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Rh-Catalyzed Reductive Cyclization of Enynes Using Ethanol as a Source of Hydrogen

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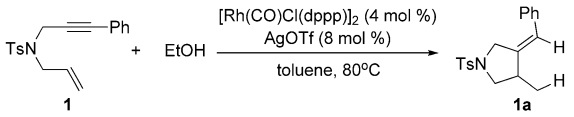
The catalytic hydrogenation has been established as a powerful and mechanistically novel strategy for carbon–carbon bond formation and is in the spotlight of synthetic chemists. In particular, Krische and co-workers played a major role in developing hydrogenation as a new method for catalytic cross-coupling.[1] Hydrogen is the cleanest and most cost-effective chemical reducing agent. Recent environmental concerns about green chemistry have prompted us to find a substitute for hydrogen. Thus, we envisioned an in situ generation of hydrogen from easily available and nontoxic chemicals and finally chose ethanol as the source of hydrogen in the absence of any oxidants.[2] The oxidant-free catalytic dehydrogenation of alcohols is well known in the presence of homogeneous[3] and heterogeneous catalysts.[4] However, the use of the in situ generated hydrogen in the hydrogen-mediated C–C bond formation is relatively rare.[1c,5] In most cases, *i*PrOH has been used as a hydrogen source. The generation of hydrogen from alcohols has been studied[6] and sometimes the generated hydrogen has been used in hydrocarbonylation reactions.[7] To yield any hydrogen-mediated C–C bond formation, a cascade of two conceptually different catalytic reactions should occur, for example, a hydrogen generation from ethanol and a hydrogenative carbon–carbon bond formation, in the presence of one or two catalysts.

Recently, there has been a demonstration of a strategy involving multifunctional catalysts in a one-pot to cooperatively catalyze a chemical reaction, which broadens the reaction scope within organic synthesis.[8] In reductive cyclization, a variety of metal compounds from base metals, such as iron and nickel to expensive and precious metals including rhodium, platinum, and palladium have been used as the catalyst.[1,9] When a palladium compound is used as a catalyst, a hydride donor such as $HSiEt_3$ has to be added. In the case of a nickel-catalyzed reaction, excess iPr_2Zn has to be added. Until now, there has been no report on the use of hydrogen generated from ethanol in the reductive cyclization. In some cases, the generated hydrogen is used in the hydrogen-transfer reaction.[10] However, they are irrelevant to a C–C bond formation. Recently, the C–C bond formation by borrowing hydrogen (dehydrogenative alcohol activation) has been developed.[11] As far as we are aware, this is the first practical use of hydrogen generated from ethanol in the reductive cyclization of enynes. An enantioselective reductive cyclization in the presence of hydrogen gas and rhodium catalyst had been reported[9b] several years ago and ethanol has been used in diene hydro-hydroxyethylation.[12] Herein we communicate our preliminary results.

According to the previous study,[13] $[Rh(CO)Cl(dppp)]_2$ is one of the best rhodium compounds in sequential dehydrogenation of ethanol and decarbonylation of acetaldehyde. However, it is well known[9a] that cationic rhodium complexes display good activity in reductive cyclization. Thus, to enable both reactions to proceed smoothly, a combination of $[Rh(CO)Cl(dppp)]_2$ and AgOTf (2 equiv) was our first trial as a catalyst (Scheme 1).



Scheme 1.

We carried out the initial study using **1** as the substrate. As shown in Scheme 1, treatment of **1** in the presence of a catalytic amount of $[Rh(CO)Cl(dppp)]_2$/AgOTf (4 mol %) in toluene/EtOH (2 mL/0.5 mL) at 80 °C for 18 h gave a reductive cyclization product **1a** in 54 % yield with a 40 % recovery of the reactant. Thus we confirmed that ethanol could be used as a hydrogen source in the reductive cyclization of **1**. Most known dehydrogenation reactions of ethanol are in the presence of heterogeneous catalysts.[14] However, in our reaction, the dehydrogenation of ethanol occurred in the presence of the homogeneous catalyst under mild reaction conditions. Furthermore, no cycloisomerized product was observed in the reaction of **1**.

Encouraged by the above result, enyne **1** was chosen as a model substrate, and $[Rh(cod)Cl]_2$/AgOTf was used as a catalyst for the optimization of reaction conditions. Initial investigations (Table 1, entries 1, 2, and 9–11) were focused on finding optimal solvents, and we found that solvent effect played a crucial role in obtaining good activity. The best yield (86 %) was obtained in $EtOH/H_2O$ (2.0 mL/0.2 mL)

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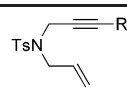
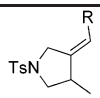
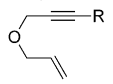
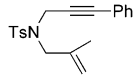
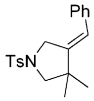
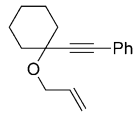
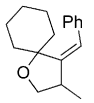
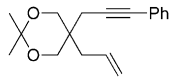
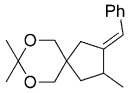
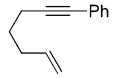
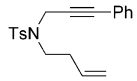
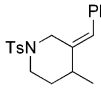
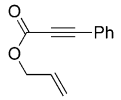
Table 1. Reaction of **1** under various reaction conditions.[a]

Entry	Additive	EtOH [mL]	Toluene [mL]	*t* [h]	**1a** [%][b]
1	dppp	0.5	2	18	54 (40)[c]
2	dppp	2	0.5	18	61[d]
3	dppe	0.5	2	24	n.r.
4	dppf	0.5	2	24	n.r.
5	BIPHEP	0.5	2	12	52[d]
6	bipyridyl	0.5	2	12	n.r
7	dcyhpp	0.5	2	12	n.r.
8	Xantphos	0.5	2	12	n.r.
9	dppp/H_2O (0.1 mL)	2	0	12	40 (50)[c]
10	dppp/H_2O (0.2 mL)	2	0	12	86[d]
11	dppp/H_2O (0.5 mL)	2	0	12	10 (80)[c]

[a] **1** (0.15 mmol), Rh dimer complex (4 mol%), AgOTf (8 mol%), and phosphine additive (8 mol%) were reacted in EtOH/toluene solvent. [b] Isolated product yield. [c] Recovered starting materials. [d] A mixture of dimers was obtained. dppe = 1,3-bis(diphenylphosphino)ethane; dppp = 1,3-bis(diphenylphosphino)propane; dppf = 1,1′-bis(diphenylphosphino)ferrocene; BIPHEP = 2,2′-bis(diphenylphosphino)-1,1′-biphenyl; dcyhpp = 1,3-bis(dicyclphexylphosphino)propane; Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene.

Table 2. Rh-catalyzed reductive cyclization of various enynes using ethanol.[a]

Entry	Reactant		Conditions[b]	Product		Yield [%][c]
						
1	R = 4-$C_6H_4OCH_3$	**2**	A		**2a**	84
2	4-C_6H_4Cl	**3**	A		**3a**	76
3	naphthyl	**4**	A		**4a**	88
4	CH_3	**5**	A		**5a**	48
						
5	R = phenyl	**6**	A		**6a**	92
6	3,5-$C_6H_3(CH_3)_2$	**7**	A		**7a**	78
7		**8**	B		**8a**	49[d]
8		**9**	B		**9a**	72
9		**10**	B		**10a**	64
10		**11**	B		**11a**	76
11[e]		**12**	B		**12a**	36[d,f]
12		**13**	B		**13a**	59

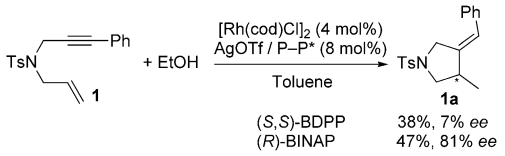
[a] Compound **1** (0.15 mmol), $[Rh(cod)Cl]_2$ (4 mol%), AgOTf (8 mol%), and dppp (8 mol%) were reacted at 80°C for 12 h. [b] Condition A: The reaction was carried out in a mixture of ethanol (2 mL) and water (0.2 mL); B: The reaction was carried out in a mixture of ethanol (0.5 mL) and toluene (2.0 mL). [c] Isolated product yield. [d] Reactant recovered. [e] Reaction time: 36 h. [f] The product was obtained with small amount of an unknown byproduct.

solution. Various additives (Table 1, entries 1 and 3–8) were subsequently evaluated for catalyst activation. Apart from BIPHEP, other additives were detrimental and no reaction was observed. A catalytic system, $[Rh(cod)Cl]_2$/BIPHEP/AgOTf, gave **1a** and **1b** in 52 and 45% yields, respectively. A brief survey of other metal complexes such as $[Ir(cod)Cl]_2$/L (L = dppp, PPh_3), and $[Ir(cod)Cl]_2$/dppp/AgOTf gave no appreciable amount of the reaction product. Thus, the catalytic system $[Rh(cod)Cl]_2$/dppp/AgOTf was the best choice. One important point to note about this is that the yield of the reaction is highly sensitive to the order of addition of the rhodium complex, the substrate, and the solvent. When the substrate was added to the alcohol solution of the rhodium catalyst, a relatively high yield was observed. However, when the alcohol was added to the mixture of the rhodium catalyst and the enyne substrate, almost no reductive cyclization was observed. We envisioned that a catalytically active rhodium species would be generated from a reaction between the rhodium catalyst and alcohol. However, a reaction of the rhodium catalyst with the enyne substrate generated a stable rhodium species, resulting in no catalytic reaction.

With the optimal reaction conditions in hand, we thus examined the scope of the multicatalytic dehydrogenation of ethanol and reductive cyclization of a variety of 1,5-enynes (Table 2). One of two reaction conditions was used depending upon the solubility of a substrate in ethanol. When the substrate showed a good solubility in ethanol, the reaction was carried out in a mixture of ethanol and water (2.0 mL/0.2 mL; conditions A). When the substrate was hardly soluble in ethanol, the reaction was carried out in a mixture of ethanol and toluene (0.5 mL/2.0 mL; conditions B). Amino, oxygenated, and C-based substrates are readily cyclized to the corresponding hetero- and carbocycles with Rh (4 mol%) at 80°C. The desired cyclized product was generated with high selectivity for the *Z*-configured alkene. Substantial structural modifications can be accommodated, as can be seen in entries 8, 11, and 12 (Table 2). For N–Ts tethered 1,6-enynes, various substrates with arylalkynyl having an electron-donating substituent (Table 2, entry 1) or having an electron-withdrawing substituent (Table 2, entry 2) at the *para* position and with sterically bulky arylalkynyl (Table 2, entry 3) had proven to be reliable substrates for the cyclization, leading to the synthesis of (*Z*)-3-benzylidene-4-methyl-1-tosylpyrrolidines in good yields (84–88%). However, the substrate with an alkylalkynyl substituent gave a moderate yield (48%, Table 2, entry 4). For O-tethered 1,6-enynes, a substituent of the alkene seems to have much more influence on the yield of the reaction than a substituent of the alkyne. An introduction of a methyl to the inner position of an alkene (Table 2, entry 7) led to the isolation of **8a** in

49% yield with a recovery of the reactant (57%). However, introduction of two methyl groups at the *meta* positions of arylalkynyl (Table 2, entry 6) or an introduction of cyclohexyl (entry 8) still gave high yields (78 and 72% yields, respectively). For carbon-tethered 1,6-enynes, malonate-tethered substrates were first tried under the optimized reaction conditions, but all the reactants were recovered. This observation is quite different from that of Krische and Jang.[6a] They observed formation of a hydrogen-mediated reductive cyclization product in high yield (80–91%) in the presence of $[Rh(cod)_2]X/BIPHEP$ (X = OTf, BF_4). However, when 1,6-enyne acetal (Table 2, entry 9) was used as a substrate, the expected reductive cyclization product was obtained in 64% yield. When an 1,7-enyne was used as a substrate, it underwent a reductive cyclization to give the expected product in 36% yield with a recovery of the reactant (64%). In the case of an allylic 2-alkynoate (Table 2, entry 12), the expected reductive cyclization product was isolated in a reasonable yield (59%).

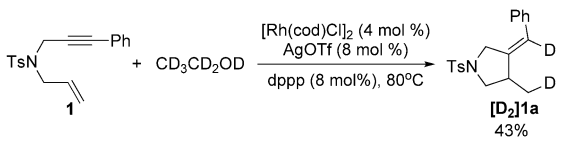
On the basis of the results in Table 2, we examined chiral diphosphine ligand for the development of its asymmetric variant.[9b] Our preliminary results showed that the reaction of **1** smoothly proceeded in the presence of (*R*)-BINAP to give **1a** with 47% and 81% *ee*, respectively (Scheme 2).[15] It is expected that optimization will give to a higher yield and higher *ee* values.



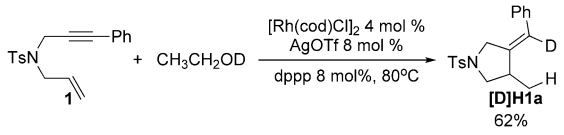
Scheme 2. An asymmetric reductive cyclization reaction using ethanol as a hydrogen source.

To gain mechanistic insights, we attempted to detect an in-situ-generated hydrogen or metal-hydride species from a reaction of ethanol in the presence of rhodium catalyst in $[D_8]$toluene at 80°C. However, we failed to observe the formation of hydrogen or a metal-hydride species in the reaction. Thus, it seems that the presence of an enyne substrate is a prerequisite to generate hydrogen or a metal-hydride species.

A reaction of tosylated amino enyne **1** with $[D_6]$ethanol was examined to discover whether or not all the hydrogen atoms used in the reductive cyclization come from ethanol (Scheme 3). The reaction of **1** with $[D_6]$ethanol in toluene at 80°C for 12 h gave the product in 43% yield. ^{1}H NMR spectra show that all the hydrogen atoms used in the reductive cyclization come from ethanol.



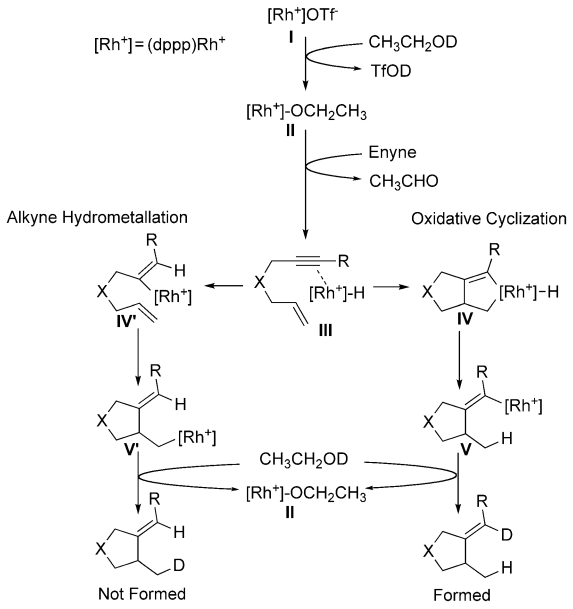
Scheme 3.



Scheme 4.

A reaction of **1** with CH_3CH_2OD was also performed (Scheme 4). The rhodium-catalyzed reductive cyclization of **1** gave **[D]H1a** in 62% yield with an isotopic label exclusively in the vinyl position of the exo alkenyl substituent.

Based on the above results, a plausible reaction mechanism is shown in Scheme 5. The dinuclear complex is proposed to be defragmented into a monometallic rhodium complex **I**. Subsequently, an alcohol reacts with the catalyst **I** liberating DOTf and giving a coordinatively unsaturated rhodium alkoxide species **II**. Then, β-hydrogen elimination from the alkoxide ligand and the coordination of the enyne give rise to a rhodium enyne hydride species **III**. In the next step, two pathways, alkyne hydrometallation and oxidative cyclization were proposed when hydrogen was used. However, they could not be differentiated by experiments. To the contrary, our experimental results showed that the oxidative cyclization was much more favorable. Thus, an enyne ligand coordinates with releasing aldehyde from the rhodium affording **IV**. During coordination, the alkyne moiety of the enyne can coordinate to the metal center and the hydride is transferred to the terminal of the alkene moiety, giving species **IV**. Finally, an oxidative addition of alcohol and a simultaneous release of the reductive cyclization product **a** generate a free coordination site to restore the coordinately unsaturated rhodium alkoxide species **II** and complete the catalytic cycle.



Scheme 5. A plausible reaction mechanism.

In conclusion, we have developed a Rh-catalyzed reductive cyclization of unactivated 1,6-enynes using an alcohol as a hydrogen donor under mild reaction conditions. The reaction is an environmentally friendly synthetic method and proceeds efficiently to give various *exo*-methylene substituted pyrrolidines, tetrahydrofuran, and cyclopentane compounds in a highly selective manner in moderate to high yields. Studies on the scope of the reaction and mechanistic studies are under way.

Experimental Section

Reaction conditions A: $[Rh(cod)Cl]_2$ (3 mg, 4 mol%), $AgSbF_6$ (3 mg, 8 mol%), dppp (4.2 mg, 8 mol%) and ethanol (2.0 mL) were added under argon gas flow to a flame-dried 50 mL Schlenk tube flask capped with a rubber septum. After the solution was stirred for 20 min, a substrate (0.15 mmol) and distilled water (0.2 mL) were put into the flask. The reaction vessel was stirred for 12 h at 80 °C. The reaction mixture was purified by flash chromatography on a silica gel column eluting with *n*-hexane/EtOAc (v/v = 10:1) to afford product.

Reaction conditions B: $[Rh(cod)Cl]_2$ (3 mg, 4 mol%), $AgSbF_6$ (3 mg, 8 mol%), dppp (4.2 mg, 8 mol%) and toluene (2.0 mL) were added under argon gas flow to a flame-dried 50 mL Schlenk tube flask capped with a rubber septum. After the solution was stirred for 20 min, ethanol (0.5 mL) was added. After a moment, a substrate (0.15 mmol) was put into the flask. The reaction vessel was stirred for 12 h at 80 °C. The reaction mixture was purified by flash chromatography on a silica gel column eluting with *n*-hexane/EtOAc (v/v = 10:1) to afford product.

Acknowledgements

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Keywords: catalysis · cyclization · enynes · ethanol · hydrogen · rhodium

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