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A Pd-Catalyzed Site-Controlled Isomerization of Terminal Olefins

Wenlong Ren,[§] Fei Sun,[§] Jianxiao Chu, and Yian Shi*

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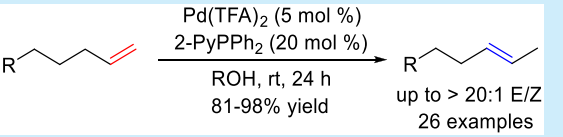
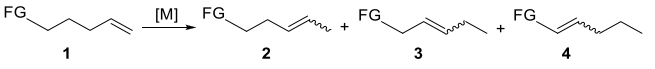
ABSTRACT: An effective Pd-catalyzed isomerization of olefins with 2-PyPPh$_2$ as the ligand is described. A wide variety of *trans*-2-olefins bearing various functional groups can be obtained with high regio- and stereoselectivity under mild reaction conditions. The ligand is crucial for the reaction.



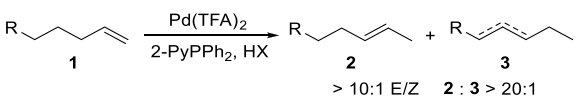
Olefins make up an important class of compounds in organic chemistry and serve as versatile intermediates for pharmaceuticals, materials, and fine chemicals. Olefin isomerization allows double bond migration from one position to another.[1] In principle, less accessible olefins can be synthesized from more readily available olefins via such a process. Terminal olefins are easy to obtain, and their isomerizations have been extensively studied (Scheme 1). Various processes have been

Scheme 1. Isomerization of Terminal Olefins



developed with Ru,[2] Pd,[3] Ir,[4] Co,[5] Ni,[6] Fe,[7] Mo,[8] Rh,[9] Zr,[10] Ti,[11] etc., as catalysts. Regio- and stereoselectivities are two key issues involved in such isomerization. A mixture of positional and geometric isomers could be produced during the reaction process. The site selectivity has been frequently controlled thermodynamically via conjugation to certain functional groups or sterically by certain branched substituents in substrates. In general, regio- and stereoselective isomerization relying on no such functional groups or substituents presents new challenges. Great progress has been made in this area, particularly with Ru,[2i,j,r] Ir,[4a,e] Co,[5b,c,e,g] and Pd[3i] catalysts. However, developing new systems with readily available catalysts is still highly desirable and appealing. During such studies, we have discovered that a simple combination of Pd(TFA)$_2$ and 2-PyPPh$_2$ is a highly effective catalyst for isomerization of terminal olefins to *trans*-2-olefins with >20:1 regioselectivity and >10:1 *E*:*Z* selectivity (Scheme 2). In this isomerization, the ligand plays an important role in directing the double bond migration. Such a catalyst-controlled process

Scheme 2. Pd-Catalyzed Regio- and Stereoselective Isomerization of Terminal Olefins



with high positional and geometric selectivities is not common for the Pd-catalyzed isomerization.

While the catalyst loading is higher than those of other related processes,[2r,4e] the current catalytic system can be prepared in situ simply from commercially available compounds. Herein, we wish to report our preliminary studies on this subject.

During our studies of Pd-catalyzed hydroesterification of olefins with HCO$_2$Ph,[12] we frequently observed some isomerized olefins in addition to the ester products. In some cases, only isomerized olefins were formed with Pd(TFA)$_2$ and 2-PyPPh$_2$. The extent of isomerization was found to be dependent on the purity of HCO$_2$Ph. We surmised that small amount of PhOH present in HCO$_2$Ph could be related to the isomerization. Considering the potential usefulness of the isomerization, we decided to carry out more detailed studies of this reaction process.

1-Dodecene (**1a**) was used as the test substrate for the initial studies. The isomerization indeed occurred when **1a** was treated with 5 mol % Pd(TFA)$_2$, 20 mol % 2-PyPPh$_2$, and 50 mol % PhOH in dichloroethane (DCE) at room temperature for 24 h, giving 2-dodecene in 44% conversion with 13:1 *E*:*Z* selectivity (Table 1, entry 1). Encouragingly, the isomerization was also regioselective with few other positional isomers being formed. Various other ligands were examined for the isomerization. Generally, poor results were observed with these ligands (Table 1, entries 2−5; for more studies, see Table S1, entries 6−10). No isomerization was detected when Pd(dba)$_2$ or Pd(OAc)$_2$ was used (Table S1, entry 11 or 12, respectively). In addition to PhOH, other proton sources were also examined for the reaction (Table 1, entries 6−14; for more studies, see the Supporting Information). Low conversions were obtained with EtOH, HFIP, and TsOH (Table 1, entries 7, 11, and 14, respectively). Good to high

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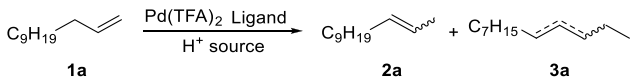
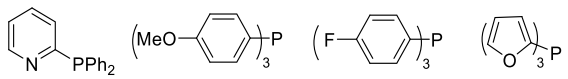
Table 1. Studies of the Reaction Conditions[a]



1a 2a 3a

entry	ligand	H^+ source	conversion (%)[b]	2a (%) (E:Z)[b]	3a (%)[b]
1	**L1**	PhOH	44	44 (13:1)	trace
2	PPh_3	PhOH	trace	–	–
3	**L2**	PhOH	0	–	–
4	**L3**	PhOH	trace	–	–
5	**L4**	PhOH	17	15 (2:3)	2
6	**L1**	F_5PhOH	99	87 (10:1)	12
7	**L1**	EtOH	trace	–	–
8[c]	**L1**	FCH_2CH_2OH	94	91 (13:1)	**3**
9	**L1**	F_2CHCH_2OH	97	89 (11:1)	8
10	**L1**	F_3CCH_2OH	75	74 (13:1)	1
11	**L1**	HFIP[d]	18	18 (10:1)	–
12	**L1**	HCOOH	87	85 (13:1)	2
13	**L1**	TFA	99	80 (5:1)	19
14	**L1**	$TsOH·H_2O$	37	36 (5:1)	1

[a]The reactions were carried out with **1a** (0.50 mmol), $Pd(TFA)_2$ (0.025 mmol), ligand (0.050 or 0.10 mmol, 4:1 P:Pd), and H^+ source (0.25 mmol) in DCE (0.30 mL) at rt (25–27 °C) for 24 h unless otherwise stated. [b]The conversion was determined by ^1H NMR analysis of the crude reaction mixture with BnOMe as the internal standard and also confirmed by ^1H NMR analysis of isolated products. The contents of **2a** and **3a** as well as the *E*:*Z* ratio of **2a** were determined by ^1H NMR analysis of isolated products (ref 13). [c]Conversion of 33% obtained with 0.10 mmol of FCH_2CH_2OH. [d]HFIP = hexafluoroisopropanol.



L1 L2 L3 L4

conversions were achieved with F_5PhOH, FCH_2CH_2OH, F_2CHCH_2OH, F_3CCH_2OH, HCOOH, and TFA (Table 1, entries 6, 8–10, 12, and 13, respectively). Somewhat lower *E*:*Z* selectivity was obtained with TFA. Overall, FCH_2CH_2OH gave the best result with regard to conversion as well as regio- and stereoselectivity. Various solvents were further investigated (Table S1, entries 25–27). Comparable results were obtained with dichloromethane (DCM). Low conversions were observed with solvents like $PhCH_3$ and THF. No isomerization occurred at 0 °C (Table S1, entry 28). The *E*:*Z* selectivity was somewhat decreased at higher reaction temperatures (Table S1, entries 29 and 30).

With the optimized reaction condition in hand, the substrate scope for the isomerization was investigated. As shown in Table 2, the isomerization process can be extended to a wide variety of alkyl terminal olefins, giving the corresponding *trans*-2-olefins in 89–98% yields (Table 2, entries 1–12). The reaction is compatible with various functionalities, including phenyl, cyclopropyl, Cl, OH, OMe, OTBDPS, CHO, acetal, CO_2H, *α*,*β*-unsaturated ester, and phthalimide. The *trans*-olefins were predominately formed with generally high *E*:*Z* selectivity (>10:1). A slightly lower *E*:*Z* ratio (8:1) was obtained for 5-hexenoic acid (Table 2, entry 10). Allyl benzenes (**1m**–**1o**), allyl phosphate (**1p**), 1-phenyl-3-buten-1-ol (**1q**), and 2-allylcyclohexanone (**1r**) were effective substrates. The corresponding *trans*-2-olefins were isolated in 81–97% yields with excellent *E*:*Z* ratios (>20:1) (Table 2, entries 13–18). The reaction process could also be applied to exocyclic olefins, giving the cyclic trisubstituted olefins in 89–95% yields (Table 2, entries 19 and 20). With substrates containing two or three terminal double bonds, all double bonds smoothly migrated to give the corresponding *trans*-2-olefins in 93–94% yields with high *E*:*Z* selectivities (Table 2, entries 21 and 22). The isomerization can proceed selectively on the monoterminal olefins when other types of olefins were present in reacting substrates (Table 2, entries 23 and 24). It should be noted that the isomerization was also highly regioselective. In nearly all cases, few (<5%) positional isomers were detected. In the case of 1-phenyl-3-buten-1-ol (Table 2, entry 17), certain amounts (~14%) of the 1-phenylbutan-1-one resulting from further isomerization of allylic alcohol **2q** were formed. The isomerization process also worked well with a nucleoside (**1y**) and a steroid (**1z**), giving the corresponding products in 83–90% yields (Scheme 3). The reaction is amenable to gram scale synthesis as illustrated in Scheme 4.

To further explore the ligand effect, several 2-$PyPPh_2$ analogues were investigated with 1-dodecene (**1a**) (see Table S2). Little isomerization was observed with **L5** and **L6** (Table S2, entries 2 and 3, respectively), indicating the pyridine nitrogen position is also crucial for the reaction. More overisomerization occurred with the 6-Me-pyridine ligand (**L7**) (Table S2, entry 4). High reactivities were displayed with ligands containing tolyl groups (**L8**–**L10**) (Table S2, entries 5–7, respectively). However, substantial overisomerization and significantly lower *E*:*Z* selectivity were obtained with **L8**. Among these ligands, ligand **L1** gave overall the best results with high *E*:*Z* selectivity and minimal overisomerization.

To further understand this catalytic system, various reaction parameters were investigated with 1-dodecene (**1a**) (see Table S3). The Pd:P ratio was found to be important (Table S3, entries 1–4). Little reaction was observed with a 1:1 or 1:2 Pd:P ratio. Control experiments showed $Pd(TFA)_2$, ligand **L1**, and the H^+ source are all required for the reaction (Table S3, entries 5–7, respectively). No reaction occurred without $Pd(TFA)_2$ or a H^+ source. Low conversion (12%) and a low *E*:*Z* ratio (2:1) were obtained without ligand **L1**. Some isomerization was observed with $Pd(TFA)_2$ alone (Table S3, entry 8). The conversion increased dramatically as more TFA was added (Table S3, entries 9–11). Only trace amounts of isomerized olefins were detected with TFA alone (Table S3, entry 12). The $Pd(TFA)_2$-catalyzed isomerization likely proceeded via the formation of a *π*-allyl Pd species and subsequent protodepalladation by TFA.[3b]

Further studies showed that the Pd source was also important for the reaction. No or little isomerization occurred with $PdCl_2$ or $Pd(OAc)_2$ (Table S3, entry 13 or 14, respectively). On the other hand, $Pd(NO_3)_2$ was as effective as $Pd(TFA)_2$ (Table S3, entry 15). No reaction occurred with $Pd(dba)_2$, **L1**, and FCH_2CH_2OH (Table S3, entry 16). The isomerization proceeded in 57% conversion with a 2:1 *E*:*Z* ratio without **L1** (Table S3, entry 17). Interestingly, results similar to those under the standard conditions were obtained with $Pd(dba)_2$, **L1**, and TFA (Table S3, entry 18 vs entry 1). The *E*:*Z* ratio dropped to 2:1 in the absence of **L1** (Table S3, entry 19), illustrating the importance of the ligand to the selective isomerization. The acidity of the H^+ source also appeared to be important for the efficiency of the reaction (Table S3, entry 16 vs entry 18). Taken together, it is likely that under the standard conditions, Pd(II) was reduced to Pd(0) and small amounts of TFA could be generated from $Pd(TFA)_2$ and FCH_2CH_2OH.

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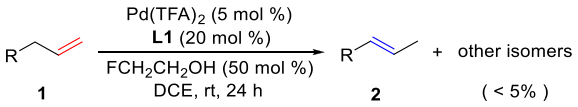
Table 2. Pd-Catalyzed Site-Controlled Isomerization of Olefins[a]



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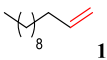
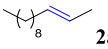
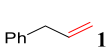
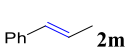
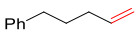
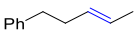
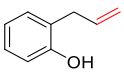
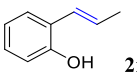
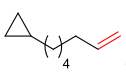
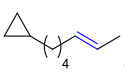
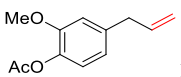
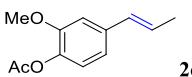
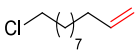
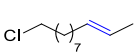
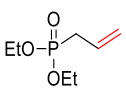
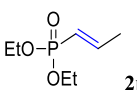
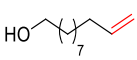
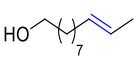
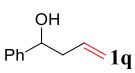
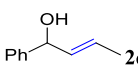
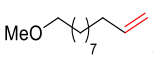
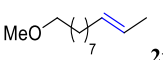
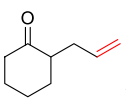
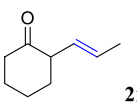
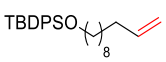
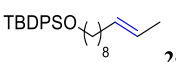
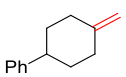
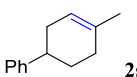
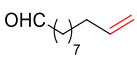
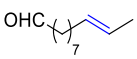
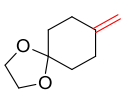
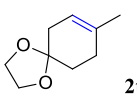
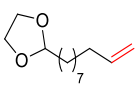
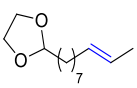
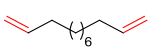
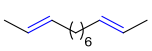
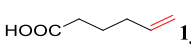
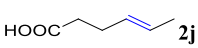
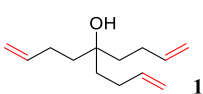
1	 1a	 2a	95 (13:1)	13	 1m	 2m	85 (20:1)
2	 1b	 2b	90 (15:1)	14	 1n	 2n	90 (> 20:1)
3	 1c	 2c	89 (13:1)	15	 1o	 2o	97 (> 20:1)
4	 1d	 2d	95 (12:1)	16[h]	 1p	 2p	90 (> 20:1)
5[c]	 1e	 2e	96 (13:1)	17[i]	 1q	 2q	81 (> 20:1)
6[d]	 1f	 2f	94 (11:1)	18[j]	 1r	 2r	91 (> 20:1)
7[e]	 1g	 2g	98 (nd)	19[h]	 1s	 2s	95 (--)
8[f]	 1h	 2h	95 (13:1)	20[h]	 1t	 2t	89 (--)
9[e]	 1i	 2i	95 (12:1)	21[k]	 1u	 2u	94 (13:1)
10	 1j	 2j	96 (8:1)	22	 1v	2v	93 (>20:1)
11	1k	2k	98 (13:1)	23[l]	1w	2w	95 (9:1)
12[g]	1l	2l	97 (14:1)	24	1x	2x	91 (12:1)

[a]The reactions were carried out with substrate **1** (0.50 mmol), $Pd(TFA)_2$ (0.025 mmol), **L1** (0.10 mmol), and FCH_2CH_2OH (0.25 mmol) in DCE (0.30 mL) at rt (25−27 °C) for 24 h unless otherwise stated. [b]Isolated yields (containing 0−11% unreacted **1**, <5% other isomers). The *E*:*Z* ratios were determined by ^1H NMR analysis of the crude reaction mixture and isolated products (ref 13); for entry 7, the *E*:*Z* ratio was not determined due to the signal overlap. [c]For 36 h without FCH_2CH_2OH. [d]With 0.30 mL of EtOH instead of FCH_2CH_2OH and DCE at 50 °C for 24 h. [e]For 36 h. [f]For 19 h. [g]With 0.30 mL of F_3CCH_2OH instead of FCH_2CH_2OH and DCE at rt for 48 h. [h]With F_5PhOH (0.50 mmol) at 50 °C for 24 h. [i]With 0.30 mL of F_3CCH_2OH instead of FCH_2CH_2OH and DCE at rt for 24 h. [j]F_5PhOH (0.10 mmol) at rt for 30 h. [k]For 30 h. [l]At 50 °C.

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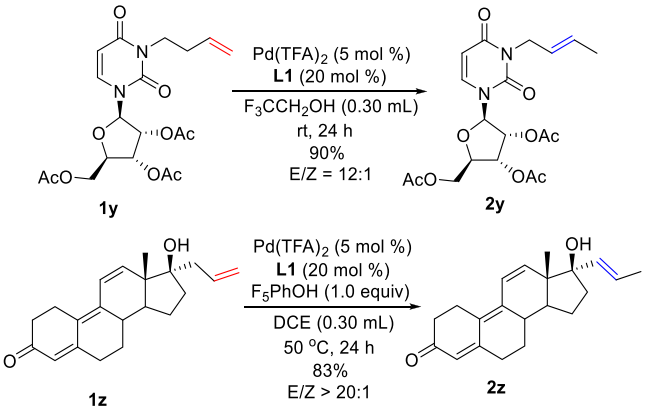
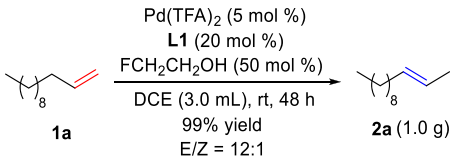
Scheme 3. Isomerization of the Functionalized Olefin

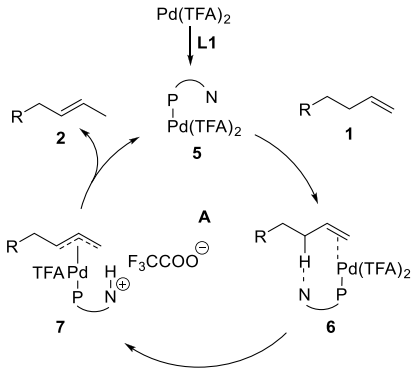


Scheme 4. Gram Scale of the Isomerization of the Olefin

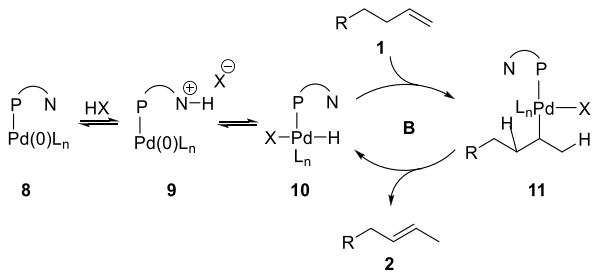


The exact mechanism is currently unclear. Two frequently proposed mechanisms are outlined in Schemes 5 and 6,

Scheme 5. Isomerization via π-Allyl Pd Species



Scheme 6. Isomerization via Pd−H Species



respectively. One involves an allylic H-abstraction of Pd−olefin complex **6** to form π-allyl Pd species **7**, which is protonated to give isomerized olefin **2** (Scheme 5).[3b,f] The other involves the formation of Pd−H species **10**, which hydropalladates the olefin to give alkyl Pd complex **11**. Isomerized olefin is subsequently generated from **11** upon β-H elimination (Scheme 6).[3c,d,k,i] It is also possible that alkyl Pd complex **11** could be generated from the olefin and complex **9** via protopalladation by direct transfer of the proton from the pyridine to the double bond.[14] Other reaction pathways cannot be ruled out at present. The pyridine could also serve as a ligand to the Pd.[15,16] NMR studies were attempted for the reaction process. No conclusive information was obtained thus far. A precise understanding of the reaction mechanism awaits further studies.

In summary, we have developed an efficient isomerization process to convert terminal olefins to *trans*-2-olefins with $Pd(TFA)_2$ as the catalyst and diphenyl-2-pyridylphosphine (**L1**) as the ligand in the presence of additives such as FCH_2CH_2OH. A variety of *trans*-2-olefins bearing various functional groups can be obtained in 81−98% yields with generally >20:1 site selectivities and >10:1 *E*:*Z* ratios under mild reaction conditions. The reaction was operationally simple and can be carried out on a gram scale. The pyridine-containing ligand is crucial for both regio- and stereoselectivities. Further understanding the reaction mechanism and developing a more effective olefin isomerization process are currently being pursued.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00168.

Experimental procedures, characterization data, and NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Yian Shi − *Institute of Natural and Synthetic Organic Chemistry, Changzhou University, Changzhou 213164, China; Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523, United States;* orcid.org/0000-0001-9016-2078; Email: Yian.Shi@colostate.edu

Authors

Wenlong Ren − *Institute of Natural and Synthetic Organic Chemistry, Changzhou University, Changzhou 213164, China;* orcid.org/0000-0002-2028-4667

Fei Sun − *Institute of Natural and Synthetic Organic Chemistry, Changzhou University, Changzhou 213164, China*

Jianxiao Chu − *Institute of Natural and Synthetic Organic Chemistry, Changzhou University, Changzhou 213164, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c00168

Author Contributions

[§]W.R. and F.S. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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