SCIENCE CHINA
Chemistry

•ARTICLES•

https://doi.org/10.1007/s11426-019-9601-7

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

Chang-Bin Yu[1†], Heng-Ding Wang[1,2†], Bo Song[1], Hong-Qiang Shen[1], Hong-Jun Fan[1*] & Yong-Gui Zhou[1*]

[1]*State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, China;*
[2]*University of Chinese Academy of Sciences, Beijing 100049, China*

Received August 24, 2019; accepted August 28, 2019; published online October 22, 2019

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

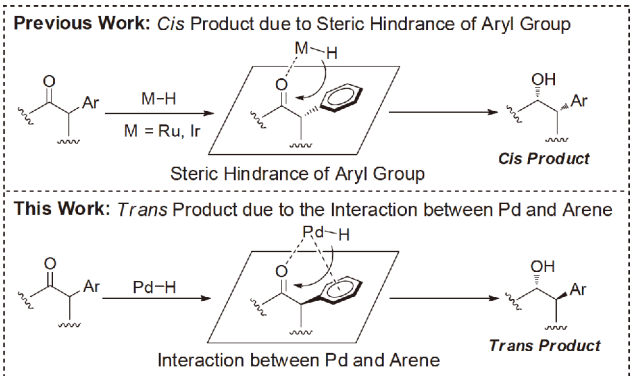
Citation: Yu CB, Wang HD, Song B, Shen HQ, Fan HJ, Zhou YG. Reversal of diastereoselectivity in palladium-arene interaction directed hydrogenative desymmetrization of 1,3-diketones. *Sci China Chem*, 2019, 62, https://doi.org/10.1007/s11426-019-9601-7

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

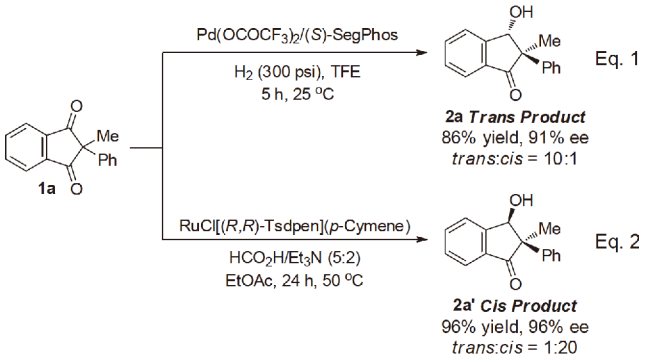
Ligand (*S*)-SegPhos (3.4 mg, 0.0055 mmol) and Pd $(OCOCF_3)_2$ (1.7 mg, 0.005 mmol) were placed in a dried Schlenk tube under nitrogen atmosphere, and degassed anhydrous acetone was added. The mixture was stirred at room temperature for 1 h. The solvent was removed under vacuum to give the catalyst. 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.

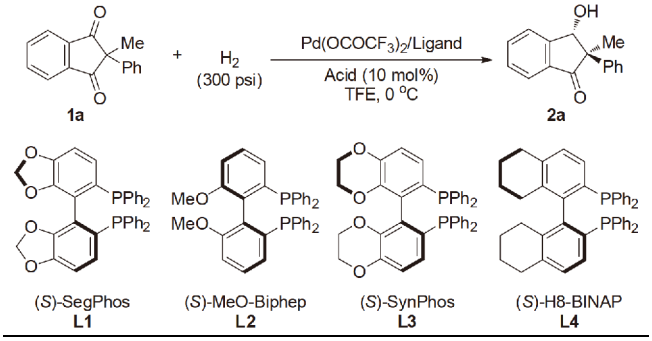
Encouraged by the above result, we next optimized the reaction conditions to further improve the diastereoselectivity. Delightedly, in the presence of additive trifluoroacetic acid (TFA), the enantio- and diastereoselectivity was improved (Table 1, entry 2). Next, when the reaction temperature was decreased, 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: $Pd(OCOCF_3)_2$/(*S*)-SegPhos/$PhCO_2H$/TFE/H_2 (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 (**1l**) 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)]

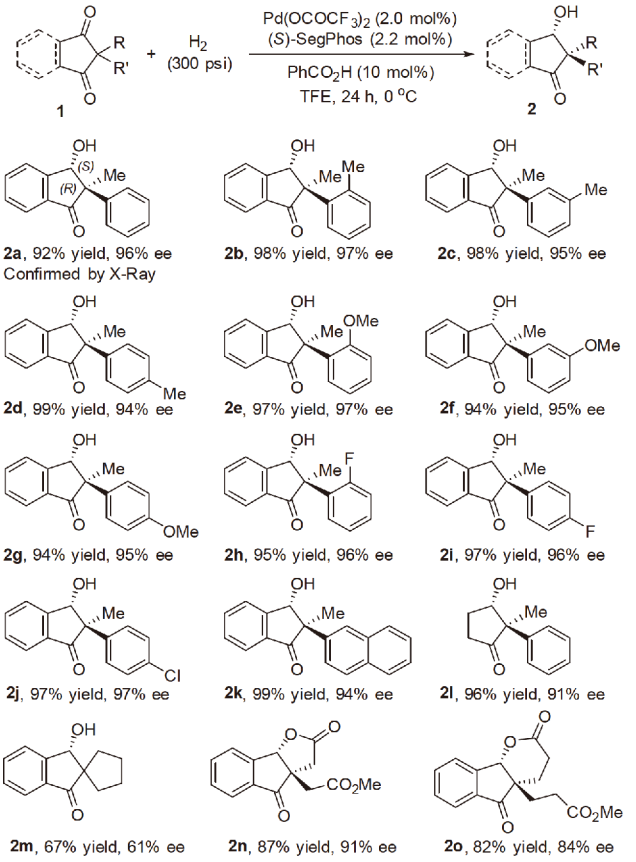


Entry	Acid	L	Yield (%)[b)]	dr[c)]	ee (%)[d)]
1[e]	–	**L1**	86	10:1	91
2[e]	TFA	**L1**	86	11:1	93
3	TFA	**L1**	89	17:1	95
4	TsOH·H_2O	**L1**	9	–	–
5	D-TA	**L1**	93	20:1	96
6	L-TA	**L1**	92	20:1	96
7	$PhCO_2H$	**L1**	92	>20:1	96
8	SA	**L1**	91	17:1	95
9	$PhCO_2H$	**L2**	80	17:1	95
10	$PhCO_2H$	**L3**	93	18:1	96
11	$PhCO_2H$	**L4**	90	19:1	95

a) Conditions: **1a** (0.25 mmol), $Pd(OCOCF_3)_2$ (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 ^{1}H NMR. d) Determined by HPLC. e) 5 h and 25 °C. TFA=trifluoroacetic acid. TsOH•H_2O=*p*-toluenesulfonic acid monohydrate. SA=salicylic acid. D-TA =D-tartaric acid.

genated, 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**–**3l**). Furthermore, the sterically hindered substituents on the

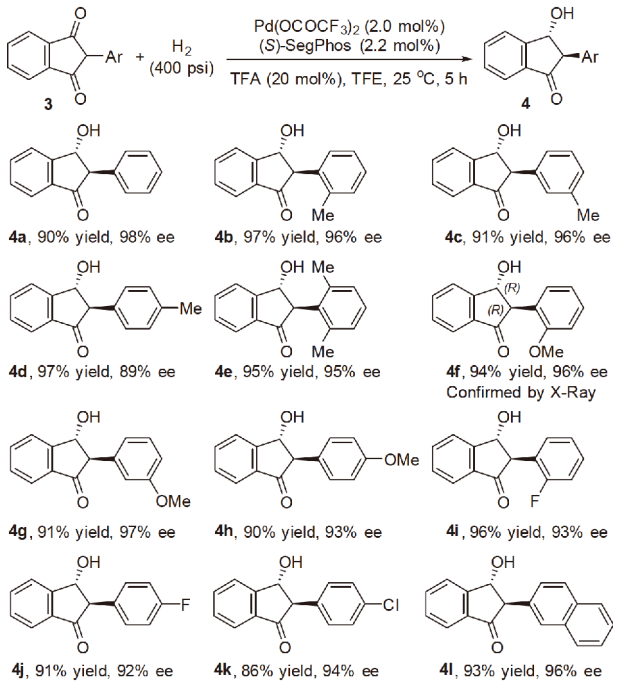


Scheme 3 Substrate scope: α-quaternary stereocenters; For **1m** and **1o**: $Pd(OCOCF_3)_2$ (5.0 mol%), (*S*)-SegPhos (6.0 mol%), trifluoroacetic acid (100 mol%), 70 °C, 42–48 h; For **1n**: $Pd(OCOCF_3)_2$ (5.0 mol%), (*S*)-SegPhos (6.0 mol%), TFA (100 mol%), 50 °C, 48 h.

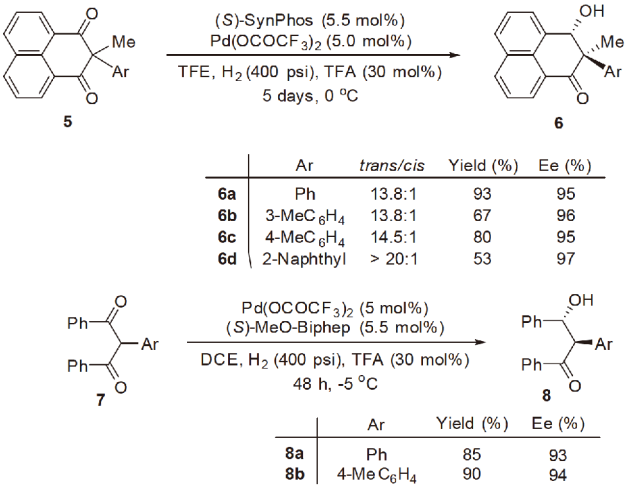
phenyl ring had negligible effect on the yield, diastereoselectivities and enantioselectivities (**3b**, **3e**, **3f** and **3i**). The absolute configuration of the desymmetrization product (2*R*,3*R*)-**4f** was determined by X-ray diffraction analysis (see Supporting Information online).

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.



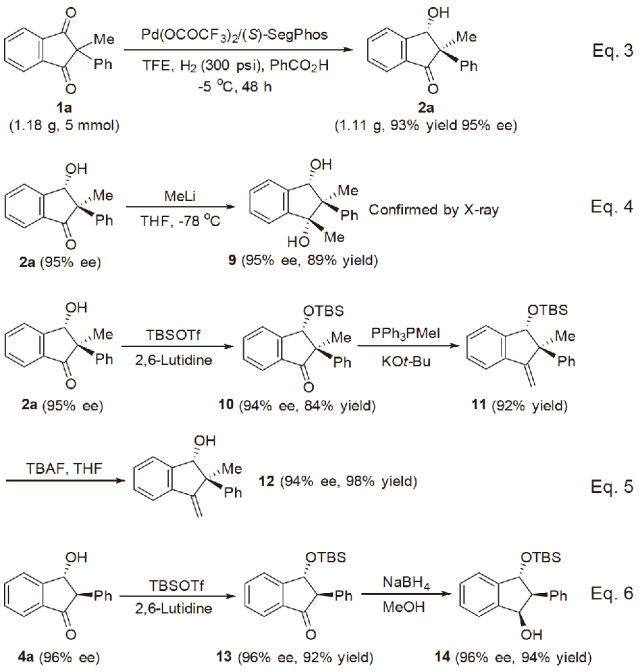
	Ar	*trans*/*cis*	Yield (%)	Ee (%)
6a	Ph	13.8:1	93	95
6b	3-MeC_6H_4	13.8:1	67	96
6c	4-MeC_6H_4	14.5:1	80	95
6d	2-Naphthyl	> 20:1	53	97

	Ar	Yield (%)	Ee (%)
8a	Ph	85	93
8b	4-MeC_6H_4	90	94

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

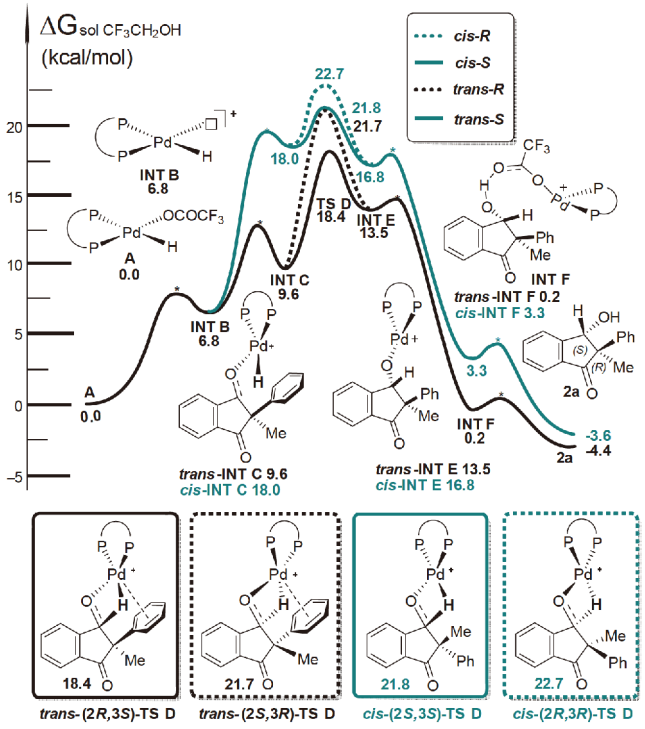
diastereoselectivity (Eq. 4). Cyclic homoallylic alcohol **12** was obtained through hydroxyl protection with TBS in the presence of lutidine, Wittig olefination and deprotection with TBAF in THF (Eq. 5). Monoprotected diol **14** with three continuous stereogenic centers could be synthesized through 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), CF_3COO^- 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 H_2 activation is pretty low, and additional acid could enhance the tranformation 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 7 DFT calculations of four types of reaction pathways for diastereoselective reversal (color online).

experiment.

Computational experiments have been carried out to give a further understanding of the observed *trans* selectivity. We first considered that possibly the selectivity arises from the interaction between the ligand and the substrate. Therefore, we removed Pd-H fragment from the optimized structure of *trans-(2R,3S)*-**TS D** and *cis-(2S,3S)*-**TS D** to direct compare total substrate/ligand interaction in the two transition states. We found the energy difference (ΔE_{total}) between *trans-(2R,3S)*-**TS D** and *cis-(2S,3S)*-**TS D** decrease dramatically from −3.9 to −1.2 kcal/mol. This result showed that the total substrate/ligand interaction is not the dominant factor for the observed *trans* selectivity. To gain more insight, the substrate/ligand interaction was analyzed with the distortion/interaction model (details in SI). We found the advantageous interaction-energy terms (ΔE_{int}) in *trans-(2R,3S)*-**TS D** is remarkably canceled by distortion energy terms (ΔE_{dist}).

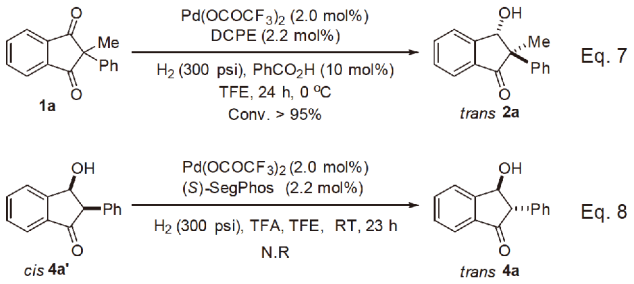
On the other hand, if the ligand was removed from the optimized structure of *trans-(2R,3S)*-**TS D** and *cis-(2S,3S)*-**TS D** the energy difference between the two transition states only changed slightly from −3.9 to −3.3 kcal/mol, which suggested that the *trans* selectivity is maintained even if the ligand is not there.

Next, the cause of Pd-H and substrate interaction leading to the *trans* product was inspected. We noticed that in the *trans* transition state the Pd(II) cation is closer to the phenyl ring of the substrate, and the negative charge of the phenyl ring points to the cationic Pd(II) center. Late transition metal-arene interaction is known in many transition metal compounds, and very recently it is found that such interactions could be very important to catalytic C–H/C–H cross coupling reaction [4a]. In our reaction system, the phenyl ring cannot coordinate strongly to the Pd(II) due to steric hindrance, however, the distance between Pd-H fragment and phenyl ring is in the range of weak interaction, and the interaction between them could be the driven force for the *trans* selectivity. To validate this idea, we have calculated the interaction energy between Pd-H and phenyl ring/methyl group of substrate **1a** with *trans*-(2*R*,3*S*)-**TS D** and *cis*-(2*S*,3*S*)-**TS D** using ADF 2018 and Interacting Quantum Atoms (IQA) method [15]. Indeed, we found that the Pd-H and phenyl interaction energy in *trans*-(2*R*,3*S*)-**TS D** is −7.0 kcal/mol, much larger than that for Pd-H and Me (−3.5 kcal/mol) in *cis*-(2*S*,3*S*)-**TS D**. The energy difference of these two interactions is −3.5 kcal/mol, which is very close to the total electronic energy difference between *trans*-(2*R*,3*S*)-**TS D** and *cis*-(2*S*,3*S*)-**TS D** (−3.9 kcal/mol), suggesting that the weak interaction of the Pd-H and phenyl ring is the dominating factor of the *trans* selectivity. Since phenyl ring does not coordinate with Pd(II) we suppose this weak interaction between Pd-H and phenyl ring mostly arise from charge-charge interaction.

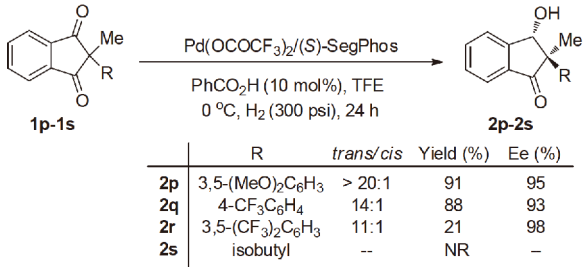
To verify this assumption, we conducted the computational experiments to study the *trans*/*cis* selectivity by replacing phenyl to other groups (such as $-NO_2$, *t*-butyl, $-CF_3$, –OTf and halogens) in the *trans*-(2*R*,3*S*)-**TS D** and *cis*-(2*R*,3*S*)-**TS D** (details in Supporting Information online). Indeed, the strong *trans* selectivity was observed for the negative charged groups, and *trans* selectivity dramatically decreased when we changed phenyl group into H atom. The bulky *t*-Butyl group, surrounded by the positively charged H atoms, is the only group which is predicted to have *cis* selectivity. These results support that the weak charge-charge interaction is the dominating factor for *trans* selectivity.

Then, some control experiments were also conducted to provide the further insight into the mechanism. Firstly, 1,3-diketone **1a** was reduced using the aliphatic ligand 1,2-bis (dicyclohexylphosphanyl)-ethane (DCPE) as to identify whether the chirality of the ligand or π-π stacking effect between the aryl in ligand and the substrate induced *trans* configuration of the product (Scheme 8, Eq. 7). *Trans* product was obtained, which proved that the ligand has no effect on diastereoselectivity, and there was also no π-π stacking effect in the transition state. When *cis*-**4a′** was conducted under the standard condition (Eq. 8), no reaction occurred, which suggested that chiral palladium complex cannot promote the isomerisation of *cis* product to thermodynamically stable *trans* product.

Next, the influence of substituents of phenyl ring on reactivity and diastereoselectivity was investigated (Scheme



Scheme 8 The control experiments.



	R	*trans*/*cis*	Yield (%)	Ee (%)
2p	3,5-$(MeO)_2C_6H_3$	> 20:1	91	95
2q	4-$CF_3C_6H_4$	14:1	88	93
2r	3,5-$(CF_3)_2C_6H_3$	11:1	21	98
2s	isobutyl	--	NR	–

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 $-CF_3$ was introduced to phenyl (**1q**), lower *trans*/*cis* (14:1) was obtained, and when two $-CF_3$ 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.

Acknowledgements This work was supported by the National Natural Science Foundation of China (21871255, 21532006, 21873096) and Chinese Academy of Sciences (XDB17020300, XDB17010200).

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.

1 (a) Jäkel C, Paciello R. *Chem Rev*, 2006, 106: 2912–2942; (b) Tang W, Zhang X. *Chem Rev*, 2003, 103: 3029–3070; (c) Verendel JJ, Pàmies O, Diéguez M, Andersson PG. *Chem Rev*, 2014, 114: 2130–2169; (d) Johnson NB, Lennon IC, Moran PH, Ramsden JA. *Acc Chem Res*, 2007, 40: 1291–1299; (e) Wang DS, Chen QA, Lu SM, Zhou YG. *Chem Rev*, 2012, 112: 2557–2590; (f) Zhang Z, Butt NA, Zhang W. *Chem Rev*, 2016, 116: 14769–14827; (g) Xie JH, Zhu SF, Zhou QL. *Chem Rev*, 2011, 111: 1713–1760

2 (a) Noyori R, Ohkuma T. *Angew Chem Int Ed*, 2001, 40: 40–73; (b) Morris RH. *Chem Soc Rev*, 2009, 38: 2282; (c) Malacea R, Poli R, Manoury E. *Coord Chem Rev*, 2010, 254: 729–752; (d) Baiker A. *Chem Soc Rev*, 2015, 44: 7449–7464; (e) Li YY, Yu SL, Shen WY, Gao JX. *Acc Chem Res*, 2015, 48: 2587–2598

3 For selected examples on asymmetric hydrogenation of α-alkyl or aryl substituted ketones: (a) Ohkuma T, Li J, Noyori R. *SynLett*, 2004, 8: 1383; (b) Lin H, Xiao LJ, Zhou MJ, Yu HM, Xie JH, Zhou QL. *Org Lett*, 2016, 18: 1434–1437; (c) Peach P, Cross DJ, Kenny JA, Mann I, Houson I, Campbell L, Walsgrove T, Wills M. *Tetrahedron*, 2006, 62: 1864–1876; (d) Nishiyama H, Park SB, Itoh K. *Tetrahedron-Asymmetry*, 1992, 3: 1029–1034; (e) Baratta W, Barbato C, Magnolia S, Siega K, Rigo P. *Chem Eur J*, 2010, 16: 3201–3206; (f) Fernández R, Ros A, Magriz A, Dietrich H, Lassaletta JM. *Tetrahedron*, 2007, 63: 6755–6763; (g) Liu C, Xie JH, Li YL, Chen JQ, Zhou QL. *Angew Chem Int Ed*, 2013, 52: 593–596; (h) Cheng LJ, Xie JH, Chen Y, Wang LX, Zhou QL. *Org Lett*, 2013, 15: 764–767

4 (a) She Z, Wang Y, Wang D, Zhao Y, Wang T, Zheng X, Yu ZX, Gao G, You J. *J Am Chem Soc*, 2018, 140: 12566–12573; (b) Mikhel IS, Ruegger H, Butti P, Camponovo F, Huber D, Mezzetti A. *Organometallics*, 2008, 27: 2937–2948

5 (a) Huber D, Kumar PGA, Pregosin PS, Mezzetti A. *Organometallics*, 2005, 24: 5221–5223; (b) Nagashima H, Fukahori T, Aoki K, Itoh K. *J Am Chem Soc*, 1993, 115: 10430–10431

6 (a) Berenguer JR, Lalinde E, Moreno MT, Sánchez S, Torroba J. *Inorg Chem*, 2012, 51: 11665–11679; (b) Falceto A, Carmona E, Alvarez S. *Organometallics*, 2014, 33: 6660–6668; (c) Fornies J, Menjon B, Gomez N, Tomas M. *Organometallics*, 1992, 11: 1187–1193; (d) McGuire R Jr., McGuire MC, McMillin DR. *Coord Chem Rev*, 2010, 254: 2574–2583

7 (a) Liu S, Rogachev AY. *ChemPhysChem*, 2018, 19: 2579–2588; (b) Elschenbroich C, Salzer A. in *Organometallics. A Concise Introduction*. 2nd ed. Weinheim: VCH, 1992. 346; (c) Belt ST, Helliwell M, Jones WD, Partridge MG, Perutz RN. *J Am Chem Soc*, 1993, 115: 1429–1440

8 (a) Maestri G, Motti E, Della Ca' N, Malacria M, Derat E, Catellani M. *J Am Chem Soc*, 2011, 133: 8574–8585; (b) Yamamoto K, Kimura S, Murahashi T. *Angew Chem Int Ed*, 2016, 55: 5322–5326; (c) Li Y, Wang WH, He KH, Shi ZJ. *Organometallics*, 2012, 31: 4397–4400; (d) Canty AJ, van Koten G. *Acc Chem Res*, 1995, 28: 406–413; (e) Falvello LR, Forniés J, Navarro R, Sicilia V, Tomás M. *Angew Chem Int Ed Engl*, 1990, 29: 891–893; (f) Cámpora J, López JA, Palma P, Valerga P, Spillner E, Carmona E. *Angew Chem Int Ed*, 1999, 38: 147–151; (g) Vignolle J, Gornitzka H, Donnadieu B, Bourissou D, Bertrand G. *Angew Chem Int Ed*, 2008, 47: 2271–2274; (h) Murahashi

T, Takase K, Oka M, Ogoshi S. *J Am Chem Soc*, 2011, 133: 14908–14911; (i) Kocovský P, Vyskocil Š, Císařová I, Sejbal J, Tišlerová I, Smrcina M, Lloyd-Jones GC, Stephen SC, Butts CP, Murray M, Langer V. *J Am Chem Soc*, 1999, 121: 7714–7715; (j) Yin J, Rainka MP, Zhang XX, Buchwald SL. *J Am Chem Soc*, 2002, 124: 71162; (k) Sköld C, Kleimark J, Trejos A, Odell LR, Nilsson Lill SO, Norrby PO, Larhed M. *Chem Eur J*, 2012, 18: 4714–4722

9 (a) Catellani M, Mealli C, Motti E, Paoli P, Perez-Carreño E, Pregosin PS. *J Am Chem Soc*, 2002, 124: 4336–4346; (b) Della Ca' N, Fontana M, Motti E, Catellani M. *Acc Chem Res*, 2016, 49: 1389

10 Tanaka D, Romeril SP, Myers AG. *J Am Chem Soc*, 2005, 127: 10323–10333

11 (a) Chen QA, Ye ZS, Duan Y, Zhou YG. *Chem Soc Rev*, 2013, 42: 497–511; (b) Xie J, Zhou Q. *Acta Chim Sin*, 2012, 70: 1427; (c) Wang YQ, Lu SM, Zhou YG. *Org Lett*, 2005, 7: 3235–3238; (d) Zhou XY, Wang DS, Bao M, Zhou YG. *Tetrahedron Lett*, 2011, 52: 2826–2829

12 (a) Raja R, Thomas JM, Jones MD, Johnson BFG, Vaughan DEW. *J Am Chem Soc*, 2003, 125: 14982–14983; (b) Goulioukina NS, Bondarenko GN, Bogdanov AV, Gavrilov KN, Beletskaya IP. *Eur J Org Chem*, 2009, 2009(4): 510–515; (c) Chen J, Liu D, Butt N, Li C, Fan D, Liu Y, Zhang W. *Angew Chem Int Ed*, 2013, 52: 11632–11636; (d) Jiang W, Zhao Q, Tang W. *Chin J Chem*, 2018, 36: 153–156

13 For coordinative group (acetamido, toluenesulfonamido and benzamido) substituted ketones, trans products could be also obtained with high enantioselectivity owing to the coordination-directed interaction, for some recent examples, see: (a) Lu B, Wu X, Li C, Ding G, Li W, Xie X, Zhang Z. *J Org Chem*, 2019, 84: 3201–3213; (b) Cotman AE, Lozinšek M, Wang B, Stephan M, Mohar B. *Org Lett*, 2019, 21: 3644–3648

14 Duan Y, Li L, Chen MW, Yu CB, Fan HJ, Zhou YG. *J Am Chem Soc*, 2014, 136: 7688–7700

15 The summed interaction between the active Pd-H and phenyl/methyl also evaluated. See details in Supporting Information.

16 During our preparation of this manuscript, a related irdium-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