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Stereoselective Alkene Isomerization over One Position

Casey R. Larsen and Douglas B. Grotjahn*

Department of Chemistry and Biochemistry, San Diego State University, San Diego, California 92182-1030, United States

Supporting Information

ABSTRACT: Although controlling both the position of the double bond and *E*:*Z* selectivity in alkene isomerization is difficult, **1** is a very efficient catalyst for selective mono-isomerization of a variety of multifunctional alkenes to afford >99.5% *E*-products. Many reactions are complete within 10 min at room temperature. Even sensitive enols and enamides susceptible to further reaction can be generated. Catalyst loadings in the 0.01−0.1 mol% range can be employed. *E*-to-*Z* isomerization of the product from diallyl ether was only $<10^{-6}$ times as fast as its formation, showing the extremely high kinetic selectivity of **1**.

Catalyzed isomerization of alkenes is an example of atom-economical chemistry.[1a,e] Particularly useful alkene isomerizations include those of allyl alcohols into the corresponding carbonyl compounds,[1] allyl ethers into their enol ethers,[2] and allylamines into their enamines.[3] Thus, alkene isomerization has attracted synthetic interest.[1e] However, the drawback of many known transition metal isomerization catalysts is the lack of *E*:*Z* selectivity of olefinic product formation.

Though many metal catalysts (e.g., Ru,[4−9] Ir,[10] Fe,[7] Ni,[11,12] Pd,[11,13] Pt,[14] and Rh[7,15]) are capable of performing alkene isomerization, challenges in the field include achieving high positional and stereochemical selectivity, substrate generality, and simplicity of catalyst use. For example, there are many *O*-allyl[2] and *N*-allyl[3] susbtrates for which isomerization over only one position is possible. Here the challenge is to obtain only the *E*- or *Z*-isomer. The preparation of enamines from allyl amines with high *E*-selectivity has been catalyzed by rhodium complexes.[15] In the oxygen case, the generation of predominately *trans*-enol ethers from allylic ethers occurs using an activated iridium catalyst,[10] whereas a Ru hydride complex generates a mixture featuring the energetically more stable *cis*-enol ether ($Z > 55$−68%).[6] These systems vary in their *cis*:*trans* selectivity, which is reported to be substrate dependent. Metathesis catalysts occasionally isomerize olefins as a side reaction;[16] subsequent modification and optimization, for example by Wipf and Donohoe, has expanded this methodology to use in natural product synthesis.[5,8,11] However, many of these systems require the use of additives, are tolerant of alkenes of only one functionality, and most importantly have difficulty controlling *E*:*Z* selectivity in a general way for all substrate classes.

We have previously disclosed complex **1** as an "alkene zipper" for isomerization of alkenes with a wide variety of functional groups under mild conditions (Figure 1).[4,17] The ability of **1** to isomerize an alkene up to 30 positions along an alkyl chain highlights its activity. In contrast, here our goal was to see if the activity of **1** could be controlled to perform

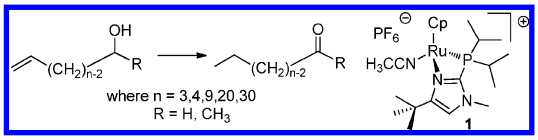

Figure 1. Alkene isomerization induced by bifunctional catalyst **1**.

selective alkene migrations *over only one bond* (mono-isomerization), while still maintaining high stereocontrol for *E*-isomeric products over a wide substrate scope. Our results here show the success of this approach, including the synthesis of sensitive enol and enamide derivatives, even in cases where further tautomerization to a carbonyl or imine function is possible.

A second general goal was to lower catalyst loading from ≥2 mol%, as we previously reported. Indeed, in many cases we find that loadings *20−200 times lower* than 2 mol% can be used.

Finally, we quantitate the extremely high kinetic selectivity of **1** by determining in one case that the rate of forming internal (*E*)-alkene from terminal isomer is over 10^6 times faster than the rate of *E*-to-*Z* isomerization.

Table 1 shows results for substrates which can only undergo a single isomerization, whereas Table 2 focuses on those compounds which can in principle be isomerized further to another alkene isomer. *In all cases, the rapid generation of exclusively (E)-alkenes was observed.* Both diallyl ether (**2**) and sulfonamide **3** gave (*E*,*E*)-dipropenyl products (Table 1, entries 1 and 2). Compound **3a** was previously unknown, whereas **2a** had been made but only as a mixture with its geometrical isomers.[18] The sulfonamide case may be slower because the larger *N*-Ts unit hinders the catalyst; in support of this notion, buildup of the intermediate (allyl)(propenyl) isomer was seen before reaction completion. Other allyl ethers (entries 3−5) are all rapidly transformed into the corresponding (*E*)-propenyl ethers as the sole product, even with as little as 0.05 mol% **1** (entry 4). Allyl-substituted cyclohexanols **8** and **9** (entries 7 and 8) show the facile production of exclusively *E*-isomer. Sensitive control using substrate sterics is shown by much slower reaction of **10** (entry 9). Presumably, 1,3-diaxial interactions as **1** acts on the allyl unit account for the observed differences between **10** and **9**. In short, a wide variety of (*E*)-propenyl-substituted compounds can be generated by catalyst **1** with very high selectivity.

Alkenyl aromatics such as *trans*-anethole and isoeugenol are important in the pharmaceutical and fragrance industries and are extracted from natural sources or generated from allyl aromatic isomers by the use of excess base and heat, thus creating large amounts of caustic waste (using aqueous NaOH or KOH,

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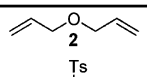
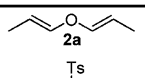
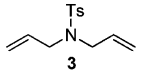
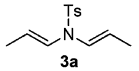
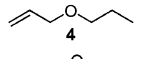
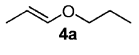
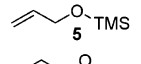
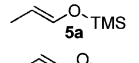
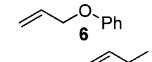
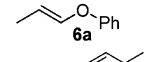
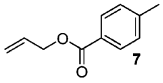
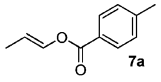
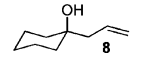
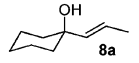
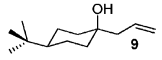
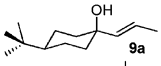
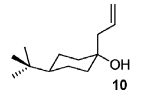
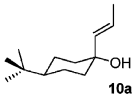
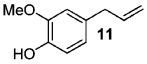
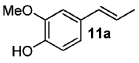
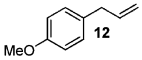
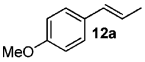
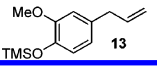
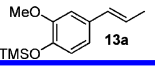
Table 1. Mono-isomerization of Linear Allyl Substrates[a]

Entry	Reactant	Product	mol% **1**	Time (h)	Yield (%)
1	 **2**	 **2a**	0.5	1.25	96
2	 **3**	 **3a**	5	24	96 (91[b])
3	 **4**	 **4a**	2	<0.1	98
4	 **5**	 **5a**	0.05	0.6	99
5	 **6**	 **6a**	2	0.25	95
6[c]	 **7**	 **7a**	2	2	96
7	 **8**	 **8a**	2	24	91
8	 **9**	 **9a**	2	24	92
9	 **10**	 **10a**	2	120	<2[d]
10	 **11**	 **11a**	0.05 0.1	0.3 <0.16	100 86[e]
11	 **12**	 **12a**	0.05	0.6	99
12	 **13**	 **13a**	0.8	<0.16	90

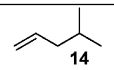
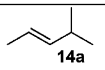
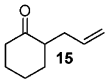
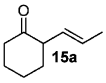
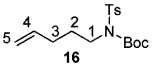
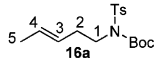
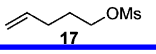
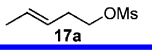
[a]Acetone-d_6 solvent, RT, NMR yield. [b]Isolated. [c]70 °C; produces ~5% of (*Z*)-**7a**. [d]No reaction (estimated limit of detection ~2%). [e]Neat reaction; product (4.59 g) isolated by distillation.

56% conversion, *E*:*Z* = 82:18 in 12 h at 200 °C).[12] Kannan catalyzed the isomerization of eugenol to isoeugenol with hydrotalcites at 200 °C (<77%, *E*:*Z* selectivity only 84:16).[12b] To overcome such drawbacks, Sharma[12a] screened $RuCl_2(PPh_3)_3$ and $RuCl_3(AsPh_3)_2$ in a variety of solvents over 3 h at 85 °C. The conversion (>99%) and selectivity for each of the valuable alkenyl aromatics were good (<95.6% *trans*); however, about 4% *cis*-isomer remained even after extensively optimizing reaction conditions.[12a]

The most impressive result to date appears to be 99% *trans*-anethole (80 °C, 15 min), in a variety of solvents, using 1 mol% $[RuCl_2(\eta^6\text{-}PhOCH_2CH_2OH)(P(OMe)_3)]$.[19] In contrast, *using much lower loadings of* **1** *without heating, both (E)-isoeugenol (**11a**) and (E)-anethole (**12a**) were afforded in >99% yield in <13 min (0.1 mol% **1**) and 40 min (0.05 mol% **1**)*, respectively, where in each case no trace of the *Z*-isomer is detected (detection limit ≈ 0.1%). *Significantly for green chemistry, **1** (0.1 mol%) acts on neat **11** within 10 min, and pure **11a** can be distilled on a multigram scale.* Moreover, even days after completion of isomerization, (*Z*)-alkenes are undetectable under our conditions.

Table 2 shows a variety of systems where a selectively mono-isomerized product can be obtained in high yield, before further alkene movement occurs. Hydrocarbon **14a** resisted further isomerization even after 48 h, forming only 9% of trisubstituted isomer, which is consistent with catalyst approach to the isopropyl C–*H* being hindered by branching. The ring of cyclohexanone derivative **15** also presents branching, and **15a** is obtained exclusively as its *E*-isomer within 45 min. The dramatic kinetic selectivity of **1** is shown by the fact that, after 77 h (100 times longer than the time required to obtain **15a**),

Table 2. Mono-isomerization of Linear Alkene Substrates

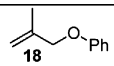
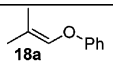
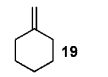
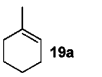
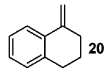
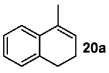
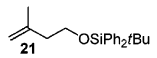
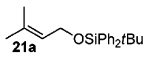
Entry	Reactant	Product	Time (h)	Yield (%)
1	 **14**	 **14a**	0.5	95
2	 **15**	 **15a**	0.75	95
3	 **16**	 **16a**	4	75[b]
4	 **17**	 **17a**	23	84[c]

[a]Acetone-d_6 solvent, RT, 2 mol% **1**, NMR yield. [b]Isolated. [c]5 mol% **1**; 11% **17** remaining (ratios of products).

only 2% of conjugated isomer **15b**[20] is formed, where this conversion may be catalyzed by **1** or by acid- or base-catalyzed enolization. Linear pent-4-en-1-yl systems **16** and **17** build up synthetically useful amounts of the *trans*-mono-isomerized species shown. The substituents on **16** may hinder catalyst approach to the H at C-2, as required for further isomerization; however, a similar result in the case of **17** suggests that other factors (e.g., substituent electronics or coordination) may play a role, which would be a subject of further investigation. In all cases shown, high selectivity for the (*E*)-2-alkene prevails.

The effects of branching presented by 1,1′-disubstituted alkenes were explored (Table 3). Of mechanistic more than

Table 3. Mono-isomerization of 1,1′-Disubstituted Alkenes to Trisubstituted Alkenes

Entry	Reactant	Product	Time (h)	Yield (%)
1	 **18**	 **18a**	29	99
2[c]	 **19**	 **19a**	2	97
3	 **20**	 **20a**	2	98
4	 **21**	 **21a**	26	30:70[b]
5[c]	**22**	**22a**	29	30:70[b]
6[c]	**23**	**23a**	20.5	20:80[b]
7[c]	**24**	**24a**	5	20:80

[a]Acetone-d_6, RT, 2 mol% **1**, NMR yield. [b]Equilibrium ratios also reached from reverse reaction. [c]70 °C.

practical interest, a polysulfone catalyst has shown to catalyze olefin migration in similar substrates at room temperature (RT) in high yields.[21] RajanBabu[11] recently optimized a multicomponent alkene isomerization system made from 5 mol% of $[(allyl)PdCl]_2$ or $[(allyl)NiBr]_2$, phosphine ligand, AgOTf, and an additive. The ratio of *E*:*Z* components within the product mixture was suggested to be based on the additive and also appeared to

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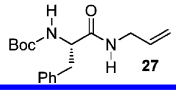
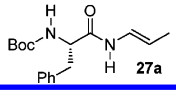
vary with substrate. In contrast, using single-component catalyst **1**, only the *E*-isomer of the product is formed, though in some cases in equilibrium with starting material. Branched alkene ether **18** is completely transformed into its enol ether **18a**, and branched hydrocarbons **19** and **20** are fully converted to trisubstituted alkenes **19a** and **20a**, respectively, all in less than 2 h. Alkenes illustrated in entries 4−7 reach an equilibrium mixture of terminal and internal alkenyl isomers. Disubstituted alkene **21**, studied previously,[4] affords an equilibrium mixture (30:70) of the starting disubstituted alkene **21** and product trisubstituted alkene **21a**. In each case, ~80% conversion to the corresponding *E*-trisubstituted product is achieved. After isomerization of **21**, **22**, and **23** to **21a**, **22a**, and **23a**, products were purified and isolated. When **21a**, **22a**, and **23a** were subjected to **1** for isomerization, each disubstituted alkene, **21**, **22**, and **23**, was regenerated in the same ratio as in the forward reaction. Trisubstituted alkenes **22a** and **23a** were subjected to RajanBabu conditions in several separate attempts but did not react, which leads to the conclusion the two catalyst systems differ in kinetic selectivity.[22] The RajanBabu catalyst system polymerized **24**, whereas entry 7 shows the mildness and functional group tolerance of **1** in its ability to isomerize **24** to (*E*)-**24a**. In summary, each disubstituted alkene is converted to the more stable trisubstituted alkene, and where an *E*:*Z* mixture is possible, only the *E*-analogue is formed.

Especially notable results (Table 4) using **1** are formation of sensitive enols and enamides. Typically enols are short-lived

Table 4. Formation of Enols and Primary Enamide Derivatives

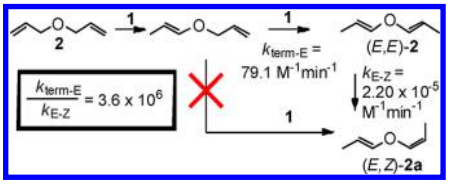
Entry	Reactant	Product	Time (min)	Yield (%)
1[a]	 **25**	 **25a**	5	96[c] (*E*:*Z* = 31:1)
2[b]	 **26**	 **26a**	60	97
3	 **27**	 **27a**	40[d] 5[b]	96 99 [78][e]

[a]Acetone-d_6, RT, 3 mol% **1**. NMR yield. [b]0.1 mol% **1**. [c]Also in mixture: 3% propanal and unreacted **25**. [d]0.6 mol% **1**. [e]Isolated.

due to favorable tautomerization to the keto forms, yet enols[23] and enamides[24] are useful synthetic intermediates and subunits in biologically active natural products, respectively. Bosnich[23a] generated simple enols via double bond migration using $[Rh(diphos)(solvent)_2]ClO_4$ activated by H_2, where it is thought that isomerization proceeds by alkene insertion into a Rh−H bond. The *cis*:*trans* ratios of the enols and the rate of subsequent tautomerization depended strongly on substrate. In the Bosnich work, allyl alcohol **25** gave 89% of enol **25a** as an isomeric mixture (*E*:*Z* = 1:1), along with 11% aldehyde, in 14 min at RT, whereas 2-phenylallyl alcohol led to 47% of the corresponding enol in all *Z*-configuration after 2 h. Table 4 illustrates the unique capability of **1** in giving (*E*)-enols and (*E*)-enamides. Remarkably, after 5 min (*E*)-enol **25a** is seen (93%) along with 3% of the *Z*-isomer, where both subsequently tautomerize to propanal. 2-Methyl-2-propenol (**26**) is quantitatively converted to the corresponding enol **26a** after 60 min with 0.1 mol% **1**, whereas according to Bosnich the keto analogue (4%) of **26a** begins to appear at 16 min and is completely tautomerized in 8 days.[23a] Amino acid allyl amides, such as **27**, were treated with Grubbs' metathesis catalyst, and isomerized products were significant components of the mixture [20% (*E*)-**27a** and 30% (*Z*)-**27a**].[24] In contrast, the action of **1** on **27** within 5 min exclusively forms (*E*)-**27a**. The success of **1** in making (*E*)-enol and enamide derivatives with very high selectivity is especially notable, because the *E* and *Z* geometrical isomers of such compounds are well-documented to be of comparable thermodynamic stability, with the *Z* form even predominating in some cases.[23,25,26]

Indeed, because *E*- and *Z*-isomers of many enols and enamides are of comparable stability, compelling evidence for unusually high kinetic selectivity using **1** comes from observing mixtures from **2** and **1** long after complete formation of **2a**. Strikingly, whereas 2 mol% of **1** isomerized **2** within 6 min, even when 20 mol% of **1** was applied, after 25 d, only 10% of (*Z*)-**2a** was seen (Scheme 1). Complete analysis of these and

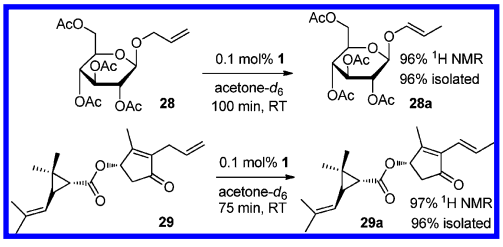
Scheme 1. Alkene Positional Isomerization Is Much Faster Than Geometrical Isomerization



similar reactions over several time points (see Supporting Information) allowed us to conclude that the ratio of rates for isomerization of **2** to (*E*)-**2a** and of further isomerization of (*E*)-**2a** to (*Z*)-**2a** must be over 3,600,000:1, a remarkable result.

Scheme 2 shows further examples of chemo- and stereoselective isomerization of polyfunctional biologically active

Scheme 2. Alkene Isomerization of Biologically Active Molecules at Low Catalytic Loading of 1



compounds by **1**. Carbohydrate **28** is a key starting material in the generation of an irreversible inhibitor of yeast hexokinase,[27] and both allyl and propenyl functional groups such as those in **28** and **28a** are used as protecting groups.[28,29] Compounds like **28a**, but with varying *E*:*Z* ratios, are made from isomers like **28** under strongly basic conditions (*t*-BuOK in DMSO[28]). Glucopyranoside **28** is converted by **1** with very low catalytic loading to (*E*)-propenyl isomer **28a**, isolated in 96% yield.

Bioallethrin (**29**) is a flexible pyrethroid pesticide[30] with three olefinic bonds. Pyrethroids demonstrate insecticidal actions based on their ability to adopt a certain conformation.[31] Novel pyrethroid **29a** is formed as a single alkene isomer, without perturbing the allylic ester functionality or the other two alkene units. Catalyst **1** enables selective structural alterations with the potential of leading to novel bioactive compounds.

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In summary, we show that very active catalyst **1** can be controlled to provide mono-isomerized alkene products with very high (>10^6:1) kinetic *E*-selectivity. These features are expected to make **1** an attractive tool in synthesis,[32] in part because the addition of an allylic substituent (e.g., to a carbonyl) is frequently easier than the installation of a propenyl analogue. Using **1**, allylic moieties can then be readily and cleanly converted to propenyl units in a controlled manner. Moreover, **1** allows facile access to the (*E*)-alkenyl aromatic compounds useful in the pharmaceutical and fragrance industries. Catalyst **1** achieves high *E*-selectivity in cases well-documented to be of comparable thermodynamic stability as their *Z*-isomers, such as enols, enol ethers, and enamides. In addition, the very mild, neutral reaction conditions under which **1** operates allow formation of enols, enamides, *β,γ*-unsaturated carbonyl compounds, and even multifunctional bioactive molecules. We believe that the heterocyclic phosphine ligand of **1** acts as a hemilabile base acting in cooperation with the metal to promote these selective transformations. Mechanistic studies are in progress to allow a greater understanding of the bifunctional system and further alter and enhance its unique reactivity, in addition to the possible applications and new chemistry catalyst **1** can provide.

■ ASSOCIATED CONTENT

Supporting Information

Details of substrate preparation, characterization, and catalysis. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

grotjahn@sciences.sdsu.edu

Notes

The authors declare no competing financial interest.

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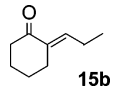

15b

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(32) Catalyst **1** is now available from Strem Chemicals. The work described here was finished before that event.

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