

Reversal of diastereoselectivity in palladium-arene interaction directed hydrogenative desymmetrization of 1,3-diketones

Chang-Bin Yu^{1†}, Heng-Ding Wang^{1,2†}, Bo Song¹, Hong-Qiang Shen¹, Hong-Jun Fan^{1*} & Yong-Gui Zhou^{1*}

¹State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, China;

²University of Chinese Academy of Sciences, Beijing 100049, China

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For the metal-catalyzed asymmetric hydrogenation of α -substituted ketones, *cis* reductive products are generally obtained due to steric hindrance of substituents. Herein, an unprecedented *trans* reductive products were observed in palladium-catalyzed hydrogenative desymmetrization of cyclic and acyclic 1,3-diketones, providing the chiral *trans* β -hydroxy ketones with two adjacent stereocenters including one α -tertiary or quaternary stereocenter with high enantioselectivity and diastereoselectivity. Mechanistic studies and DFT calculations suggested that the rarely observed diastereoselectivity reversal is ascribed to the charge-charge interaction between the palladium and aromatic ring of the substrate, which could not only result in the reversal of the diastereoselectivity, but also improve the reactivity.

palladium-arene interaction, hydrogenative desymmetrization, 1, 3-diketones

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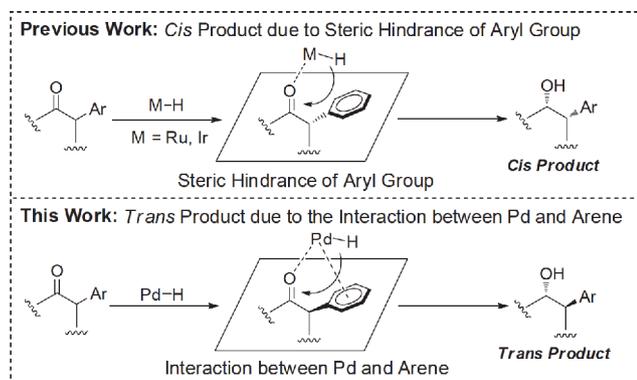
1 Introduction

Asymmetric hydrogenation represents one of the most practical methods to chiral molecules. Over the past decades, significant advances have been made in development of highly effective catalyst systems [1]. During the meantime, asymmetric hydrogenation of ketones has been a long existing interest due to the abundance of chiral alcohols in natural products and pharmaceuticals [2]. In general, *cis* products would be obtained in the hydrogenation of cyclic α -substituted ketones (Scheme 1) [3], which results from the point that when the hydrogenation takes place, active M-H species prefers to attack the carbonyl group from the less steric face.

Neutral (hetero)arenes are capable of interaction to transition metal, such as, Rh [4], Ru [5], Pt [6] and other metals [7], although the interaction is very weak. Among them, Pd-arene interactions in complexes [8] have been observed. In addition, the behavior of palladium-arene interactions was also proposed as catalytic intermediates in palladium-catalyzed reactions. For example, an intermediate was involved in palladium-catalyzed Catellani reaction [9] or palladium-catalyzed decarboxylative olefination of arene carboxylic acids [10]. Although these interactions were discovered in palladium complexes or intermediates, arenes are seldom used as auxiliary ligands, or sub-coordination group in palladium-involved reaction because of the weak interaction and a relatively limited range of substrates. Therefore, the development of an efficient strategy to extend the process scope to a wider range of substrates and realize its further application in chemistry is still of great significance. We [11]

[†]These authors contributed equally to this work.

*Corresponding authors (email: fanhj@dicp.ac.cn; ygzhou@dicp.ac.cn)



Scheme 1 Diastereoselectivity control in the hydrogenation of α -substituted ketones: *cis* and *trans* reductive products.

and others [12] have been involved in the development of palladium-catalyzed asymmetric hydrogenation of ketones. Considering (hetero)arenes could *in situ* interact with palladium, we envisaged whether 2-aryl substituted 1,3-diketones could be employed as substrates for the palladium-catalyzed asymmetric hydrogenative desymmetrization (Scheme 1), giving the *trans* chiral α -aryl substituted β -hydroxy ketones. Herein, an unprecedented *trans* reductive products were observed in palladium-catalyzed asymmetric hydrogenative desymmetrization of cyclic and acyclic 1,3-diketones, providing the chiral *trans* β -hydroxy ketones with two adjacent stereocenters including one α -tertiary or quaternary stereocenter with high enantioselectivity and diastereoselectivity. Mechanistic studies suggested that the rarely observed diastereoselectivity reversal is ascribed to the charge-charge interaction between the palladium and aromatic ring of the substrates, which could not only result in the reversal of the diastereoselectivity, but also improve the reactivity.

2 Experimental

Ligand (*S*)-SegPhos (3.4 mg, 0.0055 mmol) and Pd(OCOCF₃)₂ (1.7 mg, 0.005 mmol) were placed in a dried Schlenk tube under nitrogen atmosphere, and degassed anhydrous acetone was added. The mixture was stirred at room temperature for 1 h. The solvent was removed under vacuum to give the catalyst. This catalyst was taken into a glove box filled with nitrogen and dissolved in 2,2,2-trifluoroethanol (1.0 mL). To the mixture of 1,3-diketones (0.25 mmol) and benzoic acid (3.1 mg, 0.025 mmol) in 2,2,2-trifluoroethanol (3.0 mL) was added this catalyst solution, and then the mixture was transferred to an autoclave, which was charged hydrogen gas (300 psi). The autoclave was stirred at 0 °C for 24 h. After release of the hydrogen gas, the autoclave was opened and the reaction mixture was evaporated. Purification was performed on silica gel using hexanes/ethyl acetate as

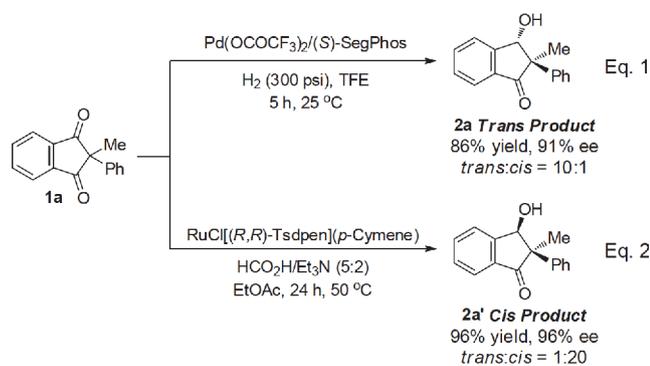
the eluent to give the chiral reductive products.

3 Results and discussion

To validate the hypothesis, we initiated our exploration by examining the palladium-catalyzed hydrogenative desymmetrization of 1,3-diketone 2-methyl-2-phenyl-1*H*-indene-1,3(2*H*)-dione (**1a**). The reaction can proceed through two possible pathways. According to previous reports, the Pd-H species would attack the carbonyl group from the less steric face leading to *cis* product. The other pathway is the addition of Pd-H to the carbonyl group from the face of aromatic ring because of the interaction between palladium and arene in substrate generated *in situ* to give the *trans* product. Delightedly, the reaction proceeded smoothly to afford the *trans* β -hydroxy ketone **2a** in 86% yield, 91% ee and 10:1 diastereoselectivity (Scheme 2, Eq. 1), and no bis-hydrogenated product was observed [13]. The absolute configuration of the desymmetrization product (2*R*,3*S*)-**2a** was determined by X-ray diffraction analysis (see the Supporting Information online). In sharp contrast, *cis* β -hydroxy ketone **2a'** was obtained with chiral ruthenium catalyst (Eq. 2). These results identified that a rare phenomenon of reversal of diastereoselectivity was involved in palladium-catalyzed hydrogenative desymmetrization.

Encouraged by the above result, we next optimized the reaction conditions to further improve the diastereoselectivity. Delightedly, in the presence of additive trifluoroacetic acid (TFA), the enantio- and diastereoselectivity was improved (Table 1, entry 2). Next, when the reaction temperature was decreased, the diastereoselectivity was improved to 17:1 (entry 3). The evaluation of acid additives indicated that no desired product was obtained in the presence of strong Brønsted acids (entry 4). However, with weak Brønsted acids, such as tartaric acid, benzoic acid and salicylic acid, both excellent yield and enantioselectivity were observed (entries 5–8). Upon further optimization from the commercially available chiral bisphosphine ligands (entries 9–11), (*S*)-SegPhos emerged as the best ligand. Thus, the optimal condition was established: Pd(OCOCF₃)₂/*(S)*-SegPhos/PhCO₂H/TFE/H₂ (300 psi)/0 °C/24 h.

With the optimized condition in hand, the scope of this hydrogenative desymmetrization was examined. This method is compatible with various functional groups (Scheme 3). In general, various 1,3-cyclopentanediones **1** were converted to chiral β -hydroxy ketones **2** bearing two adjacent stereocenters including α -quaternary stereo center with high enantioselectivity regardless of the electronic and steric properties. Notably, the non-benzofused 1,3-diketone (**11**) was also compatible. The spiro diketone **1m** could be hydrogenated with moderate 61% ee, and diketones **1n** and **1o** bearing the ester group could also be smoothly hydro-



Scheme 2 Diastereoselectivity switch in the hydrogenative desymmetrization of 1,3-diketones **1a** with Pd and Ru catalyst.

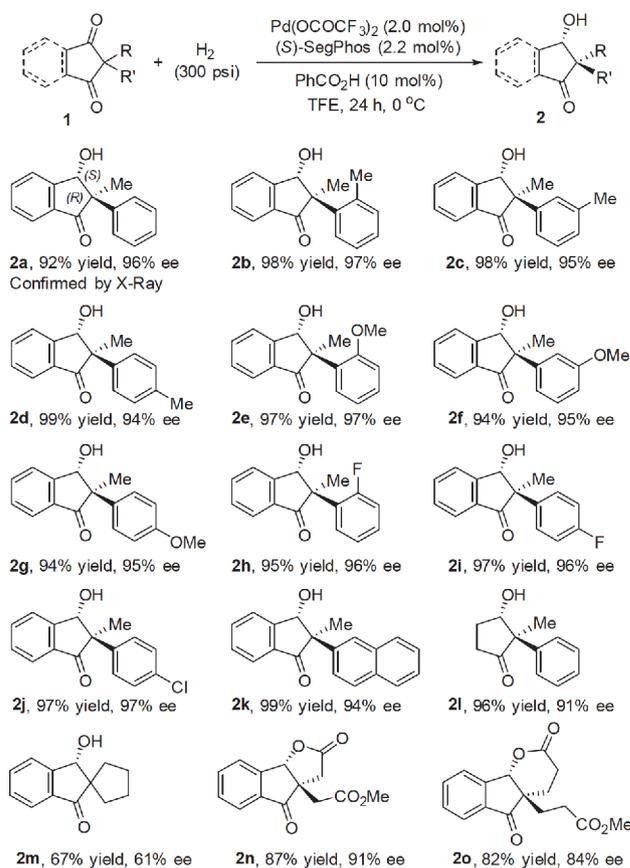
Table 1 Optimization of the reaction conditions^{a)}

Entry	Acid	L	Yield (%) ^{b)}	dr ^{c)}	ee (%) ^{d)}
1 ^{e)}	–	L1	86	10:1	91
2 ^{e)}	TFA	L1	86	11:1	93
3	TFA	L1	89	17:1	95
4	TsOH·H ₂ O	L1	9	–	–
5	D-TA	L1	93	20:1	96
6	L-TA	L1	92	20:1	96
7	PhCO ₂ H	L1	92	>20:1	96
8	SA	L1	91	17:1	95
9	PhCO ₂ H	L2	80	17:1	95
10	PhCO ₂ H	L3	93	18:1	96
11	PhCO ₂ H	L4	90	19:1	95

a) Conditions: **1a** (0.25 mmol), $\text{Pd}(\text{OCOCF}_3)_2$ (2.0 mol%), ligand (2.2 mol%), acid (10 mol%), H_2 (300 psi), TFE (4.0 mL), 0 °C, 24 h. b) Isolated yield. c) Determined by ¹H NMR. d) Determined by HPLC. e) 5 h and 25 °C. TFA=trifluoroacetic acid. TsOH·H₂O=*p*-toluenesulfonic acid monohydrate. SA=salicylic acid. D-TA =D-tartaric acid.

generated, followed by transesterification to give chiral tricyclic compounds with 91% ee and 84% ee, respectively.

The above method is also applicable to 2-aryl substituted 1,3-cyclopentanediones **3** through a simple reoptimization (see [Supporting Information online](#)). As depicted in [Scheme 4](#), both electron-donating and withdrawing substituents on the phenyl ring were tolerable, giving a series of chiral β-hydroxy ketones bearing two continuous stereocenters in excellent enantioselectivities and diastereoselectivities (**3a–3i**). Furthermore, the sterically hindered substituents on the

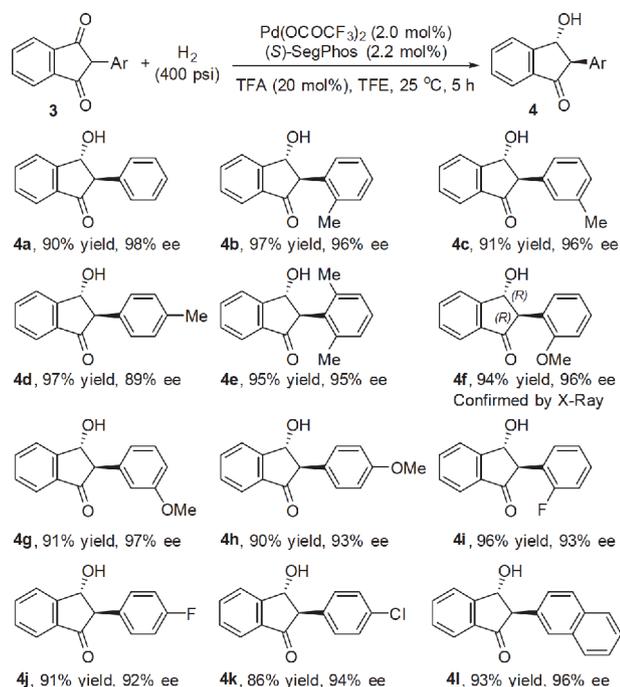


Scheme 3 Substrate scope: α-quaternary stereocenters; For **1m** and **1o**: $\text{Pd}(\text{OCOCF}_3)_2$ (5.0 mol%), $(\text{S})\text{-SegPhos}$ (6.0 mol%), trifluoroacetic acid (100 mol%), 70 °C, 42–48 h; For **1n**: $\text{Pd}(\text{OCOCF}_3)_2$ (5.0 mol%), $(\text{S})\text{-SegPhos}$ (6.0 mol%), TFA (100 mol%), 50 °C, 48 h.

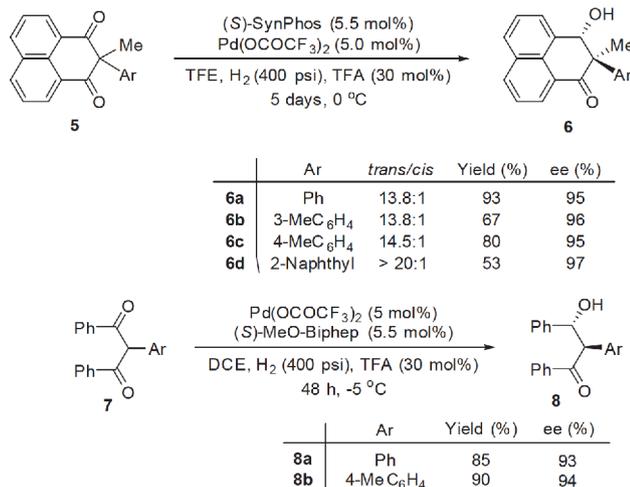
phenyl ring had negligible effect on the yield, diastereoselectivities and enantioselectivities (**3b**, **3e**, **3f** and **3i**). The absolute configuration of the desymmetrization product (*2R,3R*)-**4f** was determined by X-ray diffraction analysis (see [Supporting Information online](#)).

To further determine the substrate generality of this protocol, the naphthalene-derived 2,2-disubstituted 1,3-cyclohexanediones **5** were also investigated, and the results were summarized in [Scheme 5](#). To our delight, the hydrogenative desymmetrization afforded the chiral β-hydroxy ketones in high enantioselectivity. Besides, acyclic simple 1,3-diketones **7** were also suitable partner, giving the linear chiral β-hydroxyketones **8** with 93%–94% ee and 85%–90% yields ([Scheme 5](#)).

To demonstrate the synthetic utility of this attractive protocol, the asymmetric hydrogenation of **1a** ([Scheme 6](#), Eq. 3) was performed at gram scale to give the desired product **2a** in 93% yield and 95% ee without loss of activity, diastereoselectivity and enantioselectivity. Meanwhile, the remaining carbonyl group is an attractive functional group for further transformations. For example, nucleophilic addition with methyl lithium gave the chiral diol **9** with 89% yield and high



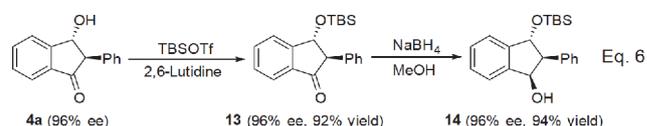
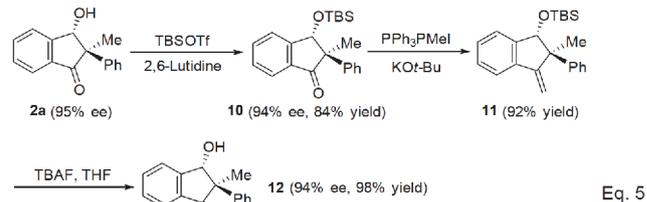
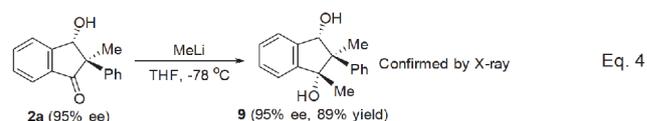
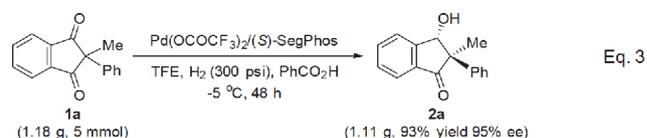
Scheme 4 Substrate scope: α -tertiary stereocenters.



Scheme 5 Substrate scopes: the naphthalene-derived 1,3-diketones and acyclic 1,3-diketones.

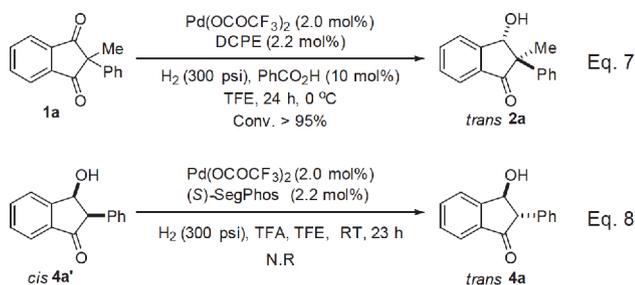
diastereoselectivity (Eq. 4). Cyclic homoallylic alcohol **12** was obtained through hydroxyl protection with TBS in the presence of lutidine, Wittig olefination and deprotection with TBAF in THF (Eq. 5). Monoprotected diol **14** with three continuous stereogenic centers could be synthesized through TBS protection and reduction with sodium borohydride with high yield (Eq. 6). Notably, for the above all transformations, no loss of optical purity was observed.

To understand the origin of unprecedented diastereoselectivity, density functional theory (M06-2X/def2-TZVP//M06-2X/def2-TZVP for Pd and 6-31g(d,p) for other atoms,

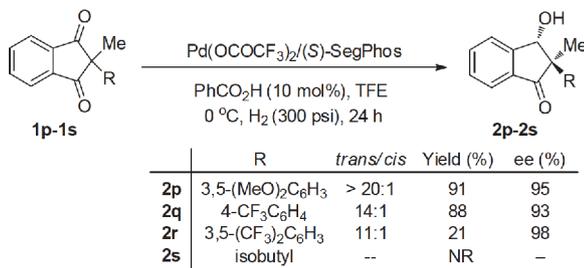


Scheme 6 Experiment at gram scale and product transformations.

details in [Supporting Information online](#)) calculations were carried out based on the optimized reaction conditions. We proposed four possible reaction mechanisms [14], four-membered ring inner-sphere model, TFA promoted four-membered ring model, outer sphere six-membered ring model, outer sphere eight-membered ring model, and found that four-membered ring inner-sphere model is the most plausible (see details in [Supporting Information online](#)). In this mechanism ([Scheme 7](#)), CF₃COO⁻ ligand is directly detached from the metal hydride **A** to generate an unoccupied site, **INT B**. The 1,3-diketone **1a** coordinates with this active center (**INT B**) to generate **INT C**. The generation of **INT E** by hydride transfer from Pd-H to **1a** is the rate-determining step (**TS D**). **INT E** reacts with TFA to generate **INT F**, following by releasing the product **2a**. TFA can be generated during the hydrogen activation step; therefore, the hydrogenation can be able to proceed without additional acid additive ([Table 1](#), entry 1). Some acid additives were found to be able to slightly increase the reactivity of the hydrogenation, we propose that this is because the concentration of TFA generated by H₂ activation is pretty low, and additional acid could enhance the transformation from **INT E** to **2a**. The key features of the reactions are similar with or without acid additives. We calculated four reaction pathways of **1a** to **2a** with four-membered inner-sphere model ([Scheme 7](#)), which showed a trend of enantioselectivity and diastereoselectivity of *trans*-(2*R*,3*S*)-**2a** > *trans*-(2*S*,3*R*)-**2a** > *cis*-(2*S*,3*S*)-**2a** > *cis*-(2*R*,3*R*)-**2a** when (*S*)-SegPhos was used as chiral ligand. Lower barriers for formation of *trans*-(2*R*,3*S*)-**2a** is in good consistent with the high diastereoselectivity observed in



Scheme 8 The control experiments.



Scheme 9 Hydrogenation of 1,3-diketones bearing different substituents.

9). When electron-donating group methoxy was introduced to phenyl (**1p**), *trans/cis* (>20:1) and full conversion was obtained. Electron-withdrawing group $-\text{CF}_3$ was introduced to phenyl (**1q**), lower *trans/cis* (14:1) was obtained, and when two $-\text{CF}_3$ were introduced (**1r**), the yield and *trans/cis* decreased to 21% and 11:1, respectively. The above results showed that the diastereoselectivity and reactivity gradually weakens with the decrease of electron cloud density on the aromatic ring, which leads to the decrease of interaction between palladium and aromatic ring. Notably, when aryl on 2-position was replaced by isobutyl, no product was obtained, which indicated that the aryl is very important to not only keep high diastereoselectivity, but also improve the reactivity.

4 Conclusions

In summary, a successful diastereoselective reversal was achieved in palladium-catalyzed asymmetric hydrogenation of 1,3-diketones through desymmetrization, providing the chiral β -hydroxy ketones bearing two adjacent stereo centers including one α -tertiary or quaternary stereocenter with high yields, enantioselectivities and diastereoselectivities [16]. The control experiments and theoretical studies based on DFT calculations revealed that the observed diastereoselectivity reversal was resulted from the charge-charge interaction between the palladium and the aromatic ring of the substrate, which also promoted the reactivity. We envision that the *in situ* interaction strategy would open a new window for the development of asymmetric synthesis.

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Conflict of interest The authors declare that they have no conflict of interest.

Supporting information The supporting information is available online at <http://chem.scichina.com> and <http://link.springer.com/journal/11426>. The supporting materials are published as submitted, without typesetting or editing. The responsibility for scientific accuracy and content remains entirely with the authors.

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- 16 During our preparation of this manuscript, a related iridium-catalyzed hydrogenative desymmetrization of 1,3-diketones was reported by Zhang's group, please see: The chiral Ir/f-ampha complex catalyst was used, and cis product was obtained. In our work, trans products were observed.. Gong Q, Wen J, Zhang X. *Chem Sci*, 2019, 10: 6350–6353