

Synthesis of Z-Alkenes from Rh(I)-Catalyzed Olefin Isomerization of β,γ -Unsaturated Ketones

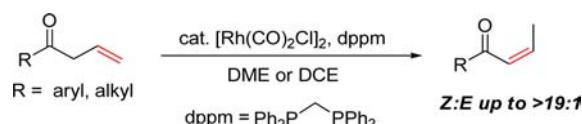
Lian-Gang Zhuo, Zhong-Ke Yao, and Zhi-Xiang Yu*

Beijing National Laboratory of Molecular Sciences (BNLMS), Key Laboratory of Bioorganic Chemistry and Molecular Engineering, College of Chemistry, Peking University, Beijing 100871, China

yuzx@pku.edu.cn

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ABSTRACT



Developing olefin isomerization reactions to reach kinetically controlled Z-alkenes is challenging because formation of *trans*-alkenes is thermodynamically favored under the traditional catalytic conditions using acids, bases, or transition metals as the catalysts. A new synthesis of Z-alkenes from Rh(I)-catalyzed olefin isomerization of β,γ -unsaturated ketones to α,β -unsaturated ketones was developed, providing an easy and efficient way to access various Z-enones.

Because alkenes are ubiquitous in molecules and they also serve as functional groups for a variety of further transformations, developing new reactions for alkene synthesis and expanding the scope of the existing alkene synthesis methods are both very significant in today's science of synthesis.¹ One powerful reaction to access substituted alkenes is to use transition-metal-catalyzed olefin isomerizations of the pre-existing C=C double bonds (Scheme 1a). These isomerization processes have been widely used in the syntheses of carbonyl compounds

(from allyl alcohols),² enamines (from allyl amines),³ enol ethers (from allyl ethers),⁴ and other internal alkenes (from terminal alkenes).^{5–11} Usually, the olefin isomerizations are catalyzed by acids or bases¹ or transition metals (e.g., Fe,⁵ Ir,⁶ Ni,⁷ Pd,^{7d,8} Pt,⁹ Rh,^{5,10} and Ru^{5,11}). A limitation of these olefin isomerizations is that, in many cases, only the *E*-alkenes are obtained. This is attributed to the facts that the olefin isomerization reactions are usually reversible and *E*-alkenes in most cases are the thermodynamically

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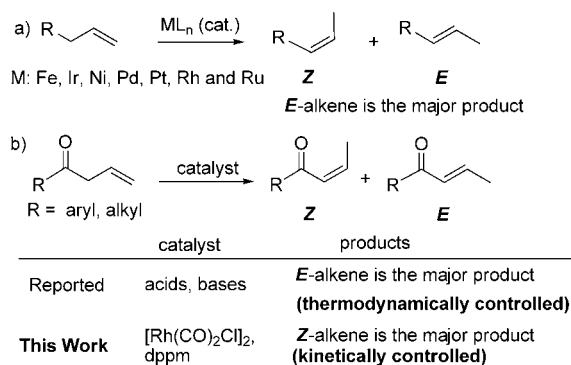
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avored products.^{8,9,11} Considering that *Z*-alkenes are required and the synthesis of these alkenes poses challenges to synthetic chemists,^{12–16} it is highly desired to develop new olefin isomerization approaches to obtain *Z*-alkenes.

Scheme 1



However, only a few reports have touched this challenge of reversing the selectivity of olefin isomerization to obtain the thermodynamically less stable products, the *Z*-alkenes. For example, Stille and Becker⁵ proposed previously that the *Z*-product could be a kinetic product in their Fe-, Ru-, or Rh-catalyzed isomerization of *N*-allylamide (only a single example using $CH_2=CHCH_2NHAc$ as the substrate was reported there). Yudin and co-workers carried out a Rh-catalyzed formation of *Z*- enamines via the alkene isomerization of very special substrates, allylaziridines.^{10b,c} Miyaoura^{6a} used Ir(I)-catalyzed isomerization of allyl silyl ethers to silyl enol ethers. In the case of $CH_2=CHCH_2OTBS$, the ratio of *E/Z* can be tuned from 99:1 (in acetone) to 1:3 (in CH_2Cl_2 /acetone solvent). It was proposed that the

Z-selectivity in these reported reactions was determined by the favored coordination of heteroatoms of the substrates to the metal atoms of the catalysts.

Here we report an unprecedented neutral Rh(I) complex catalyzed olefin isomerization of β,γ -unsaturated ketones to α,β -unsaturated ketones with high *Z*-selectivity, which is complementary to the traditional olefin isomerization catalyzed by acids or bases^{1,18} for the synthesis of *E*-alkenes (Scheme 1b).

Table 1. Screening of the *Z*-Selective Olefin Isomerization Reaction Conditions of β,γ -Unsaturated Ketone **1a**

entry	additive ^a	temp (°C)	solvent ^b	time (h)	2a-Z:2a-E ^c	conv ^c (%)	yield ^{c,d} (%)
1	none	75	DCE	18	4:1	78	51
2	AgSbF ₆	75	DCE	18	<1:19	93	72
3 ^e	none	75	DCE	23	3:1	67	35
4	dppm	75	DCE	23	6:1	89	72
5	dppe	75	DCE	23	4:1	87	74
6	dppp	75	DCE	23	2:1	91	79
7	dppb	75	DCE	23	3:1	79	63
8	PCy ₃	80	DCE	23	2:1	94	68
9	PCyPh ₂	80	DCE	23	2:1	85	64
10	P ^t Bu ₂ biphenyl	80	DCE	23	3:1	94	71
11	P(2,6-diMeO-Ph) ₃	80	DCE	23	1:2	93	64
12	dppm	75	DME	23	4:1	94	75
13	dppm	65	DME	20	6:1	87	73
14	dppm	85	DCE	32	2:1	87	54

^a dppp = 1,3-bis(diphenylphosphino)propane, dppm = bis(diphenylphosphino)methane, dppe = 1,2-bis(diphenylphosphino)ethane, dppb = 1,4-bis(diphenylphosphino)butane, Cy = cyclohexyl. ^b DCE = 1,2-dichloroethane, DME = 1,2-dimethoxyethane. ^c Determined by NMR. ^d Yield of mixture of *Z*- and *E*-enones. ^e Using 10 mol % Rh(PPh₃)₃Cl as catalyst.

When we tested the olefin isomerization of **1a** using 5 mol % catalyst of $[Rh(CO)_2Cl]_2$ in DCE at 75 °C,¹⁹ we obtained a mixture of the starting material and the targeted enones (**2a**), which have a *Z/E* ratio of 4:1 (Table 1, entry 1). Under these reaction conditions, the conversion of the reaction (78%) was not satisfactory, and only a moderate yield (51%) of **2a-Z** was obtained.

To improve the reaction yield, conversion, and especially the *Z/E* ratio, we further screened the reaction conditions. To our disappointment, cationic Rh(I) catalyst, generated by the reaction of 5 mol % of $[Rh(CO)_2Cl]_2$ and 12 mol % of AgSbF₆, gave overwhelmingly the *E*-alkene product with a *Z/E* ratio < 1:19 (Table 1, entry 2). We hypothesized that cationic Rh(I) catalyst here acted

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as a Lewis acid to facilitate the *Z* to *E* isomerization, similar to those olefin isomerizations catalyzed by Lewis acids. To avoid this Lewis acid catalysis conditions, we decided to test other neutral Rh(I) species as the potential catalysts for all further investigation. To our delight, we found that bidentate phosphine ligands such as dpmm, dppe, dppp, and dppb (Table 1, entries 4–7) all can improve the reaction conversions to about 90%. It was observed that dpmm ligand was the best one that can promote the reaction to an acceptable *Z/E* ratio of 6:1 (Table 1, entry 4). Unfortunately, a variety of other bidentate phosphine ligands (see the Supporting Information) and monodentate phosphine ligands did not exceed dpmm in the target olefin isomerization reaction (Table 1, entries 3, 8–11). Several solvents (Table 1, entry 12, and the Supporting Information) were examined under the reaction conditions of using 5 mol % [Rh(CO)₂Cl]₂ and 12 mol % dpmm as the catalyst at 75 °C, showing that DCE is the best solvent at this temperature. Interestingly, at a lower temperature (65 °C) in DME solution (Table 1, entry 13), the olefin isomerization reaction gave the final products with yields comparable to those in DCE at 75 °C. It was found that longer reaction time or higher reaction temperature can increase the conversion of the isomerization reaction slightly, both the *Z/E* ratio and the yield of the reaction, unfortunately, decreased dramatically (Table 1, entry 14).

Initially, we tried to study the scope (Tables 2 and 3) of the olefin isomerization reactions by using the conditions given in entry 4 (at 75 °C in DCE) or 13 (at 65 °C in DME) in Table 1. However, we found that some substrates gave dramatically different results in DCE and DME, in contrast to the reactions of **1a**. For example, the isomerization of 4-Cl-substituted substrate **1b** (Table 2, entry 2) gave the *Z/E* ratio of final products as 7:1 at 65 °C in DME in 20 h, but this ratio dropped to 2:1 if the reaction was carried out at 75 °C in DCE (the reaction conversions were almost the same in both solvents). Similar phenomenon can be found in other case (Table 2, entry 3). Therefore, we carried out most of the olefin isomerizations in DME instead of DCE solvent. For substrates that gave poor results in DME, we then performed their reactions in DCE solvent to get improved yields and *Z*-selectivities.

We were happy to find that almost all substrates **1** with both electron-withdrawing and electron-donating groups can undergo the olefin isomerizations in DME at 65 °C with excellent conversions and decent to high *Z*-selectivities (Table 2). Only substrate **1k** (Table 2, entry 11) with two electron-donating groups had to be subjected to DME solution at 75 °C. For substrate **1f** with a *p*-methyl group and substrate **1j** with an *o*-methoxy group, their isomerizations had to be carried out at 75 °C in DCE to get better results (Table 2, entries 6 and 10). We scaled the reaction from 0.3 to 1.5 mmol, finding that similar conversions and selectivities can be obtained (entries 13 and 14). Meanwhile, we were happy to find that the isolated yields of pure **2m-Z** can be improved from 53% (0.3 mmol scale) to 73% (1.5 mmol scale).²⁰

It is noteworthy that substrates with alkyl substituents (**3a–i**, Table 3) can also isomerize to the corresponding

Table 2. Scope of the *Z*-Selective Olefin Isomerization Reaction of β,γ -Unsaturated Ketones **1**^a

entry	Ar	temp (°C)	solvent	time (h)	2-Z:2-E ^b	conv ^b (%)	yield ^{b,c} (%)
1	1a , Ph	75	DCE	23	6:1	89	72
		65	DME	20	6:1	87	73
2	1b , 4-ClC ₆ H ₄ -	75	DCE	23	2:1	93	80
		65	DME	20	7:1	>95	85
3	1c , 2-ClC ₆ H ₄ -	75	DCE	23	1:1	>95	88
		65	DME	16	>19:1	>95	93
4	1d , 3-ClC ₆ H ₄ -	65	DME	19	12:1	84	75
5	1e , 4-FC ₆ H ₄ -	65	DME	16	11:1	87	79
6	1f , 4-MeC ₆ H ₄ -	75	DCE	23	4:1	93	80
7	1g , 3-MeC ₆ H ₄ -	65	DME	24	5:1	90	65
8	1h , 4-MeOC ₆ H ₄ -	65	DME	20	5:1	92	74
9	1i , 3-MeOC ₆ H ₄ -	65	DME	19	10:1	89	67
10	1j , 2-MeOC ₆ H ₄ -	75	DCE	23	3:1	80	66
11	1k , 3,4-di-MeOC ₆ H ₄ -	75	DME	19	7:1	>95	90
12	1l , 4-PhC ₆ H ₄ -	65	DME	16	3:1	85	82
13	1m , 2-naphthyl-	65	DME	19	11:1	92	78 (53 ^d)
14 ^e	1m , 2-naphthyl-	65	DME	20	13:1	94	81 (73 ^d)

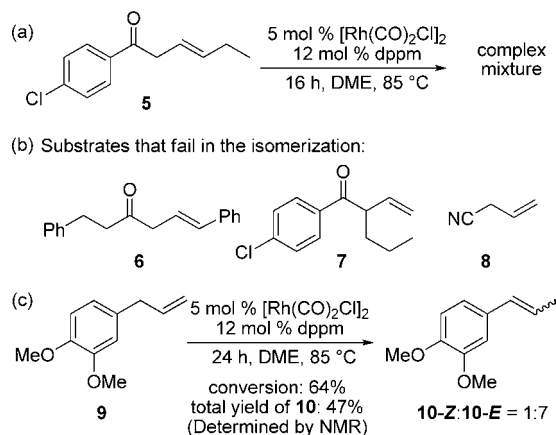
^a 1.5 mL of solvent and 0.3 mmol of β,γ -unsaturated ketones were used. ^b Determined by NMR. ^c Yield of mixture of *Z*- and *E*-enones. ^d Isolated pure **2m-Z** yield (by column chromatography). ^e 6 mL of DME and 1.5 mmol of β,γ -unsaturated ketone were used.

Table 3. Scope of the *Z*-Selective β,γ -Unsaturated Ketone Isomerization Reaction of **3**^a

entry	R	time	4-Z:4-E ^b	conv ^b	yield ^{b,c}
1	3a , <i>n</i> -C ₆ H ₁₃	24 h	6:1	75%	68%
2	3b , Ph	21 h	>19:1	88%	88%
3	3c , Ph	23 h	>19:1	94%	73%
4	3d , Cyclohexyl	24 h	7:1	86%	65%
5	3e , TBSO-CH ₂ CH ₂ CH ₂ -	24 h	6:1	84%	67%
6	3f , isopropyl	23 h	7:1	88%	69%
7	3g , isobutyl	23 h	7:1	81%	75%
8	3h , 2-methyl-2-butyl	17 h	7:1	86%	70%
9	3i , Ph	23 h	6:1	92%	70%

^a 1.5 mL of DME and 0.3 mmol of β,γ -unsaturated ketones were used. ^b Determined by NMR. ^c Yield of mixture of *Z*- and *E*-enones.

Scheme 2



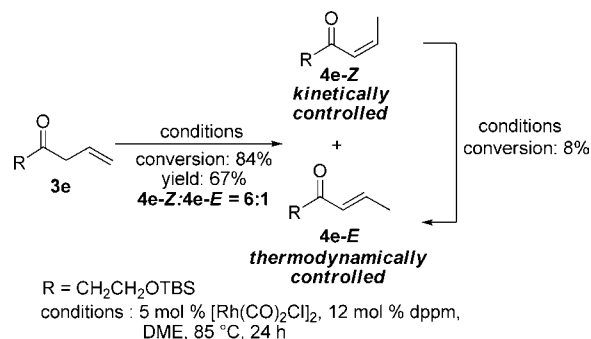
α,β -unsaturated ketones, with the *Z*-alkenes as the major products. In all cases, higher temperature (85 °C in DME) was required. We speculated that this is because alkyl-substituted ketones have stronger C–H bonds at their α positions than their counterparts in the aryl-substituted β,γ -unsaturated ketones, and consequently the isomerization of these substrates in Table 3 becomes more difficult than substrates in Table 2.

Further studies (Scheme 2) showed that neither the terminally substituted substrates **5** and **6** nor the α -substituted substrate **7** could undergo the Rh(I)-catalyzed *Z*-selective olefin isomerization. The carbonyl group is very important in the isomerization reaction: substrate **8** with a CN instead of a carbonyl group failed in the isomerization reaction, while substrate **9** without carbonyl group gave *E*-alkene instead of *Z*-alkene dominantly.

Preliminary studies to elucidate the reaction mechanism were performed (Scheme 3). Our chemical intuition suggests that formations of the *E*-alkene isomers were the thermodynamically controlled products, while the *Z*-alkenes in the present reaction were the kinetically controlled products. To prove this, we carried out the *Z* to *E* isomerization process of **4e-Z** under the same reaction conditions, finding that a mixture of *Z* and *E* isomers was obtained with a conversion of 8%. This agrees with the

(20) The substrates and *Z*-enones from the isomerizations have close R_f (retention factor) values in chromatography, and their separation was not satisfactory when the reactions were conducted on a small scale.

Scheme 3. *Z*-Enone to *E*-Enone Transformation



experimental observation that the *Z/E* ratio decreased under higher temperature with prolonged reaction time.²¹ These results suggested the *Z*-isomers were the kinetically favored products and the *Z* to *E* isomerization processes are very slow. Because of this, the isomerization of ketones under the catalysis of Rh can give *Z*-alkenes kinetically as the major products. Further study using both experiments and DFT calculations is ongoing to elucidate the detailed reaction mechanism and the stereochemistry. At present, we hypothesized that carbonyl group's oxygen coordination to the Rh catalyst could be the major reason for the observed *Z*-selectivity.

In summary, we have developed the first neutral Rh(I)-complex catalyzed *Z*-selective olefin isomerization of β,γ -unsaturated ketones to α,β -unsaturated ketones, providing an efficient and versatile approach to the synthetically challenging *Z*-alkenes.

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Supporting Information Available. Experimental details. This material is available free of charge via the Internet at <http://pubs.acs.org>.

(21) Stille and Becker also found that the *Z/E* ratio decreased with time (see ref 5).

The authors declare no competing financial interest.