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Rhodium-Catalyzed Cycloisomerization of *N*-Propargyl Enamine Derivatives

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Since the pioneering studies of Stork,[1] enamines have remained among the most widely used nucleophiles for the construction of C−C bonds under mild reaction conditions. The profound impact of enamine chemistry on organic synthesis is well manifested by its widespread utility in a variety of reactions.[2] While a broad range of electrophiles, such as alkyl and acyl halides, aldehydes, and Michael acceptors, have been employed in reactions with enamines, the use of enamines in transition metal catalysis is surprisingly rare, limited to the processes involving a metallo-π-allyl intermediate.[3] Given the exceptional scope of enamine and transition metal chemistry, the merger of these two domains would embrace immense potential for the development of new synthetic methodologies.

It has been established that alkynes can be mobilized by coordination with transition metals to form vinylidene complexes and undergo catalytic 1,1-addition processes.[4] In connection with our interest in transition metal vinylidene-mediated catalysis,[5] we were intrigued by the potential of enamines to engage in a reaction with metal vinylidene complexes that would lead to C−C bond formation (Scheme 1). While such a notion could be complicated by a possible pericyclic process involving the C_α=C_β bond (path A),[6] we envisioned that direct addition of the enamine to the C_α=M bond would produce a zwitterionic intermediate that might allow for catalyst turnover via proton shunting,[7] thus accomplishing a C−C bond-forming cyclization (path B).[8] In this communication, we report the Rh(I)-catalyzed cycloisomerization of *N*-propargyl enamine derivatives that enables the efficient synthesis of six-membered azacycles, important structural motifs ubiquitously encountered in a number of natural products as well as pharmaceutical agents.

The evaluation of our proposition was initiated by testing the reaction of enamide **1** with the rhodium catalyst system proven for vinylidene complex generation (Table 1).[10] Upon treatment with $[Rh(C_2H_2)_2Cl]_2$/P(4-F−C_6H_4)$_3$ in DMF at 85 °C for 24 h, enamide **1** was transformed into its cyclic isomer **2** in 30% yield (entry 1). Despite the low yield, the formation of the Alder-ene product **2** as a single isomer was promising and led us to speculate that the reaction would be sensitive to conditions affecting the migration of proton. Indeed, the yield and rate of the reaction were enhanced by the addition of bases (entries 2−5). In the presence of DABCO, the reaction could be performed at ambient temperature to provide **2** in 95% yield (entry 6). Further screening experiments revealed nonpolar solvents to be poor media for the reaction, suggesting the intermediacy of a polar species (entries 8−10).

Having established the optimal reaction conditions, we next examined the scope of the reaction with an assortment of substrates (Table 2). The survey showed that the rhodium-catalyzed protocol is feasible with a wide variety of *N*-propargyl enamine derivatives to afford the corresponding cyclization products in good yields. While the electronic variation of the *N*-benzoyl group had little influence on the efficiency or selectivity of the reaction, the *N*-tosyl group completely reoriented the selectivity to the formation of the isomeric *endo*-1,3-diene **13** (entries 1 vs 2). Dihydropyridines **14**−**18** were obtained as the exclusive products when the formation of

Scheme 1. Reactions of Transition Metal Vinylidene with Enamine

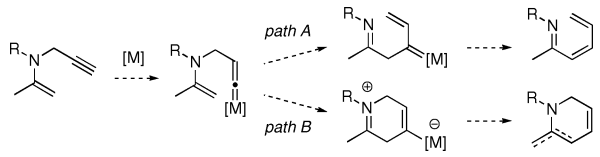
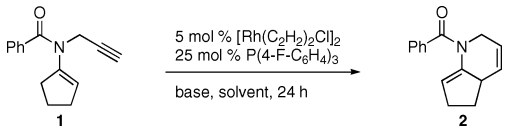


Table 1. Rh-Catalyzed Cycloisomerization of Enamide **1**[a]



1 **2**

entry	base	solvent	temp (°C)	conversion (%)	yield[b] (%)
1		DMF	85	100	30
2	2,6-DTBP[c]	DMF	85	100	40
3	TEA	DMF	85	100	45
4	DBU	DMF	85	100	93
5	DABCO	DMF	85	100	95
6	**DABCO**	**DMF**	**25**	**100**	**95**
7	DABCO	DMSO	85	100	85
8	DABCO	toluene	85	<10	trace
9	DABCO	THF	85	<10	trace
10	DABCO	CH_2Cl_2	85	<10	trace

[a] All reactions were performed with 0.2 mmol of enamide **1** and base at 0.1 M for 24 h. [b] Isolated yield. [c] 2,6-DTBP = 2,6-di-*tert*-butylpyridine.

the exo-isomer could create strain (entry 3) or was inaccessible (entries 4−7). It is worth noting that deactivated enamines **7**−**9** also participated well in the cyclization process, although a higher reaction temperature (85 °C instead of 25 °C) was required in these cases (entries 5−7). Notably, substrates possessing a propargylic stereogenic center underwent facile cyclization to furnish single regio- and diastereomers **19** and **20** in excellent yields (entries 8 and 9).

The new cycloisomerization process is amenable to the expedient assembly of indolizidine and quinolizidine skeletons from readily available building blocks. As depicted in Scheme 2, the requisite *N*-propargyl enamides **21** and **23** were prepared in single steps by three- and four-component coupling reactions.[11] Under the standard rhodium-catalyzed conditions, the monocyclic enamides **21** and **23** were cleanly converted to their bicyclic isomers, which, upon exposure to H_2 (1 atm) in the same pot, underwent chemoselective hydrogenations to give rise to **22** and **24** in 60 and 83% yields, respectively. Considering the synthetic flexibility of the multicomponent coupling approach and the operational simplicity of the two-stage rhodium catalysis, this sequence should allow for expeditious entry to a diverse array of 1-azabicyclo[4.4.0] and [4.3.0] frameworks that constitute a major class of physiologically important alkaloids.[12]

While further investigations are currently in progress for a detailed understanding of this reaction, a simple mechanistic picture may be put forward in which two catalytic cycles account for the observed regiochemical dichotomy (Scheme 3). It is proposed that the reaction is initiated by the formation of a rhodium vinylidene

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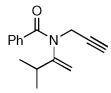
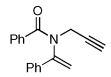
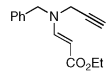
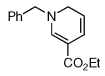
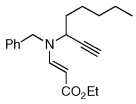
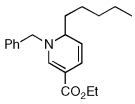
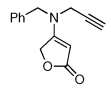
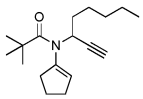
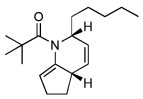
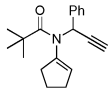
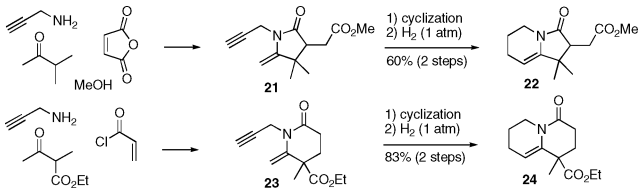
Table 2. Rh-Catalyzed Cyclization of *N*-Propargyl Enamines[a]

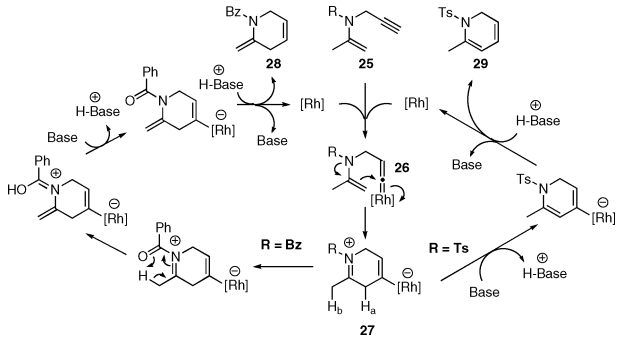
entry	reactant	product	yield[b] %
1	 **3a** R = *p*-NO_2-Bz **3b** R = *p*-Br-Bz **3c** R = *p*-MeO-Bz		**12a** 82 **12b** 90 **12c** 93
2	 **4**		**13** 83
3	 **5**		**14** 81
4	 **6**		**15** 67
5[c]	 **7**		**16** 53
6[c]	 **8**		**17** 69
7[c]	 **9**		**18** 52
8[d]	 **10**		**19** 95
9[d]	 **11**		**20** 99

[a] All reactions were performed with 5 mol % of $[Rh(C_2H_2)_2Cl]_2$, 25 mol % of P(4-F−C_6H_4)$_3$, and 1.0 equiv of DABCO in DMF (0.1 M) at 25 °C for 24 h unless otherwise noted. [b] Isolated yields. [c] The reaction was conducted at 85 °C. [d] Obtained as single diastereomers.

Scheme 2. Synthesis of Indolizidine and Quinolizidine Skeletons



Scheme 3. Proposed Mechanism for Cycloisomerization



complex **26** and subsequent addition of the pendant enamine to the α-carbon of the vinylidene. In the case of R = Bz, the resulting zwitterion **27** undergoes a 1,5-H shift prior to the deprotonation−protodemetalation sequence to form the 1,4-diene **28**, whereas selective removal of an endocyclic proton (H_a) takes places with the *N*-tosyl substrate (R = Ts) to result in the formation of a 1,3-diene **29**.

The reaction described in this paper represents a new mode of reactivity arising from the union of an enamine and a nonclassical electrophile (rhodium vinylidene). The unique mechanistic feature permits a broad spectrum of *N*-propargylic enamines to undergo an unprecedented cycloisomerization that produces six-membered azacyclic products under simple and mild reaction conditions.

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

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