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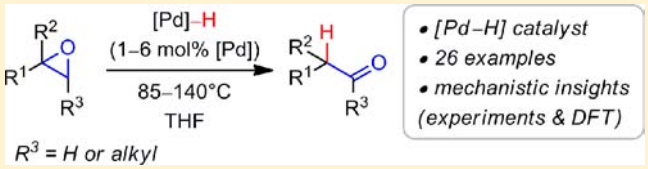
Isomerization of Terminal Epoxides by a [Pd−H] Catalyst: A Combined Experimental and Theoretical Mechanistic Study

Devendra J. Vyas,[†] Evgeny Larionov,[†] Céline Besnard,[‡] Laure Guénée,[‡] and Clément Mazet*[,†]

[†]Department of Organic Chemistry, University of Geneva, Quai Ernest Ansermet 30, 1211 Geneva 4, Switzerland
[‡]Laboratoire de Crystallographie, University of Geneva, Quai Ernest Ansermet 24, 1211 Geneva 4, Switzerland

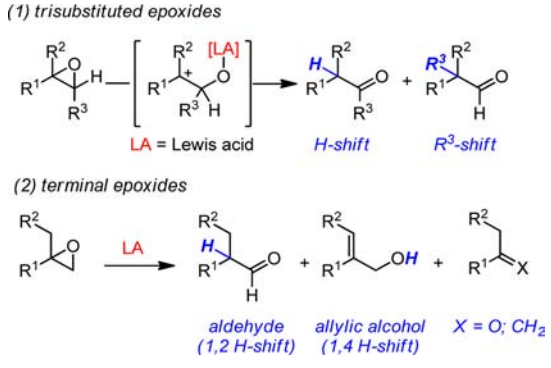
Supporting Information

ABSTRACT: An unusual palladium hydride complex has been shown to be a competent catalyst in the isomerization of a variety of terminal and internal epoxides. The reaction displayed broad scope and synthetic utility. Experimental and theoretical evidence are provided for an unprecedented hydride mechanism characterized by two distinct enantio-determining steps. These results hold promise for the development of an enantioselective variant of the reaction.



The isomerization of epoxides into the corresponding carbonyl derivatives is a reaction that bears substantial synthetic potential.[1,2] Starting from readily accessible substrates, it provides a straightforward access to either ketones or aldehydes—arguably two of the most valuable and prevalent functions in synthesis. Surprisingly, this seemingly simple isomerization still belongs to the repertoire of promising chemical reactions for which the potentialities have yet to be fully revealed. Indeed, although many Lewis acids have been employed to perform this transformation, the number of catalytic rather than stoichiometric versions remains limited.[3] More importantly, the outcome of the reaction strongly depends on the substitution pattern of the starting epoxide and the often modest regioselectivity of the transformation usually delivers complex mixtures of products. From a mechanistic standpoint, the lack of predictability is usually attributed to the competition between hydrogen migration and alkyl migration upon opening of the epoxide after activation by the Lewis acid (Scheme 1, eq 1). Examples of stereospecific isomerizations of epoxides are very rare.[4] Although the kinetic resolution of racemic 2,3-disubstituted and trisubstituted epoxides has been documented, the main focus was to access either enantioenriched epoxides or enantioenriched allylic alcohols.[5] A variant of this transformation using terminal epoxides yet remains to be developed. Importantly, such a *redox economical*[6] process would provide a direct route to chiral aldehydes with a tertiary α-stereocenter. Strategies to access this family of stereolabile compounds in high enantiopurity are quite limited.[7,8]

Scheme 1. Lewis Acid Mediated or Catalyzed Rearrangement of Epoxides



Herein, we report on the preparation of a well-defined Pd(II)-hydride which catalyzes the isomerization of a variety of epoxides with perfect regioselectivity and in practical yields. In the case of 2,2-disubstituted epoxides, evidence is provided for an unprecedented stereodivergent mechanism characterized by two distinct enantio-determining steps which highlights the potential of this method in asymmetric catalysis.

Mechanistic studies on the isomerization of trisubstituted epoxides are scarce and the rearrangement shown in Scheme 1 has been generally admitted rather than truly demonstrated. Alternatives have been proposed in rare occasions.[9−11] Terminal epoxides tend to undergo additional rearrangements and, aside from the desired aldehydes, allylic alcohols, alkenes or ketones are often formed in substantial amounts (Scheme 1, eq 2).[3d]

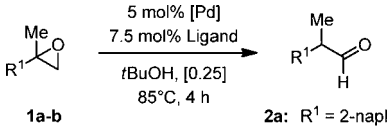
Kulawiec and co-workers have reported that a catalytic combination of $Pd(OAc)_2$ and PPh_3 efficiently isomerized a few 2,3-disubstituted epoxides in *t*BuOH at elevated temperatures.[11c] Isomerization of 2-methyl-2-(2-naphthyl)-oxirane **1a** into 2-(naphthyl)-propanal **2a** was the sole example involving a terminal epoxide; a reaction for which a S_N2-type mechanism was proposed.[11c,d] It was also shown that **2a** enolizes under the protic reaction conditions employed.[11b] Despite this significant shortcoming, we considered this study as a potential entry for

Received: January 11, 2013
Published: March 25, 2013

dx.doi.org/10.1021/ja400325w | J. Am. Chem. Soc. 2013, 135, 6177−6183

the development of an asymmetric isomerization of terminal epoxides. Although we were able to reproduce the result reported by Kulawiec and co-workers, more representative epoxides such as **1b** were unreactive under the same conditions (Table 1). Much to our delight, the use of a chelating ligand

Table 1. Optimization Study



1a-b

2a: R^1 = 2-naphthyl
2b: R^1 = phenyl

entry[a]	epoxide	[Pd]	ligand	conv. (%)[b]
1	**1a**	$Pd(OAc)_2$	PPh_3[c]	98[d]
2	**1b**	$Pd(OAc)_2$	PPh_3[c]	nr[e]
3	**1b**	$Pd(OAc)_2$	dppp	98
4	**1b**	$Pd(PPh_3)_4$		nr
5	**1b**	$Pd(dba)_2$		nr
6	**1b**	$Pd(PtBu_3)_2$		nr
7	**1b**	$Pd(dba)_2$	dppp	nr
8	**1b**	$Pd(PtBu_3)_2$	dppp	38
9	**1b**	$Pd(PtBu_3)_2$	dippp	98

[a]Average of two experiments. [b]Determined by GC. [c]15 mol %. [d]Repeated according to ref 11c. [e]No reaction.

(dppp = 1,3-bis-(diphenylphosphino)-propane) restored the catalytic activity and **2b** was obtained quantitatively (entry 1−3). A rapid survey of the most common organic solvents revealed a dichotomous situation since only *t*BuOH proved viable whereas all other options left the substrate unreacted (see Supporting Information). Questioning whether the initial step of the catalytic cycle proposed by Kulawiec and co-workers would really consist in reduction of Pd(II) to Pd(0), we evaluated various commercially available Pd(0) sources (entry 4−9). Neither $[Pd(PPh_3)_4]$, $[Pd(dba)_2]$ (dba = dibenzylideneacetone), $[Pd(PtBu_3)_2]$, nor a mixture of $[Pd(dba)_2]$ and dppp, proved competent in the isomerization of **1b**. Under otherwise identical conditions, a combination of $[Pd(PtBu_3)_2]$ and dppp delivered **2b** in 38% conversion (entry 8). The more sterically demanding and electron-rich dippp ligand (dippp = 1,3-bis(di-*iso*propylphosphino)propane) afforded **2b** in 98% conversion (entry 9).

Suspecting a [Pd−H] species might be responsible for the catalytic activity in the isomerization of **1b** to **2b**, we attempted to isolate a well-defined complex following a protocol similar to that developed by Bunel and co-workers.[12] Reaction of $[Pd(PtBu_3)_2]$ with 1.8 equiv of dippp in toluene at 70 °C, afforded the known dinuclear palladium complex $[Pd_2(dippp)_3]$.[13] Subsequent treatment with 1.35 equivalents (per Pd) of trifluoromethanesulfonic acid in diethyl ether at room temperature provided quantitatively the corresponding dinuclear palladium hydride **3**. The solution structure of **3** was established by spectroscopic and spectrometric analyses and was found to be consistent with the result of an X-ray diffraction study (Figure 1).[14] In the solid state, each Pd atom is chelated by one dippp ligand in a boat-like conformation (P−Pd−P = 93.60° and 99.37°) and both are bridged by the third dippp. The hydrides have been located *cis* to the monodentate P-donor. Each Pd atom lies in a slightly distorted square planar geometry and, while one [(dippp)PdH] unit is nearly coplanar with the linear propane chain of the bridging dippp ligand, the other is almost perpendicular.

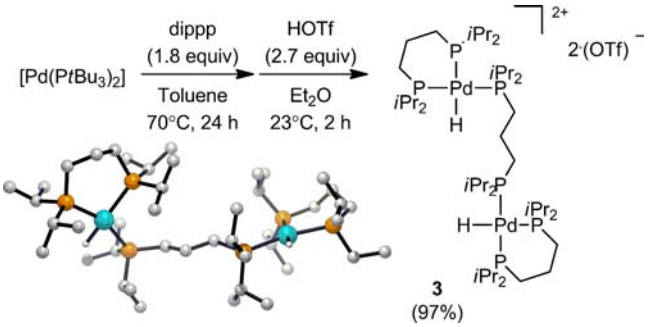


Figure 1. Synthesis and X-ray analysis for complex **3**.

We next investigated the aptitude of complex **3** to perform the isomerization of **1b** into **2b**. Among the different solvents surveyed (toluene, benzene, DMF, dioxane, acetone), THF turned out to be the best option. With as low as 2 mol % in [Pd], complete conversion was reached in THF at 85 °C after only 4 h and aldehyde **2b** was isolated in 77% yield.

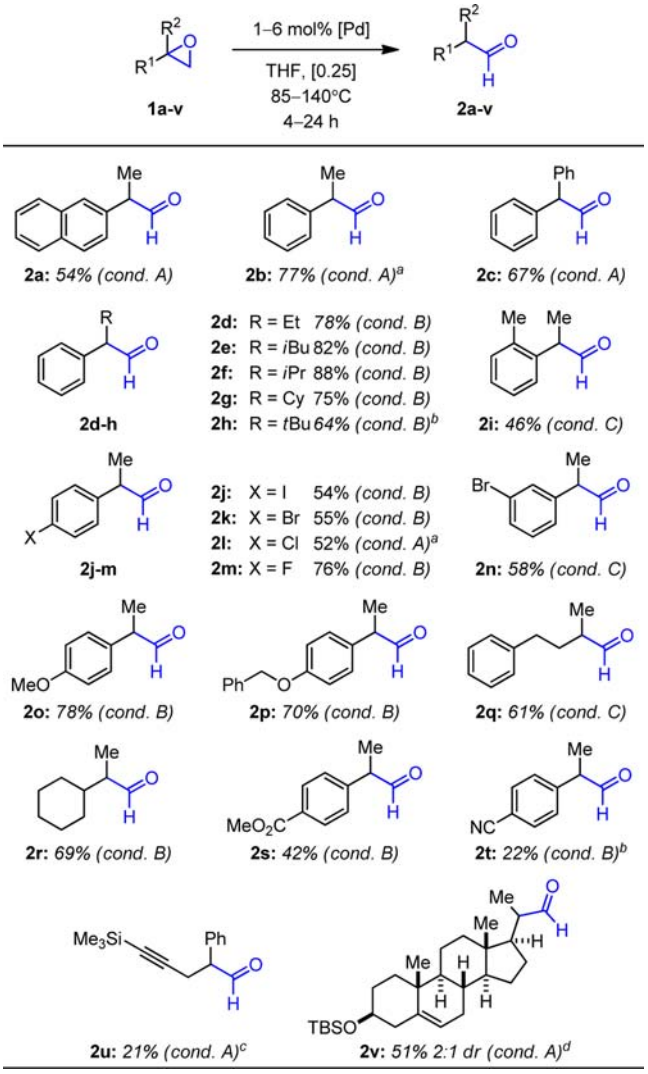
Using only 1 mol % in [Pd], aldehydes **2a** and **2c** were obtained in good yield (54 and 67%, respectively). Two other sets of reaction conditions (B−C) were applied to a variety of epoxides (Scheme 2). Substrates with primary (**2d**,**e**), secondary (**2f**,**g**) and tertiary (**2h**) alkyl substituents R^2 were all isomerized in good yield with consistently perfect regioselectivity. A wide range of functional groups potentially sensitive to Pd catalysis is also well-tolerated.[15] In particular, synthetically useful halogenated products **2j**−**n** were all isolated in practical yields (52−76%). Similarly, substrates **1o**−**p** with para-methoxy and benzyloxy substituents were isomerized into **2o**−**p** in 78 and 70% yield respectively.[16] Substrates possessing two alkyl groups also underwent efficient isomerization (**2q** in 61% yield and **2r** in 69% yield). Epoxides bearing ester (**1s**), cyano (**1t**), as well as silylated alkyne (**1u**) also afforded the corresponding aldehydes. Although the yields were sometimes modest, products that would result from reduction by the Pd−H catalyst were not observed. Remarkably, isomerization of epoxide **1v**, derived from the pregnenolone scaffold, delivered aldehyde **2v** in 51% as a 2:1 mixture of C-20 diastereoisomers. Interestingly, the silyloxy substituent was well-tolerated and no isomerization of the internal double bond was observed, underscoring further the functional group tolerance of the [Pd−H] catalyst.

Although our initial focus was the isomerization of terminal epoxides, we also explored the ability of complex **3** to isomerize internal epoxides (Scheme 3). Reactions were performed in THF using 2 mol % in [Pd−H] at 85 °C and monitored by GC. After 12 h, 2,3-disubstituted epoxide **1w** was fully isomerized and phenylpropane-2-one **2w** was isolated in 82% yield as the sole product of the reaction. Isomerization of *cis*-**1x** and *trans*-**1x** gave in each case ketone **2x** exclusively (86%). Cyclic epoxides such as **1y** and **1z** also underwent smooth isomerization into **2y** and **2z**. Of note, the presence of the carbonyl functionality in **1z** was well-tolerated.

In order to gain insight into the exact role of the dinuclear palladium hydride precursor in the isomerization of terminal epoxides, we performed a series of complementary experiments. The use of 2,6-di-*tert*-butyl-4-methylpyridine does not inhibit the reaction and rules out the decomposition of **3** into triflic acid (See Supporting Information). When the typical reaction using **1b** was carried out in the presence of 10 mol % of TEMPO no product formation was observed (See Supporting

dx.doi.org/10.1021/ja400325w | J. Am. Chem. Soc. 2013, 135, 6177−6183

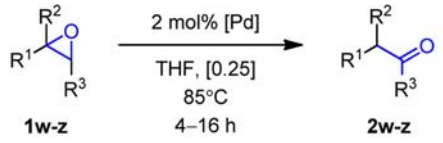
Scheme 2. Substrate Scope (Terminal Epoxides)[a]



[a][Pd–H]-catalyzed isomerization of epoxides using **3** (0.25 mmol scale, yields of isolated product). Conditions A: 1 mol % in [Pd], 85 °C, 4 h; Conditions B: 4 mol % in [Pd], 100 °C, 24 h; Conditions C: 6 mol % in [Pd], 140 °C, 24 h. [a] 2 mol % in [Pd]. [b] 120 °C, 48 h. [c] 10 mol % in [Pd]. [d]4 mol % in [Pd], 24 h.

Information).[17] Isomerization of (*R*)-**1b** (*ee* = 94%), delivered **2b** quantitatively but in racemic form (Figure 2A). Taken individually, this result suggests this isomerization is a stereoconvergent process. Whereas heating a THF solution of (*R*)-**2b** (*ee* = 88%) for 4 h did not lead to an erosion of enantiopurity (Figure 2B), partial racemization was noticed in the presence of complex **3** (2 mol % in [Pd]) (Figure 2C). These results indicate that racemization involves direct participation of the active form of the palladium hydride catalyst. Labeling experiments were also conducted using **1b**-d_{10} and various amounts of **3** (Figure 2D). When 12 mol % in [Pd–H] were employed, H-incorporation was observable only at the benzylic and aldehydic positions (9% and 2% respectively). At higher loadings in palladium (29 and 51 mol %), incorporation was seen at the same positions. In all cases, incorporation was not complete and signals of unreacted Pd–H which integrated for the remainder of "hydrogen content" were observed by ^{1}H NMR at δ = −6.9 ppm (1, 10 and 29% respectively).[18] Collectively these data indicate that a [Pd–H]

Scheme 3. Substrate Scope (2,3- and Tri-substituted Epoxides)[a]



epoxide	time	product	isolated yield
1w	12 h	**2w**	82%
cis-**1x**	16 h	**2x**	86%
trans-**1x**	16 h	**2x**	86%
1y	4 h	**2y**	62%
1z (2.5:1.0 dr)	4 h	**2z** (2.0:1.0 dr)	72%[a]

[a][Pd–H]-catalyzed isomerization of epoxides using **3** (0.25 mmol, yields of isolated product). [a]Reaction performed on a 1.0 mmol scale.

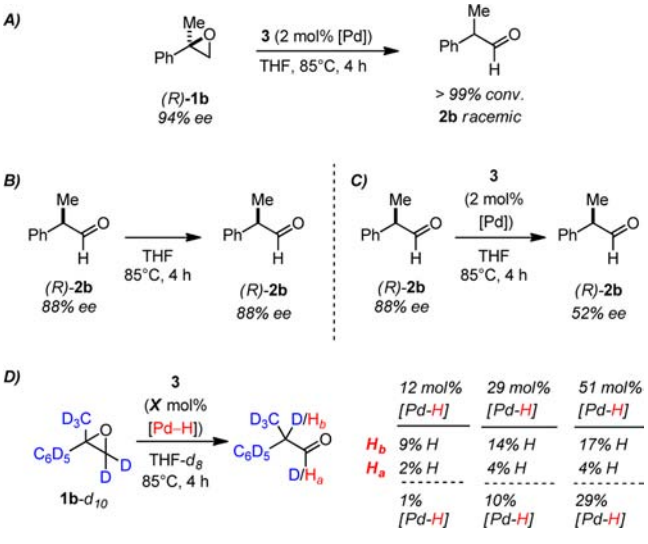


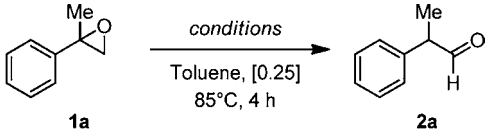
Figure 2. Mechanistic experiments. (A) Isomerization of an enantioenriched epoxide by **3**. Racemization experiments (B) with and (C) without **3**. (D) Labeling experiments.

dx.doi.org/10.1021/ja400325w | *J. Am. Chem. Soc.* 2013, 135, 6177–6183

species is involved in the isomerization of 2,2-disubstituted epoxides and, as will be shown hereafter, entry into the catalytic cycle likely proceeds via reversible dissociation of the bridging dippp ligand in **3**. H-incorporation in the aldehydic position is consistent with involvement of the [Pd−H] in a reversible last step (*vide infra*).

In the perspective of developing an asymmetric version of this [Pd−H]-catalyzed isomerization of 2,2-disubstituted epoxides, we have optimized an *in situ* protocol that avoids systematic isolation of well-defined [Pd−H] complexes when precious chiral ligands are employed (Table 2).

Table 2. Optimization of Reaction Conditions for *In Situ* Catalysis



entry	[Pd] (4 mol %)	ligand (6 mol %)	additive (10 mol %)	conv. (%)[a]
1	**3**			99[b]
2	$[Pd_2(dippp)_3]$			nr[c]
3	$[Pd_2(dippp)_3]$		*t*BuOH	nr
4	$[Pd_2(dippp)_3]$		4-CN-C_6H_4OH	95
5	$[Pd(PtBu_3)_2]$	dippp		nr
6	$[Pd(PtBu_3)_2]$	dippp	*t*BuOH	nr
7		dippp	4-CN-C_6H_4OH	nr
8	$[Pd(PtBu_3)_2]$		4-CN-C_6H_4OH	nr
9	$[Pd(PtBu_3)_2]$	dippp	4-CN-C_6H_4OH	98
10	$[Pd(PtBu_3)_2]$	dippp	4-CN-C_6H_4OH	98[b]

[a]Determined by GC. [b]Reaction performed in THF. [c]No reaction.

This approach was again inspired by the work of Bunel and co-workers who showed that formation of [Pd−H] is directly linked to the pK_a of the protic additive employed.[12] Although it could be used as a solvent, *t*BuOH (pK_a = 19) did not prove viable as an additive. In contrast, 4-cyanophenol (pK_a = 4.5) revealed as the protic additive of choice. When $[Pd_2(dippp)_3]$ is used, 4-cyanophenol is the only necessary additive. In the case of $[Pd(PtBu_3)_2]$, both added dippp and 4-cyanophenol were required. Notably, THF and toluene were equally competent solvents for the reactions performed *in situ*.

We next attempted to develop an enantioselective variant of the isomerization of terminal epoxides using substrate **1f** and the *in situ* protocol ($[Pd(PtBu_3)_2]$, 4-cyanophenol and chiral ligand). A mixture of toluene and THF was employed to ensure complete solubility of all reaction components. Ligand **4** was initially selected for its steric and electronic resemblance with dippp (Figure 3). A conversion of 18% was reached after 4 h at 60 °C. Recovered **1f** was obtained in 13% *ee* (*S* = 4.4) and aldehyde **2f** in 10% *ee* (*S* = 1.3). Prolonged heating (16 h, *C* = 51%) led to further racemization of **2f** (**1f**: 48% *ee*, *S* = 4.1; **2f**: 13% *ee*, *S* = 1.1). This indicates a kinetic resolution (i.e., a stereodivergent process) rather than a dynamic kinetic resolution (i.e., a stereoconvergent process) has taken place. Of important note, the discrepancy observed between the selectivity factors calculated for (*S*)-**1f** and (*S*)-**2f** is in line with the partial racemization observed in Experiments B and C (Figure 2).

On the basis of the experiments detailed in Figure 2 and 3, a mechanistic proposal that accounts for the isomerization of

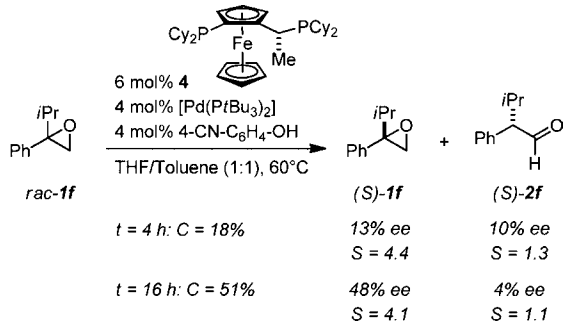


Figure 3. Kinetic resolution of **1f**.

terminal epoxides using **3** is depicted in Figure 4. Initial decoordination of the monodentate dippp ligand allows binding

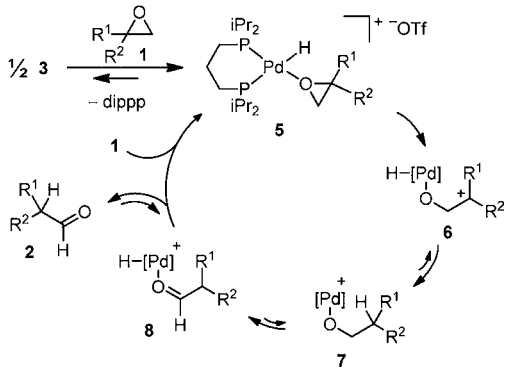


Figure 4. Proposed catalytic cycle.

of the epoxide and entry of monomeric [Pd−H] units **5** into the catalytic cycle. Opening of the epoxide generates the most stable carbocationic intermediate (**6**), hydride transfer (**7**) and a subsequent *β*-hydride elimination of a methylenic proton delivers the aldehyde and concomitantly regenerates the [Pd−H] intermediate. This manifold is consistent with the results of the labeling experiments (Figure 2C). The result of Experiment A supports formation of a sp^2 hybridized carbocationic intermediate. We propose that the formation of **6** is both the rate-determining step of the reaction and the selectivity-determining step that accounts for enantio-enrichment of the epoxide. The enantioselection could occur either by selective binding of one of the two enantiomeric epoxides to the palladium center or by selective opening of one of the two diastereomeric intermediates of type **5**. Remarkably, the subsequent hydride transfer (**6** → **7**) is likely to be the enantio-determining step during product formation. To the best of our knowledge, the observation of distinct enantio-determining steps in a kinetic resolution has been rarely documented.[19] On the sole basis of our experimental results, we initially hypothesized that reversible formation of the carbocationic intermediate (**2** → **8** → **7** → **6**) could explain partial racemization of the aldehyde.

To further substantiate our mechanistic model, we performed a series of DFT calculations using dtbpp as a model ligand (dtbpp =1,3-bis(di-*tert*- butylphosphino)-propane). We first investigated the thermodynamics of the dissociation of dinuclear palladium complex $[(dtbpp)_3(PdH)_2]^{2+}$ **3b** into mononuclear species (Figure 5). Dissociation of $[(dtbpp)_3(PdH)_2]^{2+}$ **3b** into two monomeric palladium hydride complexes $[(dtbpp)(PdH)]^+$ **3b-1** and

dx.doi.org/10.1021/ja400325w | *J. Am. Chem. Soc.* 2013, 135, 6177−6183

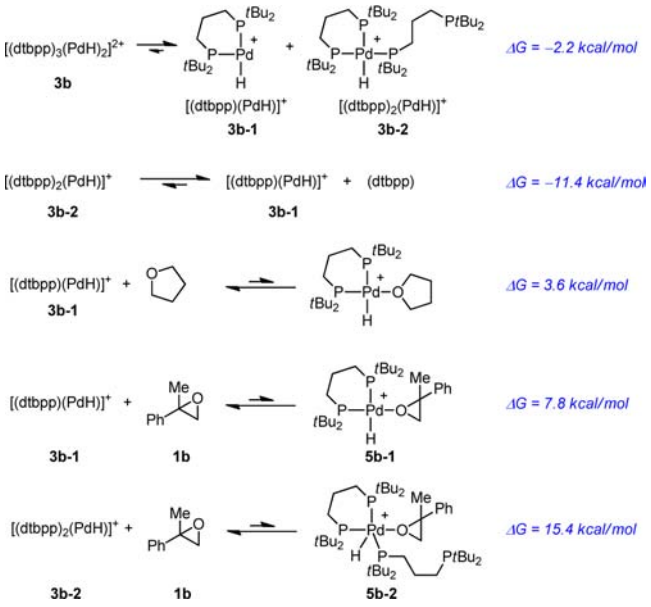


Figure 5. Generation of mononuclear [Pd−H] units from dimer **3b**. DFT method: B3LYP/[LANL2DZ on Pd, 6-31G(d) on H, C, O, P], PCM in THF at the same level.

$[(dtbpp)_2(PdH)]^+$ **3b-2** was found to be slightly exergonic (−2.2 kcal/mol). Further dissociation of one dtbpp ligand in **3b-2** to generate the coordinatively unsaturated palladium complex **3b-1** is formally spontaneous (−11.4 kcal/mol).

In contrast, coordination of one explicit molecule of THF or one molecule of substrate **1b** to **3b-1** were identified as endergonic processes, with the latter being slightly disfavored (3.6 vs. 7.8 kcal/mol, respectively). These results are in line with the incomplete dissociation of **3** in the labeling experiments at high catalyst concentration (Figure 2, D). An hypothetical associative mechanism involving $[(dtbpp)_2(PdH)]^+$ **3b-2** and substrate **1b** leading to intermediate **5b-2** displayed a ΔG value of 15.4 kcal/mol indicating such a mechanism is less likely to occur.

Next, starting from mononuclear complex **3b-1** a reasonable reaction profile has been calculated (Figure 6).[20,21] Complex **5b-1** lies 7.8 kcal/mol higher in energy than the coordinatively unsaturated complex (**1b** + **3b-1**). Ring-opening of the epoxide followed by hydride transfer in overall activation free energy of 26.4 kcal/mol leads to the pallada-alkoxy intermediate **7b** and constitutes the rate-determining step of the transformation. This value is in good agreement with the experimental reaction conditions (T = 85 °C for isomerization of **1b**). The sequence passes through the carbocationic intermediate **6b** which is consistent with the collective results of experiments A−D (Figure 2) and the kinetic resolution described in Figure 3. Aldehyde **2b** is liberated after a β-hydride abstraction (facilitated by an agostic interaction in **7b**) and subsequent decoordination in a slightly exergonic process.

Unexpectedly, we found that epimerization of the aldehyde occurs by a formal 1,2-addition of the Pd−H into the carbonyl (**9b**) followed by β-hydride elimination of the benzylic proton to generate the enol-bound intermediate **10b** rather than by the reverse reaction from (**2b** + **3b-1**) to **6b**. This route is more favorable by 23.4 kcal/mol (47.7 kcal/mol vs 24.3 kcal/mol). This observation prompted us to consider alternative tautomerization pathways that could account for postreaction racemization of the enantioenriched aldehyde (Figure 7). The O-bound enol isomer **10b′** was found to be almost isoenergetic to the C-bound enol **10b**, and to further evolve into dissociated enol **11b** and the coordinatively unsaturated palladium complex **3b-1** (ΔG = −15.2 kcal/mol).

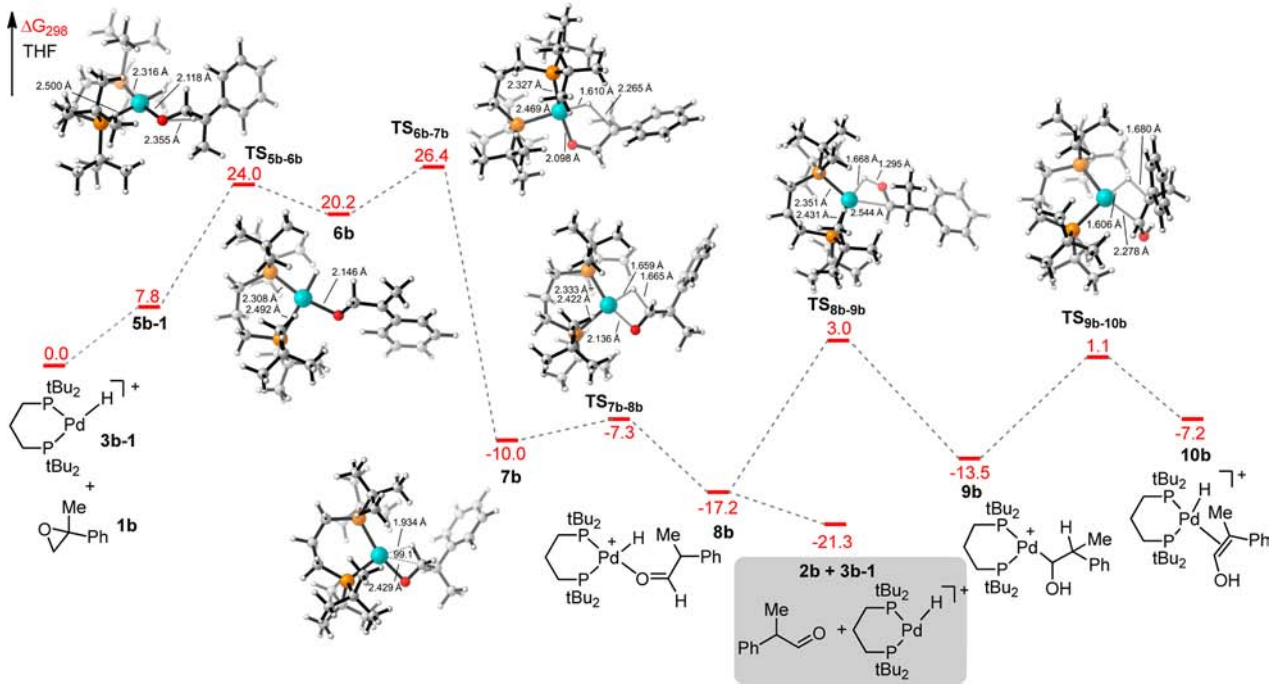


Figure 6. Computed reaction profile using dtbpp (1,3-bis(di-*tert*-butylphosphino)propane) as a model ligand. The most relevant intermediates and transition states are shown. DFT method: B3LYP/[LANL2DZ on Pd, 6-31G(d) on H, C, O, P], PCM in THF at the same level. ΔG values are given in kcal/mol.

dx.doi.org/10.1021/ja400325w | J. Am. Chem. Soc. 2013, 135, 6177−6183

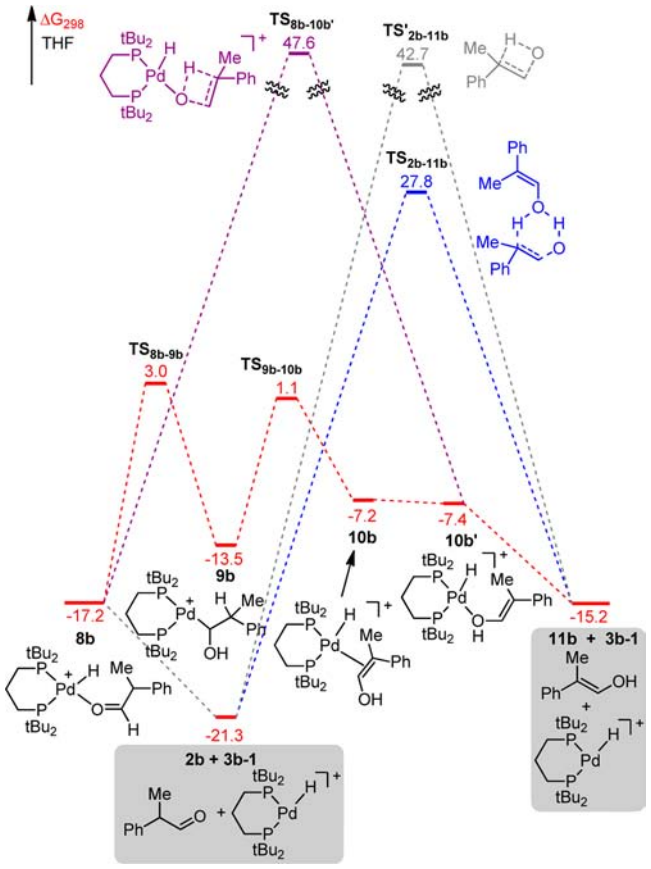


Figure 7. Competing tautomerization pathways. DFT method: B3LYP/[LANL2DZ on Pd, 6-31G(d) on H, C, O, P], PCM in THF at the same level. ΔG values are given in kcal/mol.

Metal-free tautomerization of **2b** to **11b** can occur either in a unimolecular (gray) or a bimolecular (blue) process. The latter was found to be more favorable and the corresponding 6-membered Zimmerman-Traxler transition state $\mathbf{TS_{2b-11b}}$ lied at 27.8 kcal/mol ($\Delta G^{\ddagger}_{298}$ = 49.1 kcal/mol; **2b** → **11b**); far above the [Pd−H]-catalyzed tautomerization route (in red in Figure 7). These values are in agreement with the results of experiments B and C reported in Figure 2. Finally, tautomerization *via* an enolate Lewis acid-assisted pathway was found to be unrealistic as the corresponding transition state $\mathbf{TS_{8b-10b'}}$ lied at 47.6 kcal/mol (purple).

In conclusion, we have synthesized and characterized a well-defined Pd−H dinuclear complex which proved competent in the selective isomerization of terminal epoxides into aldehydes. Experimental and theoretical investigations point to an unprecedented hydride-type mechanism. Preliminary observations revealed two distinct enantio-determining steps for the kinetic resolution of racemic epoxides. A pathway that accounts for partial racemization of the enantio-enriched aldehyde and that lies off the productive catalytic cycle was also identified. Importantly, although far from practicality, these results clearly set a precedent that will serve as a blueprint for further developments of a more efficient asymmetric isomerization of terminal epoxides. Future work will be aimed at the identification of highly enantioselective catalysts for this isomerization and for related transformations.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectral, crystallographic for complex **3**, computational data, and full reference 20. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

clement.mazet@unige.ch

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the University of Geneva and Roche. We thank the SMS platform of the University of Geneva for mass spectrometric measurements and Prof. Tomasz A. Wesolowski (University of Geneva) for offering us access to his computational facilities. Mr. Houhua Li is acknowledged for technical assistance in the preparation of substrates **1v** and **1z**. This article is dedicated to Prof. Lutz H. Gade (University of Heidelberg) on the occasion of his 50th birthday.

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