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Communication

Palladium-Catalyzed Autotandem Hydrogenolysis/Hydrogenation for the Synthesis of Hexahydro-β-carbolines Containing Three Contiguous Stereocenters

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ABSTRACT: Autotandem catalysis is an efficient and step-economical reaction involving two or more mechanistically distinct reaction processes under the action of only a single catalyst. Herein, an unprecedented asymmetric autotandem catalysis reaction merging hydrogenolysis and hydrogenation of hydroxylactam-fused indoles through a dynamic kinetic resolution process with palladium hydride as the same active species was developed, affording hexahydro-β-carbolines containing three contiguous stereocenters with excellent enantio- and diastereoselectivity. Versatile synthetic transformations of the chiral heterocyclic products were carried out without loss of enantiomeric purity, even affording octahydroindole derivatives containing up to five contiguous stereocenters. Mechanistic studies including deuterium-labeling experiments and control experiments supported that the dynamic kinetic resolution process is crucial for excellent diastereoselectivity performance.

Autotandem catalysis (ATC) is a fascinating process involving two or more mechanistically distinct elementary processes that are facilitated by a single catalyst,[1] in which the process enables the catalyst to perform multiple roles and avoids isolation of intermediates, thereby cutting waste and enhancing efficiency with an eco-friendly manner. Therefore, ATC has received considerable attention in recent decades. Despite progress in this field,[2] the reports of asymmetric autotandem catalysis reactions are limited, because it is challenging to establish highly efficient catalytic systems compatible with multiple mechanistically different catalytic cycles.[3] Therefore, developing new asymmetric autotandem catalysis processes is desirable. Transition-metal-catalyzed hydrogenolysis is indispensable in organic synthesis, which has been successfully applied in synthetic methods and industrial processes.[4,5] In addition, transition-metal-catalyzed asymmetric hydrogenation has emerged as a fundamental transformation in modern organic synthesis, due to its high atom economy, environmental friendliness and simple workup procedure, which is regarded as one of the most successful methods in the field of industrial applications (Scheme 1, upper part).[6] Therein, the key metal-hydride[7] is the same active species involved in both hydrogenolysis and asymmetric hydrogenation, which provides a chance for the realization of an asymmetric autotandem catalysis reaction merging hydrogenolysis and asymmetric hydrogenation.

Chiral indoline motifs containing multiple contiguous stereocenters are widely found in many structurally complex and diverse natural products as well as biologically active molecules (Figure 1).[8] Notably, these chiral molecules not only exhibit extremely rich biological and medicinal activities but also have long been a source of inspiration in drug design.

However, traditional methods for constructing these complex skeletons typically require tedious step-by-step processes.[9] This gradual approach often leads to low synthetic efficiency, limiting their widespread application in organic synthesis and drug development. Therefore, developing more efficient and concise synthetic pathways to these important chiral indoline structural units is of great significance for promoting the discovery and development of innovative drugs. Among the most common methods, the direct asymmetric reduction of corresponding indole compounds is one of the most straightforward and efficient approaches to obtain chiral indolines. Over the past decades, asymmetric reduction of corresponding indoles was successful for synthesis of 2/3-monosubstituted[10] and 2,3-disubstituted[11] indolines with excellent enantioselectivities. However, the asymmetric reduction of indoles for the synthesis of chiral indolines with multiple contiguous stereocenters remains a challenge that has been rarely explored to date. Considering that dynamic kinetic resolution (DKR) is an efficient strategy for achieving a single enantiomer from multiple enantiomers with 100% theoretical yield, this method has been widely used for the synthesis of compounds with one or two, or even multiple contiguous stereogenic centers.[11a,b,12,13] Moreover, indole derivatives with hydroxyl groups are readily available,[14] and the hydroxyl groups can easily undergo hydrogenolysis reaction in the presence of metal hydride.[4] In addition, metal hydride active species have successfully achieved asymmetric hydrogenation of indoles.[10a−k,11] In our continuous efforts in homogeneous palladium-catalyzed hydrogenolysis and asymmetric hydro-

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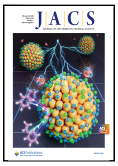

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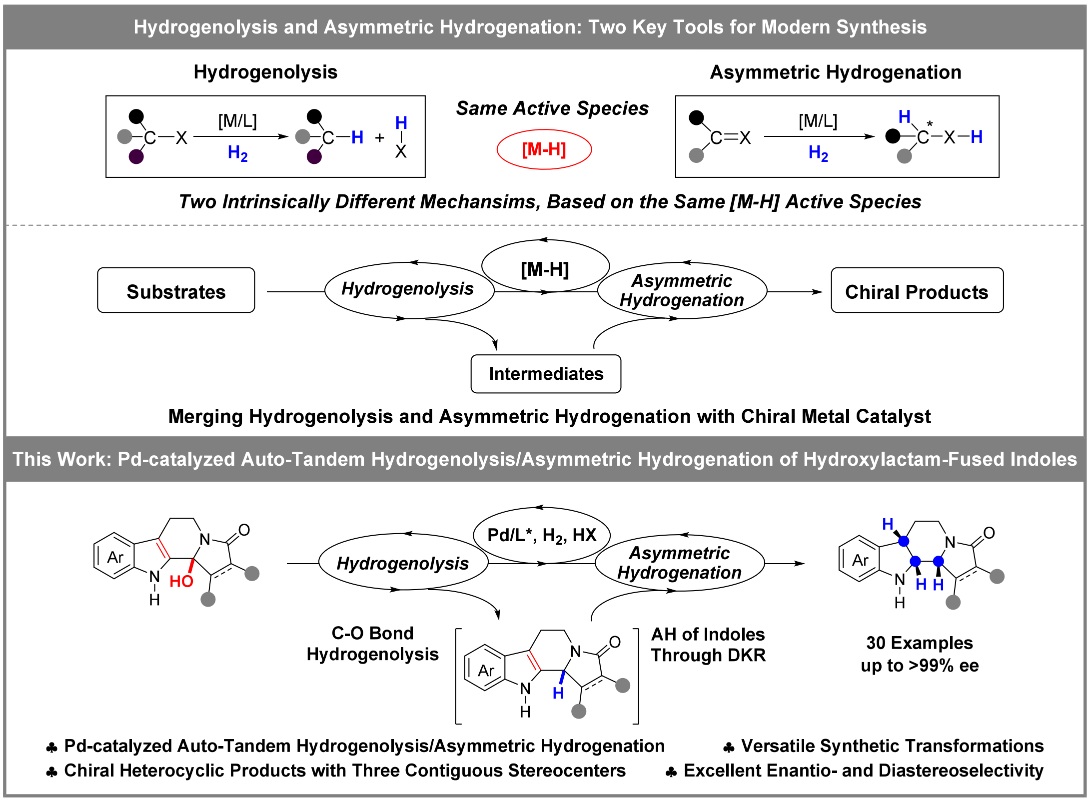
Scheme 1. Palladium-Catalyzed Autotandem Hydrogenolysis/Asymmetric Hydrogenation



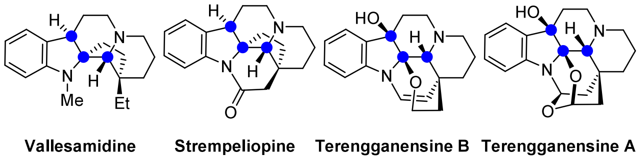
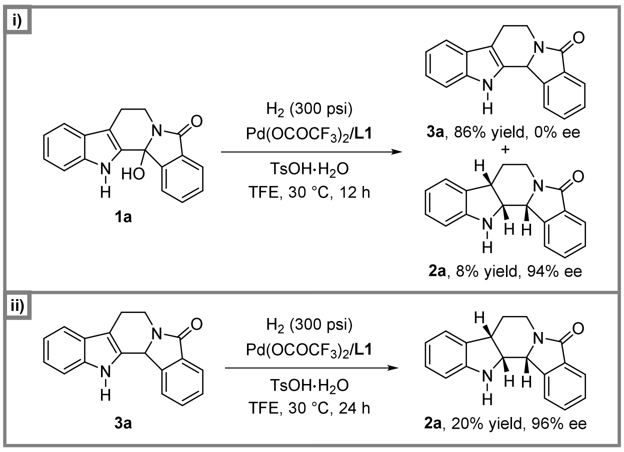


Figure 1. Indoline alkaloids containing vicinal stereocenters.

genation[4b,15,16] with the same palladium hydride (Pd−H) active species, we envisioned whether it is a possibility to achieve the synthesis of indoline alkaloid analogues containing multiple contiguous stereocenters through a palladium-catalyzed autotandem process involving hydrogenolysis of C−O bonds and asymmetric hydrogenation of indoles via DKR. However, this ATC reaction still faces several challenges, such as 1) the sequence of hydrogenolysis, asymmetric hydrogenation and DKR processes, 2) the compatibility between metal hydrides and ATC, 3) the control of chemoselectivity, enantioselectivity, and diastereoselectivity. Herein, we reported a palladium-catalyzed autotandem hydrogenolysis/asymmetric hydrogenation involving a DKR process to synthesize the hexahydro-*β*-carbolines containing three contiguous stereocenters with excellent enantio- and diastereoselectivity (Scheme 1, bottom part). In addition, the versatile synthetic transformations of the chiral heterocyclic products were conducted, and octahydroindole derivatives containing five contiguous stereocenters could even be conveniently prepared.

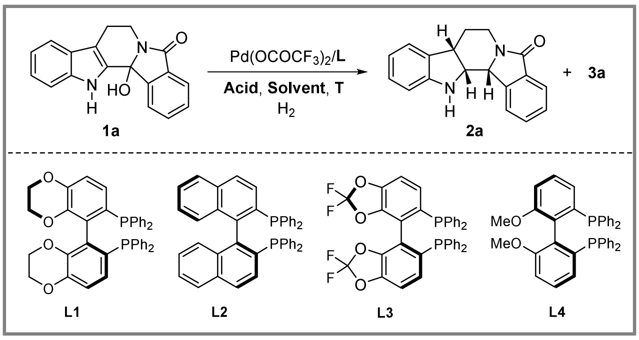
Motivated by the aforementioned vision, we began the initial attempt of a palladium-catalyzed autotandem hydrogenolysis/asymmetric hydrogenation (Scheme 2). First of all, hydroxylactam-fused indole **1a** was chosen as the model substrate, and a Pd$(OCOCF_3)_2$/(*S*)-SynPhos complex was used as the catalyst in the presence of hydrogen as the hydride source and TsOH·H_2O as the Brønsted acid in 2,2,2-trifluoroethanol (TFE) at 30 °C for 12 h. The hydrogenolysis product **3a** was observed with 86% yield and 0% ee, while the desired product **2a** was also detected in 8% yield with 94% ee (Scheme 2i). Next, hydrogenolysis product **3a** was subjected to hydrogenation under the same conditions with the reaction time extended to 24 h. The desired product **2a** was obtained with 20% yield and 96% ee (Scheme 2ii). The anticipated and gratifying results demonstrated that the proposed concept, autotandem hydrogenolysis/asymmetric hydrogenation relying on a single Pd−H active species, is feasible.

Scheme 2. Initial Attempt of Pd-Catalyzed Autotandem Hydrogenolysis/Asymmetric Hydrogenation of Hydroxylactam-Fused Indoles



According to the above experimental findings, we systematically investigated the reaction parameters of the autotandem reaction to establish the optimal conditions (Table 1, see SI, Supporting Information). To achieve a high yield and enantioselectivity, the autotandem reaction was conducted at 80 °C and 750 psi H_2. First, the effect of solvents on the reactivity and enantioselectivity was examined; TFE gave a better yield and enantioselectivity (entry 3). Next, various Brønsted acids were examined (entries 3–6) and exhibited distinct behavior. Among them, the methanesulfonic acid ($MeSO_3H$) afforded the best result (entry 4). When a weak Brønsted acid, such as benzoic acid, was added, the reaction yielded hydrogenolysis product **3a** in 98% yield (entry 6). Further screening of various chiral bisphosphine ligands showed that **L4**, (*S*)-MeOBiPhep, was the optimal choice (entry 9). Finally, the reaction parameters were fine-tuned to promote this autotandem catalysis process. Lowering either temperature (entry 10) or hydrogen pressure (entry 11) had slightly adverse effects on the yield and ee value of the desired product **2a**. When the catalyst loading was decreased to 2.0 mol %, or the amounts of TFE was reduced to 2.0 mL, the reaction proceeded smoothly without deterioration of the yield and ee value (entries 12, 13). Therefore, the optimal conditions were established: $Pd(OCOCF_3)_2$/**L4**, $MeSO_3H$, TFE, and H_2 (750 psi) were measured at 80 °C.

Table 1. Condition Optimization[a]



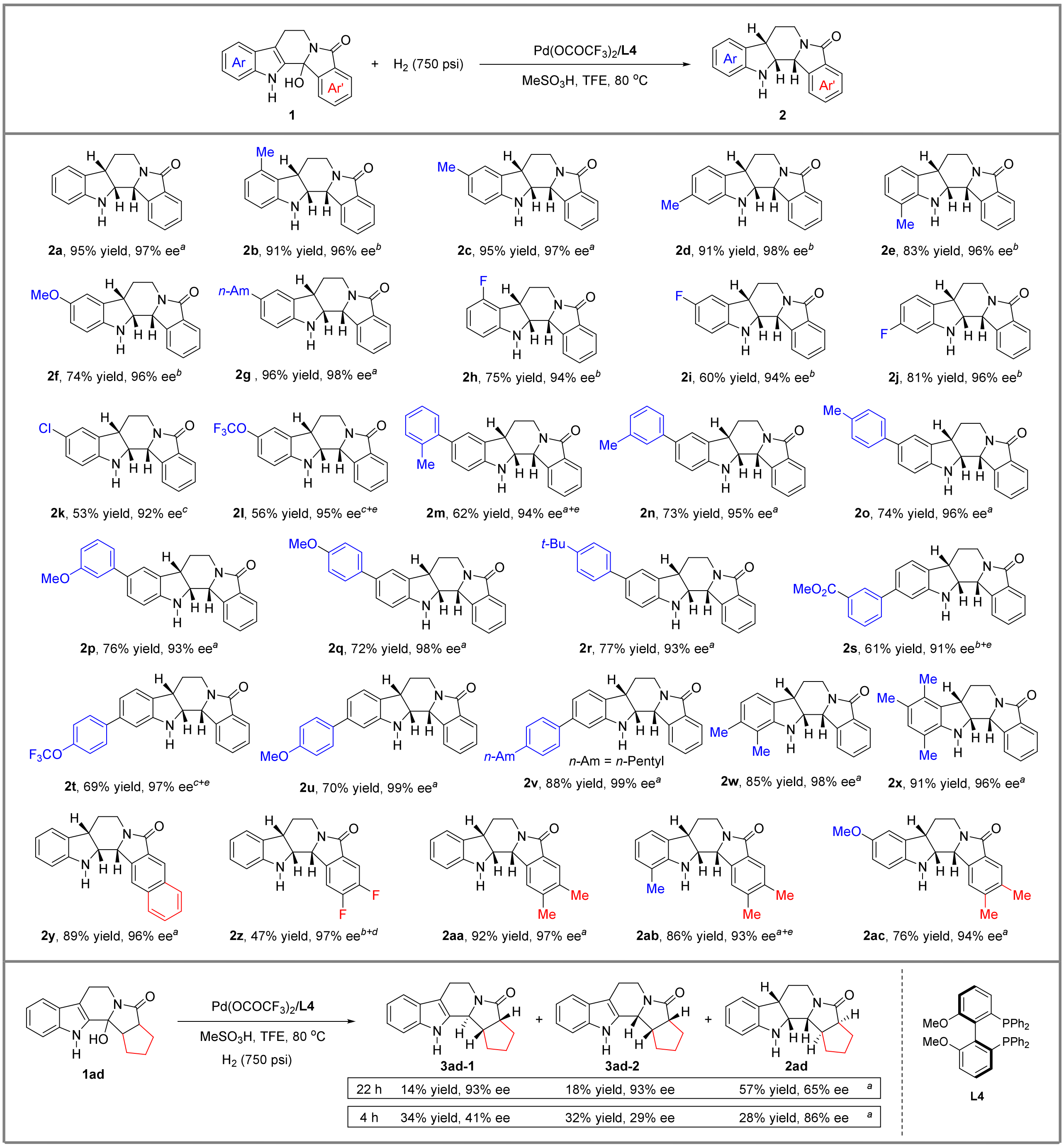
				2a	
Entry	Solvent	Acid	L	Yield (%)[b]/ ee (%)[c]	3a Yield (%)[b]
1	DCM	$TsOH·H_2O$	**L1**	28/86.1	72
2	HFIP	$TsOH·H_2O$	**L1**	86/95.0	13
3	TFE	$TsOH·H_2O$	**L1**	94/95.1	5
4	TFE	$MeSO_3H$	**L1**	97/96.9	<5
5	TFE	CF_3CO_2H	**L1**	19/72.4	80
6	TFE	$PhCO_2H$	**L1**	−/−	98
7	TFE	$MeSO_3H$	**L2**	98/92.3	<5
8	TFE	$MeSO_3H$	**L3**	90/95.5	10
9	TFE	$MeSO_3H$	**L4**	99/97.5	<5
10[d]	TFE	$MeSO_3H$	**L4**	98/95.2	<5
11[e]	TFE	$MeSO_3H$	**L4**	95/95.5	<5
12[f]	TFE	$MeSO_3H$	**L4**	98/97.1	<5
13[g]	**TFE**	**$MeSO_3H$**	**L4**	**99/97.1**	**<5**

[a] Reaction conditions: **1a** (58 mg, 0.2 mmol), $Pd(OCOCF_3)_2$ (2.0 mg, 3.0 mol %), **L** (3.3 mol %), Solvent (3.0 mL), H_2 (750 psi.), 80 °C, 24 h. [b] Conversions and yields were determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard, and all conversion was >95%. [c] Determined by chiral HPLC. [d] 70 °C. [e] H_2 (500 psi.). [f] $Pd(OCOCF_3)_2$ (1.3 mg, 2.0 mol %), **L4** (2.6 mg, 2.2 mol %). [g] $Pd(OCOCF_3)_2$ (1.3 mg, 2.0 mol %), **L4** (2.6 mg, 2.2 mol %), TFE (2.0 mL).

Under the optimal conditions, we examined the substrate scope (Scheme 3). The desired product hexahydro-*β*-carboline **2a** was obtained from model substrate **1a** in 95% yield with 97% ee. Subsequently, the substrates bearing various substituents on the benzene ring of the indole moiety were investigated. The substrates containing electron-donating and electron-withdrawing substituents at different positions of the indole moiety performed well, affording the desired products (**2b–2l**) with excellent enantioselectivities and moderate to excellent yields. To further broaden the range of substrates, the substrates bearing various substituted phenyls on the indole moiety were subjected to the reaction, achieving autotandem reaction successfully and yielding corresponding chiral products (**2m–2v**) with satisfactory results. Besides, both disubstituted and trisubstituted substrates at the indole moiety afforded the chiral products **2w** and **2x** in excellent enantioselectivities and yields, respectively. Furthermore, various substituents on the hydroxylactam moiety were also investigated. Naphthyl (**1y**), *o*-difluorophenyl (**1z**), and *o*-dimethylphenyl (**1aa**) hydroxylactams reacted effectively to give the corresponding chiral products with excellent enantiocontrol. Consequently, based on substrate **1aa**, we further investigated substrates bearing a 7-methyl group and 5-methoxy group at the indole moiety, and the chiral products (**2ab–2ac**) were obtained with good yields and excellent enantioselectivities. Additionally, the substrate **1ad** derived from alkyl-substituted anhydride smoothly converted to the desired product **2ad** containing five contiguous stereocenters through a DKR process, as well as hydrogenolysis products **3ad-1** and **3ad-2** containing three contiguous stereocenters via a kinetic resolution (KR) process. Due to the aforementioned process, the yield and enantioselectivity of the corresponding products depend on the reaction time. When the reaction proceeded for 22 h, the hydrogenolysis products **3ad-1** and **3ad-2** were obtained with high ee, affording the product **2ad** in low ee. Reducing to 4 h, the enantioselectivities of the corresponding hydrogenolysis products **3ad-1** and **3ad-2** became worse, the desired product **2ad** was obtained with 86% ee.

In order to demonstrate the synthetic value of this methodology, the palladium-catalyzed autotandem reaction of substrate **1a** was processed at gram scale, and the desired product (−)-**2a** was isolated in 94% yield with 97% ee without loss of reactivity and enantioselectivity (Scheme 4a). The fused pentacyclic products containing three contiguous stereocenters could serve as versatile synthons to access more elaborate scaffolds, thereby highlighting their significant potential in both organic synthesis and medicinal chemistry. The ee of (−)-**2a** was upgraded to 99% through recrystallization, and subsequently, versatile transformations were performed using the purified (−)-**2a** (99% ee) (Scheme 4b). The indoline moiety of (−)-**2a** could be readily transformed to the *N*-Ts product (−)-**4**. Meanwhile, the absolute configuration was determined to be 8a*S*,13a*R*,13b*R* by X-ray crystal diffraction analysis (see SI). Tetrahydro-*β*-carboline (+)-**5** was obtained through oxidation aromatization of the indoline moiety of (−)-**2a**. Furthermore, (−)-**2a** was treated with varying equivalents of pyridinium tribromide, providing monobrominated product (−)-**6** and dibrominated product (−)-**7**, respectively. The highly diastereoselective reduction of the indoline moiety of (−)-**2a** proceeded smoothly, giving the fused pentacyclic

Scheme 3. Substrate Scope[f]



[a] $[Pd(OCOCF_3)_2]$ (2.0 mg, 2.0 mol %), **L4** (3.9 mg, 2.2 mol %). [b] $[Pd(OCOCF_3)_2]$ (4.0 mg, 4.0 mol %), **L4** (7.7 mg, 4.4 mol %). [c] $[Pd(OCOCF_3)_2]$ (8.0 mg, 8.0 mol %), **L4** (15.4 mg, 8.8 mol %), $MeSO_3H$ (2.4 equiv). [d] $Cu(OAc)_2$ (5.5 mg, 10 mol %). [e] **L3** instead of **L4**. [f] **Reaction conditions:** **1** (0.30 mmol), $MeSO_3H$ (1.2 equiv), TFE (0.1 M), 12 to 72 h.

product (−)-**8** containing five contiguous stereogenic centers. The amide group of (−)-**2a** was reduced to afford the corresponding chiral amine (−)-**9**. Besides, (−)-**2ad** was subjected to dibromination and oxidative dehydrogenative aromatization of the indoline moiety, affording the corresponding dibrominated product (−)-**10** and the tetrahydro-*β*-carboline (+)-**11**, respectively. The absolute configuration of (−)-**10** was determined to be 3a*S*,7a*S*,12a*R*, 12b*R*, and 12c*R* by X-ray crystal diffraction analysis (see SI). Notably, for the above all derivatization procedures, no erosion of enantiomeric purity was observed.

To gain insight into the reaction mechanism, we conducted the deuterium-labeling experiments (Scheme 4c) and the control experiments (Scheme 4d). When the palladium-catalyzed autotandem reaction was performed in TFE-D_3 and TsOD, the deuterium atoms of the deuterated product **D-2a′** were incorporated at the 8a- and 13b-positions with 91%, respectively (eq 1), which clearly indicated that a fast and reversible process of protonation and deprotonation existed,

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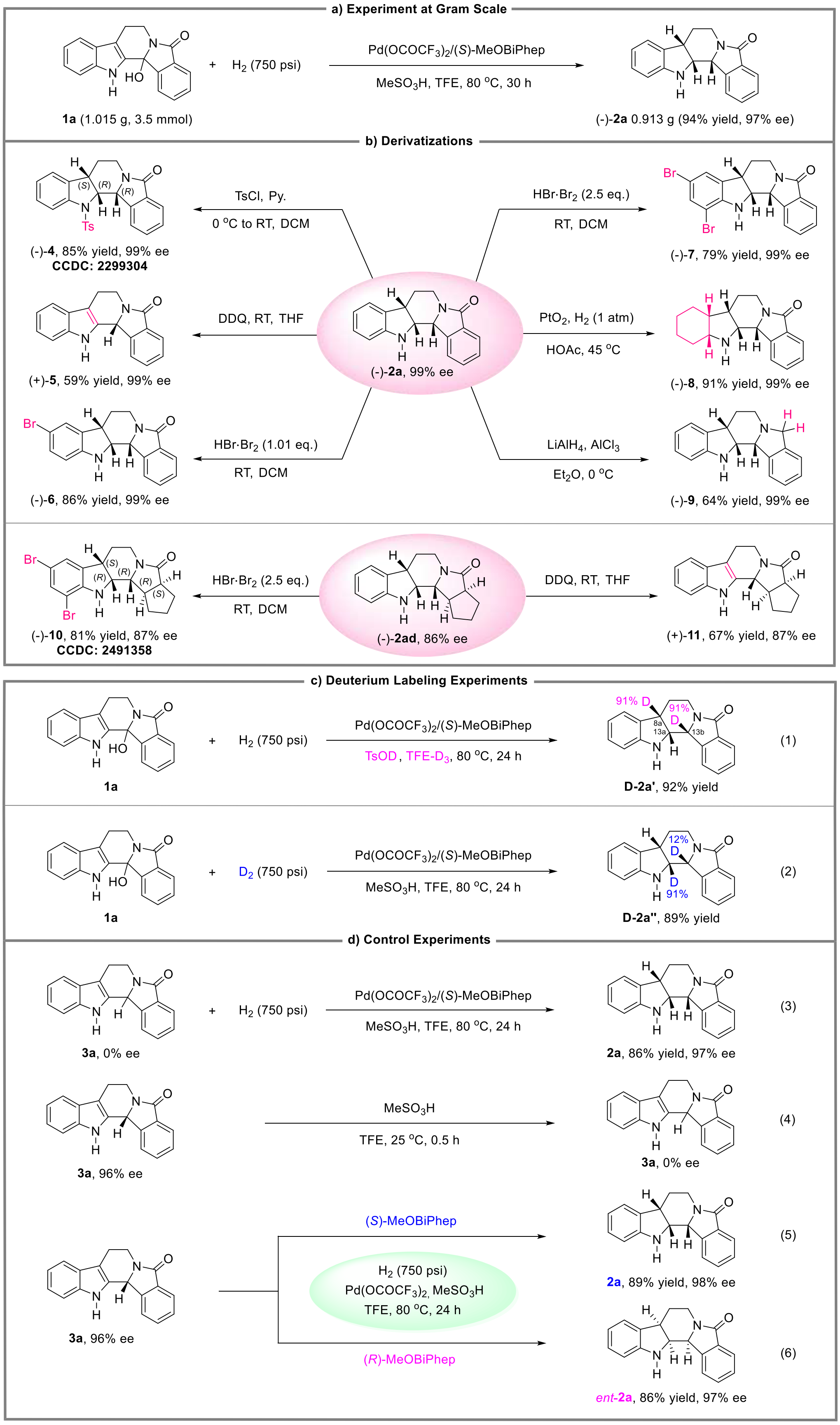
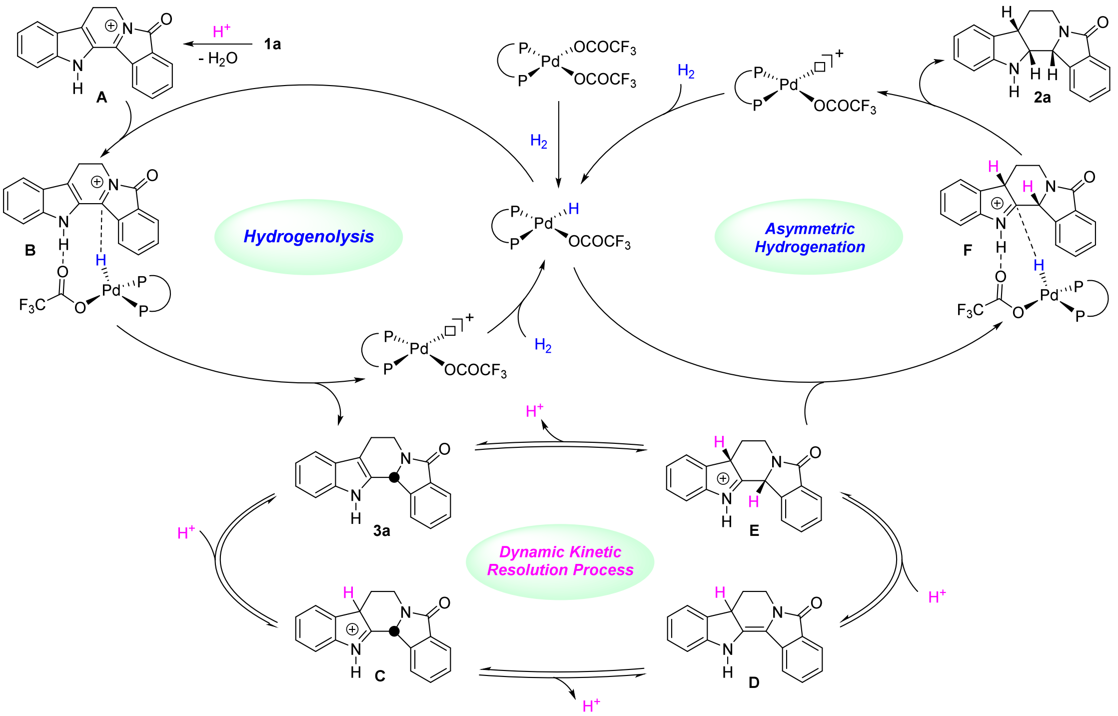
Scheme 4. Experiment at Gram Scale, Derivatizations and Mechanistic Study Experiments



Scheme 5. Proposed Mechanism for Pd-Catalyzed Autotandem Hydrogenolysis/Asymmetric Hydrogenation



and the equilibrium was faster than the hydrogenation. When **1a** was subjected to autotandem reaction with D_2, the deuterated product **D-2a′′** was obtained with 91% incorporation at the 13a-position and with 12% incorporation at the 13b-position (eq 2). The results suggested that the hydrogenation of the lactam-fused indoles can be activated by Brønsted acid to form iminium *in situ*; the favorable enantiomeric intermediate is directly hydrogenated, leading to 12% incorporation at the 13b-position, whereas the unfavorable enantiomeric intermediate goes through protonation and deprotonation under acidic conditions *via* DKR to form the favorable iminium salt intermediate and then was hydrogenated by the chiral palladium catalyst. To explore the origin of enantioselectivity, racemic hydrogenolysis product **3a** was subjected to hydrogenation under standard conditions, and the desired product **2a** was obtained with 86% yield and 97% ee (eq 3). Furthermore, the chiral hydrogenolysis product **3a** (96% ee) was treated with Brønsted acid, leading to the 0% ee of **3a** (eq 4). We subjected chiral hydrogenolysis product **3a** (96% ee) to hydrogenation reactions employing (*S*)-MeOBiPhep and (*R*)-MeOBiPhep, respectively. The (*S*)-MeOBiPhep afforded the product **2a** with 89% yield and 98% ee (eq 5); for the (*R*)-MeOBiPhep, the product *ent*-**2a** was given in 97% ee with 86% yield (eq 6). These experimental results confirmed that hydrogenolysis product **3a** undergoes rapid protonation and deprotonation in the presence of a Brønsted acid, resulting in fast racemization, and the enantioselectivity of the product is entirely determined by the chiral palladium catalyst. Based on the mechanistic experiments and the literature precedence,[10,11] a plausible mechanism of palladium-catalyzed autotandem hydrogenolysis/asymmetric hydrogenation involving a DKR process is proposed (Scheme 5), and the corresponding details are described in the SI.

In conclusion, we have developed the palladium-catalyzed autotandem hydrogenolysis/asymmetric hydrogenation involving a DKR process to synthesize hexahydro-β-carbolines containing three contiguous stereocenters with excellent enantio- and diastereoselectivity. The versatile transformations of the chiral heterocyclic products were conducted, and octahydroindole derivatives containing up to five contiguous stereocenters could even be obtained. Furthermore, the mechanism studies supported that the DKR process is crucial for control of the excellent enantio- and diastereoselectivity of products, which was determined by the chiral palladium catalyst. The utility of this autotandem asymmetric catalysis reaction and the development of new asymmetric autotandem reactions via metal hydride are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.5c20093.

Detailed experimental procedures, characterization of new compounds, spectra and X-ray data (PDF)

Accession Codes

Deposition Numbers 2299304 and 2491358 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via the joint Cambridge Crystallographic Data Centre (CCDC) and Fachinformationszentrum Karlsruhe Access Structures service.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Reviews on autotandem catalysis: (a) Fogg, D. E.; dos Santos, E. N. Tandem Catalysis: A Taxonomy and Illustrative Review. *Coord. Chem. Rev.* **2004**, *248*, 2365−2379. (b) Shindoh, N.; Takemoto, Y.; Takasu, K. Auto-Tandem Catalysis: A Single Catalyst Activating Mechanistically Distinct Reactions in a Single Reactor. *Chem.—Eur. J.* **2009**, *15*, 12168−12179. (c) Camp, J. E. Auto-Tandem Catalysis: Activation of Multiple, Mechanistically Distinct Process by a Single Catalyst. *Eur. J. Org. Chem.* **2017**, *2017*, 425−433.

(2) For selected examples on nonasymmetric autotandem catalysis: (a) Evans, P. A.; Robinson, J. E. Regio- and Diastereoselective Tandem Rhodium-Catalyzed Allylic Alkylation/Pauson-Khand Annulation Reactions. *J. Am. Chem. Soc.* **2001**, *123*, 4609−4610. (b) Chen, J.-R.; Li, C.-F.; An, X.-L.; Zhang, J.- J.; Zhu, X.-Y.; Xiao, W.-J. Ru-Catalyzed Tandem Cross-Metathesis/Intramolecular-Hydroarylation Sequence. *Angew. Chem., Int. Ed.* **2008**, *47*, 2489−2492. (c) Venning, A. R. O.; Kwiatkowski, M. R.; Roque Peña, J. E.; Lainhart, B. C.; Guruparan, A. A.; Alexanian, E. J. Palladium-Catalyzed Carbocyclizations of Unactivated Alkyl Bromides with Alkenes Involving Auto-tandem Catalysis. *J. Am. Chem. Soc.* **2017**, *139*, 11595−11600. (d) Chen, P.; Chen, Z.-C.; Li, Y.; Ouyang, Q.; Du, W.; Chen, Y.-C. Auto-Tandem Cooperative Catalysis Using Phosphine/Palladium: Reaction of Morita-Baylis-Hillman Carbonates and Allylic Alcohols. *Angew. Chem., Int. Ed.* **2019**, *58*, 4036−4040. (e) Maddigan-Wyatt, J. T.; Blyth, M. T.; Ametovski, J.; Coote, M. L.; Hooper, J. F.; Lupton, D. W. Redox Isomerization/(3 + 2) Allenoate Annulation by Auto-Tandem Phosphine Catalysis. *Chem.—Eur. J.* **2021**, *27*, 16232−16236. (f) Sahoo, H.; Zhang, L.; Cheng, J.; Nishiura, M.; Hou, Z. Auto-Tandem Copper-Catalyzed Carboxylation of Undirected Alkenyl C-H Bonds with CO_2 by Harnessing β-Hydride Elimination. *J. Am. Chem. Soc.* **2022**, *144*, 23585−23594.

(3) For selected examples on asymmetric autotandem catalysis: (a) Kanbayashi, N.; Takenaka, K.; Okamura, T.; Onitsuka, K. Asymmetric Auto-Tandem Catalysis with a Planar-Chiral Ruthenium Complex: Sequential Allylic Amidation and Atom-Transfer Radical Cyclization. *Angew. Chem., Int. Ed.* **2013**, *52*, 4897−4901. (b) Long, J.; Yu, R.; Gao, J.; Fang, X. Access to 1,3-Dinitriles by Enantioselective Auto-Tandem Catalysis: Merging Allylic Cyanation with Asymmetric Hydrocyanation. *Angew. Chem., Int. Ed.* **2020**, *59*, 6785−6789. (c) Zhu, J.-X.; Chen, Z.-C.; Du, W.; Chen, Y.-C. Asymmetric Auto-Tandem Palladium Catalysis for 2,4-Dienyl Carbonates: Ligand-Controlled Divergent Synthesis. *Angew. Chem., Int. Ed.* **2022**, *61*, No. e202200880. (d) Peters, B. B. C.; Zheng, J.; Krajangsri, S.; Andersson, P. G. Stereoselective Iridium-*N*,*P*-Catalyzed Double Hydrogenation of Conjugated Enones to Saturated Alcohols. *J. Am. Chem. Soc.* **2022**, *144*, 8734−8740. (e) Sun, L.; Wang, H.; Bai, D.; Yu, C.-B.; Wu, B.; Liao, R.-Z.; Zhou, Y.-G. Asymmetric Auto-Tandem Palladium Catalysis for α,β-Unsaturated Lactones: Merging Olefin and Ester Hydrogenation. *CCS Chem.* **2024**, *6*, 1987−1999. (f) Kondoh, A.; Kato, T.; Chen, H.; Terada, M. Asymmetric Auto-Tandem Catalysis with Chiral Organosuperbases: Intramolecular Cyclization/Enantioselective Direct Mannich-Type Addition Sequence. *Org. Lett.* **2024**, *26*, 6523−6528.

(4) For selected examples on hydrogenolysis of carbon-oxygen bonds: (a) Zheng, J.; Jongcharoenkamol, J.; Peters, B. B. C.; Guhl, J.; Ponra, S.; Ahlquist, M. S. G.; Andersson, P. G. Iridium-Catalysed Enantioselective Formal Deoxygenation of Racemic Alcohols *via* Asymmetric Hydrogenation. *Nat. Catal.* **2019**, *2*, 1093−1100. (b) Li, X.; Wang, G.-W.; Liu, L.-X.; Yu, C.-B.; Zhou, Y.-G. Palladium-Catalyzed Asymmetric Hydrogenolysis of Aryl Triflates for Construction of Axially Chiral Biaryls. *Angew. Chem., Int. Ed.* **2023**, *62*, No. e202301337. For selected examples on hydrogenolysis of carbon-carbon bonds: (f) Wilsily, A.; Nguyen, Y.; Fillion, E. Hydrogenolysis of Unstrained Carbon-Carbon σ Bonds: Stereoselective Entry into Benzylic Tertiary Centers. *J. Am. Chem. Soc.* **2009**, *131*, 15606−15607. For selected examples on hydrogenolysis of carbon-halogen bonds: (g) Kündig, E. P.; Chaudhuri, P. D.; House, D.; Bernardinelli, G. Catalytic Enantioselective Hydrogenolysis of [$Cr(CO)_3$(5,8-Dibromonaphthalene)]. *Angew. Chem., Int. Ed.* **2006**, *45*, 1092−1095. For selected examples on hydrogenolysis of carbon-nitrogen bonds: (h) Zhang, Y.-Q.; Vogelsang, E.; Qu, Z.-W.; Grimme, S.; Gansäuer, A. Titanocene-Catalyzed Radical Opening of *N*-Acylated Aziridines. *Angew. Chem., Int. Ed.* **2017**, *56*, 12654−12657. For selected examples on hydrogenolysis of silicon-oxygen bonds: (i) Nishibayashi, Y.; Takei, I.; Hidai, M. Novel Catalytic Hydrogenolysis of Trimethylsilyl Enol Ethers by the Use of an Acidic Ruthenium Dihydrogen Complex. *Angew. Chem., Int. Ed.* **1999**, *38*, 3047−3050.

(5) (a) Poutsma, M. L. Free-radical Thermolysis and Hydrogenolysis of Model Hydrocarbons Relevant to Processing of Coal. *Energy Fuels* **1990**, *4*, 113−131. (b) Shen, X.; Zhang, C.; Han, B.; Wang, F. Catalytic Self-Transfer Hydrogenolysis of Lignin with Endogenous Hydrogen: Road to the Carbon-Neutral Future. *Chem. Soc. Rev.* **2022**, *51*, 1608−1628.

(6) (a) Horner, L.; Siegel, H.; Büthe, H. Asymmetric Catalytic Hydrogenation with an Optically Active Phosphine Rhodium Complex in Hhomogeneous Solution. *Angew. Chem., Int. Ed.* **1968**, *7*, 942−942. (b) Knowles, W. S.; Sabacky, M. J. Catalytic asymmetric hydrogenation employing a soluble, optically active, rhodium complex. *J. Chem. Soc. Chem. Commun.* **1968**, 1445−1446. (c) Blaser, H.-U.; Pugin, B.; Spindler, F. Progress in Enantioselective Catalysis Assessed from an Industrial Point of View. *J. Mol. Catal. A: Chem.* **2005**, *231*, 1−20. (d) Seo, C. S. G.; Morris, R. H. Catalytic Homogeneous Asymmetric Hydrogenation: Successes and Opportunities. *Organometallics* **2019**, *38*, 47−65. (e) Wen, J.; Wang, F.; Zhang, X. Asymmetric Hydrogenation Catalyzed by First-Row Transition Metal Complexes. *Chem. Soc. Rev.* **2021**, *50*, 3211−3237.

(7) (a) Grushin, V. V. Hydrido Complexes of Palladium. *Chem. Rev.* **1996**, *96*, 2011−2034. (b) Morris, R. H. Brønsted-Lowry Acid Strength of Metal Hydride and Dihydrogen Complexes. *Chem. Rev.*

2016, *116*, 8588−8654. (c) Peng, J.; Bai, R.; Lan, Y. How to Achieve Hydrogenation/Hydrofunctionalization *via* Metal Hydride Complexes. *Acc. Chem. Res.* **2025**, *58*, 1484−1495.

(8) (a) Walser, A.; Djerassi, C. Alkaloid-Studien LII. Die Alkaloide aus Vallesia dichotoma RUIZ et PAV. *Helv. Chim. Acta* **1965**, *48*, 391−404. (b) Brown, S. H.; Djerassi, C.; Simpson, P. G. Alkaloid Studies. LIX. Structure and Absolute Configuration of Vallesamidine. *J. Am. Chem. Soc.* **1968**, *90*, 2445−2446. (c) Laguna, A.; Novotný, L.; Dolejš, L.; Buděšínský, M. Alkaloids from Roots of Strempeliopsis Strempelioides-Structures of Strempeliopine and Strempeliopidine. *Planta Med.* **1984**, *50*, 285−288. (d) Hajicek, J.; Trojanek, J. (−)-Strempeliopine Stereoselective Total Synthesis and the Determination of Absolute Configuration. *Collect. Czech. Chem. Commun.* **1986**, *51*, 1731−1742. (e) Uzir, S.; Mustapha, A. M.; Hadi, A. H. A.; Awang, K.; Wiart, C.; Gallard, J.-F.; Païs, M. Terengganensines A and B, dihydroeburnane alkaloids from Kopsia terengganensis. *Tetrahedron Lett.* **1997**, *38*, 1571−1574.

(9) (a) Wang, X.; Xia, D.; Qin, W.; Zhou, R.; Zhou, X.; Zhou, Q.; Liu, W.; Dai, X.; Wang, H.; Wang, S.; Tan, L.; Zhang, D.; Song, H.; Liu, X.-H.; Qin, Y. Radical Cascade Enabling Collective Syntheses of Natural Products. *Chem.* **2017**, *2*, 803−816. (b) Liu, X.-H.; Qin, Y. Indole Alkaloid Synthesis Facilitated by Photoredox Catalytic Radical Cascade Reactions. *Acc. Chem. Res.* **2019**, *52*, 1877−1891. (c) Ramakrishna, G. V.; Latif, Z.; Romiti, F. Enantioselective Total Syntheses of Vallesamidine and Schizozygane Alkaloids. *J. Am. Chem. Soc.* **2025**, *147*, 4613−4623.

(10) For selected examples on asymmetric metal reduction of 2/3-monosubstituted indoles: (a) Kuwano, R.; Sato, K.; Kurokawa, T.; Karube, D.; Ito, Y. Catalytic Asymmetric Hydrogenation of Heteroaromatic Compounds. Indoles. *J. Am. Chem. Soc.* **2000**, *122*, 7614−7615. (b) Kuwano, R.; Kashiwabara, M. Ruthenium-Catalyzed Asymmetric Hydrogenation of *N*-Boc-Indoles. *Org. Lett.* **2006**, *8*, 2653−2655. (c) Wang, D.-S.; Chen, Q.-A.; Li, W.; Yu, C.-B.; Zhou, Y.-G.; Zhang, X. Pd-Catalyzed Asymmetric Hydrogenation of Unprotected Indoles Activated by Brønsted Acids. *J. Am. Chem. Soc.* **2010**, *132*, 8909−8911. (d) Baeza, A.; Pfaltz, A. Iridium-Catalyzed Asymmetric Hydrogenation of *N*-Protected Indoles. *Chem.—Eur. J.* **2010**, *16*, 2036−2039. (e) Núñez-Rico, J. L.; Fernández-Pérez, H.; Vidal-Ferran, A. Asymmetric Hydrogenation of Unprotected Indoles using Iridium Complexes Derived from P-OP Ligands and (Reusable) Brønsted Acids. *Green Chem.* **2014**, *16*, 1153−1157. (f) Wen, J.; Fan, X.; Tan, R.; Chien, H.-C.; Zhou, Q.; Chung, L. W.; Zhang, X. Brønsted-Acid-Promoted Rh-Catalyzed Asymmetric Hydrogenation of *N*-Unprotected Indoles: A Cocatalysis of Transition Metal and Anion Binding. *Org. Lett.* **2018**, *20*, 2143−2147. (g) Ge, Y.; Wang, Z.; Han, Z. N.; Ding, K. Iridium-Catalyzed Enantioselective Hydrogenation of Indole and Benzofuran Derivatives. *Chem.—Eur. J.* **2020**, *26*, 15482−15486. (h) Wu, B.; Yang, J.; Hu, S.-B.; Yu, C.-B.; Zhao, Z.-B.; Luo, Y.; Zhou, Y.-G. Diboron-Mediated Palladium-Catalyzed Asymmetric Transfer Hydrogenation Using the Proton of Alcohols as Hydrogen Source. *Sci. China Chem.* **2021**, *64*, 1743−1749. (i) Wang, K.; Yu, Y.-J.; Wang, X.-Q.; Bai, Y.-Q.; Chen, M.-W.; Zhou, Y.-G. Palladium-Catalyzed Asymmetric Hydrogenation of Unprotected 3-Substituted Indoles. *J. Org. Chem.* **2022**, *87*, 10398−10407. (j) Zhang, Fu.; Sasmal, H. S.; Daniliuc, C. G.; Glorius, F. Ru-NHC-Catalyzed Asymmetric, Complete Hydrogenation of Indoles and Benzofurans: One Catalyst with Dual Function. *J. Am. Chem. Soc.* **2023**, *145*, 15695−15701. (k) Rong, N.; Zhou, A.; Liang, M.; Wang, S.-G.; Yin, Q. Asymmetric Hydrogenation of Racemic 2-Substituted Indoles *via* Dynamic Kinetic Resolution: An Easy Access to Chiral Indolines Bearing Vicinal Stereogenic Centers. *J. Am. Chem. Soc.* **2024**, *146*, 5081−5087. For selected examples on asymmetric metal-free reduction of 2/3-monosubstituted indoles: (l) Zhao, W.; Zhang, Z.; Feng, X.; Yang, J.; Du, H. Asymmetric Transfer Hydrogenation of *N*-Unprotected Indoles with Ammonia Borane. *Org. Lett.* **2020**, *22*, 5850−5854. (m) Yang, K.; Lou, Y.; Wang, C.; Qi, L.-W.; Fang, T.; Zhang, F.; Xu, H. L.; Zhou, L.; Li, W.; Zhang, G.; Yu, P.; Song, Q. Chiral Brønsted Acid from Chiral Phosphoric Acid Boron Complex and Water: Asymmetric Reduction of Indoles. *Angew. Chem., Int. Ed.* **2020**, *59*, 3294−3299.

(11) For selected examples on asymmetric reduction of 2,3-disubstituted indoles: (a) Wang, D.-S.; Tang, J.; Zhou, Y.-G.; Chen, M.-W.; Yu, C.-B.; Duan, Y.; Jiang, G.-F. Dehydration Triggered Asymmetric Hydrogenation of 3-(*α*-Hydroxyalkyl)indoles. *Chem. Sci.* **2011**, *2*, 803−806. (b) Duan, Y.; Li, L.; Chen, M.-W.; Yu, C.-B.; Fan, H.-J.; Zhou, Y.-G. Homogenous Pd-Catalyzed Asymmetric Hydrogenation of Unprotected Indoles: Scope and Mechanistic Studies. *J. Am. Chem. Soc.* **2014**, *136*, 7688−7700. (c) Yang, Z.; Chen, F.; He, Y.; Yang, N.; Fan, Q.-H. Highly Enantioselective Synthesis of Indolines: Asymmetric Hydrogenation at Ambient Temperature and Pressure with Cationic Ruthenium Diamine Catalysts. *Angew. Chem., Int. Ed.* **2016**, *55*, 13863−13866. (d) Touge, T.; Arai, T. Asymmetric Hydrogenation of Unprotected Indoles Catalyzed by *η*6-Arene/*N*-Me-sulfonyldiamine-Ru(II) Complexes. *J. Am. Chem. Soc.* **2016**, *138*, 11299−11305. (e) Liu, G.; Zheng, L.; Tian, K.; Wang, H.; Chung, L.; Zhang, X.; Dong, X.-Q. Ir-Catalyzed Asymmetric Hydrogenation of Unprotected Indoles: Scope Investigations and Mechanistic Studies. *CCS Chem.* **2023**, *5*, 1398−1410.

(12) (a) Vedejs, E.; Jure, M. Efficiency in Nonenzymatic Kinetic Resolution. *Angew. Chem., Int. Ed.* **2005**, *44*, 3974−4001. (b) Pellissier, H. Recent Developments in Dynamic Kinetic Resolution. *Tetrahedron* **2011**, *67*, 3769−3802. (c) Bhat, V.; Welin, E. R.; Guo, X.; Stoltz, B. M. Advances in Stereoconvergent Catalysis from 2005 to 2015: Transition-Metal-Mediated Stereoablative Reactions, Dynamic Kinetic Resolutions, and Dynamic Kinetic Asymmetric Transformations. *Chem. Rev.* **2017**, *117*, 4528−4561.

(13) (a) Steward, K. M.; Gentry, E. C.; Johnson, J. S. Dynamic Kinetic Resolution of *α*-Keto Esters *via* Asymmetric Transfer Hydrogenation. *J. Am. Chem. Soc.* **2012**, *134*, 7329−7332. (b) Chen, M.-W.; Cai, X.-F.; Chen, Z.-P.; Shi, L.; Zhou, Y.-G. Facile Construction of Three Contiguous Stereogenic Centers *via* Dynamic Kinetic Resolution in Asymmetric Transfer Hydrogenation of Quinolines. *Chem. Commun.* **2014**, *50*, 12526−12529. (c) Touge, T.; Sakaguchi, K.; Tamaki, N.; Nara, H.; Yokozawa, T.; Matsumura, K.; Kayaki, Y. Multiple Absolute Stereocontrol in Cascade Lactone Formation *via* Dynamic Kinetic Resolution Driven by the Asymmetric Transfer Hydrogenation of Keto Acids with Oxo-Tethered Ruthenium Catalysts. *J. Am. Chem. Soc.* **2019**, *141*, 16354−16361. (d) Yang, D.; Wu, X.; Zheng, X.-J.; Xie, J.-H.; Zhou, Q.-L. Dynamic Kinetic Resolution of *γ*-Substituted Cyclic *β*-Ketoesters *via* Asymmetric Hydrogenation: Constructing Chiral Cyclic *β*-Hydroxyesters with Three Contiguous Stereocenters. *Org. Lett.* **2021**, *23*, 5153−5157.

(14) Yin, Q.; Wang, S.-G.; You, S.-L. Asymmetric Synthesis of Tetrahydro-*β*-carbolines *via* Chiral Phosphoric Acid Catalyzed Transfer Hydrogenation Reaction. *Org. Lett.* **2013**, *15*, 2688−2691.

(15) (a) Chen, M.-W.; Chen, Q.-A.; Duan, Y.; Ye, Z.-S.; Zhou, Y.-G. Asymmetric Hydrogenolysis of Racemic Tertiary Alcohols, 3-Substituted 3-Hydroxyisoindolin-1-ones. *Chem. Commun.* **2012**, *48*, 1698−1700. (b) Yu, C.-B.; Zhou, Y.-G. Palladium-Catalyzed Asymmetric Hydrogenolysis of *N*-Sulfonyl Aminoalcohols *via* Achiral Enesulfonamide Intermediates. *Angew. Chem., Int. Ed.* **2013**, *52*, 13365−13368. (c) Song, B.; Yu, C.-B.; Huang, W.-X.; Chen, M.-W.; Zhou, Y.-G. Formal Palladium-Catalyzed Asymmetric Hydrogenolysis of Racemic *N*-Sulfonyloxaziridines. *Org. Lett.* **2015**, *17*, 190−193.

(16) (a) Wang, D.-S.; Chen, Q.-A.; Lu, S.-M.; Zhou, Y.-G. Asymmetric Hydrogenation of Heteroarenes and Arenes. *Chem. Rev.* **2012**, *112*, 2557−2590. (b) Chen, Q.-A.; Ye, Z.-S.; Duan, Y.; Zhou, Y.-G. Homogeneous Palladium-Catalyzed Asymmetric Hydrogenation. *Chem. Soc. Rev.* **2013**, *42*, 497−511.

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