Rhodium-catalyzed tandem cyclization–cycloaddition reactions of enynebenzaldehydes: construction of polycyclic ring systems†

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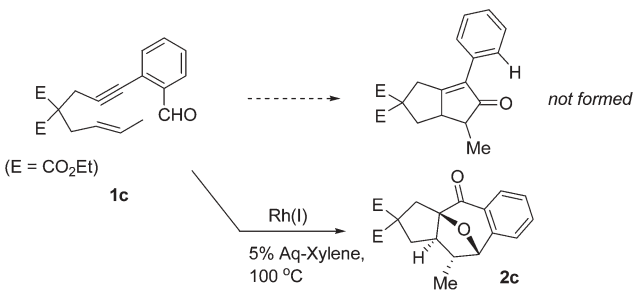
***o*-(1,6-Enynyl)benzaldehydes underwent a novel mode of cycloaddition using Rh(I)-precatalyst, *via* [3 + 2] cycloaddition of presumed dipolar carbonyl ylide intermediate generated by Rh-catalyst and the utility of this mechanistically intriguing enyne cyclization can be found in a number of polycyclic natural product skeletons.**

Transition metal-catalyzed cyclizations of enynes and related π-precursors has been an area of intense study in past decades, and has emerged as one of the most expeditious and versatile routes for construction of carbo- and heterocyclic compounds of medicinal and materials interest.[1] In an important subset of these reaction, *i.e.* [1 + *m* + *n*] cycloaddition, Rh(I)[2] complex has played a pivotal role in generating various modes of cyclization, such as [2 + 2 + 1], [5 + 2 + 1], and [4 + 2 + 2], *etc*.[3] We now report our discovery of novel Rh(I)-catalyzed cycloaddition among appropriately tethered alkyne, alkene, and aldehyde functionalities (Scheme 1).

In connection with our interest in the metal-catalyzed cyclization of enynes,[4] we were originally intrigued by the possibility of intramolecular Pauson–Khand-type transfer carbonylation of *o*-(1,6-enynyl)benzaldehyde **1c**. In this vein, we treated **1c** with $Rh(PPh_3)_3Cl$ in xylene at 120 °C for 6 h (entry 1, Table 1). Surprisingly, we found the unusual polycyclic compound **2c** formed in 34% yield instead of the expected Pauson–Khand-type product, along with decomposed unidentified products. The structural identification and stereochemical assignment of **2c** followed from ^1H, ^{13}C, COSY, HSQC, and 1-D NOE NMR experiments and finally from HRMS.[5,6] From the screening of catalyst precursors and ligand, it was found that combination of $[Rh(COD)Cl]_2$ and dppp gave the highest yield of **2c** (entries 1–3), while use of cationic Rh(I) complex gave inferior conversion



Scheme 1

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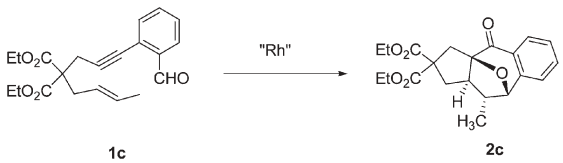
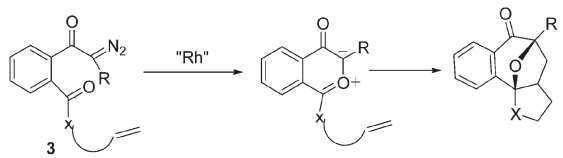
(entry 5). It is noteworthy that cyclization proceeds more effectively in the presence of a small amount of water. For example, treatment of **1c** with $[Rh(COD)Cl]_2$ (5 mol %) and dppp (10%) in refluxing aqueous xylene (containing 5 wt% H_2O) gave **2c** in 86% yield, while the same reaction in dry xylene (dried over Na) led to extensive decomposition of the starting material (entries 3, 4, and 7, Table 1). Among commercially available Rh-complexes tested, 5 mol % of $[Rh(COD)Cl]_2$ along with dppp (10%) gave the highest conversion in 5% aqueous xylene (86% yield, entry 7, Table 1).

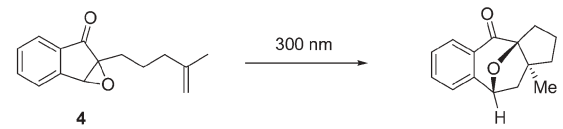


(1)

It is also interesting to note that Padwa *et al.* and Feldman *et al.* independently reported the formation of the polyoxacyclic skeleton of **2c** from α-diazocarbonyl compound **3** *via* intermediacy of carbonyl ylide generated under Rh(II)-catalysis, and from photochemical reaction of α,β-epoxyketone **4** (eqn (2) and (3)), respectively.[7] The present reaction has apparent advantages in that (1) multiple bonds formed efficiently from readily available starting material, leading to complex polyoxacyclic skeleton, and (2) the reaction is highly atom-economical. Several natural products can be projected to be generated from this methodology, including barbatusol, pisiferin, faveline, and xochitlolone.[8]



(2)



(3)

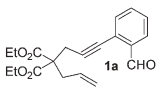
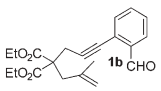
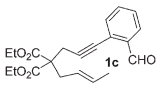
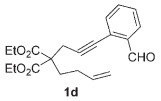
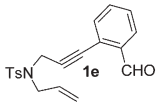
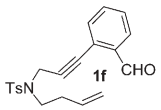
In order to demonstrate the scope of present reaction, we prepared various *o*-(enynyl)benzaldehydes **1a–g** and tested these substrates under our optimized conditions: $[Rh(COD)Cl]_2$ (5 mol%), dppp (10%) in 5% aqueous xylene (Table 2). The reaction is highly tolerant of the substitution pattern in alkene and both terminal as well as internal alkenes **1c** underwent efficient cyclization (Table 2, entries 2 and 3) in satisfactory yields without any isomerization. Heteroatoms enyne (Table 2, **1e–1f**) can be well accommodated in the present methodology (Table 2, entries 5–7). Finally, 1,7-enyne substrates **1d** and **1f** substrates gave higher

Table 1 Reactions of **1c** with various metal complexes under different solvents

Entry	Catalyst[a]	Conditions	Yield[b] (%)
1	$Rh(PPh_3)_3Cl$	xylene (commercial), 120 °C, 6 h	34[c]
2	$[Rh(CO)_2Cl]_2$	xylene (commercial), 120 °C, 0.5 h	45[c]
3	$[Rh(COD)Cl]_2$/dppp	xylene (commercial), 120 °C, 12 h	81
4	$[Rh(COD)Cl]_2$/dppp	xylene (dired over Na), 120 °C, 48 h	decomposition
5	$[Rh(COD)Cl]_2$/dppp/AgOTf	5% aq. xylene, 120 °C, 6 h	63[c]
6	$Pd(PPh_3)_4$	5% aq. xylene, 120 °C, 24	No reaction
7	**$[Rh(COD)Cl]_2$,/dppp**	**aq. 5% aq. xylene, 110 °C, 12h**	**86**

[a] At 5 mol% Rh. 10% of ligand (if any). [b] Isolated yields. [c] The rest of material was decomposed product.

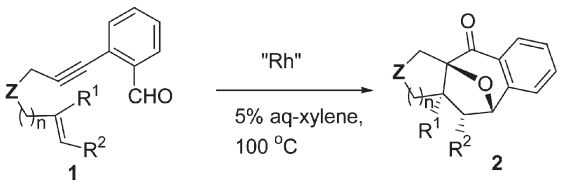
Table 2 Reactions of various *o*-enynebenzaldehydes **1a–g**

Entry	Substrate (1)	Temp (°C)/Time (h)	Product **2**	Yield (%)
1		100, 12	**2a**	83
2		100, 12	**2b**	76
3		100, 12	**2c**	86
4		110, 12	**2d**	68
5		80, 8	**2e**	87
6		80, 8	**2f**	81

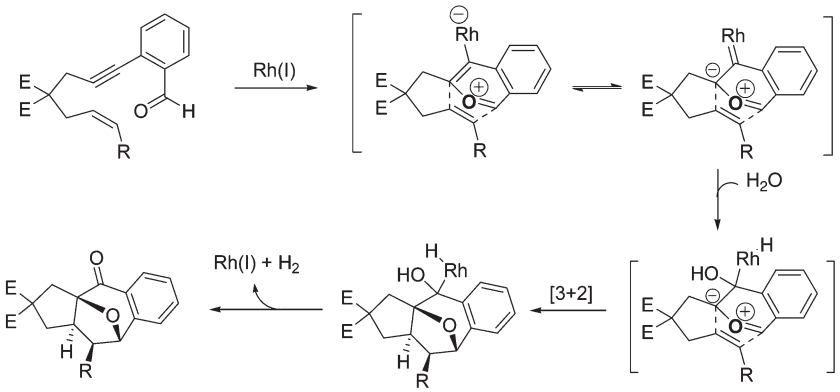
homologs **2d** and **2f** smoothly, albeit in slightly diminished yields (Table 2, entries 4 and 6).

While detailed mechanism should await further study, we suggest Scheme 2 as a working hypothesis. We postulated the formation of **2** is initiated by activation of alkyne by Rh(I) species to generate Rh-carbenoid carbonyl ylide (Scheme 2).[9,10] Successive *tandem* [3 + 2] cycloaddition with tethered alkene would lead to the observed oxabicyclic product **2**. Addition of water could occur at any stage, regenerationg Rh(I) and molecular hydrogen. Yamamoto *et al.* recently reported that similar substrates undergo Au(III)-catalyzed [4 + 2] cycloaddition to give benzannulation product.[11] Presumably, fine reactivity control by putting *gem*-disubstituent directs the reaction manifold into [3 + 2] cycloaddition instead of [4 + 2] pathway.

In summary, we have demonstrated a highly efficient, atom-economical route to various polycyclic compounds from *o*-(enynyl)benzaldehydes. Further study aimed at elucidating this novel and mechanistically intriguing mode of cyclization is currently underway. We are also pursuing the applications of this methodology for the construction of various polycyclic natural product skeletons.



(4)



Scheme 2 Proposed mechanism of Rh(I)-catalyzed polycyclization.

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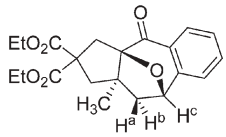
5 **General Experimental Procedure for the preparation of compound 2a–g**: Into a 10 mL round bottomed flask was taken: 1 mmol of enynebenzaldehyde, 5 mol% $[Rh(COD)Cl]_2$, dimer and 10 mol% of dppp. To this, 5% aqueous xylene (2 mL) was added through a glass syringe. The reaction mixture was first stirred for 10 min at room temperature and then kept in a preheated oil bath at 100–110 °C. After completion of the reaction, it was cooled, diluted with diethyl ether and filtered through celite. The solvent was evaporated and subjected to column chromatography to obtain the pure compound.

6 A representative stereochemical assignment of **2b** is shown below, which is based on the coupling constants (400 MHz for ^1H) and NOE experiments. The molecular model indicates H^a–C–C–H^c dihedral angle of **2b** of *ca.* 20°, and H^b–C–C–H^c of 90 °C. 1-D NOE experiments are consistent with this stereochemistry.



2b

Protons	Coupling constants	1D-NOE information
H^a-H^c	J = 7.0 Hz	1.7 % (irradiation of H^c)
H^b-H^c	J = ~0 Hz	0.3 % (irradiation of H^c)
H^a-Me		1.9 % (irradiation of Me)
H^b-Me		~0 % (irradiation of Me)

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