-dienes from enynes selectivity using either titanium or iron catalysts, respectively.

Intramolecular Alder-ene reactions of allene–ynes are not as widely studied and only a few examples are known. Both Malacria[7] and Livinghouse[8] used cobalt to effect an intramolecular allenic Alder-ene reaction. Malacria used this cycloisomerization reaction in a synthesis of steroidal analogs,[9] while the triene was obtained as a by-product in 33% yield by Livinghouse. Sato[10] demonstrated an allenic Alder-ene reaction using stoichiometric amounts of titanium.

Recently, rhodium has stepped into the limelight and proven itself as a useful and powerful transition metal catalyst for the Alder-ene reaction.[11] In 2000, Zhang demonstrated the first Rh(I)-catalyzed Alder-ene reaction with 1,6-enynes, yielding 1,4-dienes.[12] Rhodium was beneficial over ruthenium, cobalt, or iron because reactions could be performed at room temperature and the ligands on the catalyst could be easily tuned to accommodate steric or electronic factors in the substrates.[13]

We have previously reported the reaction of Rh(I) with allenynes to produce cross-conjugated trienes. One example is shown in Scheme 1, where allenyne **1** affords an 85% yield of triene **2**.[14] This formal allenic Alder-ene reaction is unique from others because the reaction conditions are used to direct which double bond of the allene reacts. For example, Malacria[7] and Sato[10] reported the same reactivity pattern using cobalt and titanium, respectively; however, π-bond selectivity was obtained using substrate control (sterics and ring strain).[15] Rhodium, unlike other transition metals, was found to give selective cyclization with the distal double bond of the allene regardless of the substitution pattern on the allene or tether length.[16]



1 **2**
[E : Z] = 5 : 1

Scheme 1. Rh(I)-catalyzed allenic Alder-ene reaction.

Cross-conjugated trienes are seldom found in the literature, which may be attributed to a lack of general procedures for

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the formation of these highly unsaturated systems.[17] Brummond et al. have shown that the formal Alder-ene reaction gives high yields of trienes with moderate *E*/*Z* selectivity for a variety of substrates and that rhodium biscarbonyl chloride dimer is a general catalyst. The *E*/*Z* selectivity was increased by changing the neutral Rh(I) catalyst to a cationic Rh(I) or Ir(I) catalyst; altering selectivity from 5:1 to 13:1 or 99:1, respectively.[14]

The high yields and mild conditions of the Rh(I)-catalyzed allenic Alder-ene reaction motivated us to examine its value in natural product synthesis. The application of this carbocyclization process to the ovalicin/fumagillol class of sesquiterpenoids was the most exciting, due in part to the potentially rapid access to the entire carbocyclic skeleton and the interesting biological activity associated with these compounds (Fig. 1).

Fumagillin (**5**), ovalicin (**4**), and analogs of these compounds have been shown to inhibit angiogenesis in vivo.[18] Angiogenesis is essential for tumor growth and by suppressing this process the tumor does not grow beyond a few cubic millimeters, nor does it metastasize.[19] Fumagillol (**3**) and the analog TNP-470 (**6**) have been found to have an inhibitory effect on the growth and metastasis of various cancers including breast, colon, gastric, renal, ovarian, and prostate.[20] It is known that endothelial cells play a necessary role in angiogenesis, and both ovalicin and TNP-470 were found to inhibit endothelial cell proliferation. However, the mechanism of action for this inhibition is still unclear. Clardy[21] illustrated that fumagillin, ovalicin, and TNP-470 covalently bind to a cobalt-containing enzyme called methionine amino peptidase (MetAP-2), but do not bind to the closely related MetAP-1. It is significant that this binding is selective since inhibition of both MetAP-1 and MetAP-2 is lethal.[22] Methionine amino peptidase-2 removes methionine residues from the N-termini of proteins in a critical co-translational processing event and there is a strong correlation between inhibition of endothelial cell proliferation and inhibition of MetAP-2.[23] However, the significance of the binding is still under great debate since recently it was reported that MetAP-2 function is independent of endothelial cell production.[24] Despite the enigmatic mechanisms of action for these natural products, they are still under investigation in the biological and clinical sector and are synthetically popular targets.[25]

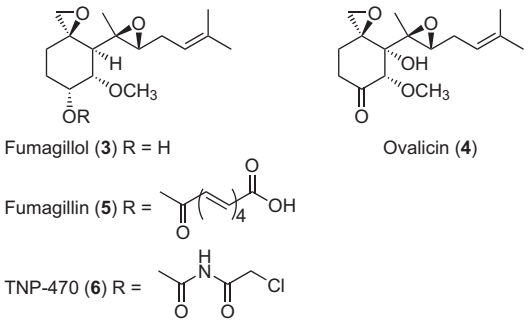


Figure 1. Structure of fumagillol, fumagillin, TNP-470, and ovalicin.

Corey was the first to synthesize (±)-ovalicin in 1985 in 12 steps. After the novel formation of an epoxy ketone, he stereoselectively added the lithiated diene to give the desired carbocyclic skeleton (Fig. 2).[26] Subsequently, Corey published an asymmetric synthesis of ovalicin by preparing the epoxy ketone via an asymmetric dihydroxylation reaction.[27] Bath[28] and Barco[29] gain access to (−)-ovalicin by manipulating naturally occurring optically pure building blocks L-quebrachitol and (−)-quinic acid, respectively. The most recent syntheses of (−)-ovalicin were reported by Takahashi who starts with a simple sugar, D-mannose, while also featuring ring closing metathesis and Hayashi whose approach is similar to that of Corey.[30]

Our retrosynthetic analysis of ovalicin (**4**) is outlined in Scheme 2. Conversion of **7** to ovalicin will be accomplished by a stereoselective hydroxyl directed epoxidation of the double bond, and conversion of the primary hydroxyl group into the terminally trisubstituted double bond via an oxidation and homologation sequence similar to the strategy used by Taber in his synthesis of fumagillin.[31] The highly functionalized cyclohexanone **7**, in turn, can be prepared via a series of selective oxidations carried out on triene **8**.

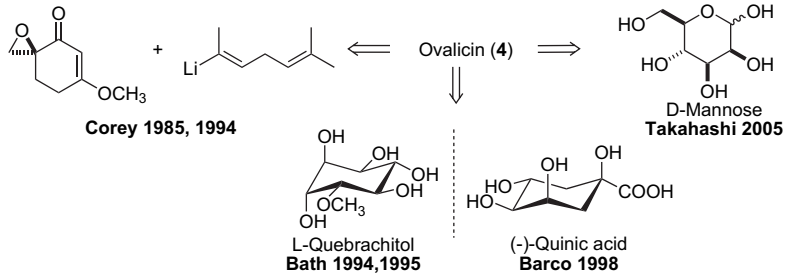
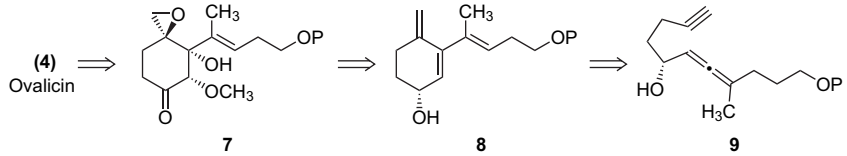


Figure 2. Previous synthetic strategies.



Scheme 2. Retrosynthetic analysis of ovalicin (**7**).