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Rh^I-Catalyzed Cycloisomerization of Vinyl Bicyclopropyl Compounds to Azabicyclo[3.2.2]nona-2,8-dienes

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Nitrogen-containing azabicycles are an important class of structural motif ubiquitous in natural alkaloids. New synthetic methods for these compounds are thus of immense importance to the pharmaceutical field.[1] During our ongoing endeavor searching for a new transition-metal-catalyzed reaction pathways, we recently discovered that azabicyclo-[3.2.2]nona-2,8-diene (**1a**) could be synthesized via Rh^I-catalyzed cycloisomerization of vinyl bicyclopropyl (VBC) derivatives.

The azabicyclo[3.2.2]nona-2,8-diene is a higher homologue of tropane alkaloids[2] such as cocaine and atropine. Moreover, it is also an analogue of morphinomimetic isopavines (Figure 1).[3] These kinds of natural opioid alkaloids are known to function in the central nervous system (CNS) by strong binding to G-protein-coupled receptors (GPR).[4] The detailed mechanism of the interactions between GPR and binding ligands in the CNS remains elusive, though a variety of chemical modifications of such opioid alkaloids are necessary not only for drug addiction treatments but also for potential remedies for neurological disorders such as Alzheimer's and Parkinson's disease, as well as depression and schizophrenia.[5]

Although there have been a number of synthetic approaches for the construction of the azabicyclo[3.2.2]nona-2,8-diene skeleton, they are still limited.[2,6] As far as we are aware, the catalytic formation of azabicyclo[3.2.2]nona-2,8-dienes from the VBCs is the first observation of this kind. Herein we communicate the synthesis of such compounds from VBCs in the presence of a Rh^I catalyst and also present the result of DFT calculations about the reaction mechanism.

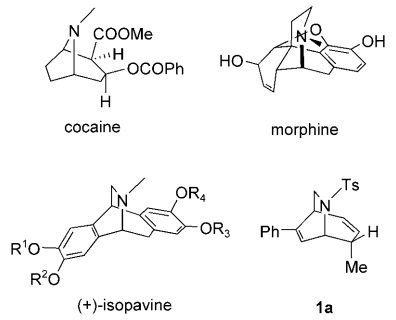
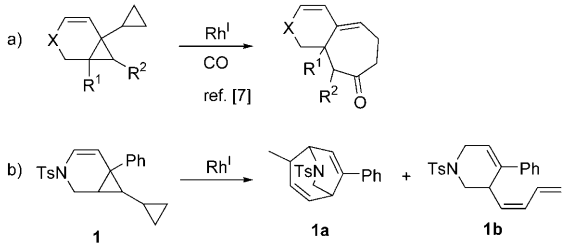


Figure 1. Structures of cocaine, morphine, (+)-isopavine, and **1a**.

Recently, we reported a Rh^I-catalyzed carbonylative [3+3+1] cycloaddition of the VBC derivatives under atmospheric CO condition (Scheme 1a).[7]



Scheme 1. Rh^I-catalyzed cyclization of modified VBC (7-cyclopropyl-3-azabicyclo[4.1.0]hept-4-enes, CABH).

When a structurally modified VBC (7-cyclopropyl-3-azabicyclo[4.1.0]hept-4-enes, CABH)[8] bearing a phenyl group at 6-position (**1**) was applied to the catalytic reaction in the presence of Rh^I catalyst without CO pressure, a new

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type of an azabicyclo[3.2.2]nona-2,8-diene (**1a**), which structure was confirmed by an X-ray diffraction study (Figure 2), was produced along with a concomitant formation of a triene derivative (**1b**). Being an interesting molecule **1a** as described earlier, the observation of such a compound with a subtle modification of the reaction conditions from our previous work encouraged us to investigate this reaction in more detail.

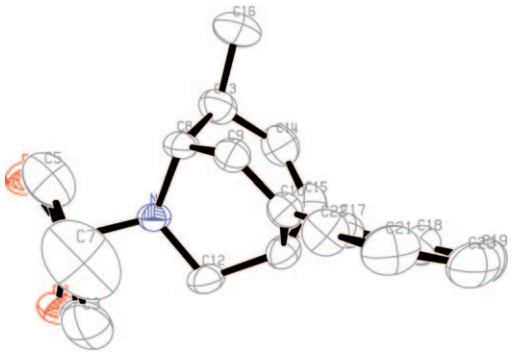


Figure 2. X-ray crystallographic structure of **1a**.[12]

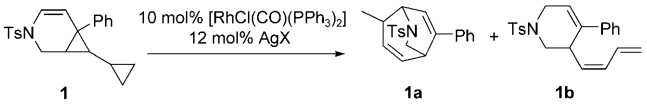
Firstly we attempted to establish the reaction conditions that would yield **1a** rather than **1b**. The optimized reaction conditions were readily achieved after a number of screening processes (Table 1). The reaction was not catalyzed by the use of $[RhCl(CO)(PPh_3)_2]$ nor $AgSbF_6$, giving rise to the recovery of the starting material (entries 1 and 2). The desired compound **1a** was produced only when the Rh^I species was used which was generated in situ by $[RhCl(CO)(PPh_3)_2]/AgSbF_6$. An initial attempt with this catalyst system in 1,2-dichloroethane at 80 °C gave 64 % of **1a** with 15 % of **1b**. When toluene was used, the results were even worse. Only 36 % of **1a** with a comparable amount of **1b** (21 %) was produced along with the recovery of the reactant (41 %, entry 4). In 1,4-dioxane, the result was similar to that obtained in 1,2-dichloroethane (entry 6).

The yield of **1a** was greatly improved when the reaction temperature was elevated. The best yield (96 %) was achieved in 1,4-dioxane at 100 °C (entry 7). In toluene, raising the reaction temperature to the refluxing point did improve the yield of **1a**. Moreover, the formation of **1b** still persisted. Employing $AgBF_4$ or AgOTf instead of $AgSbF_6$ gave rather poor results (entries 8 and 9). Any attempts to reduce catalyst amount were not successful (entry 10).

Under the optimized reaction conditions, we tested cycloisomerization reactions with a series of VBCs (Table 2). The 7-cyclopropylbicyclo[4.1.0]hept-4-ene derivatives used in this study (**1**–**14**) were readily obtained by $PtCl_2$-catalyzed cycloisomerization of the corresponding enynes (Scheme 2).[9]

Various 7-cyclopropyl-6-aryl-3-azabicyclo[4.1.0]hept-4-ene derivatives with a substituent at the *para*-position of 6-aryl group could participate in the reaction (entries 2–6). Although varying degrees of electronic effects by these substituents were seemingly obvious, a clear trend in the prod-

Table 1. Optimization of Rh^I-catalyzed transformation of **1** to **1a** and **1b**.[a]

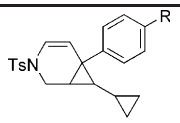
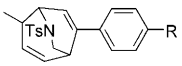
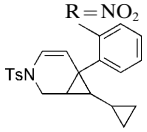
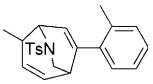
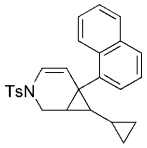
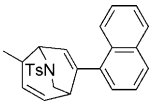
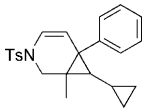
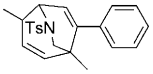
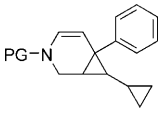
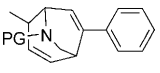
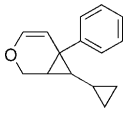
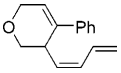


1 1a 1b

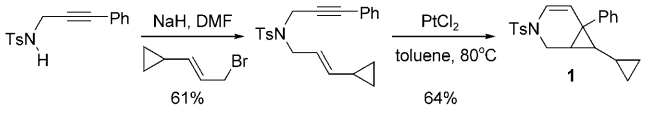
Entry	AgX	Solvent	T [°C]	Yield [%]		
				1	**1a**	**1b**
1[b]	–	$ClCH_2CH_2Cl$	80	87		
2[c]	$AgSbF_6$	$ClCH_2CH_2Cl$	80	73		
3	$AgSbF_6$	$ClCH_2CH_2Cl$	80		64	15
4	$AgSbF_6$	toluene	80	41	36	21
5	$AgSbF_6$	toluene	110		72	7
6	$AgSbF_6$	1,4-dioxane	80		65	20
7	$AgSbF_6$	1,4-dioxane	100		96	
8	$AgBF_4$	1,4-dioxane	100		82	
9	AgOTf	1,4-dioxane	100		60	
10[d]	$AgSbF_6$	1,4-dioxane	100		85	

[a] Conditions: 10 mol % $[RhCl(CO)(PPh_3)_2]$, 12 mol % AgX, solvent (6 mL), 24 h. [b] Without AgX. [c] Without Rh catalyst. [d] 5 mol % $[RhCl(CO)(PPh_3)_2]$, 6 mol % $AgSbF_6$.

Table 2. Rh^I-catalyzed cycloisomerization to **a**.[a]

Entry	Substrate	Product	Yield [%]
			
1	R = H	**1**	96 (**1a**)
2	R = Me	**2**	68 (**2a**)
3	R = OMe	**3**	76 (**3a**)
4	R = Cl	**4**	92 (**4a**)
5	R = Br	**5**	95 (**5a**)
6	$R = NO_2$	**6**	75 (**6a**)
7		**7**	 48 (**7a**)[b]
8		**8**	 43 (**8a**)
9		**9**	 77 (**9a**)
			
10	PG = Ms	**10**	94 (**10a**)
11	$PG = PhSO_2$	**11**	61 (**11a**)
12	PG = Cbz	**12**	44 (**12a**)
13	PG = Boc	**13**	19 (**13a**)[c]
14		**14**	 55 (**14b**)[d]

[a] Conditions: 10 mol % $[RhCl(CO)(PPh_3)_2]$, 12 mol % $AgSbF_6$, 1,4-dioxane (6 mL), 100 °C, 18 h. [b] 20 % of the reactant was recovered. [c] 46 % of the reactant was recovered. [d] 2 h.



Scheme 2. Preparation of modified VBCs (7-cyclopropylbicyclo-[4.1.0]hept-4-enes).

uct yield was not observed for this series. The yield of the reaction seemed to be affected by the steric effect rather than by the electronic effect of the 6-aryl group. When the aryl group was *o*-tolyl, the yield was only 48% with a 20% recovery of the reactant (entry 7). In case of 1-naphthyl group, the desired product was obtained in 43% (entry 8). Another important factor that affects the reaction yield was the nature of the protecting group on the nitrogen tether (see entries 1, 10–13). When sulfonyl groups were used as protecting groups, the yield was moderate (entry 11, 61%) to high (entry 1, 96% and entry 10, 94%). However, substrates with carbamate protecting groups gave rise to low yields (entry 12, 44% and entry 13, 19%). In contrast to the N-tethered substrates, a triene **14b** was isolated in 55% yield for an oxygen-tethered substrate **14** (entry 14).

To elucidate the reaction mechanism, we performed DFT calculations.[10] Initially, a cationic $[Rh(CO)(PPh_3)_2]$ might coordinate to the CABH. This complex can enter the catalytic cycle by losing one phosphine ligand since a 14-electron Rh species is commonly accepted as an active catalyst in the Rh^I-catalyzed cycloaddition of vinyl cyclopropanes (VCPs).[11] Thus we started the calculation from the structure formed by the complexation between CABH and $[Rh(CO)(PPh_3)]$. Among many possible conformations of the reactant state, **PR** was chosen based on the previously reported structural information of the CABH with an *R* configuration at the C7 atom.[8c] This conformation leads to oxidative addition of the C1-C6-C7 cyclopropyl (CP) ring exclusively leaving another CP ring (C8-C9-C10) peripheral. The $(\eta^1$-alkyl$)(\eta^3$-allyl$)Rh^{III}$ intermediate (**PI1**) was formed (Figure 3). This type of the catalytic initiation of VCP by Rh^I catalyst has been revealed via DFT study by Houk et al.[11a] Successive cleavage of the peripheral CP ring gives rise to another $(\eta^1$-alkyl$)(\eta^3$-allyl$)Rh^{III}$ intermediate (**PI2**), which then evolves to $(\eta^2$-alkenyl$)(\eta^3$-allyl$)Rh^{III}H$ (**PI3**) via β-hydride elimination. The β-hydride elimination step requires 37.4 kcal mol^{-1} of activation free energy, which is the highest among the six transition states involved in the catalytic cycle, and thus be a rate-determining step. The **PI3** has a trigonal bipyramid geometry with the hydride being positioned at the axial *trans* to the carbonyl group. **PI4** is the intermediate structure where the repositioning of the hydride atom necessary for the subsequent metal-to-ligand hydride transfer is conducted. At **PI4**, the distance between the metal hydride and terminal C10 atom becomes only 2.44 Å, short enough for the efficient hydride transfer reaction to occur. The final step of the cycle can be best described by migratory reductive elimination with an activation free energy of only 9.1 kcal mol^{-1}. Demetalation of the catalyst wraps up the catalytic cycle.

In summary, we have demonstrated that VBC can be efficiently transformed to azabicyclo[3.2.2]nona-2,8-dienes in the presence of a Rh^I catalyst. The overall reaction pathway obtained by the DFT calculations shows the catalytic cycle can be described as 1) complexation between Rh^I catalyst and CABH, 2) oxidative addition by the CP ring cleavage, 3) migratory insertion of the second CP ring, 4) β-hydride elimination, 5) rearrangement of the hydride, 6) metal-to-ligand hydride transfer, 7) migratory reductive elimination, and 8) demetalation. Further efforts on the synthetic utility of the reactions as well as more detailed mechanistic investigations that include the conformation dependent mechanistic variation are in progress.

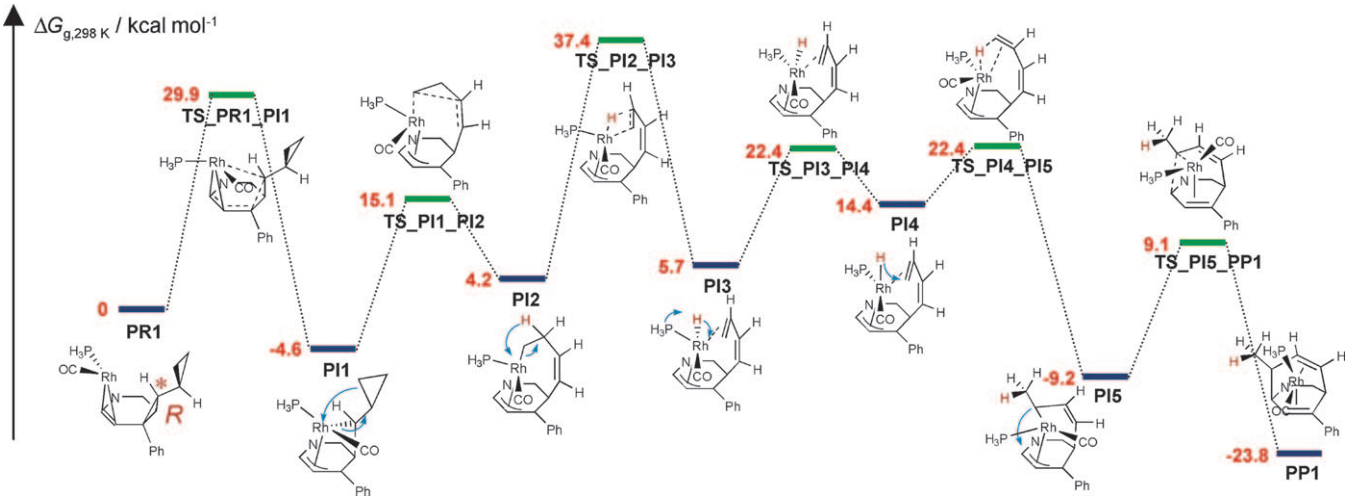


Figure 3. Free energy reaction profile of Rh^I-catalyzed transformation of CABH to azabicyclo[3.2.2]nona-2,8-dienes. Geometries of all stationary points are optimized structures via DFT at the B3LYP/6-31G(d) and LANL2DZ level. Zero-point energy (ZPE) corrected free energies calculated in gas phase are given in kcal mol^{-1}.

Experimental Section

General procedure: $[RhCl(CO)(PPh_3)_2]$ (0.03 mmol), $AgSF_6$ (0.04 mmol) and 1,4-dioxane (2 mL) were added to a tube-type Schenk flask equipped with a stirring bar and capped with a rubber septum. The reaction mixture was stirred at room temperature for 5 min. Then a substrate (0.3 mmol) and 1,4-dioxane (4 mL) were added to the flask. The resulting mixture was stirred until the substrate was completely disappeared (as checked by TLC) at 100 °C. The reaction products were purified by flash chromatography on a silica gel column eluting with *n*-hexane/ethyl acetate (v/v, 6:1).

Acknowledgements

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Keywords: alkaloids · bicyclic compounds · cycloisomerization · rhodium

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[9] The synthetic procedures and spectroscopic data of new compounds are summarized in the Supporting Information.

[10] In the computational model, the PPh_3 ligand was represented by PH_3. Tosyl group at the nitrogen atom was replaced with H. For more details about the calculations, see the Supporting Information.

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[12] CCDC-716233 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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