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Dynamic Kinetic Resolution of γ-Substituted Cyclic β-Ketoesters via Asymmetric Hydrogenation: Constructing Chiral Cyclic β-Hydroxyesters with Three Contiguous Stereocenters

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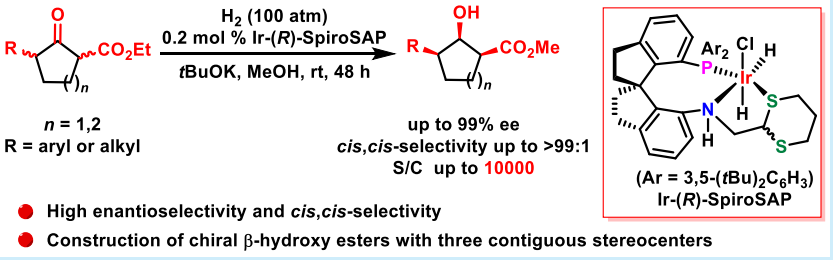

ABSTRACT: An efficient asymmetric hydrogenation of racemic γ-substituted cyclic β-ketoesters via dynamic kinetic resolution to provide chiral cyclic β-hydroxy esters with three contiguous stereocenters is reported. Using a chiral spiro iridium catalyst (*R*)-**5** (Ir-SpiroSAP), a series of racemic γ-aryl/alkyl substituted cyclic β-ketoesters were hydrogenated to the corresponding chiral cyclic β-hydroxy esters in high yields (84−97%) with good to excellent enantioselectivities (69−>99% ee) and *cis*,*cis*-selectivities (up to >99:1).

Transition-metal catalyzed asymmetric hydrogenation represents a very useful and versatile method for the preparation of optically active chiral compounds.[1] By contrast, the catalytic asymmetric hydrogenation of configurationally labile α-substituted β-ketoesters via dynamic kinetic resolution (DKR) holds the potential of providing chiral β-hydroxy esters bearing two vicinal chiral centers with high efficiency (Scheme 1a) and has been successfully applied to the synthesis of chiral drugs and bioactive natural products.[2] The success of this process relies upon the acidity of the α-C−H that facilitates the racemization of α-chiral center through an achiral enolate intermediate.[3] However, the resolution of racemic α,γ-disubstituted β-ketoesters for the construction of chiral β-hydroxy esters with three contiguous stereocenters through catalytic asymmetric hydrogenation remains a significant challenge due to the less acidic γ-C−H of β-ketoesters (Scheme 1b),[1] despite its enormous potential synthetic utility. Thus, Genêt and co-workers employed the asymmetric hydrogenation of γ-amino α-methyl-β-ketoester derived from (*S*)-proline with Ru-(*S*)-MeO-BIPHEP for the enantioselective synthesis of iso-dolaproine[4] (Scheme 1c). Herein, we report the first highly efficient enantioselective dynamic kinetic resolution asymmetric hydrogenation (DKR-AH) of racemic α,γ-disubstituted β-ketoesters, allowing the direct access to enantiomerically enriched β-hydroxy esters with three contiguous stereocenters in excellent enantioselectivities (up to 99% ee) and *cis*,*cis*-selectivities (up to >99:1) (Scheme 1d).

Upon initial investigation, we noticed that chiral cyclic β-hydroxy esters with contiguous stereocenters are important structural motifs widely found in bioactive natural products and pharmaceuticals (Figure 1).[5] Therefore, we first intended to study the asymmetric hydrogenation of γ-substituted cyclic β-ketoesters with chiral spiro ruthenium complex $RuCl_2$-(*S*)-Xyl-SDP/(*R*,*R*)-DPEN ((*S*$_a$,*R*,*R*)-**3**),[6] an efficient catalyst for the asymmetric hydrogenation of racemic α-substituted aldehydes and ketones via DKR in the presence of strong base such as *t*BuOK.[7] We selected ethyl 3-phenyl-2-oxocyclohexane-1-carboxylate (**1a**) as a model substrate and performed the hydrogenation under the general conditions in the presence of 0.2 mol % of (*S*$_a$,*R*,*R*)-**3**, and no hydrogenation product was observed (Scheme 2). This result showed that chiral spiro ruthenium catalyst (*S*$_a$,*R*,*R*)-**3** is not effective for the asymmetric hydrogenation of β-ketoesters even in the presence of considerable amounts of *t*BuOK as a cocatalyst. We then tested chiral spiro iridium catalysts Ir-(*R*)-SpiroPAP ((*R*)-**4**)[8] and Ir-(*R*)-SpiroSAP ((*R*)-**5**),[9] which are extremely efficient for the asymmetric hydrogenation of β-ketoesters. The

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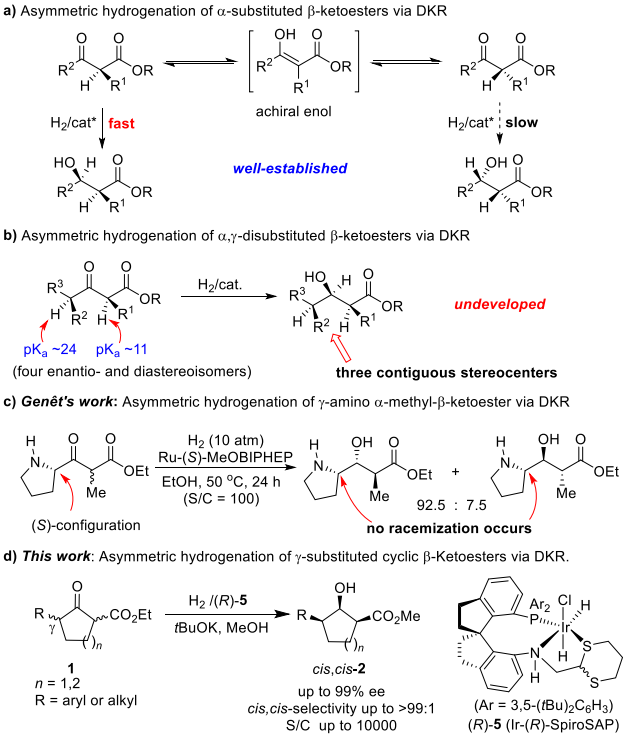
Scheme 1. Asymmetric Hydrogenation of α-Substituted and α,γ-Disubstituted β-Ketoesters via DKR



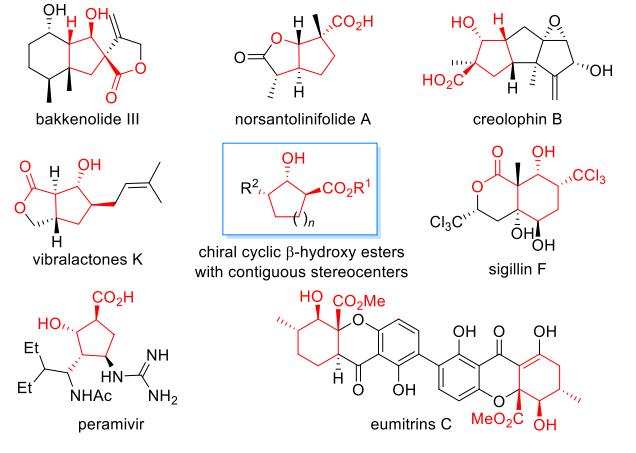
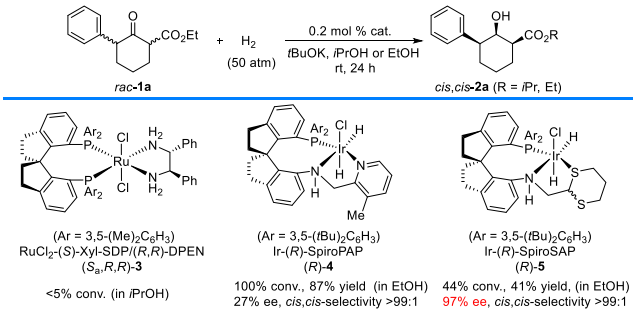


Figure 1. Examples of natural products and pharmaceuticals containing chiral cyclic β-hydroxy ester motifs with contiguous stereocenters.

catalyst (*R*)-**4** provided **2a** (R = Et) in 87% yield and >99:1 *cis*,*cis*-selectivity but with a low enantioselectivity of 27% ee. In contrast, excellent enantioselectivity (97% ee) and *cis*,*cis*-selectivity (>99:1) were achieved by using the catalyst (*R*)-**5**, albeit with a moderate yield of 41%. These results indicated that the use of catalytic amounts of *t*BuOK as a base is efficient to racemize the less acidic γ-C−H, leading to the formation of *cis*,*cis*-γ-substituted cyclic β-hydroxy ester *cis*,*cis*-**2a** in optically active form.

Thus, we choose (*R*)-**5** as the catalyst of choice for further optimization (see the Supporting Information). We found that the reaction was completed within 48 h and provided **2a** in 92% yield with 97% ee and >99:1 *cis*,*cis*-selectivity if increasing the H_2 pressure to 100 atm. Furthermore, we proved that the solvent also has considerable influence on the reaction rate of

Scheme 2. Evaluation of Chiral Catalysts for Asymmetric Hydrogenation of 1a[a]



[a]Reaction conditions: **1a** (0.5 mmol), cat./*t*BuOK/**1a** = 1:50:500, solvent (2 mL), 50 atm of H_2, room temperature (25−30 °C), 24 h, isolated yield and the *cis*,*cis*-selectivities and ee values of *cis*,*cis*-product were determined by ^{1}H NMR and HPLC using chiral column, respectively.

the hydrogenation. MeOH as the solvent gave higher yield (94%) and higher enantioselectivity (98% ee). In contrast, *n*PrOH and *i*PrOH as the solvent significantly lowered the conversions (64% and 31%, respectively) with a slight decrease in enantioselectivities. In addition to *t*BuOK, other bases such as *t*BuONa, K_2CO_3, and KOH also provided comparable results. Furthermore, when the amount of *t*BuOK was increased from 5 to 10 mol % or decreased to 1 mol %, similar results were also observed. To our delight, even though the catalyst loading was decreased to 0.01 mol % (S/C = 10 000), the hydrogenation could still proceed smoothly and afforded **2a** in 91% yield with 97% ee and >99:1 *cis*,*cis*-selectivity within 96 h.

Under the optimized reaction conditions, we examined a series of racemic γ-aryl substituted cyclic β-ketoesters **1a**−**o**. As summarized in Scheme 3, the electronic properties of the substituents on the phenyl ring of substrates **1a**−**e** have no obvious effect on the reaction rates and the enantioselectivities. The corresponding hydrogenated products **2a**−**e** were obtained in 92−97% yields with 97−99% ee and 98:2−>99:1 *cis*,*cis*-selectivities. Substrates **1f** and **1g** possessing substituents on the *meta*-position of the phenyl ring also gave comparable outcomes under the optimized conditions. However, higher catalyst loading (1 mol %) and longer reaction times (72 h) were required to complete the hydrogenation when using *ortho*-substituted ketoesters **1h** and **1i**, providing **2h** and **2i** in 93% yield with >99% ee and 91% yield with >99% ee, respectively. Substrate bearing a heterocyclic moiety, such as 2-furanyl (**1n**), also underwent the hydrogenation to afford the corresponding chiral product **2n** in high yield and enantioselectivity (84% yield, 94% ee). The substrate **1o** bearing a five-membered ring was also evaluated, providing the product **2o** in 92% yield with 92% ee and 98:2 *cis*,*cis*-selectivity. In addition, the absolute configuration of the hydrogenated product **2c** was determined as (1*S*,2*R*,3*S*) by a single crystal X-ray diffraction analysis (see the Supporting Information, CCDC 2049701).

Several racemic γ-alkyl substituted cyclic β-ketoesters **1p**−**u** were also evaluated under the optimized reaction conditions (Scheme 3). The hydrogenations proceeded smoothly to provide the six-membered ring products **2p**−**t** in 89−96% yields with 96−98% ee and >99:1 *cis*,*cis*-selectivities. The substrate **1u** bearing a five-membered ring also provided the corresponding product **2u** in high yield and high *cis*,*cis*-

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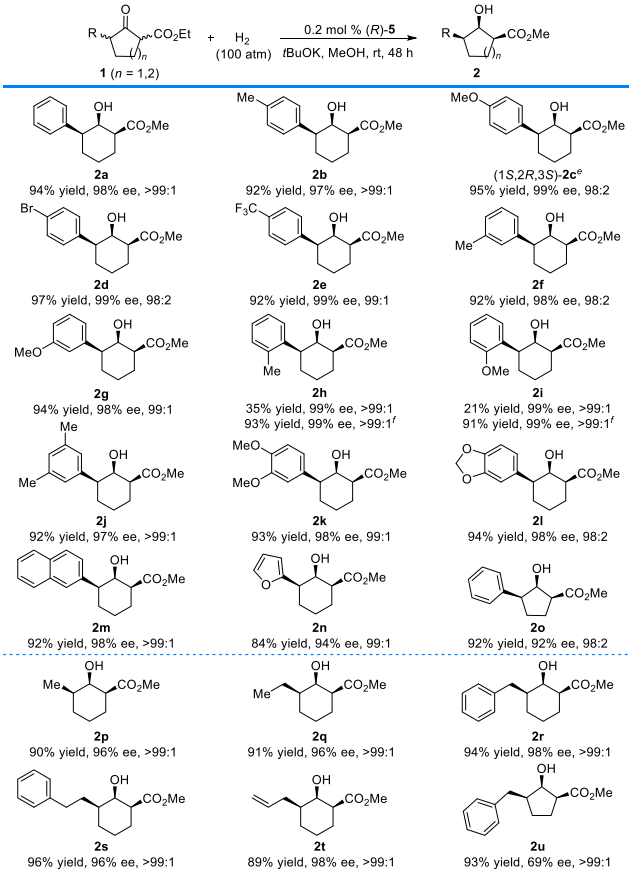
Scheme 3. Asymmetric Hydrogenation of Racemic γ-Aryl/alkyl Substituted Cyclic β-Ketoesters 1[a−d]



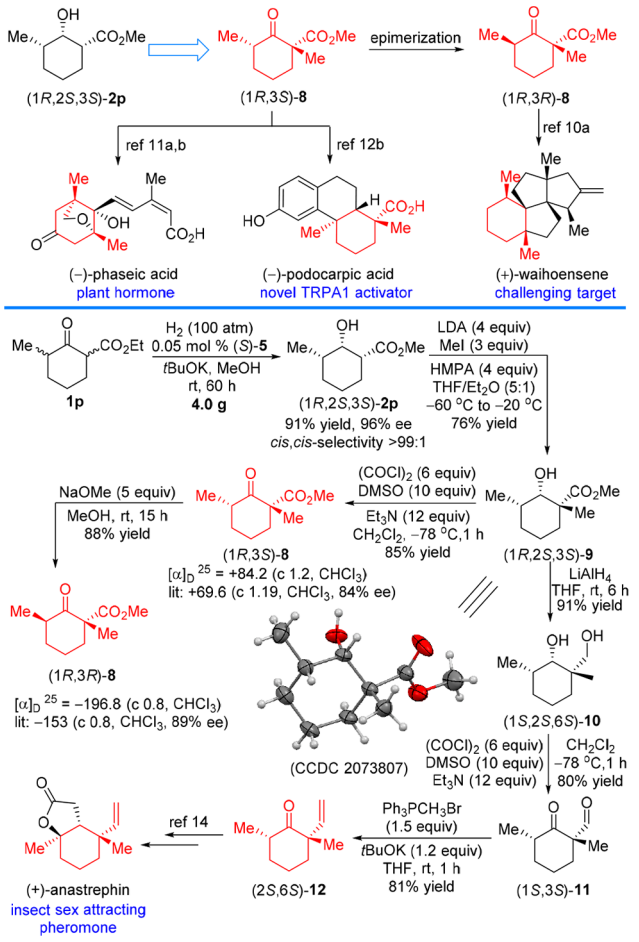
[a]Reaction conditions: substrate (0.5 mmol), (*R*)-**5**/*t*BuOK/substrate = 1:50:500, MeOH (2 mL), 100 atm of H_2, room temperature (25−30 °C) for 48 h. [b]Isolated yield. [c]The *cis*,*cis*-selectivities of products **2** were determined by ^{1}H NMR spectroscopy. [d]The ee values were determined by HPLC using chiral columns. [e]The configuration of product **2c** was determined as the (1*S*,2*R*,3*S*)-configuration by single-crystal X-ray analysis. [f]1.0 mol % of (*R*)-**5**, 72 h.

selectivity but with moderate enantioselectivity (69% ee). Overall, this represents the first highly efficient enantioselective dynamic kinetic resolution using an asymmetric hydrogenation of racemic α,γ-disubstituted β-ketoesters.

Encouraged by these results, we explored the enantioselective asymmetric hydrogenation of racemic acyclic α,γ-disubstituted β-ketoesters via dynamic kinetic resolution, for example, ethyl 2-methyl-4-phenyl-3-oxopentanoate (**6**). The hydrogenation was completed within 48 h, affording the corresponding β-hydroxy ester **7** in 89% yield as a 92:8 mixture of two isomers, and the ee value of the major one was 69% (see the Supporting Information).

To demonstrate the synthetic utility of this method, we decided to pursue the synthesis of chiral 1,3-dimethyl-2-oxocyclohexane-1-carboxylates (1*R*,3*R*)-**8** and (1*R*,3*S*)-**8**, which are potential important chiral intermediates for the total synthesis of bioactive natural products such as (+)-waihoensene,[10] (−)-phaseic acid,[11] and (−)-podocarpic acid[12] (Scheme 4). The synthesis commenced from the hydrogenation of racemic **1p** with (*S*)-**5** on a multigram scale. With 0.05 mol % (S/C = 2000) of (*S*)-**5** and under the optimal reaction conditions for 60 h, *rac*-**1p** was hydrogenated to (1*R*,2*S*,3*S*)-**2p** in 96% yield with 96% ee and >99:1 *cis*,*cis*-

Scheme 4. Enantioselective Synthesis of Chiral Intermediates to Natural Products (+)-Waihoensene, (−)-Phaseic Acid, (−)-Podocarpic Acid, and (+)-Anastrephin



selectivity. The subsequent methylation of (1*R*,2*S*,3*S*)-**2p** with methyl iodide in the presence of lithium diisopropylamide (LDA) as a base delivered (1*R*,2*S*,3*S*)-**9** in 76% yield, and the configuration of **9** was determined by X-ray diffraction analyses (see the Supporting Information, CCDC 2073807). Subsequently, the Swern oxidation of (1*R*,2*S*,3*S*)-**9** furnished (1*R*,3*S*)-**8** in 85% yield. The epimerization of the methylated chiral tertiary center adjacent to the ketone group of (1*R*,3*S*)-**8** in the presence of NaOMe as a base was proceeded smoothly, affording the desired (1*R*,3*R*)-**8** in 88% yield. In a word, we completed the enantioselective synthesis of (1*R*,3*S*)-**8** [[α] = +84.2 (*c* 1.2, $CHCl_3$) (lit.[12b] = +69.6 (*c* 1.19, $CHCl_3$), 84% ee)] and (1*R*,3*R*)-**8** [[α] = −196.8 (*c* 0.8, $CHCl_3$) (lit.[12b] = −153 (*c* 0.8, $CHCl_3$), 89% ee)] from the hydrogenated product (1*R*,2*S*,3*S*)-**2p** in 65% and 57% yield, respectively, via two and three steps. To the best of our knowledge, our work provides the first catalytic asymmetric synthesis of such chiral 1,3-dimethyl-2-oxocyclohexane-1-carboxylates.[13]

With chiral intermediate (1*R*,2*S*,3*S*)-**9** in hand, we further studied the enantioselective synthesis of chiral ketone (2*S*,6*S*)-**12**,[14] a key intermediate to an insect sex attracting pheromone (+)-anastrephin[15] (Scheme 4). The direct reduction of the ester group of (1*R*,2*S*,3*S*)-**9** with lithium aluminum hydride followed by the Swern oxidation of the resulting diols (1*S*,2*S*,6*S*)-**10** provided aldehyde-ketone (1*S*,3*S*)-**11** in a

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yield of 73% via two steps. A selective Wittig reaction of the aldehyde group of (1*S*,3*S*)-**11** with methyltriphenylphosphonium bromide using *t*BuOK as a base produced the ketone (2*S*,6*S*)-**12** in 81% yield. Therefore, an efficient approach to (2*S*,6*S*)-**12** was developed in 45% yield and four steps from the hydrogenated product (1*R*,2*S*,3*S*)-**2p**.

In conclusion, we have achieved the highly efficient asymmetric hydrogenaion of racemic γ-substituted cyclic β-ketoesters via DKR for the enantioselective synthesis of optically active chiral cyclic β-hydroxy esters with three contiguous stereocenters. Using chiral spiro Ir-(*R*)-SpiroSAP ((*R*)-**5**) as the catalyst, a series of racemic γ-aryl/alkyl substituted cyclic β-ketoesters were hydrogenated to the corresponding optically active cyclic β-hydroxy esters in high yields (84−97%) with good to excellent enantioselectivities (69−>99% ee) and *cis*,*cis*-selectivities (up to >99:1). The hydrogenation could be performed smoothly at a low catalyst loading of 0.01 mol % (S/C = 10 000) without the erosion of the yield and enantioselectivity. With this highly efficient protocol, we developed efficient routes for the enantioselective synthesis of the chiral key intermediates for the preparation of bioactive natural products such as (+)-waihoensene, (−)-phaseic acid, (−)-podocarpic acid, and (+)-anastrephin.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01689.

Synthesis and characterization, detailed experimental procedures, NMR spectra (PDF)

Accession Codes

CCDC 2049701 and 2073807 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For selected recent reviews see: (a) de Vries, J.-G., Elsevier, C.-J., Eds. *The Handbook of Homogeneous Hydrogenation*; Wiley-VCH: Weinheim, 2007. (b) Xie, J.-H.; Zhou, Q.-L. New Progress and Prospects of Transition Metal-Catalyzed Asymmetric Hydrogenation. *Acta Chim. Sinica* **2012**, *70*, 1427−1438. (c) Ayad, T.; Phansavath, P.; Ratovelomanana-Vidal, V. Transition-Metal-Catalyzed Asymmetric Hydrogenation and Transfer Hydrogenation: Sustainable Chemistry to Access Bioactive Molecules. *Chem. Rec.* **2016**, *16*, 2754−2771. (d) Seo, C.-S.-G.; Morris, R.-H. Catalytic Homogeneous Asymmetric Hydrogenation: Successes and Opportunities. *Organometallics* **2019**, *38*, 47−65.

(2) For selected recent reviews see: (a) Ohkuma, T.; Noyori, R. In *The Handbook of Homogeneous Hydrogenation*; de Vries, J.-G., Elsevier, C.-J., Eds.; Wiley-VCH: Weinheim, 2007; pp 1105−1164. (b) Pellissier, H. Recent Developments in Dynamic Kinetic Resolution. *Tetrahedron* **2011**, *67*, 3769−3802. (c) Xie, J.-H.; Zhou, Q.-L. Catalytic Asymmetric Hydrogenation of Substituted Ketones and Aldehydes via Dynamic Kinetic Resolution: Efficient Approach to Chiral Alcohols. *Aldrichim. Acta* **2015**, *48*, 33−40. (d) Betancourt, R.-M.; Echeverria, P.-G.; Ayad, T.; Phansavath, P.; Ratovelomanana-Vidal, V. Recent Progress and Application of Transition-Metal-Catalyzed Asymmetric Hydrogenation and Transfer Hydrogenation of Ketones and Imines through Dynamic Kinetic Resolution. *Synthesis* **2020**, *53*, 30−50.

(3) For selected papers for catalytic asymmetric hydrogenation of racemic α-substituted β-ketoesters via dynamic kinetic resolution, see: (a) Noyori, R.; Ikeda, T.; Ohkuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Akutagawa, S.; Sayo, N.; Saito, T.; Taketomi, T.; Kumobayashi, H. Stereoselective Hydrogenation via Dynamic Kinetic Resolution. *J. Am. Chem. Soc.* **1989**, *111*, 9134−9135. (b) Genet, J.-P.; Pinel, C.; Mallart, S.; Juge, S.; Thorimbert, S.; Laffitte, J.-A. Asymmetric Synthesis. Practical Production of D and L Threonine. Dynamic Kinetic Resolution in Rhodium and Ruthenium Catalyzed Hydrogenation of 2-Acyclamino-3-Oxobutyrates. *Tetrahedron: Asymmetry* **1991**, *2*, 555−567. (c) Makino, K.; Goto, T.; Hiroki, Y.; Hamada, Y. Stereoselective Synthesis of anti-β-Hydroxy-α-Amino Acids through Dynamic Kinetic Resolution. *Angew. Chem., Int. Ed.* **2004**, *43*, 882−884. (d) Makino, K.; Hiroki, Y.; Hamada, Y. Dynamic Kinetic Resolution Catalyzed by Ir Axially Chiral Phosphine Catalyst: Asymmetric Synthesis of Anti Aromatic β-Hydroxy-α-Amino Acids Esters. *J. Am. Chem. Soc.* **2005**, *127*, 5784−5785. (e) Hou, C.-J.; Hu, X.-P. Sterically Hindered Chiral Ferrocenyl P,N,N-Ligands for Highly Diastereo-/Enantioselective Ir-Catalyzed Hydrogenation of α-Alkyl-β-Ketonesters via Dynamic Kinetic Resolution. *Org. Lett.* **2016**, *18*, 5592−5595. (g) Gu, G.; Lu, J.; Yu, Q.; Wen, J.; Yin, Q.; Zhang, X. Enantioselective and Diastereoselective Ir-Catalyzed Hydrogenation of α-Substituted β-Ketoesters via Dynamic Kinetic Resolution. *Org. Lett.* **2018**, *20*, 1888−1892.

(4) (a) Lavergne, D.; Mordant, C.; Ratovelomanana-Vidal, V.; Genet, J.-P. Stereoselective Synthesis of *iso*-Dolaproine via Dynamic Kinetic Resolution. *Org. Lett.* **2001**, *3*, 1909−1912. (b) Mordant, C.; Reymond, S.; Ratovelomanana-Vidal, V.; Genêt, J.-P. Synthesis of Both *syn* and *anti* Diastereoisomers of Boc-Dolaproine from (*S*)-Proline through DKR Using Ruthenium-Catalyzed Hydrogenation: A

Dramatic Role of *N*-Protecting Groups. *Tetrahedron* **2004**, *60*, 9715−9723.
(5) (a) Wu, T.-S.; Kao, M.-S.; Wu, P.-L.; Lin, F.-W.; Shi, L.-S.; Teng, C.-M. Antiplatelet Principles from the Root of *Petasites Formosanus*. *Phytochemistry* **1999**, *52*, 901−905. (b) Wu, T.-S.; Kao, M.-S.; Wu, P.-L.; Lin, F.-W.; Shi, L.-S.; Liou, M.-J.; Li, C.-Y. The Bakkenolides from the Root of *Petasites Formosanus* and Their Cytotoxicity. *Chem. Pharm. Bull.* **1999**, *47*, 375−382. (c) Wang, G.-Q.; Wei, K.; Zhang, L.; Li, Z.-H.; Wang, Q.-A.; Liu, J.-K. Three New Vibralactone-Related Compounds from Cultures of Basidiomycete *Boreostereum Vibrans*. *J. Asian Nat. Prod. Res.* **2014**, *16*, 447−452. (d) Steinbiss, M.; Maczka, M.; Langewald, J.; London, B.; Vallinayagam, R.; Jones, P.-G.; Bastiaans, H.; Schulz, S. Sigillins from Springtails are Potent Natural Insecticides. *J. Nat. Prod.* **2020**, *83*, 468−472.
(6) (a) Xie, J.-H.; Zhou, Q.-L. Chiral Diphosphine and Monodentate Phosphorus Ligands on a Spiro Scaffold for Transition-Metal-Catalyzed Asymmetric Reactions. *Acc. Chem. Res.* **2008**, *41*, 581−593. (b) Xie, J.-H.; Wang, L.-X.; Fu, Y.; Zhu, S.-F.; Fan, B.-M.; Duan, H.-F.; Zhou, Q.-L. Synthesis of Spiro Diphosphines and Their Application in Asymmetric Hydrogenation of Ketones. *J. Am. Chem. Soc.* **2003**, *125*, 4404−4405.
(7) (a) Liu, S.; Xie, J.-H.; Wang, L.-X.; Zhou, Q.-L. Dynamic Kinetic Resolution Allows A Highly Enantioselective Synthesis of *cis*-α-Aminocycloalkanols by Ruthenium-Catalyzed Asymmetric Hydrogenation. *Angew. Chem., Int. Ed.* **2007**, *46*, 7506−7508. (b) Xie, J.-H.; Zhou, Z.-T.; Kong, W.-L.; Zhou, Q.-L. Ru-Catalyzed Asymmetric Hydrogenation of Racemic Aldehydes via Dynamic Kinetic Resolution: Efficient Synthesis of Optically Active Primary Alcohols. *J. Am. Chem. Soc.* **2007**, *129*, 1868−1869. (c) Yang, D.; Yang, A.-J.; Chen, Y.; Xie, J.-H.; Zhou, Q.-L. Asymmetric Hydrogenation of Racemic 6-Aryl 1,4-Dioxaspiro[4.5]decan-7-ones to Functionalized Chiral β-Aryl Cyclohexanols via a Dynamic Kinetic Resolution. *Org. Lett.* **2021**, *23*, 1616−1620.
(8) (a) Xie, J.-H.; Liu, X.-Y.; Xie, J.-B.; Wang, L.-X.; Zhou, Q.-L. An Additional Coordination Group Leads to Extremely Efficient Chiral Iridium Catalysts for Asymmetric Hydrogenation of Ketones. *Angew. Chem., Int. Ed.* **2011**, *50*, 7329−7332. (b) Xie, J.-H.; Zhou, Q.-L. Migical Chiral Spiro Ligands. *Acta Chim. Sinica* **2014**, *72*, 778−797.
(9) (a) Bao, D.-H.; Wu, H.-L.; Liu, C.-L.; Xie, J.-H.; Zhou, Q.-L. Development of Chiral Spiro P-N-S Ligands for Iridium-Catalyzed Asymmetric Hydrogenation of β-Alkyl-β-Ketoesters. *Angew. Chem., Int. Ed.* **2015**, *54*, 8791−8794. (b) Bao, D.-H.; Gu, X.-S.; Xie, J.-H.; Zhou, Q.-L. Iridium-Cayalyzed Asymmetric Hydrogenation of Racemic β-Keto Lactams via Dynamic Kinetic Resolution. *Org. Lett.* **2017**, *19*, 118−121.
(10) Selected papers for the total synthesis of waihoensene, see: (a) Lee, H.; Kang, T.; Lee, H.-Y. Total Synthesis of (±)-Waihoensene. *Angew. Chem., Int. Ed.* **2017**, *56*, 8254−8257. (b) Qu, Y.; Wang, Z.; Zhang, Z.; Zhang, W.; Huang, J.; Yang, Z. Asymmetric Total Synthesis of (+)-Waihoensene. *J. Am. Chem. Soc.* **2020**, *142*, 6511−6515. (c) Peng, C.; Arya, P.; Zhou, Z.; Synder, S.-A. A Concise Total Synthesis of (+)-Waihoensene Guided by Quaternary Center Analysis. *Angew. Chem., Int. Ed.* **2020**, *59*, 13521−13525. (d) Rosenbaum, L.-C.; Häfner, M.; Gaich, T. Total Synthesis of the Diterpene Waihoensene. *Angew. Chem., Int. Ed.* **2021**, *60*, 2939−2942.
(11) Selected papers for the total synthesis of phaseic acid, see: (a) Kitahara, T.; Touhara, K.; Watanabe, H.; Mori, K. Stereocontrolled Synthesis of Both the Enantiomers of Phaseic Acid and Its Methyl Ester, A Pivotal Metabolite of Abscisic Acid. *Tetrahedron* **1989**, *45*, 6387−6400. (b) Abrams, G.-D.; Abrams, S.-R.; Nelson, L.-A.-K.; Gusta, L.-V. Total Synthesis of (±)-Phaseic Acid. *Tetrahedron* **1990**, *46*, 5543−5554. (c) Tu, W.; Ning, C.; Xu, J. Enantioselective Synthesis of (−)-Phaseic Acid. *Org. Chem. Front.* **2018**, *5*, 29−31.
(12) Selected papers for the total synthesis of podocarpic acid, see: (a) Hao, X.-J.; Node, M.; Fuji, K. Total Synthesis of (+)-Podocarpic and (+)-Lambertic Acids. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1505−1509. (b) Katoh, T.; Awasaguchi, K.-i.; Mori, D.; Kimura, H.; Kajimoto, T.; Node, M. Lipase-Catalyzed Asymmetric Dealkoxylcarbonylation of σ-Symmetrical β-Ketodiesters and Its Application to the Synthesis of (−)-Podocarpic Acid. *Synlett* **2005**, *2005*, 2919−2922.
(13) Selected papers for the synthesis of 1,3-dimethyl-2-oxocyclohexane-1-carboxylates, see: (a) Huang, P.-Q.; Zhou, W.-S. Efficient Syntheses of a New Chiral Diene and a New Bridgehead Enone for a Diels-Alder Approach to Kaura-9(11)-16-dien-19-oic Acid. *Tetrahedron: Asymmetry* **1991**, *2*, 875−878. (b) Mohr, J.-T.; Behenna, D.-C.; Harned, A.-M.; Stoltz, B.-M. Deracemization of Quaternary Stereocenters by Pd-Catalyzed Enantioconvergent Decarboxylative Allylation of Racemic β-Ketoesters. *Angew. Chem., Int. Ed.* **2005**, *44*, 6924−6927. (c) Richter, M.-J.-R.; Schneider, M.; Brandstätter, M.; Krautwald, S.; Carreira, E.-M. Total Synthesis of (−)-Mitrephorone A. *J. Am. Chem. Soc.* **2018**, *140*, 16704−16710.
(14) Walse, S.-S.; Kuzmich, D. Diastereoselective Synthesis of (±)-Epianastrephin, (±)-Anastrephin and Analogs Thereof. US2017305874 A1, 2017.
(15) Selected papers for the total synthesis of anastraphin, see: (a) Tadano, K.; Isshiki, Y.; Minami, M.; Ogawa, S. Samarium(II) Iodide-Mediated Reductive Cyclization Approach to Total Synthesis of the Insect Sex Attractant (−)-Anastrephin. *Tetrahedron Lett.* **1992**, *33*, 7899−7902. (b) Wada, K.; Sakai, M.; Kawashima, H.; Ogawa, N.; Kobayashi, Y. Efficient Synthesis of Anastrephin via the Allylic Substitution for Quaternary Carbon Construction. *Synlett* **2016**, *27*, 1428−1432.

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