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Cationic Rhodium(I)/BINAP Complex-Catalyzed Isomerization of Secondary Propargylic Alcohols to α,β-Enones

Ken Tanaka* and Takeaki Shoji

Department of Applied Chemistry, Graduate School of Engineering, Tokyo University of Agriculture and Technology, Koganei, Tokyo 184-8588, Japan

tanaka-k@cc.tuat.ac.jp

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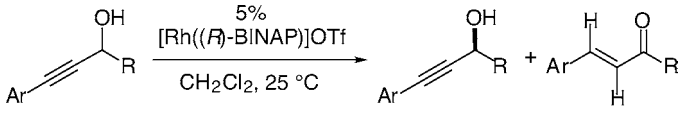
ABSTRACT



kinetic resolution

selectivity factor = up to 11.5

We have developed a cationic rhodium(I)/BINAP complex-catalyzed isomerization of secondary propargylic alcohols to α,β-enones. The asymmetric variant of this reaction, a kinetic resolution of secondary propargylic alcohols, was also developed with good selectivity. The mechanistic study revealed that the isomerization proceeds through intramolecular 1,3- and 1,2-hydrogen migration pathways.

α,β-Unsaturated carbonyl compounds are useful building blocks in organic synthesis. For their preparation, isomerization of propargylic alcohols to α,β-enones or α,β-enals is one of the most efficient methods due to the easy access to propargylic alcohols and high atom economy.[1] However, such isomerizations are relatively rare compared with well established isomerizations of allylic alcohols.[2]

The isomerization of propargylic alcohols to α,β-enones or α,β-enals was developed by using Ru,[3,4] Ir,[5] and Pd[6] catalysts. Although there are many examples of rhodium-catalyzed isomerizations of allylic alcohols,[7] only one example of rhodium-catalyzed isomerization of propargylic alcohols was reported. The isomerization of hydroxy alkyne esters proceeded in the presence of 3% $RhCl(PPh_3)_3$ and 5% n-Bu_3P in toluene at 110 °C.[8] In this paper, we describe a cationic rhodium(I)/BINAP complex-catalyzed isomerization of secondary propargylic alcohols to α,β-enones.

Table 1 shows various rhodium(I) catalysts (5% based on propargylic alcohols) that we examined for their ability to isomerize propargylic alcohol **1a** at room temperature. Among the catalysts examined, [Rh(*rac*-BINAP)]BF_4 was the most effective (entry 7). The best result was obtained by using [Rh(*rac*-BINAP)]BF_4 as a catalyst at 80 °C for 1 h, which furnished the desired α,β-enone **2a** in >95% yield with complete trans:cis selectivity (100:0, entry 8).

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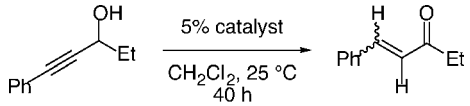
Table 1. Screening of Catalysts for Rhodium-Catalyzed Isomerization of Propargylic Alcohol **1a**



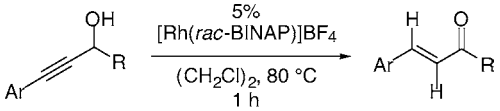
1a **2a**

entry	alcohol	conversion (%)[a]	yield (%)[a]	trans:cis
1	$RhCl(PPh_3)_3$	<1	<1	
2	$[Rh(PPh_3)_2]BF_4$	<1	<1	
3	$[Rh(n\text{-}Bu_3P)_2]BF_4$	<1	<1	
4	[Rh(dppe)]BF_4	<1	<1	
5	[Rh(dcpe)]BF_4	40	32	41:59
6	[Rh(dppf)]BF_4	<1	<1	
7	[Rh(*rac*-BINAP)]BF_4	27	27	91:9
8[b]	[Rh(*rac*-BINAP)]BF_4	100	>95	100:0

[a] Determined by ^1H NMR. [b] Reaction was conducted in $(CH_2Cl)_2$ at 80 °C for 1 h.

A series of secondary propargylic alcohols **1a**−**h** was subjected to the above optimal reaction conditions (Table 2). Primary (entries 1−3), secondary (entry 4), and tertiary

Table 2. Cationic Rhodium(I)/BINAP Complex-Catalyzed Isomerization of Propargylic Alcohols



1a–h **2a–h**

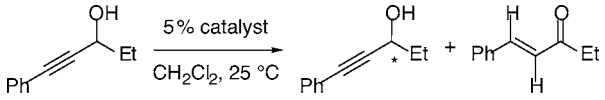
entry	alcohol	Ar	R	ketone	yield (%)[a]	trans:cis
1	**1b**	Ph	Me	**2b**	99	100:0
2	**1a**	Ph	Et	**2a**	98	100:0
3	**1c**	Ph	*n*-Bu	**2c**	95	100:0
4	**1d**	Ph	*i*-Pr	**2d**	98	100:0
5	**1e**	Ph	*t*-Bu	**2e**	96	100:0
6	**1f**	4-$MeOC_6H_4$	Et	**2f**	98	100:0
7	**1g**	4-$CF_3C_6H_4$	Et	**2g**	99	100:0
8	**1h**	2-MeC_6H_4	Et	**2h**	94	67:33

[a] Isolated yield.

(entry 5) alkyl-substituted propargylic alcohols cleanly afforded the corresponding α,β-enones **2a**−**e** in almost quantitative yield with complete trans:cis selectivity (100:0). The electronic nature of the aromatic substituent did not affect the yield or the trans:cis ratio of α,β-enones **2f**,**g** (entries 6 and 7), but a sterically demanding substituent on the phenyl decreased the trans:cis ratio of α,β-enone **2h** (entry 8). Although the isomerization of aryl-ethynyl/alkyl carbinols proceeded cleanly, that of alkyl-ethynyl/alkyl[9] or alkynyl/aryl[10] carbinols did not proceed cleanly due to significant side reactions.

Next, a kinetic resolution of secondary propargylic alcohol **1a** was investigated using chiral rhodium(I) or iridium(I)/

Table 3. Screening of Catalysts for Rhodium-Catalyzed Kinetic Resolution of Secondary Propargylic Alcohol **1a**



1a ***kinetic resolution*** **1a** **2a**

entry	catalyst	time (h)	% ee of unreacted alcohol (% conversion[a])	*s* (selectivity factor)
1	[Rh((*R*)-BINAP)]BF_4	78	47 (46)	5.2
2	[Rh((*R*)-Tol-BINAP)]BF_4	40	22 (34)	3.1
3	[Rh((*R*)-H8-BINAP)]BF_4	40	33 (46)	3.1
4	[Rh((*S*)-Segphos)]BF_4	88	9 (14)	3.8
5[b]	[Rh((*R*)-BINAP)]Cl	38	10 (20)	2.5
6[b]	[Ir((*R*)-BINAP)]BF_4	15	8 (70)	1.2
7	[Rh((*R*)-BINAP)]SbF_6	40	41 (52)	3.3
8	[Rh((*R*)-BINAP)]OTf	72	76 (59)	7.3

[a] Determined by ^1H NMR. [b] Reaction was conducted in $(CH_2Cl)_2$ at 80 °C.

modified−BINAP complexes (Table 3).[11−14] Among the modified BINAP ligands examined (Figure 1), BINAP was

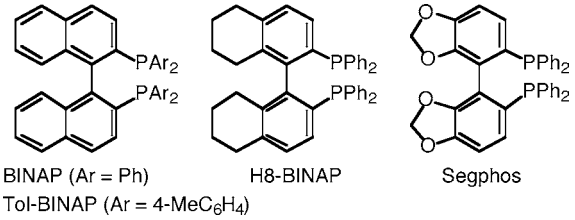


Figure 1. Structures of modified BINAP ligands.

the most effective (Table 3, entry 1). The use of a neutral rhodium(I) complex or a cationic iridium(I) complex led to

(9) Isomerization of 3-octyn-2-ol gave a mixture of olefinic ketones.

(10) The isomerization of 1-phenyl-2-heptyn-1-ol gave a complex mixture of the products contaning olefinic ketones and 3-butylindan-1-one. For the formation of indanones utilizing rhodium 1,4-migration, see: (a) Yamabe, H.; Mizuno, A.; Kusama, H.; Iwasawa, N. *J. Am. Chem. Soc.* **2005**, *127*, 3248−3249. (b) Shintani, R.; Okamoto, K.; Hayashi, T. *J. Am. Chem. Soc.* **2005**, *127*, 2872−2873.

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(12) For examples of transition-metal-catalyzed kinetic resolutions of allylic alcohols, see: (a) Kitamura, M.; Manabe, K.; Noyori, R. *Tetrahedron Lett.* **1987**, *28*, 4719−4720. (b) Wiles, J. A.; Lee, C. E.; McDonald, R.; Bergens, S. H. *Organometallics* **1996**, *15*, 3782−3784.

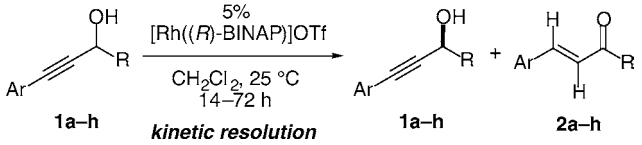
(13) For a kinetic resolution of propargylic alcohols with a planar-chiral DMAP derivative, see: Tao, B.; Ruble, C.; Hoic, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **1999**, *121*, 5091−5092.

(14) For a recent example of an enzymatic kinetic resolution of propargylic alcohols, see: Raminelli, C.; Comasseto, J. V.; Andrade, L. H.; Porto, A. L. M. *Tetrahedron: Asymmetry* **2004**, *15*, 3117−3122 and references therein.

messy reactions, and the selectivity factors were very low (entries 5 and 6). Changing the counterion from BF_4 to OTf improved the selectivity factor (entry 8).[15]

A series of secondary propargylic alcohols **1a**−**h** can be resolved using Rh(I)$^+$/(*R*)-BINAP as a catalyst (Table 4).

Table 4. Cationic Rhodium(I)/(*R*)-BINAP Complex-Catalyzed Kinetic Resolution of Secondary Propargylic Alcohols



1a–h 1a–h 2a–h

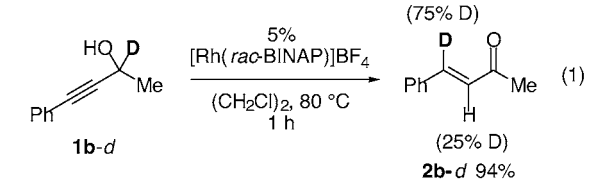
entry	alcohol	Ar	R	% ee of unreacted alcohol (% conversion[a])	*s* (selectivity factor)
1	**1b**	Ph	Me	42 (58)	2.8
2	**1a**	Ph	Et	76 (59)	7.3
3	**1c**	Ph	*n*-Bu	82 (60)	8.2
4	**1d**	Ph	*i*-Pr	58 (51)	6.1
5[b]	**1e**	Ph	*t*-Bu	62 (58)	4.7
6	**1f**	4-$MeOC_6H_4$	Et	62 (55)	5.8
7	**1g**	4-$CF_3C_6H_4$	Et	78 (60)	7.2
8	**1h**	2-MeC_6H_4	Et	80 (55)	11.5

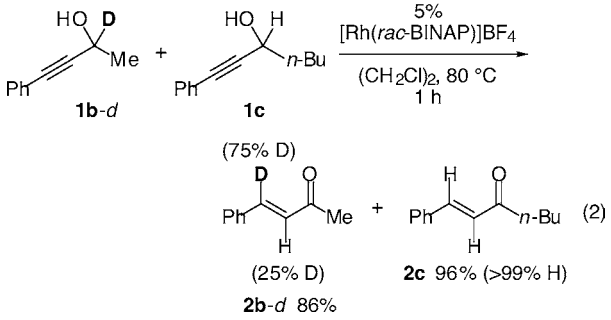
[a] Determined by ^{1}H NMR. [b] Performed with 5% [Rh((*R*)-BINAP)]BF_4.

The length and steric demand of the alkyl groups affected the enantioselectivity of the isomerization (entries 1−5). Good selectivity factors were observed in Et-, *n*-Bu-, and *i*-Pr-substituted propargylic alcohols (entries 2−4). Although the electronic nature of the aromatic substituent appeared to have a modest impact on the selectivity factor (entries 6 and 7), sterically demanding substituents on the aryl ring improved the selectivity factor (entry 8).

The reaction of a deuterated propargylic alcohol was investigated to gain mechanistic insight into this reaction. Deuterium from the propargylic alcohol **1b**-*d* was incorporated into the α-position (25% D) and *β*-position (75% D) of the α,*β*-enone **2b**-*d* (eq 1). Furthermore, we have established that the migration is an intramolecular process. Treatment of a 1:1 mixture of deuterated propargylic alcohol **1b**-*d* and nondeuterated propargylic alcohol **1c** with [Rh(*rac*-BINAP)]BF_4 furnishes deuterated **2b**-*d* and nondeuterated **2c** (eq 2).[16]

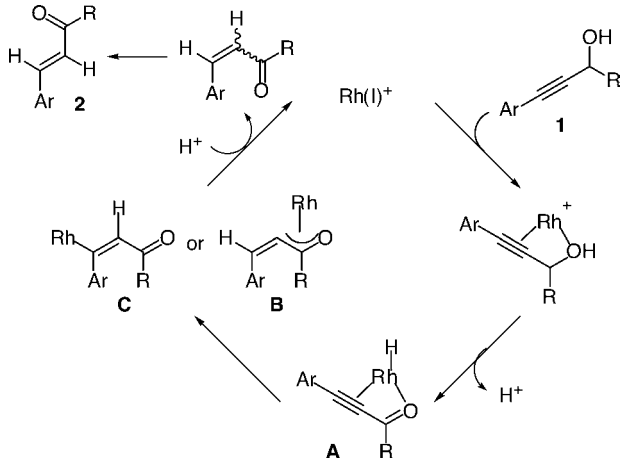
Scheme 1 depicts a plausible mechanism for this reaction. We believe that reaction of a rhodium(I) catalyst with a propargylic alcohol **1** furnishes rhodium hydride complex **A**. Addition of rhodium hydride to alkyne furnishes *π*-oxallyl rhodium intermediate **B** or alkenyl rhodium intermediate **C**, which is protonated to give an α,*β*-enone and regenerate the





rhodium(I) catalyst. The isomerization to thermodynamically stable *trans*-α,*β*-enone **2** may occur through heating in the presence of the cationic rhodium(I) catalyst.

Scheme 1



In conclusion, we have developed a cationic rhodium(I)/BINAP complex-catalyzed isomerization of secondary propargylic alcohols to α,*β*-enones. The asymmetric variant of this reaction, a kinetic resolution of secondary propargylic alcohols, was also developed with good selectivity. Furthermore, we have determined that the isomerization proceeds through intramolecular 1,3- and 1,2-hydrogen migration pathways. Expansion of the scope and a detailed mechanistic study of this reaction are underway in our laboratory.

Acknowledgment. We thank Takasago International Corporation for the gift of modified BINAP ligands.

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

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(15) A similar counterion effect was observed in the enantioselective isomerization of geraniol with Rh(I)$^+$/BINAP; see ref 11d.

(16) Deuterium labeling studies revealed that the isomerization of allylic alcohols proceeds through 1,3-hydrogen migration pathway, see: (a) McGrath, D. V.; Grubbs, R. H. *Organometallics* **1994**, *13*, 224−235. (b) Trost, B. M.; Kuliawec, R. J. *J. Am. Chem. Soc.* **1993**, *115*, 2027−2036. (c) Bergens, S. H.; Bosnich, B. *J. Am. Chem. Soc.* **1991**, *113*, 958−967. Also, see ref 11b.