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[Pd(μ-Br)(P^{t}Bu$_3$)]$_2$ as a Highly Active Isomerization Catalyst: Synthesis of Enol Esters from Allylic Esters

Patrizia Mamone, Matthias F. Grünberg, Andreas Fromm, Bilal A. Khan, and Lukas J. Gooßen*

FB Chemie – Organische Chemie, TU Kaiserslautern, Erwin-Schrödinger-Str. Geb. 54,
67663 Kaiserslautern, Germany

goossen@chemie.uni-kl.de

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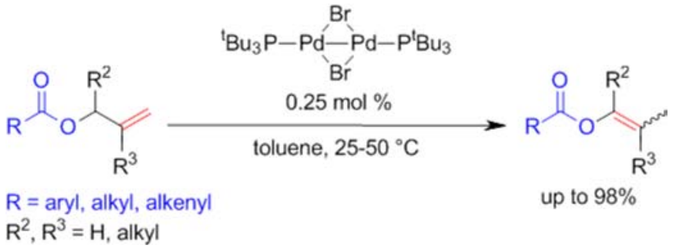
ABSTRACT



The dimeric Pd(I)-complex [Pd(μ-Br)(P^{t}Bu$_3$)]$_2$ was found to be highly active for catalyzing double-bond migration in various substrates such as unsaturated ethers, alcohols, amides, and arenes, under mild conditions. It efficiently mediates the conversion of allylic esters into enol esters, rather than inserting into the allylic C–O bond. The broad applicability of this reaction was demonstrated with the synthesis of 22 functionalized enol esters.

Enol esters are important precursors in a variety of organic transformations such as aldol- and Mannich type reactions,[1] asymmetric hydrogenations,[2] cycloadditions,[3] or other cyclization reactions to afford, e.g., heterocycles or chromones.[4] They are employed as auxiliary reagents in the desymmetrization of alcohols,[5] as well as in the synthesis of vinylic amino alcohols and diols.[6]

Classical approaches to their synthesis involve transesterification between alkyl esters and enol acetates, or *O*-acylation of enolates.[7] However, these require stoichiometric amounts of bases, acids, or toxic mercury salts. Modern, catalytic syntheses of enol esters include the Zr-catalyzed methylalumination of alkynes,[8] the Cu-catalyzed oxidative esterification of aldehydes with β-dicarbonyl compounds,[9] the Au-catalyzed intramolecular rearrangements of propargylic esters and alcohols,[10] the Fe-catalyzed asymmetric coupling of ketenes with aldehydes,[11] and the addition of carboxylic acids to alkynes catalyzed by Ru,[12] Ru–Re,[13] or Rh complexes.[14]

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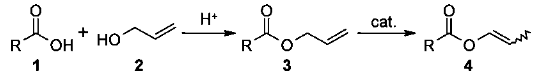
10.1021/ol301563g

Scheme 1. Synthesis of Enol Esters via Catalytic Isomerization



The catalytic isomerization of allylic esters to enol esters would be an attractive alternative to the above approaches, because the starting materials are easily accessible by esterification of carboxylic acids (Scheme 1). However, because of the weak thermodynamic driving force for the double-bond migration and the tendency of many metal catalysts to insert into the C(allyl)–O bond with formation of stable carboxylate complexes,[15] this reaction is beyond the performance limit of most isomerization catalysts. Even for unsubstituted allyl esters, only two reports of double-bond migrations exist. Iranpoor et al. found that stoichiometric amounts of $Fe_3(CO)_{12}$ promote this reaction when irradiated with UV light.[16] Krompiec et al. achieved up to eight catalytic turnovers for the double-bond migration, along with C(allyl)–O bond cleavage, using the ruthenium hydride complex $RuClH(CO)(PPh_3)_3$.[17] Mechanistic studies by Tokunaga et al. confirmed the low catalytic activity of Ru complexes for this type of substrate.[18]

In the context of our research on isomerizing functionalizations of fatty acids,[19] we had thoroughly investigated the activity of various isomerization methods involving acid[20] or base mediators,[21] as well as metal catalysts reported for the isomerization of alkenes,[22] allylic benzenes,[23] allylic ethers,[15,24] allylic silyl ethers,[25] alkenyl alcohols,[26] allylic amines and amides.[27] However, none of these systems permitted to convert our test substrate, oleic acid, into an equilibrium mixture of isomers within a few hours at catalyst loadings below 1%.[19]

In our search for new lead structures for highly active isomerization catalysts, reports by Mingos/Vilar and Hartwig on the dimeric palladium complex $[\mathrm{Pd}(\mu\text{-Br})(\mathrm{P}^t\mathrm{Bu}_3)]_2$ caught our attention.[28] They discovered that this unusual, dimeric Pd^{I} species, which has found applications in catalytic cross-coupling reactions,[29] can be converted into hydridopalladium(II) complexes under remarkably mild conditions. We reasoned that a metal complex with such strong tendency to form Pd–H species, which are known to add across C–C double-bonds,[22,30] should also be an excellent catalyst for alkene isomerization. Indeed, oleic acid was converted to an equilibrium mixture of double-bond isomers with only 0.5 mol % of $[\mathrm{Pd}(\mu\text{-Br})(\mathrm{P}^t\mathrm{Bu}_3)]_2$ within less than an hour.[31]

The high activity of this one-component system led us to evaluate the catalytic activity of the Pd^{I} dimer as the catalyst for double-bond migrations in a range of standard test substrates. As a reference system, we used a mixture of $Pd(dba)_2$, isobutyryl chloride, and tri(*tert*-butyl)phosphine. This catalyst has been shown by Lindhardt and Skrydstrup to set new standards with regard to catalytic activity and functional group tolerance for single-carbon migrations of various double bonds.[32] The examples in Scheme 2 demonstrate that the Pd^{I} dimer is an effective catalyst for double-bond migrations in allylic arenes (**5**), amides (**7**), ethers (**9**), and alcohols (**11** and **13**). In each case, the catalyst loading was reduced to the minimum effective level, in order to differentiate between the systems. For all substrate classes, the Pd^{I} dimer compared favorably even to the state-of-the-art Pd-catalyst for single-carbon migration of the double-bond. It is also able to move the bond over longer alkyl chains. Thus, hexanal (**14**) was obtained from 5-hexen-1-ol (**13**) in high yield and selectivity.

The most striking result obtained in this series of test reactions was that allyl benzoate (**3a**) was cleanly converted to the corresponding enol ester **4a**. Using only 0.25 mol % of Pd^{I} in toluene, near-quantitative conversion to 1-propenyl benzoate (**4a**) was achieved within 2 h at 50 °C, with a product (*E*/*Z*)-ratio of 1:2. The only other component detected in the reaction mixture was 2% of the

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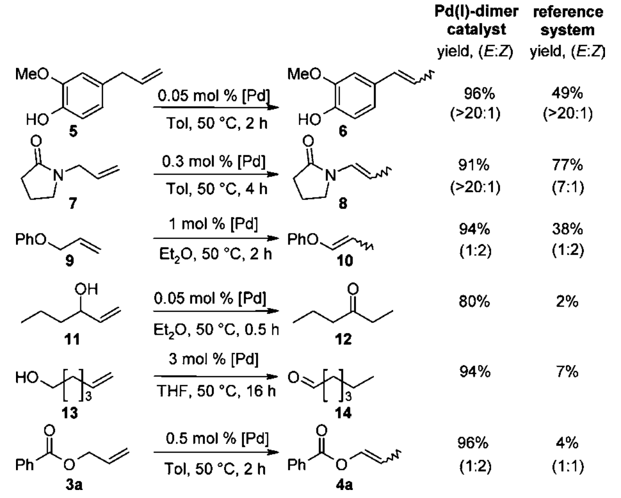
Scheme 2. Double-Bond Migration with the Pd^I Catalyst[33]



starting material **3a**, which did not disappear even after a prolonged reaction time, indicating that the equilibrium had been reached. In view of the rich chemistry of allylic acetate activation by palladium catalysts, it was surprising that no trace of benzoic acid arising from C(allyl)−O bond cleavage was observed.[34,15]

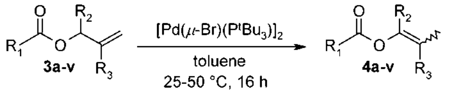
Encouraged by the observation that equilibration occurs so rapidly and that its position lies so far on the side of the enol esters, we optimized the catalyst loading and reaction conditions[33] and then explored the scope of the reaction protocol. As can be seen from the examples in Table 1, the reaction is broadly applicable with regard both to the carboxylate and allyl alcohol side of the esters.[35]

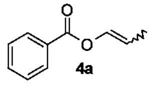
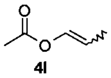
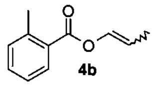
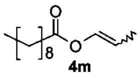
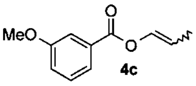
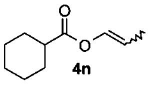
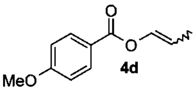
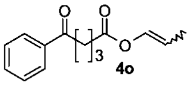
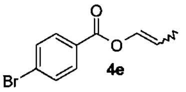
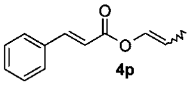
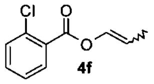
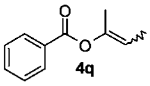
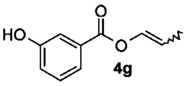
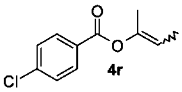
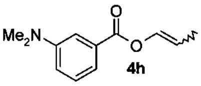
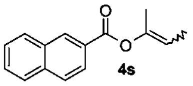
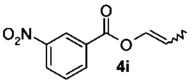
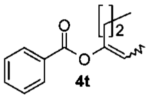
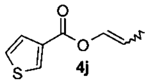
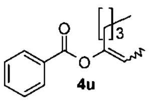
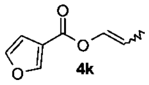
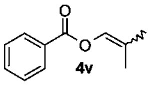
Allylic esters of electron-rich and electron-deficient aromatic (**4a**−**i**), heteroaromatic (**4j**,**k**), aliphatic (**4l**−**o**), and cinnamic (**4p**) carboxylates were successfully converted.

A variety of functionalities including alkoxy (**4c**,**d**), hydroxy (**4g**), amino (**4h**), nitro (**4i**), and keto groups (**4o**) were tolerated. Even halogen-containing substrates reacted smoothly without any indication of competing Heck-type reactions (**4e**,**f**). In all cases, (*E*:*Z*)-ratios between 1:2 and 1:5 were obtained.

The allyl residue can be linear or branched in the 1- and/or 2-positions (**4q**−**v**). Enol esters branched in the 1-position are of considerable interest as substrates for enantioselective hydrogenations, but because of their limited availability, there are only few reports on such reactions.[2,36] We were thus pleased to find that compounds **4q**−**u** can be hydrogenated in high yields and enantiomeric excess (Scheme 3).[37] This demonstrates the viability of

Table 1. Isomerization of Allylic Esters to Enol Esters[f]



product	yield [%]/(*E*:*Z*)	product	yield [%]/(*E*:*Z*)
 **4a**	90 (1:2)	 **4l**	97[a,c] (1:2)
 **4b**	98 (1:2)	 **4m**	89 (1:2)
 **4c**	90 (1:2)	 **4n**	80 (1:2)
 **4d**	91 (1:2)	 **4o**	88 (1:2)
 **4e**	73 (1:2)	 **4p**	96 (1:2)
 **4f**	91[a] (1:2)	 **4q**	83[a] (1:3)
 **4g**	98[b] (1:2)	 **4r**	93[a] (1:3)
 **4h**	91[b] (1:2)	 **4s**	95[a] (1:3)
 **4i**	87[b] (1:1)	 **4t**	87[a,d] (1:5)
 **4j**	56[b] (1:2)	 **4u**	88[a,d] (1:5)
 **4k**	76 (1:2)	 **4v**	77[e]

[a] $[\mathrm{Pd}(\mu\text{-Br})(\mathrm{P}^t\mathrm{Bu}_3)]_2$ (0.50 mol %). [b] $[\mathrm{Pd}(\mu\text{-Br})(\mathrm{P}^t\mathrm{Bu}_3)]_2$ (2.50 mol %). [c] Yield and (*E*/*Z*)-selectivity was determined by NMR with anisole as internal standard. [d] 25 °C, 10% of other isomers. [e] $[\mathrm{Pd}(\mu\text{-Br})(\mathrm{P}^t\mathrm{Bu}_3)]_2$ (1.00 mol %). [f] Reaction conditions: Allylic esters **1a**−**v** (1.00 mmol), $[\mathrm{Pd}(\mu\text{-Br})(\mathrm{P}^t\mathrm{Bu}_3)]_2$ (0.25 mol %), 2 mL of toluene, 50 °C, 16 h, isolated yields. (*E*/*Z*)-selectivity was determined by GC.

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(33) For details, see the Supporting Information.

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(35) Synthesis of 1-propenyl benzoate (**4a**): Under a nitrogen atmosphere, a 50 mL vessel was charged with di-*μ*-bromobis(tri-*tert*-butylphosphine)dipalladium(I) (27.2 mg, 35.0 *μ*mol), allyl benzoate (**3a**) (1.76 g, 10.0 mmol), and toluene (20 mL). The mixture was stirred at 50 °C for 16 h, diluted with diethyl ether (40 mL), and filtered through a pad of celite (5 g), and the solvent was removed in vacuo (50 mbar, 40 °C). The crude product was purified by column chromatography (SiO_2, diethyl ether/*n*-pentane gradient) to give prop-1-enyl benzoate (**4a**) (1.65 g, 94% yield, *E*:*Z* 1:2) as colorless liquid.

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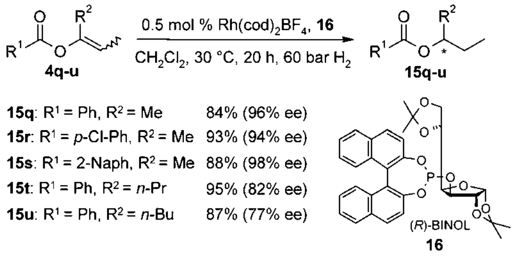
Scheme 3. Rh-Catalyzed Asymmetric Hydrogenation of Enol Esters

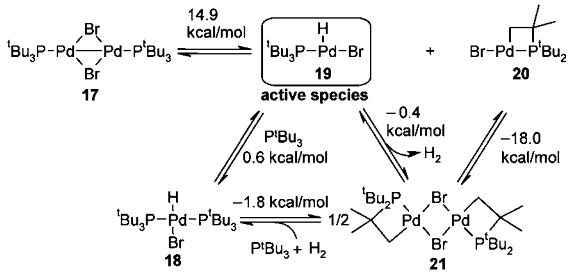


enantioselective syntheses via a double-bond isomerization/asymmetric hydrogenation sequence.

In order to evaluate how the catalytically active species may form from the Pd$^{\mathrm{I}}$ dimer, we calculated the standard Gibbs free energy ($\Delta_{\mathrm{R}}G^{\ominus}$) for the formation of various Pd-hydride species using the B3LYP density functional.[33] The lowest energy expenditure was calculated for the formation of Pd hydride **19** along with the monomeric palladacycle **20** ($\Delta_{\mathrm{R}}G^{\ominus}$ = 14.9 kcal/mol) (see Table S3 (Supporting Information) and Scheme 4). Since this reaction proceeds via an endergonic pathway, the driving force for the formation of **19** is the concomitant dimerization of **20** to the stable palladacycle **21** ($\Delta_{\mathrm{R}}G^{\ominus}$ = −18 kcal/mol).

The Pd−H complex **19** likely acts as the catalytically active species, but because of its high reactivity, we were not surprised to detect the oxidized dimeric palladacycle **21** as major signal when monitoring the catalytic reaction by ^{1}H and ^{31}P NMR (^{31}P NMR: −8.6 ppm). A minor signal at −9.0 ppm also appeared, which might originate from an isomer of **21**. It is known that **21** can also form from Pd−H species **18**, with concomitant release of a phosphine and hydrogen gas.[38] Moreover, **21** may result from the decomposition of **19** after it has achieved the double bond migration. Another experimental result that supports **19** as the catalytically active species is that upon trapping with tri-*tert*-butylphosphine, the more stable bis(*tert*-butylphosphino)palladium hydride complex **18** was detected (^{1}H NMR: triplet at −15.6 ppm).[28a]

Scheme 4. Proposed Activation of the Pd$^{\mathrm{I}}$ Dimer



Starting from **19**, a possible mechanism for the isomerization reaction would involve an insertion of the alkene into the Pd−hydride **19** followed by β-hydride elimination with formation of the isomerized olefin and regeneration of the initial Pd−hydride **19**. Further mechanistic investigations to elucidate the origin of the high isomerization activity of [Pd(μ-Br)(P^{t}Bu$_3$)]$_2$ are underway.

In conclusion, the Pd$^{\mathrm{I}}$ dimer [Pd(μ-Br)(P^{t}Bu$_3$)]$_2$ possesses a new level of reactivity for catalyzing double bond migrations in a wide range of unsaturated substrate classes. It even catalyzes the isomerization of allylic esters to the corresponding enol esters, which are valuable starting materials, e.g., for asymmetric hydrogenation.

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Supporting Information Available. Screening table, experimental procedures, characterization of all new compounds, and data of DFT calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.