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Rhodium-Catalyzed Stereoselective Formation of *Z*-Enamines from Allylaziridines

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Enols, metal enolates, and enamines are the most important carbon nucleophiles in both biological and chemical synthesis.[1] Many useful reactions owe their efficiency to selective formation of *E* or *Z* metal enolates (Figure 1). In contrast, the chemistry of enamines is limited to reactions of the *E*-isomers. The reason is simple: a classical condensation between an amine and a carbonyl compound is an equilibrium process that affords the thermodynamically more stable *E*-isomer. Transition-metal-catalyzed approaches to enamines include metal-catalyzed isomerization of *N*-allylamines,[2] amination of alkenyl halides,[3] hydroamination of alkynes,[4] and oxidative amination of olefins.[5] Likewise, all of these methods give the thermodynamic product. There are no useful, kinetically controlled, reactions that result in *Z*-enamine formation. Although strong base-promoted isomerization of *N*-allylamines to *Z*-enamines have been reported,[6] attempts to isolate the *Z*-product result in *Z*-to-*E* isomerization and/or hydrolysis. The present contribution examines an unexpected rhodium-catalyzed route to chromatographically stable *Z*-enamines from *N*-allylaziridines. Since the aziridine ring is widely considered to be a stepping stone to other amines via diverse ring-opening processes,[7] this chemistry may find useful synthetic applications.

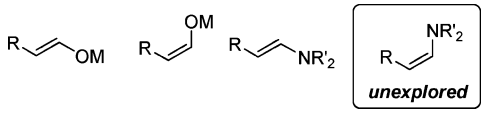


Figure 1. Carbon nucleophiles of fundamental significance.

We recently reported that unsubstituted aziridines undergo facile palladium-catalyzed allylic amination with allyl acetates and carbonates in good to excellent yields and with high enantioselectivities.[8] The allylaziridines thus obtained were chosen for transition-metal-catalyzed allylic isomerization. Cationic Rh(I) diphosphine complexes[2a,9] are known to induce selective isomerization of *N*-allylamines into *E*-enamines. A generally accepted mechanistic description of the reaction is depicted in Scheme 1.[2a] Upon C−H activation at the allylic position, organometallic species **A**, stabilized through iminium complex **B**, is generated. Subsequent hydride migration to the terminal olefinic carbon affords intermediate **C** which undergoes decomplexation, releasing the enamine product. As an indirect piece of evidence of iminium complex formation, cationic rhodium(I) catalysts failed to isomerize allylamines derived from ethylene imine.[10] With our new approach to allylaziridines,[8] we investigated the isomerization of *N*-allylcyclohexene imine **1a** with 1.5 mol % of [Rh(BINAP)(COD)]OTf as the source of rhodium(I) prepared in situ from $[Rh(COD)_2]OTf$ and *rac*-BINAP in THF (60 °C, 16 h). In contrast to previous reports, we did obtain the *N*-(1-propenyl)aziridine **2a**, albeit with a low 25% conversion. Interestingly, unexpected selectivity for the *Z*-isomer **2a** was observed (Table 1, entry 1).[11] There was no evidence for isomerization into the *E*-isomer in the course of isolation.[12] The enamine **2a** was isolated as a chromatographically stable oil.

Scheme 1

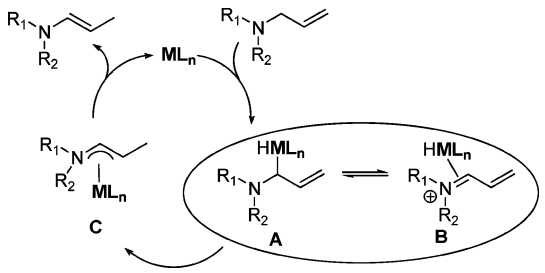
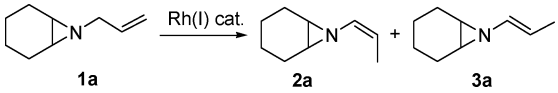


Table 1. Effect of Rhodium(I) Source and Temperature on Isomerization of *N*-Allylaziridine **1a** to *N*-Alkenylaziridines **2a** and **3a**[a]



entry	catalyst	temp (°C), time (h)	conv. (%)[c]	*Z*/*E* selectivity (%)[c]
1[b]	[Rh(BINAP)(COD)]OTf	60, 16	25	60:40
2	$RhH(CO)(PPh_3)_3$	60, 0.2	100	85:15
3	$RhH(CO)(PPh_3)_3$	20, 3	100	92:8
4	$RhH(CO)(PPh_3)_3$	−78, 24	100	95:5

[a] [Substrate] = 0.7 M, [substrate]/[Rh] = 66 in THF under nitrogen. [b] Prepared in situ from $[Rh(COD)_2]OTf$ and 2 equiv of *rac*-BINAP. [c] Determined by GC.

When we evaluated $RhH(CO)(PPh_3)_3$[13] as the source of Rh(I) in our system, full conversion of *N*-allylcyclohexene imine **1a** to enamine **2a** was achieved in THF in just over 10 min. The *Z*-stereoselectivity was increased to 95:5 when the reaction was performed at −78 °C (Table 1, entries 2−4). The same selectivity was observed in toluene and dichloromethane. The double bond migration consistently afforded high *Z*-selectivity with other substrates giving *N*-(1-propenyl)aziridines in excellent isolated yields (Table 2). The GC analysis of *N*-allylcyclohexene imine **1a** isomerization, performed with 1.5 mol % of $RhH(CO)(PPh_3)_3$ in THF at room temperature, indicated that *E*- and *Z*-isomers do not interconvert under the reaction conditions.[14] Substitution at the allylic position was found to slow the reaction presumably due to higher barrier for initial C−H activation. Notably, subjecting allyl morpholine to the $RhH(CO)(PPh_3)_3$-catalyzed isomerization resulted in exclusive formation of the *E*-enamine.

A mechanistic scenario consistent with the observed kinetic *Z*-selectivity would involve C−H bond activation to give intermediate **D**, hydride migration, and C−H bond reductive elimination from metallocycle **E** (Scheme 2, path a).[15] This deviation from the accepted tertiary allylamine isomerization mechanism (Scheme 2, path b) would result from kinetic inaccessibility of the intermediate **F**.

A glimpse into intriguing and potentially useful properties of the *Z*-aziridine enamines was obtained in a preliminary study of

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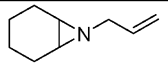
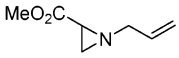
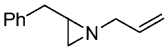
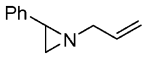
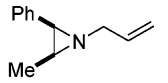
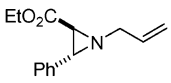
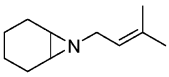
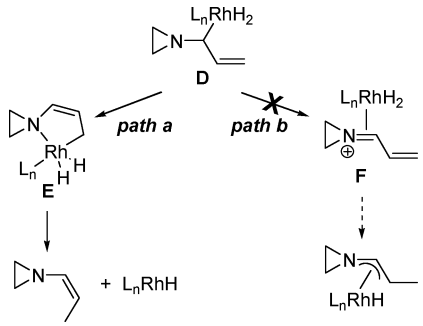
Table 2. Substrate Scope for Isomerization of *N*-Allylaziridines to *N*-Alkenylaziridines with $RhH(CO)(PPh_3)_3$ Catalyst[a]

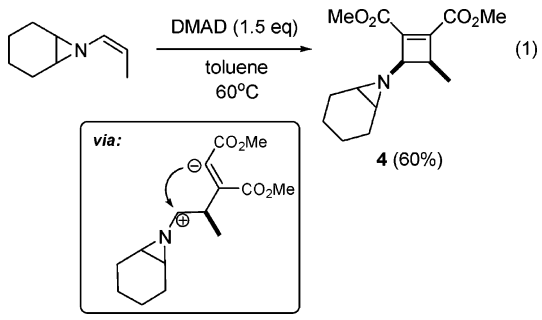
entry	substrate		conv. (%)[b]	*Z*/*E* selectivity(%)[b]
1		**1a**	100	95:5
2[c]		**1b**	100	82:18
3[d]		**1c**	100	76:24
4[e]		**1d**	100	91:9
5		**1e**	100	96:4
6[c]		**1f**	80	75:25
7[f]		**1g**	trace	-

[a] [Substrate] = 0.7 M, [substrate]/[Rh] = 66 at −78 °C in THF under nitrogen. [b] Determined by GC. [c] [Substrate]/[Rh] = 10 at 60 °C, 72 h. [d] [Substrate]/[Rh] = 20 at 60 °C, 24 h. [e] [Substrate]/[Rh] = 66 at 20 °C, 24 h. [f] Only the starting material was recovered.

Scheme 2



cycloaddition with DMAD (dimethyl acetylene dicarboxylate). The *syn* cyclobutene stereoisomer **4** was isolated in 60% yield upon heating (*Z*)-7-(prop-1-enyl)-7-azabicyclo[4.1.0]heptane **2a** with DMAD (eq 1). The preservation of *syn* stereochemistry implies that the cycloaddition mechanism involves a zwitterionic intermediate with a lifetime that is short relative to rotation around the C−N bond, which would have generated the more stable *E*-isomer.[16]



(1)

In summary, we have uncovered a novel and highly selective rhodium-catalyzed pathway from allylaziridines to stable *Z*-enamines. The observed stereoselectivity favors the formation of *Z*-isomers not seen with other systems that produce the thermodynamically more stable *E*-enamines. This simple process should facilitate metal-catalyzed access to *Z*-enamines, which belong to an under-explored class of carbon nucleophiles of fundamental significance (Figure 1). Synthetic applications and detailed mechanistic studies of these reactions are underway.

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

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(14) See Supporting Information for details.
(15) A mechanism involving β-hydride elimination is less likely as it is known to proceed with *E*-selectivity (see ref 2b).
(16) A concerted pathway cannot be ruled out at this point.

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