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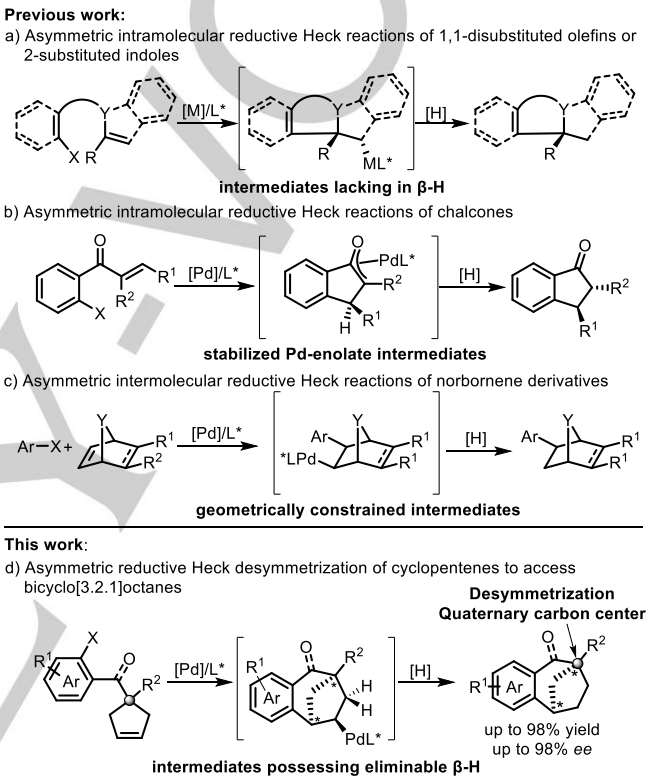
Palladium-catalyzed Asymmetric Intramolecular Reductive Heck Desymmetrization of Cyclopentenes: Access to Chiral Bicyclo[3.2.1]octanes

Zhenbo Yuan, Ziwen Feng, Yuye Zeng, Xiaobin Zhao, Aijun Lin* and Hequan Yao*

Dedication ((optional))

Abstract: A palladium-catalyzed asymmetric reductive Heck reaction of unactivated aliphatic alkenes with eliminable β-H has been realized for the first time. A series of optically active bicyclo[3.2.1]octanes bearing a chiral quaternary and a tertiary carbon stereocenters were obtained in good yields with excellent enantioselectivities, exhibiting good functional group tolerance and scalability. Moreover, the deuterated optically active bicyclo[3.2.1]octanes could also be obtained in high efficiency.

In 1983, Cacchi and co-workers described a palladium-catalyzed cross-coupling reaction between aryl halides and enones or enals to form conjugate adducts in the presence of hydride species, which now is known as the reductive Heck reaction.[1] After that, such reaction has been proved as an efficient and tempting method to construct saturated C-C bond due to the avoidance of air- and moisture-sensitive organometallic reagents, and it has been widely applied in the synthesis of natural products and pharmaceuticals.[2] However, because of the high propensity of β-H elimination pathway (Heck reaction), the asymmetric version of the reductive Heck reaction is still immature. Prior works on the asymmetric intramolecular reductive Heck reactions of 1,1-disubstituted olefins or 2-substituted indoles have been realized by Diaz,[3a] Jia,[3b,c] Zhu,[3d,e] Lautens,[3f] Tong[3g] and Zhang,[3h] respectively (Scheme 1a). In these elegant works, the in situ-generated alkylpalladium intermediates could be efficiently trapped by the hydride donors to deliver the asymmetric reductive Heck products because they lacked in β-H. Besides, Buchwald,[4a] Zhou,[4b] de Vries and Minnaard[4c] independently disclosed another type of asymmetric intramolecular reductive Heck reactions with (pseudo)halide substituted chalcones, in which the stabilized trans-configured H-bound Pd-enolate intermediates were hard to occur β-H elimination to form the Heck products (Scheme 1b). Moreover, specific bicyclic alkenes, such as norbornene and its derivatives have also been employed in the asymmetric reductive Heck reactions (Scheme 1c).[5] In these reactions, the rigidity of the carbocyclic frameworks forbade the alkylpalladium intermediates to undergo rotation and β-H elimination. Very recently, the racemic reductive Heck reactions of unactivated aliphatic alkenes possessing eliminable β-H have been realized by Loh[6a] and Engle.[6b] However, to the best of our knowledge, protocols that enable asymmetric reductive Heck reactions of unactivated aliphatic alkenes have not been described until now.



Scheme 1. Asymmetric reductive Heck reactions.

Bicyclo[3.2.1]octane, as a kind of intricate polycyclic structure was widely found in natural products and bioactive molecules with antibacterial and antithrombotic activities.[7] The skeleton commonly contain multiple chiral quaternary carbon and tertiary carbon centers. In the past few decades, constructing such framework has aroused great interest from chemists.[8] Herein, we will describe an unprecedented palladium-catalyzed asymmetric intramolecular reductive Heck desymmetrization reaction of cyclopentenes to construct chiral bicyclo[3.2.1]octanes in good yields with excellent enantioselectivities (Scheme 1d). In this reaction, inhibition of the competitive β-H elimination pathway remains difficult.

To validate our hypothesis, we chose 1-(2-iodobenzoyl)-cyclopent-3-ene **1a** as the substrate to identify systems capable

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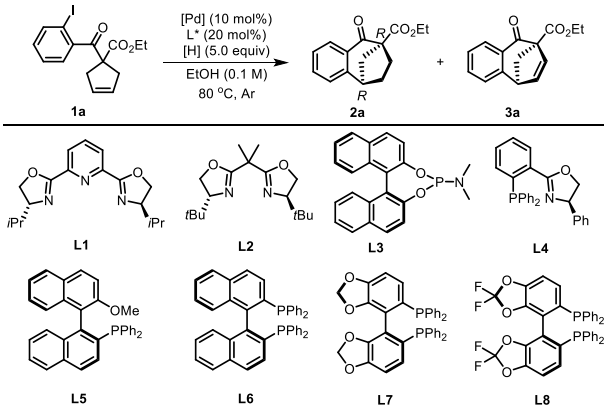
Table 1. Optimization of Reaction Conditions.[a]

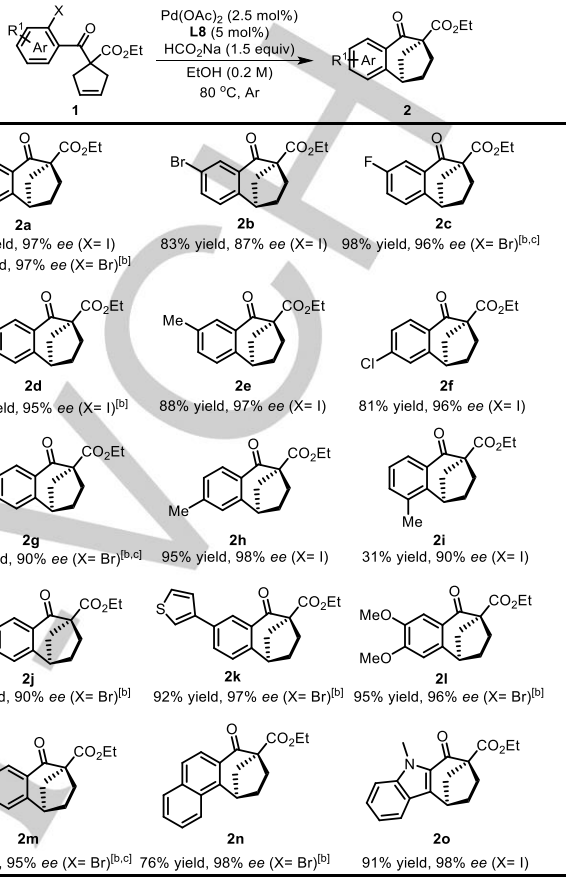


Entry	[Pd]	Ligand	**2a**	*ee* of **2a**	**3a**
1	$Pd(OAc)_2$	**L1**	11	2	36
2	$Pd(OAc)_2$	**L2**	18	-6	15
3	$Pd(OAc)_2$	**L3**	9	9	58
4	$Pd(OAc)_2$	**L4**	14	4	52
5	$Pd(OAc)_2$	**L5**	<2	-	88
6	$Pd(OAc)_2$	**L6**	99	78	<2
7	$Pd(OAc)_2$	**L7**	98	92	<2
8	$Pd(OAc)_2$	**L8**	98	95	<2
9	$[Pd(allyl)Cl]_2$	**L8**	15	58	52
10	$Pd_2dba_3{\cdot}CHCl_3$	**L8**	43	89	53
11[b]	$Pd(OAc)_2$	**L8**	98	96	<2
12[b,c]	$Pd(OAc)_2$	**L8**	98	96	<2
13[b,c,d]	$Pd(OAc)_2$	**L8**	98	97	<2
14[b,d,e]	$Pd(OAc)_2$	**L8**	<2	-	<2

[a] Reaction conditions: **1a** (0.10 mmol), [Pd] (10 mol%), ligand (20 mol%), HCO_2Na (0.50 mmol) in 1.0 mL EtOH, at 80 °C, 12 h, under argon; isolated yields with *ee* values determined by chiral HPLC. [b] 2.5 mol% $Pd(OAc)_2$ and 5.0 mol% **L8** were used. [c] 1.5 equiv HCO_2Na was added. [d] in 0.5 mL EtOH. [e] Without HCO_2Na.

of mediating this palladium-catalyzed asymmetric reductive Heck desymmetrization reaction. Take it into consideration that the ligands may play a crucial role in controlling the enantioselectivity, and stabilizing the in situ- generated alkylpalladium intermediate to avoid the β-H elimination, we firstly tested different types of ligands, such as the N,N,N-ligand **L1**, N,N-ligand **L2**, N,P-ligands **L3**–**4**, P,O-ligand **L5** and P,P-ligand **L6** (Table 1, entries 1–6). The desired product **2a** was achieved in 99% yield with 78% *ee* when **L6** was used. Further screening of the bisphosphine ligands with different bidentate angles and electric properties showed that the *ee* value could be improved to 95% when (*S*)-Difluorphos **L8** was employed (Table 1, entries 7–8). Other palladium catalysts gave inferior results compared with $Pd(OAc)_2$ (Table 1, entries 9–10).[9]

Table 2. Substrate Scope of Haloaryl Moiety.[a]



[a] Reaction conditions: **1** (0.10 mmol), 2.5 mol% $Pd(OAc)_2$, 5.0 mol% **L8**, HCO_2Na (0.15 mmol) in 0.5 mL EtOH, 80 °C, 12 h, under argon; isolated yields with *ee* values determined by chiral HPLC. [b] 24 h. [c] 5.0 mol% $Pd(OAc)_2$ and 10.0 mol% **L8** were used.

To our delight, reducing the amount of the palladium catalyst to 2.5 mol%, the yield and *ee* value could be well maintained (Table 1, entry 11). Decreasing the amount of HCO_2Na to 1.5 equiv and EtOH to 0.5 mL did not affect the reaction efficiency (Table 1, entries 12–13). The reaction was drastically prohibited in the absence of HCO_2Na (Table 1, entry 14). The structure and absolute configuration of (*R*,*R*)-**2a** were confirmed by ^1H and ^{13}C NMR spectroscopy,[10] mass spectrometry, and single-crystal X-ray diffraction analysis.[11]

With the optimum conditions in hand, we then investigated the substrate scope and generality of the reaction. The effect of the haloaryl moiety in cyclopentenes **1** was first tested and the results are summarized in Table 2. Other than aryl iodine, aryl bromine could also furnish the reaction well, offering the product **2a** in 97% yield with 97% *ee* after prolonging the reaction time to 24 h. In view of the commercial availability, synthetic compatibility and similar outcomes, some substrates with aryl bromine were employed in the reaction. Halogen groups (-F, -Cl, -Br), electron-donating groups (-Me, -OMe) or electron-withdrawing groups (-CF_3) installed at the 4- or 5-positions of the benzene ring all performed well, affording **2b–h** in good to excellent yields with 87–98% *ee*. The substrate **1i** with a methyl group at the 3-position of the benzene ring offered **2i** in 31% yield with 90% *ee* due to the steric hindrance. Substrates with phenyl or thienyl groups

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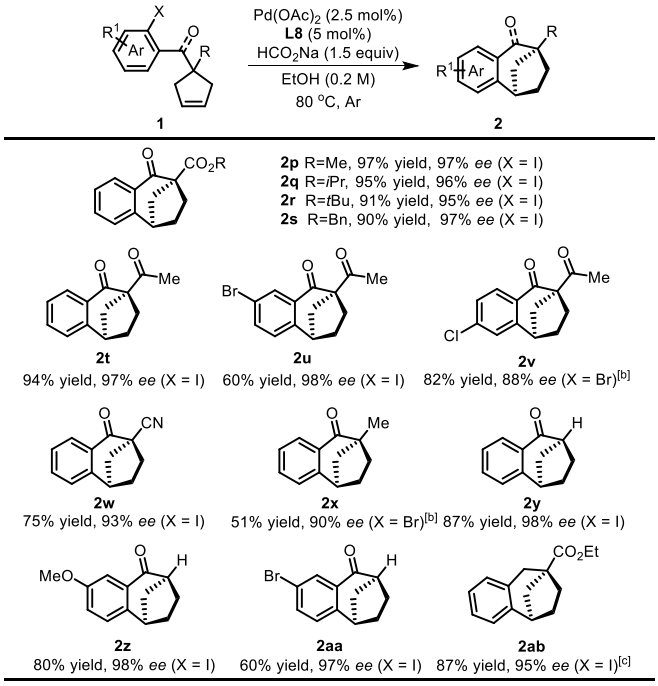
Table 3. Substrate Scope of other components of cyclopentenes.[a]

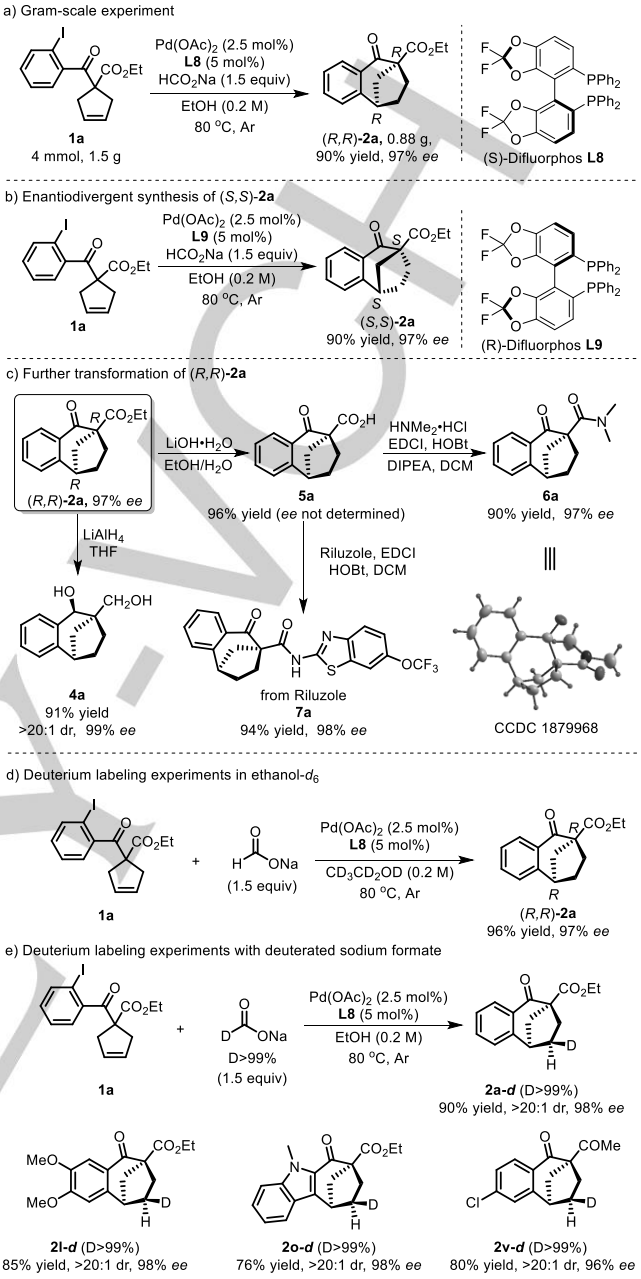


[a] Reaction conditions: **1** (0.10 mmol), 2.5 mol% $Pd(OAc)_2$, 5.0 mol% **L8**, HCO_2Na (0.15 mmol) in 0.5 mL EtOH, 80 °C, 12 h, under argon; isolated yields with *ee* values determined by chiral HPLC. [b] 24 h. [c] HCO_2NH_4 (0.20 mmol) was used.

delivered **2j** and **2k** in 81% and 92% yields with 90% and 97% *ee*. Dimethoxy-substituted product **2l**, as well as the difluoro-substituted product **2m** could be obtained in good yields (95% and 86%) with excellent enantioselectivities (96% and 95% *ee*). In addition, the naphthyl and indole units, which broadly exist in the natural products and pharmaceuticals could be efficiently assembled into **2n** and **2o** in good yields with excellent enantioselectivities.

After checking the character of the haloaryl moiety, we then turned our attention to check other components of the cyclopentenes **1**, and the results are shown in Table 3. Varying the ethyl ester group to the methyl, isopropyl, *tert*-butyl, and benzyl ester groups, products **2p**–**s** were produced in good yields (90–97%) with high levels of enantioselectivities (95–97% *ee*). Acetyl- or cyano- substituted cyclopentenes were also good candidates for this reaction, offering the corresponding products **2t–w** in good efficiency. Additionally, this asymmetric reductive Heck reaction could be further extended to the alkyl substituted cyclopentene **1x**, and the product **2x** was achieved in 90% *ee*. Minimizing the R group to hydrogen atom, products **2y–aa** were produced in 97–98% *ee*. Alkyl linked cyclopentene **1ab** could also deliver the desired product **2ab** in 87% yield with 95% *ee*.

To further gain insight into the utility of the reaction, the bicyclo[3.2.1]octane (*R,R*)-**2a** (0.88 g) was synthesized in 4 mmol scale in 90% yield with 97% *ee* (Scheme 2a). It is well known that obtaining both enantiomers is highly desirable, yet challenging in organic chemistry and medicinal chemistry, because enantiomers always exhibit distinct biological activities. Producing both enantiomers from the same substrate will be the most ideal and efficient method. To our great delight, the (*S,S*)-**2a** could be

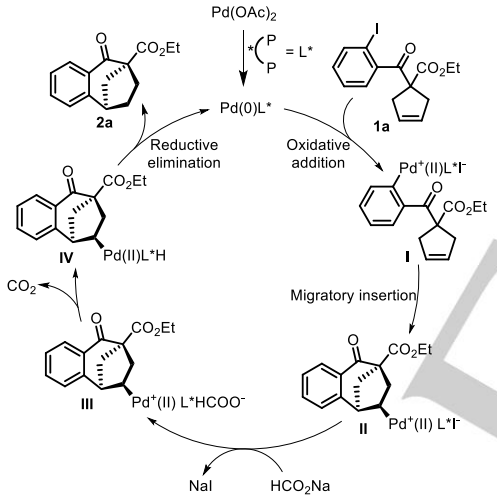


Scheme 2. Further investigation of the reaction.

efficiently synthesized by employing (*R*)-Difluorphos **L9** (Scheme 2b). Reduction of the ester and carbonyl groups of **2a** simultaneously produced the chiral 1,3-diols **4a** in 91% yield with high diastereoselectivity (>20:1 *dr*) and enantiospecificity (99% *ee*).[10] Dimethylcarbamoyl-substitued product **6a** could be synthesized through hydrolysis and amidation in 86% yield without the loss of enantiopurity (97% *ee*). Moreover, the structure and absolute configuration of **6a** was confirmed by single-crystal X-ray diffraction analysis.[11] Riluzole,[12] a signal transduction modulator treating for Parkinson's disease, Huntington's disease and other neurologic diseases, could be well late-stage functionalized to form compound **7a** in 94% yield and 98% *ee*.

To confirm the source of hydride, deuterium labelling experiments with different deuterated reagents were carried out.

When **1a** was subjected to the optimized conditions in the presence of ethanol-d_6, product **2a** was achieved in 96% yield with 97% *ee* (Scheme 2c). When deuterated sodium formate was used, the deuterated **2a-*d*** was obtained in 90% yield with >20:1 dr and 98% *ee* (Scheme 2d). These results indicated that the sodium formate was the hydride donor of the reaction. Additionally, careful NOE analysis of **2a-*d*** revealed that the deuterium was *syn* to the benzene ring.[10] As is known that the introduction of deuterium atom into drug molecules can efficiently change the absorption, distribution, metabolism and excretion properties of the drugs.[13] To further illustrate the synthetic utility of the reaction, the D-labeled (D>99%) bicyclo[3.2.1]octanes **2l-*d***, **2o-*d*** and **2v-*d*** were successfully produced in good yields with excellent diastereo- and enantioselectivities (Scheme 2d). What is more, to figure out the real ratio of the palladium catalyst and the ligand for the chiral induction, nonlinear effect studies with different enantiopurity levels of ligands were carried out. A linear correlation (R^2 = 0.99) between *ee* of the products and the ligands was found, indicating that the active catalyst species was consistent with a monomeric nature during the stereodetermining migratory insertion event.[14]



Scheme 3. Proposed mechanism.

On the basis of the above mentioned results and previous literatures,[3f, 4a, 6b] a proposed mechanism of this reaction is figured in Scheme 3. Firstly, **1a** undergoes oxidative addition of the active palladium catalyst to give the cationic Pd(II) intermediate **I**. Next, intramolecular *syn*-migratory insertion of **I** leads to the alkylpalladium intermediate **II**, which undergoes anion exchange with HCO_2Na to deliver the intermediate **III**. It should be noted that the competitive β-H elimination process (Heck reaction) of the intermediate **II** is well suppressed by employing an exquisite catalytic system. The intermediate **III** converts to the hydropalladium species **IV** by releasing a molecular CO_2. Finally, reductive elimination of the intermediate **IV** delivers product **2a**, and regenerates the palladium catalyst to the next catalytic cycle.

In conclusion, we have described a palladium-catalyzed asymmetric intramolecular reductive Heck desymmetrization reaction of cyclopentenes with eliminable β-H to achieve chiral bicyclo[3.2.1]octanes bearing a quaternary and a tertiary carbon stereocenters in good yields and excellent enantioselectivities. Additionally, the reaction could incorporate deuterium in the bicyclo[3.2.1]octanes with complete deuteration, excellent diastereo- and enatioselectivities.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric catalysis • reductive Heck • desymmetrization • bicyclo[3.2.1]octanes • palladium

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[9] See Supporting Information for more details on the optimization conditions of the asymmetric reductive Heck reaction and the asymmetric Heck reaction.

[10] See Supporting Information for more details on NOE results of **2a**, **4a** and **2a-*d***.

[11] CCDC1842844 (**2a**) and CCDC1879968 (**6a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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[14] See Supporting Information for details on NLE experiments.

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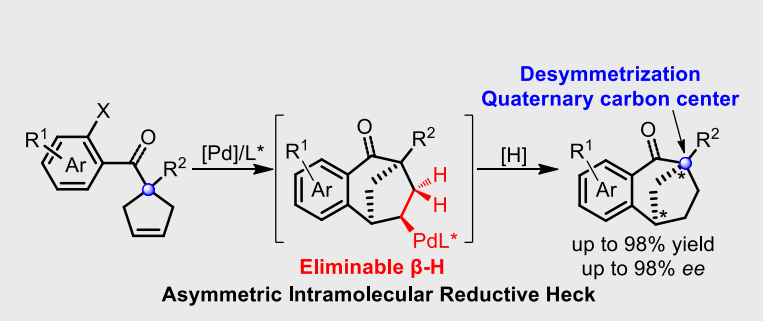

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