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Asymmetric hydrogenation of exocyclic γ,δ -unsaturated β -ketoesters to functionalized chiral allylic alcohols *via* dynamic kinetic resolution†

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An iridium catalyzed asymmetric hydrogenation of racemic exocyclic γ,δ -unsaturated β -ketoesters *via* dynamic kinetic resolution to functionalized chiral allylic alcohols was developed. With the chiral spiro iridium catalysts Ir-SpiroPAP, a series of racemic exocyclic γ,δ -unsaturated β -ketoesters bearing a five-, six-, or seven-membered ring were hydrogenated to the corresponding functionalized chiral allylic alcohols in high yields with good to excellent enantioselectivities (87 to >99% ee) and *cis*-selectivities (93 : 7 to >99 : 1). The origin of the excellent stereoselectivity was also rationalized by density functional theory calculations. Furthermore, this protocol could be performed on gram scale and at a lower catalyst loading (0.002 mol%) without the loss of reactivity and enantioselectivity, and has been successfully applied in the enantioselective synthesis of chiral carbocyclic δ -amino esters and the β -galactosidase inhibitor isogalactofagomine.

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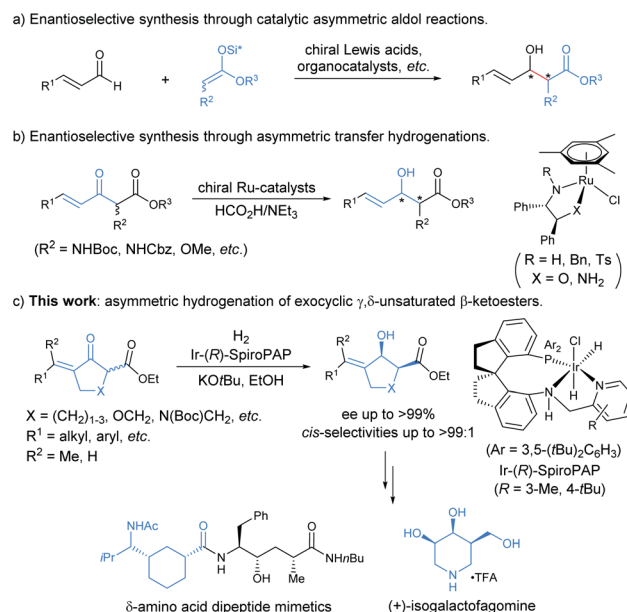
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Introduction

Chiral allylic alcohols not only are highly valuable and versatile chiral building blocks in organic synthesis but also represent common structural motifs in a variety of natural products and biologically active compounds. As a result, substantial efforts have been devoted to the development of a variety of catalytic asymmetric reactions allowing efficient and enantioselective syntheses of chiral allylic alcohols.¹ Among them, catalytic asymmetric hydrogenation of enones has been demonstrated to be one of the most efficient, practical, and atom-economical approaches.² However, despite long-standing interest, the enantioselective synthesis of highly functionalized chiral allylic alcohols such as γ,δ -unsaturated β -hydroxy esters with two contiguous stereocenters remains rare and challenging.² The reported catalytic asymmetric methods for the synthesis of optically active chiral γ,δ -unsaturated β -hydroxy esters with two contiguous stereocenters are limited to asymmetric aldol reactions (Scheme 1a)³ and ruthenium catalyzed asymmetric transfer hydrogenation of racemic α -substituted γ,δ -

unsaturated β -ketoesters *via* a dynamic kinetic resolution (DKR) (Scheme 1b).⁴ However, most of these methodologies are restricted to provide noncyclic chiral γ,δ -unsaturated β -hydroxy esters containing two contiguous stereocenters, and no reports have been published on the enantioselective synthesis of such types of highly functionalized chiral allylic alcohols through



Scheme 1 Enantioselective synthesis of chiral allylic alcohols with two contiguous stereocenters.

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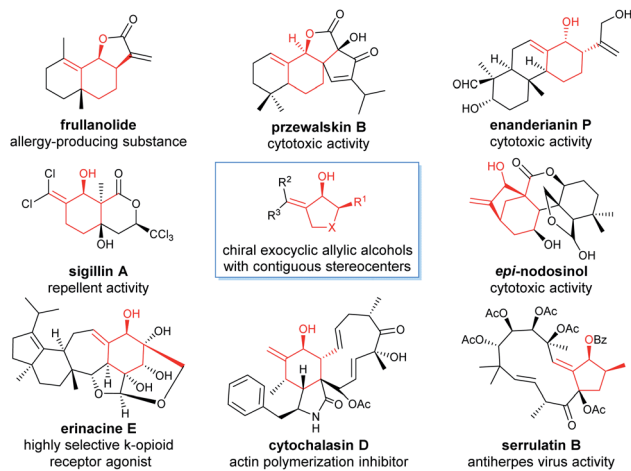


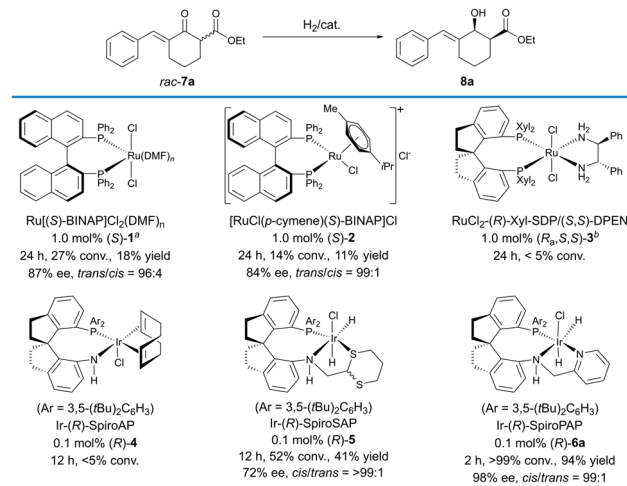
Fig. 1 Representative biologically active natural products containing chiral exocyclic allylic alcohol substructures.

direct asymmetric hydrogenation of the corresponding racemic enone esters *via* DKR.⁵

In recent years, we were interested in the development of highly efficient asymmetric hydrogenations for the syntheses of chiral alcohols with multiple chiral stereocenters, which could serve as valuable chiral building blocks to facilitate the concise and rapid construction of the chiral core structures of natural products.⁶ We noticed that chiral exocyclic allylic alcohols with contiguous stereocenters are widely found in biologically active natural products (Fig. 1).⁷ Inspired by these fascinating substructural features, we envisioned an asymmetric hydrogenation of racemic exocyclic γ,δ -unsaturated β -ketoesters *via* DKR for the synthesis of ester-functionalized chiral cyclic allylic alcohols with two contiguous stereocenters. We found that chiral spiro iridium catalysts Ir-SpiroPAP⁸ were highly efficient for these transformations, providing the corresponding functionalized chiral allylic alcohols with two contiguous stereocenters in high yields and excellent enantioselectivities (Scheme 1c). We successfully employed this efficient asymmetric hydrogenation as a key step for the scalable enantioselective total synthesis of the monoterpene indole alkaloid (–)-goniomitine.⁹ In this study, we showcase the details of the asymmetric hydrogenation of such γ,δ -unsaturated racemic cyclic β -ketoesters *via* DKR¹⁰ and the application of this method in the enantioselective synthesis of chiral carbocyclic δ -amino esters and the β -galactosidase inhibitor (+)-isogalactofagomine (Scheme 1c).

Results and discussion

The study commenced with the evaluation of chiral catalysts in the hydrogenation of a racemic δ -aryl substituted exocyclic enone ester bearing a six-membered ring, **7a** (Scheme 2). We initially evaluated the Ru–BINAP complex Ru[(*S*)-BINAP]Cl₂(DMF)_{*n*} ((*S*)-1),¹¹ a type of efficient chiral catalyst for asymmetric hydrogenation of racemic α -substituted β -ketoesters *via* DKR. Under the general conditions (1 mol% (*S*)-1, MeOH, 50 °C, 100 atm H₂), **8a** was obtained in 18% yield and 87% ee with 96 : 4



Scheme 2 Evaluation of chiral catalysts for asymmetric hydrogenation of **7a**. Reaction conditions: 1.0 mmol scale, **7a**/cat. = 100 : 1, MeOH (4.0 mL), 50 atm H₂, 50 °C, 24 h for Ru-catalysts (*S*)-1, (*S*)-2, and (*R_{a,S,S}*)-3; 1.0 mmol scale, **7a**/KOtBu/cat. = 1000 : 10 : 1, EtOH (4.0 mL), 10 atm H₂, 25–30 °C, 12 h for Ir-catalysts (*R*)-4 and 5, and 2 h for Ir-catalyst (*R*)-6a unless otherwise specified. The conversions of **7a** were determined by ¹H NMR spectroscopy. The yields are isolated yields of *cis*- and *trans*-isomers of **8a**. The enantiomeric excesses (ee) of the major diastereomers and the *cis/trans* values were determined by HPLC analysis using a chiral column. ^a100 atm H₂. ^b5 mol% KOtBu, *i*PrOH, 25–30 °C.

trans-selectivity. Then, another type of Ru–BINAP complex, [RuCl(*p*-cymene)(*S*)-BINAP]Cl ((*S*)-2), was also evaluated,¹² which provided **8a** in 11% yield and 84% ee with 99 : 1 *trans*-selectivity. The chiral spiro Ru–SDP complex RuCl₂(*R*)-Xyl-SDP/(*S,S*)-DPEN ((*R_{a,S,S}*)-3)¹³ and the iridium complex Ir-(*R*)-SpiroPAP ((*R*)-4),^{2f} developed by us previously, showed low reactivity (<5% conv.). The chiral spiro iridium complex Ir-(*R*)-SpiroSAP ((*R*)-5)¹⁴ displayed higher reactivity but a moderate ee value (41% yield, 72% ee and >99 : 1 *cis*-selectivity). However, promising results were observed by using the chiral spiro iridium complex Ir-(*R*)-SpiroPAP ((*R*)-6a),⁸ providing the desired product **8a** in a high yield (94%) with excellent enantioselectivity (98% ee) and high *cis*-selectivity (99 : 1).

Subsequently, the evaluation of other Ir-(*R*)-SpiroPAPs showed that the catalysts (*R*)-6b gave the highest enantioselectivity (99% ee) and *cis*-selectivity (>99 : 1) (Table 1, entries 1–7). In addition to KOtBu, other bases (NaOtBu, LiOtBu and K₂CO₃) could also be used, but the enantioselectivity and *cis*-selectivity were slightly lower, and a longer reaction time was needed when using K₂CO₃ as the base (Table 1, entries 8–10). When the H₂ pressure was decreased to 1 atm, the reaction time was increased to 2 h with the enantioselectivity and *cis*-selectivity being maintained (Table 1, entry 11). It is worth noting that when the catalyst loading was reduced to 0.002 mol% (S/C = 50 000) at 50 atm H₂, the hydrogenation still occurred smoothly without change in reactivity (98% yield) and enantioselectivity (99% ee) (Table 1, entry 12).

With the optimized reaction conditions in hand, we first investigated the hydrogenation of racemic δ -aryl substituted



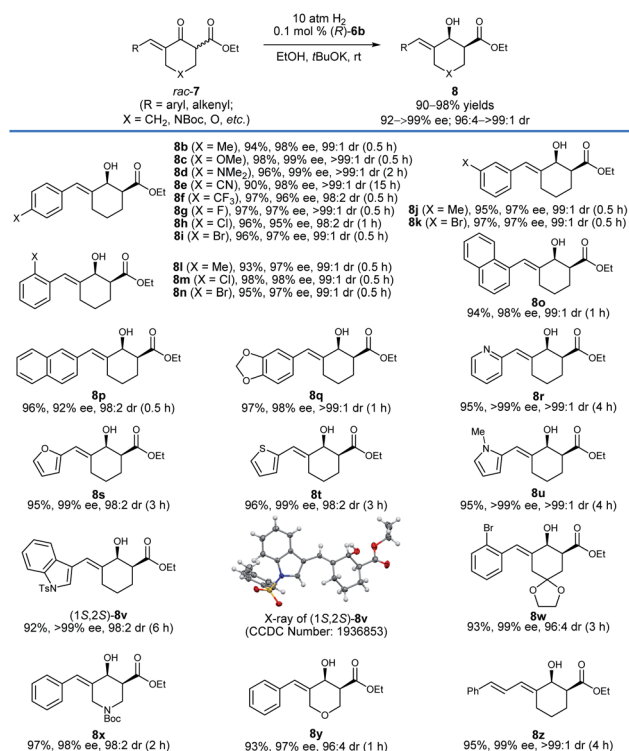
Table 1 Asymmetric hydrogenation of **7a** with (*R*)-**6** under optimized reaction conditions^a

Entry	(<i>R</i>)- 6	Base	Time (h)	Yield ^b (%)	<i>cis/trans</i> ^c	ee ^c (%)
1	(<i>R</i>)- 6a	KOtBu	2.0	94	99 : 1	98
2	(<i>R</i>)- 6b	KOtBu	0.5	96	>99 : 1	99
3	(<i>R</i>)- 6c	KOtBu	0.5	95	99 : 1	98
4	(<i>R</i>)- 6d	KOtBu	0.5	95	98 : 2	98
5	(<i>R</i>)- 6e	KOtBu	0.5	96	99 : 1	55
6	(<i>R</i>)- 6f	KOtBu	0.5	97	99 : 1	98
7	(<i>R</i>)- 6g	KOtBu	0.5	95	>99 : 1	98
8	(<i>R</i>)- 6b	NaOtBu	0.5	97	99 : 1	98
9	(<i>R</i>)- 6b	LiOtBu	0.5	94	99 : 1	98
10	(<i>R</i>)- 6b	K ₂ CO ₃	10.0	95	99 : 1	98
11 ^d	(<i>R</i>)- 6b	KOtBu	2.0	97	>99 : 1	99
12 ^e	(<i>R</i>)- 6b	KOtBu	24	98	99 : 1	99

^a Reaction conditions: 1.0 mmol scale, **7a**/base/(*R*)-**6** = 1000 : 10 : 1, EtOH (4.0 mL), 25–30 °C, >99% conversion (determined by ¹H NMR spectroscopy). ^b Isolated yields of *cis*- and *trans*-isomers of **8a**. ^c The enantiomeric excesses (ee) of the major diastereomer and the *cis/trans* values were determined by HPLC analysis using a chiral column. ^d 1 atm H₂. ^e 5.2 g (20 mmol) scale, **7a**/KOtBu/(*R*)-**6b** = 50 000 : 100 : 1, 50 atm H₂ (initial), EtOH (50 mL).

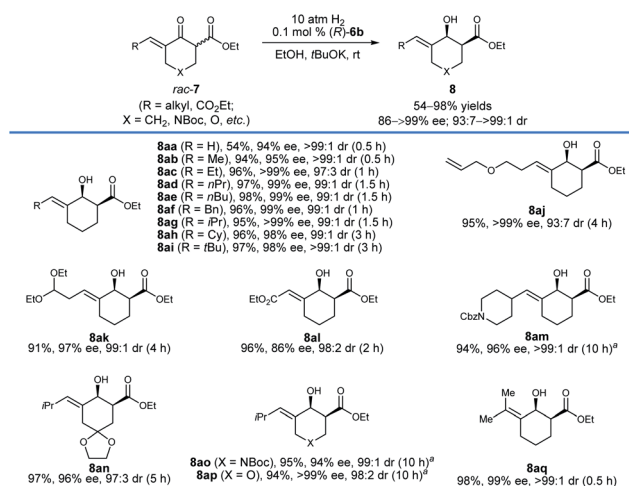
exocyclic enone esters **7** bearing a six-membered ring (Scheme 3). The electronic properties and the positions of the substituents on the phenyl ring have no obvious effect on the reactivity or enantioselectivity, and the corresponding hydrogenated products **8b–q** were obtained in high yields (90–98%) with excellent enantioselectivity (92–99% ee) and *cis*-selectivity (dr = 98 : 2 to >99 : 1). The substrates **7r–v** containing a heteroaryl ring, such as 2-pyridinyl (**7r**) and 2-thienyl (**7t**), also provided the desired products **8r–v** in comparable yields (92–96%) and *cis*-selectivities (99 to >99% ee, 96 : 4 to >99 : 1 dr). The hydrogenation of substrates **7w–y** derived from 1,4-cyclohexanedione monoacetal (**7w**), *N*-Boc piperidin-4-one (**7x**), and tetrahydropyran-4-one (**7y**), respectively, also occurred smoothly and afforded chiral allylic alcohols **8w–y** in high yields (93–97%), enantioselectivities (97–99% ee) and *cis*-selectivities (96 : 4 to 98 : 2 dr). The substrate **7z** with a dienone moiety was also a suitable candidate, providing dienyl alcohol **8z** in 95% yield with excellent enantioselectivity (99% ee) and *cis*-selectivity (>99 : 1 dr). The stereochemistry of the hydrogenation can be determined using the single crystals of **8v**. The X-ray diffraction analysis of the crystal structure of **8v** showed that the hydrogenation with the catalyst (*R*)-**6b** gave **8v** with a 1*S*,2*S*-configuration.

A series of racemic δ-alkyl substituted six-membered exocyclic enone esters **7** were also evaluated with (*R*)-**6b** under the same conditions (Scheme 4). The size of the alkyl groups of the



Scheme 3 Asymmetric hydrogenation of δ-aryl substituted exocyclic enone esters bearing a six-membered ring, **7**. Reaction conditions: 1.0 mmol scale, **7**/tBuOK/(*R*)-**6b** = 1000 : 10 : 1, EtOH (4.0 mL), 25–30 °C, 0.5–15 h. The yields are isolated yields of *cis*- and *trans*-isomers of **8**. The enantiomeric excesses (ee) of the major diastereomer and the diastereomeric ratio (dr) values were determined by HPLC analysis using a chiral column.

substrates has no significant effect on the enantioselectivity, and chiral allylic alcohols **8aa–aq** were obtained in high yields (54–98%) with 86 to >99% ee and 93 : 7 to >99 : 1 *cis*-selectivity.



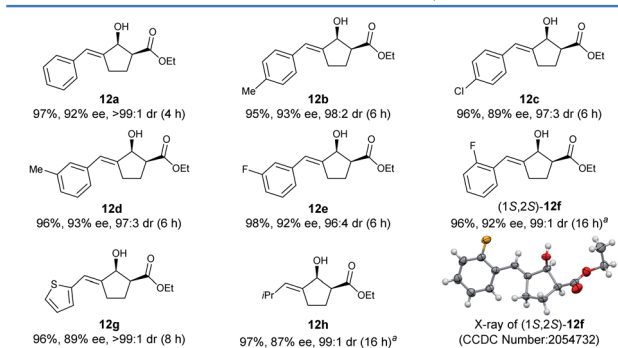
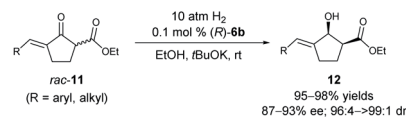
Scheme 4 Asymmetric hydrogenation of δ-alkyl substituted exocyclic enone esters bearing a six-membered ring, **7**. Reaction conditions: 1.0 mmol scale, **7**/tBuOK/(*R*)-**6b** = 1000 : 10 : 1, EtOH (4.0 mL), 25–30 °C, 0.5–10 h. The yields are isolated yields of *cis*- and *trans*-isomers of **8**. The enantiomeric excess (ee) of the major diastereomer and the diastereomeric ratio (dr) values were determined by HPLC analysis using a chiral column. ^a**7**/tBuOK/(*R*)-**6b** = 500 : 50 : 1.



However, a longer reaction time was required for the substrates with a relatively bulky alkyl group. The substrate **7aa** with a terminal double bond gave **8aa** in 54% yield with 94% ee and >99 : 1 *cis*-selectivity. The reason for the lower yield was that the catalyst (*R*)-**6b** hydrogenated the less hindered terminal C=C double bond of **8aa**, leading to the production of the corresponding saturated alcohol with both the C=C and C=O double bonds being hydrogenated successively.¹⁵ Notably, functional groups such as allyl ether (**7aj**), aldehyde acetal (**7ak**), ester (**7al**), and amide (**7am**) could be tolerated, and the corresponding chiral allylic alcohols **8aj–am** were delivered in great reactivity with 86 to >99% ee and 93 : 7 to >99 : 1 *cis*-selectivity. The hydrogenation of substrates **7an–ap** worked well and provided chiral allylic alcohols **8an–ap** in high yields (94–97%) and enantioselectivities (94 to >99% ee). In addition, the hydrogenation of the more challenging tetrasubstituted enone ester **7aq** could also be completed within 0.5 h and it provided the allylic alcohol **8aq** in 98% yield with 99% ee and >99 : 1 *cis*-selectivity.

Subsequently, we found that (*R*)-**6b** was also highly efficient for the asymmetric hydrogenation of racemic exocyclic enone esters bearing a seven-membered ring, **9** (Scheme 5). The hydrogenations could be completed within 2 h which afforded chiral exocyclic allylic alcohols **10** in high yields (90–96%) with excellent enantioselectivities (98 to >99% ee) and *cis*-selectivities (>99 : 1). Likewise, the substrates bearing coordinating heteroaryl moieties such as 2-pyridinyl (**9g**) and 2-furanyl (**9h**) have no significant effect on both the reactivity and enantioselectivity of the hydrogenations.

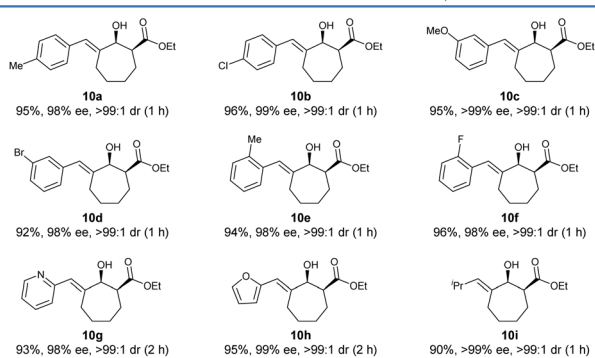
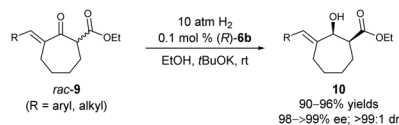
The aforementioned asymmetric hydrogenation of racemic exocyclic enone esters bearing a five-membered ring has been successfully applied in the enantioselective synthesis of the monoterpene indole alkaloid (–)-goniomitine,⁹ but the



Scheme 6 Asymmetric hydrogenation of exocyclic enone esters bearing a five-membered ring, **11**. Reaction conditions: 1.0 mmol scale, **11**/*t*BuOK/(*R*)-**6b** = 1000 : 10 : 1, EtOH (4.0 mL), 25–30 °C, 4–16 h. The yields are isolated yields of *cis*- and *trans*-isomers of **12**. The enantiomeric excesses (ee) of the major diastereomer and the diastereomeric ratio (dr) values were determined by HPLC analysis using a chiral column. ^aWith (*R*)-**6g** as the catalyst.

substrate scope was not widely studied. Thus, we also tested the asymmetric hydrogenation of racemic exocyclic enone esters bearing a five-membered ring, **11**, with the catalyst (*R*)-**6b** (Scheme 6). We found that (*R*)-**6b** provided 89–93% ee and 96 : 4 to >99 : 1 *cis*-selectivity for the hydrogenation of **11a–e** with a *para*- or *meta*-substituent on the phenyl ring. When the five-membered substrate **11f** with an *ortho*-F on the phenyl ring was hydrogenated, the catalyst (*R*)-**6g** with a 4-*t*Bu on the pyridinyl ring gave the corresponding allylic alcohol product **12f** in 96% yields with 92% ee and 99 : 1 *cis*-selectivity. The heteroaryl substituted allylic alcohol **12g** (2-thienyl) could be obtained with 89% ee and >99 : 1 *cis*-selectivity using (*R*)-**6b** as the catalyst. Moreover, the hydrogenation of the alkyl substituted substrate **11h** (R = *i*Pr) with the catalyst (*R*)-**6g** provided allylic alcohol **12h** (97%, 87% ee) with relatively low enantioselectivity and excellent *cis*-selectivity (99 : 1). The absolute configuration of **12f** was determined to be 1*S*,2*S* by single-crystal X-ray crystallography. This result showed that the asymmetric hydrogenation of five-membered exocyclic enone esters **11** with (*R*)-**6b** or **6g** shares a similar stereochemical control with the asymmetric hydrogenation of six-membered exocyclic enone esters **7**.

To understand the origins of the stereoselectivity, density functional theory (DFT) calculations were performed based on an outer-sphere mechanism.¹⁶ Fig. 2 showcases the proposed models of the interaction between the substrate **7ab** and catalyst (*R*)-**6b** according to the crystal structure of Ir-SpiroPAP.^{8b} To minimize steric repulsion, the substrate **7ab** approaches the catalyst (*R*)-**6b** with the ester group of the substrate away from the catalyst. Thus, the hydride from the Ir (Ir–H) and the proton from the nitrogen (N–H) of the catalyst (*R*)-**6b** prefer to transfer through six-membered-ring transition states **TS-SS** and **TS-RR** to the keto-carbonyl groups of the (*S*)- or (*R*)-isomer of the substrate **7ab**. Comparing the calculated energies of **TS-SS** (0.0 kcal mol^{–1}) and **TS-RR** (2.5 kcal mol^{–1}), an activation Gibbs



Scheme 5 Asymmetric hydrogenation of exocyclic enone esters bearing a seven-membered ring, **9**. Reaction conditions: 1.0 mmol scale, **9**/*t*BuOK/(*R*)-**6b** = 1000 : 10 : 1, EtOH (4.0 mL), 25–30 °C, 1–2 h. The yields are isolated yields of *cis*- and *trans*-isomers of **10**. ^cThe enantiomeric excesses (ee) of the major diastereomer and the diastereomeric ratio (dr) values were determined by HPLC analysis using a chiral column.



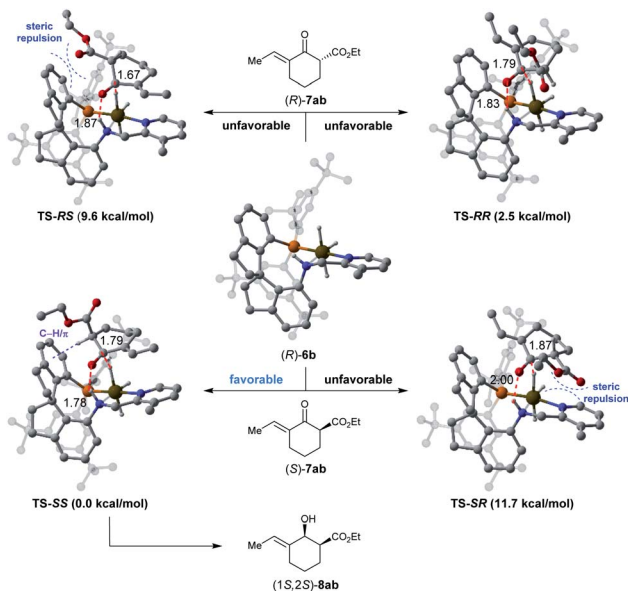
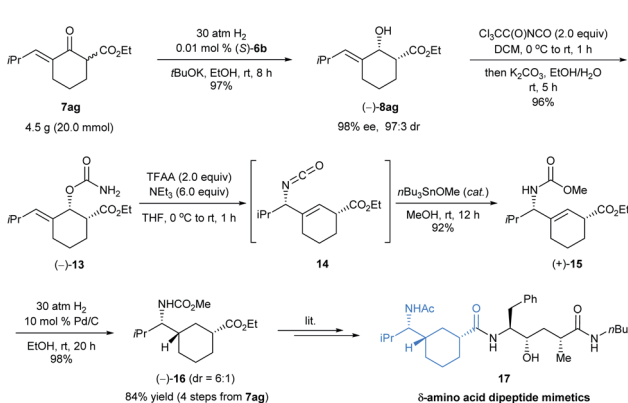


Fig. 2 Diastereomeric hydride/proton transfer transition states. Relative Gibbs free energies are reported in parentheses. The C–H/ π interactions are depicted in purple dashed lines.

free energy difference of $2.5 \text{ kcal mol}^{-1}$ was found between them. These results suggested that the catalyst (*R*)-**6b** tends to preferentially afford (1*S*,2*S*)-**8ab**, which is consistent with the experimental observation. The analysis of the non-covalent interactions (NCIs) with the independent gradient model (IGM) method also indicated that **TS-SS** was calculated to be more stable than **TS-RR**, owing to the attractive C–H/ π interaction¹⁷ between the α -C–H bond of the ester group and one of the phenyl ring of the spiro backbone in **TS-SS** (for details, see the ESI†). Therefore, the 1*S*,2*S*-configured product was preferentially formed with excellent enantioselectivity.

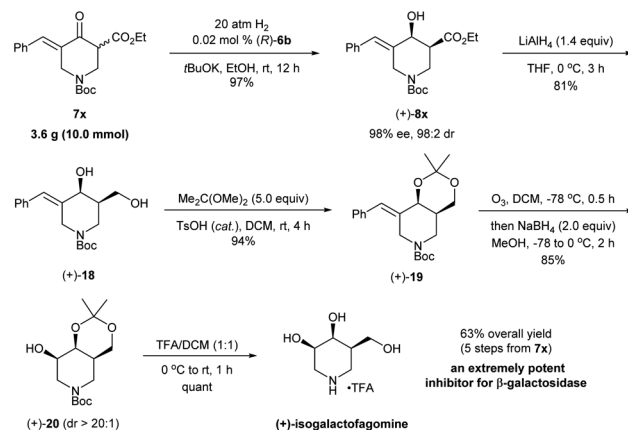
To exemplify the potential utility of this highly efficient asymmetric hydrogenation methodology, we initially selected δ -amino acids and their derivatives as targets. Chiral δ -amino acids are an important class of biomolecules used extensively as peptidomimetics and in the development of pharmaceuticals.¹⁸ We noticed that carbocyclic δ -amino acid ester **16** is a key chiral



Scheme 7 Enantioselective synthesis of carbocyclic δ -amino acid ester **16**.

intermediate to peptidomimetic **17** (Scheme 7), which showed submicromolar activity on β -site amyloid precursor protein cleavage enzyme-1 (BACE-1).¹⁹ However, long synthetic sequences (at least 11 steps) were required to complete the synthesis of such a δ -amino acid and its derivatives.^{19b} Our synthetic route started from the asymmetric hydrogenation of **7ag** with (*S*)-**6b** on the multi-gram scale at 0.01 mol% catalyst loading. The hydrogenation was completed within 8 h under 30 atm H_2 pressure and it afforded (–)-**8ag** in 97% yield with 98% ee and 97 : 3 *cis*-selectivity. Carbamoylation of (–)-**8ag** with trichloroacetyl isocyanate followed by dehydration with trifluoroacetic anhydride (TFAA) in the presence of NEt_3 yielded an allylic isocyanate intermediate **14**, which was then converted to allylic amine (+)-**15** in 88% yield (2 steps) *via* an Ichikawa rearrangement²⁰ and trapping with MeOH promoted by Bu_3SnOMe according to Stecko's procedure.²¹ Hydrogenation of allylic amine (+)-**15** on Pd/C afforded *N*-methoxycarbonyl δ -amino acid ester (–)-**16** in 98% yield with 6 : 1 diastereoselectivity. Thus, we completed the enantioselective synthesis of the δ -amino acid derivative (–)-**16** in 4 steps with 84% overall yield from exocyclic enone ester **7ag** and provided an efficient and concise access to carbocyclic δ -amino acid esters.

The synthetic utility was further demonstrated through the enantioselective synthesis of (+)-isogalactofagomine from exocyclic enone ester **7x** (Scheme 8). Isogalactofagomine (4-*epi*-isogalactofagomine) is one of the most interesting members of azasugars and is an extremely potent and selective β -galactosidase inhibitor ($\text{IC}_{50} = 12 \text{ nM}$; $\text{K}_i = 4 \text{ nM}$).²² While several synthetic routes have been reported to access such azasugars, these approaches rely on chiral starting materials²³ and chiral resolution by enzymes.²⁴ The gram-scale asymmetric hydrogenation of **7x** with (*R*)-**6b** provided (+)-**8x** in 97% yield with 98% ee and 98 : 2 *cis*-selectivity within 12 h. The reduction of (+)-**8x** with LiAlH_4 followed by the reaction with 2,2-dimethoxypropane yielded the cyclic imino derivative (+)-**18** in 76% yield. Then, ozonolysis followed by reduction with NaBH_4 in a one-pot procedure converted (+)-**19** to the alcohol product (+)-**20** in 85% yield with >20 : 1 diastereoselectivity. The treatment of (+)-**20** with trifluoroacetic acid (TFA) afforded the target molecule (+)-isogalactofagomine in quantitative yield. The NMR



Scheme 8 Enantioselective synthesis of (+)-isogalactofagomine.



spectroscopic data and the optical rotation ($[\alpha]_{\text{D}}^{25} = +2.6$ ($c = 1.0$, H_2O); lit.²⁴ $[\alpha]_{\text{D}}^{22} = +2.5$ ($c = 1.0$, H_2O)) of our synthetic (+)-isogalactofagomine are identical to those reported in the previous synthesis.²⁴ In short, with the asymmetric hydrogenation of exocyclic enone ester **7x** as the key step, (+)-isogalactofagomine was synthesized enantioselectively in 63% overall yield *via* 5 steps. This represents the first example of transition-metal catalyzed asymmetric synthesis of (+)-isogalactofagomine.

Conclusions

In conclusion, we developed an efficient asymmetric hydrogenation of racemic exocyclic enone esters to functionalized chiral allylic alcohols. With chiral spiro iridium catalysts (*R*)-**6b** and **6g**, a series of racemic exocyclic enone esters bearing a five-, six-, or seven-membered ring were hydrogenated to the corresponding functionalized chiral allylic alcohols in high yields with good to excellent enantioselectivities (87 to >99% ee) and *cis*-selectivities (93 : 7 to >99 : 1). The asymmetric hydrogenation of six- and seven-membered exocyclic enone esters **7** and **9** afforded better enantioselectivities (95 to >99% ee) than those for five-membered exocyclic enone esters **11** (87–93% ee). The origin of excellent enantioselectivity and *cis*-selectivity in the catalysis was revealed by DFT calculations to be an attractive C–H/ π interaction and stereo-repulsion between the substrate and the catalyst in the favored transition state. This asymmetric hydrogenation could be performed on gram scale and at a lower catalyst loading (0.002 mol%) without the loss of enantioselectivity. Based on this highly efficient asymmetric hydrogenation, the concise and efficient approaches to chiral carbocyclic δ -amino esters and the β -galactosidase inhibitor isogalactofagomine were developed.

Author contributions

H.-Y. B. performed the experiments and prepared the ESI[†] and paper. L. C. and C.-L. Z. prepared some substrates and repeated some experiments. X. W. carried out all computational work. X.-H. Y., J.-H. X. and Q.-L. Z. conceived and directed the project.

Conflicts of interest

There are no conflicts to declare.

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