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Ir/f-Ampha complex catalyzed asymmetric sequential hydrogenation of enones: a general access to chiral alcohols with two contiguous chiral centers†

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A general and highly efficient method for asymmetric sequential hydrogenation of α,β-unsaturated ketones has been developed by using an iridium/f-Ampha complex as the catalyst, furnishing corresponding chiral alcohols with two contiguous stereocenters in high yields with excellent diastereo- and enantioselectivities (up to 99% yield, >20 : 1 dr and >99% ee). Control experiments indicated that the C=C and C=O bonds of the enones were hydrogenated sequentially, and the final stereoselectivities were determined by the dynamic kinetic resolution of ketones. Moreover, DFT calculations revealed that an outer sphere pathway was involved in both reduction of C=C and C=O bonds of enones. The synthetic utility of this method was demonstrated by a gram-scale reaction with very low catalyst loading (S/C = 20 000) and a concise synthetic route to key chiral intermediates of the antiasthmatic drug CP-199,330.

Introduction

Owing to the perfect atom-economy, environmental benignancy and operational simplicity, asymmetric hydrogenation has been widely investigated both in academia and in industry, and it has emerged as one of the most important approaches to prepare chiral molecules.[1] In this context, the selective asymmetric hydrogenation of C=O[2] or C=C[3] bonds of α,β-unsaturated ketones has been well established by choosing a well-designed ligand combined with optimization of reaction conditions. In comparison, asymmetric sequential hydrogenation of multiply substituted α,β-unsaturated ketones in one step is rarely exploited although it provides a powerful strategy for the construction of molecules with multi-chiral centers.[4] The possible reasons may be attributed to the following challenges: first, the reaction mechanism of asymmetric hydrogenation of ketones is different from that of alkenes, it usually needs different catalysts and different reaction conditions to obtain good results in the asymmetric hydrogenation of ketones or olefins, thus it's very difficult to achieve the asymmetric sequential hydrogenation of multisubstituted enones with high yields and excellent stereoselectivities by using a single catalyst in one step. In addition, the first formed chiral center usually has an impact on the stereocontrol of the next chiral center generated, which makes it difficult to obtain high diastereoselectivity. Moreover, due to the different reactivities of ketones and olefins in asymmetric hydrogenation and different coordination models between the metal catalyst and substrate (inner sphere *vs.* outer sphere), it's a challenge to obtain high turnover numbers (TONs) for the sequential reduction of α,β-unsaturated ketones. For example, the Ru–PHOX–Ru catalytic system developed by the Zhang group exhibited excellent performance in the selective asymmetric hydrogenation of the C=O bonds of exocyclic α,β-unsaturated pentenones (S/C is up to 10 000), but failed to complete both reduction of C=O and C=C bonds even by increasing the catalyst loading (S/C = 100), hydrogen pressure and reaction temperature, only less than 50% sequential reduction product was obtained with poor diastereoselectivity (2 : 1) (Scheme 1-2).[2a] As a result, the asymmetric sequential hydrogenation of enones could be achieved only in a few cases, and most of them featured moderate diastereoselectivity, low turnover number and limited substrate scope.[4b–f] To date, multistep reduction is still the main method to achieve both asymmetric reduction of C=O and C=C bonds of enones.[2a–c,3j] Thus, it's highly desirable to develop new

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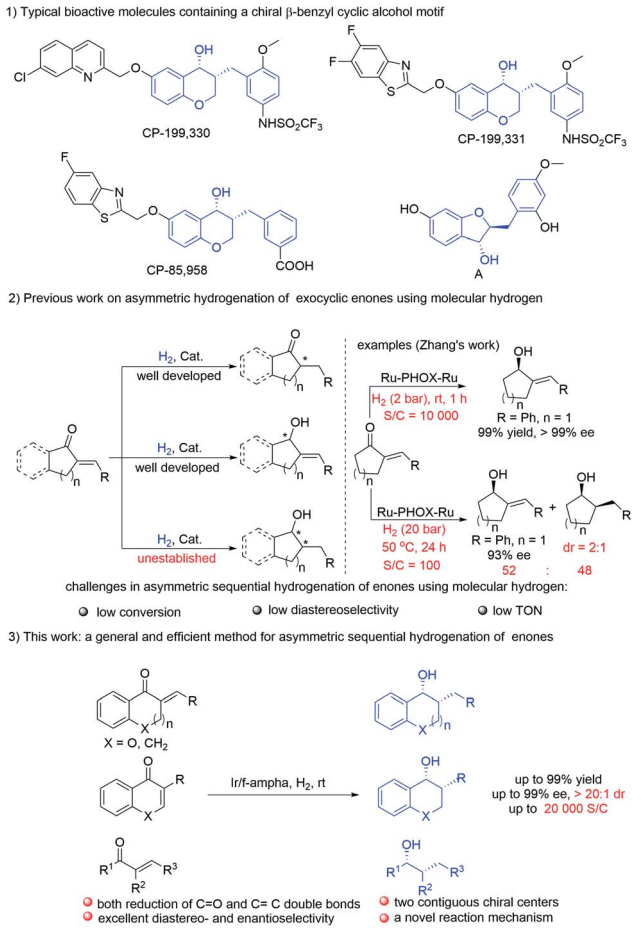


Scheme 1 Asymmetric hydrogenation of exocyclic enones using H_2 and typical bioactive molecules containing a chiral β-benzyl cyclic alcohol unit.

protocols to achieve asymmetric sequential hydrogenation of multiply substituted α,β-unsaturated ketones in a simple and efficient manner.

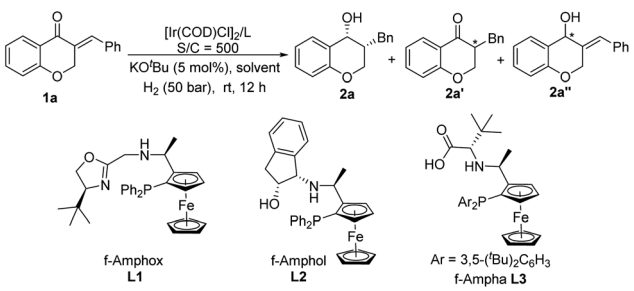
Chiral 4-chromanols and their derivatives are privileged structural motifs widely occurring in natural products and drug lead compounds (Scheme 1-1).[5] Particularly, chiral 3-alkylchroman-4-ols are known to be medicinally important motifs with a wide range of biological activities. For instance, CP-199,330 and CP-199,331 are potent cysteinyl leukotriene-1 (LT1) receptor antagonists, targeted for the treatment of asthma.[5a,i] CP-85,958 is useful in the treatment of arthritis and asthma.[5f,g] Compound A, which was isolated from dehulled adlay seeds, displays an anti-inflammatory effect.[6] Considerable efforts have been directed toward the synthesis of chiral chromanols.[5a,f,g] However, protocols for their enantioselective preparation are still very limited. To our surprise, asymmetric sequential reduction of exocyclic α,β-unsaturated ketones using molecular hydrogen, one of the most straightforward methods to synthesize chiral 3-alkylchroman-4-ols, has not been established.[7] Devising new methods for the asymmetric synthesis of 3-alkylchroman-4-ols is urgently needed.

Recently, our group developed a series of ferrocene-based tridentate amino-phosphine ligands, such as f-Amphox,[8] f-Ampha[9] and f-Amphol,[10] which showed excellent performance in the Ir-catalyzed asymmetric hydrogenation of prochiral ketones. We envision that the active Ir–H species may react with multiply substituted enones through 1,4-addition to form α-substituted ketones, followed by dynamic kinetic resolution (DKR) of ketones to achieve the asymmetric sequential hydrogenation of enones with high diastereo- and enantioselectivity. Herein, we report a general and efficient approach for the synthesis of chiral alcohols with two contiguous chiral centers by the Ir/f-Ampha complex enabled asymmetric sequential hydrogenation of α,β-unsaturated ketones.

Results and discussion

Our initial studies began with the optimization of reaction conditions by using the asymmetric hydrogenation of (*E*)-3-benzylidene chroman-4-one **1a** as a model reaction. With 0.1 mol% $[Ir(COD)Cl]_2$ and 5 mol% KO^{t}Bu in ^{i}PrOH at room temperature, a set of chiral tridentate ligands developed by our group were evaluated. When f-Amphox **L1** was used, only 13% *syn* 3-benzylchroman-4-ol **2a** was obtained along with a large amount of the ketone reduction product **2a″** (Table 1, entry 1). f-Amphol **L2** and f-Ampha **L3** exhibited good reactivity for sequential reduction of enone **1a**, both of them only afforded target product **2a** with excellent yields and good ee values (Table

Table 1 Ligand and solvent screening for the Ir-catalyzed asymmetric hydrogenation of (*E*)-3-benzylidenechroman-4-one (**1a**)[a]



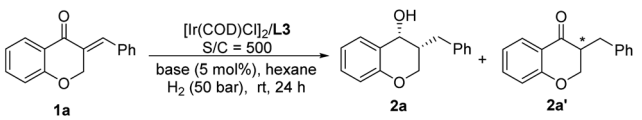
Entry	Ligand	Solvent	Conv.[b] (%)	**2a**/**2a′**/**2a″**[b]	dr[b] (**2a**)	ee[c] (%)
1	**L1**	^{i}PrOH	>99	13/0/87	>20 : 1	>99
2	**L2**	^{i}PrOH	>99	100/0/0	>20 : 1	87
3	**L3**	^{i}PrOH	>99	100/0/0	>20 : 1	90
4	**L3**	Dioxane	>99	14/86/0	>20 : 1	90
5	**L3**	Toluene	>99	65/35/0	>20 : 1	97
6	**L3**	Hexane	>99	100/0/0	>20 : 1	98
7	**L3**	THF	>99	36/64/0	>20 : 1	92
8	**L3**	DCM	>99	21/79/0	>20 : 1	83
9	**L3**	DCE	>99	5/95/0	>20 : 1	11
10	**L3**	EtOH	>99	31/69/0	>20 : 1	19
11	**L3**	TFE	>99	3/97/0	>20 : 1	—

[a] $[Ir(COD)Cl]_2$/ligand/**1a** (0.1 mmol) ratio of 0.5 : 1.1 : 500 in 1.0 mL solvent. In all cases described in this manuscript, little ^{i}PrOH as the solvent of the catalyst was introduced into the reaction mixture. [b] Determined by ^{1}H NMR analysis. [c] Determined by HPLC analysis using a chiral stationary phase. The configuration of **2a** was determined by comparing the specific rotation of **2a** with the data in the literature.[7a]

1, entries 2–3). Considering the product distribution and enantioselectivity, **L3** was chosen as the best ligand. Then, solvent screening was conducted and the results disclosed that solvents have a significant impact on the yield and the enantioselectivity of **2a**. Most of the solvents tested here, such as dioxane, dichloromethane, dichloroethane, tetrahydrofuran, ethanol, and trifluoroethanol, are mainly beneficial for the reduction of C=C double bonds, delivering the α-chiral ketone **2a′** as the main product (Table 1, entry 4 and entries 7–11). Fortunately, the desired product **2a** was obtained in a quantitative yield with excellent enantioselectivity by using hexane as the solvent (Table 1, entry 6).

Subsequently, the effect of bases was investigated and the results are summarized in Table 2. The reaction did not occur in the absence of a base (Table 2, entry 1). Strong bases and moderately strong bases, such as NaOH, NaOMe, NaO^{t}Bu, KO^{t}Bu, and Cs_2CO_3, were good choices for this transformation, giving **2a** with high yields and excellent stereoselectivities (Table 2, entries 2–6). When Na_2CO_3 was used, only 65% conversion was obtained and more than half of the converted starting material was only transformed to the product hydrogenated at the C=C double bond, which indicated that weak bases had a detrimental impact on the sequential hydrogenation of **1a** (Table 2, entry 7). To screen out the best base, a series of bases were re-evaluated under 0.05 mol% catalyst loading (S/C = 2000), and the results show that NaOH was superior to others (Table 2, entries 8–11). In addition, the effect of catalyst loading was also investigated. To our delight, on decreasing the catalyst loading to 0.01 mol% (S/C = 10 000), there was no loss of yield or diastereo- and enantioselectivity (Table 2, entry 12).

Table 2 Base screening for asymmetric hydrogenation of (*E*)-3-benzylidenechroman-4-one (**1a**)[a]



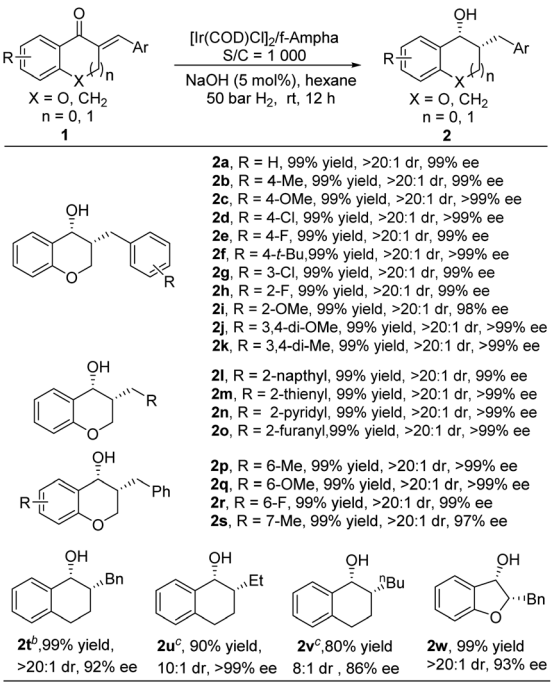
Entry	Base	Conv.[b] (%)	**2a** : **2a′**[b]	dr[b] (**2a**)	ee[c] (%)
1	—	NR	NA	NA	NA
2	NaOH	99	>20 : 1	>20 : 1	98
3	NaOMe	99	15 : 1	>20 : 1	97
4	NaO^{t}Bu	99	>20 : 1	15 : 1	98
5	KO^{t}Bu	99	>20 : 1	>20 : 1	98
6	Cs_2CO_3	99	>20 : 1	>20 : 1	98
7	Na_2CO_3	65	0.9 : 1	15 : 1	94
8[d]	NaOH	99	>20 : 1	>20 : 1	99
9[d]	Cs_2CO_3	99	2.3 : 1	17 : 1	97
10[d]	KO^{t}Bu	99	0.1 : 1	>20 : 1	87
11[d]	NaO^{t}Bu	99	>20 : 1	15 : 1	99
12[e]	NaOH	99	>20 : 1	>20 : 1	99

[a] Unless otherwise mentioned, all reactions were carried out with a [Ir(COD)Cl]$_2$/f-Ampha/**1a** (0.1 mmol) ratio of 0.5 : 1.1 : 500 in 1.0 mL of hexane. [b] Determined by ^{1}H NMR analysis. [c] Determined by HPLC analysis using a chiral stationary phase. [d] S/C = 2000. [e] S/C = 10 000. NR = no reaction. NA = not available.

With the optimal conditions in hand, the substrate scope of this reaction was explored with 0.1 mol% catalyst and the results are summarized in Table 3. Delightfully, the reaction exhibited good tolerance to a variety of exocyclic α,β-unsaturated ketones, furnishing the corresponding products in quantitative yields with excellent diastereo- and enantioselectivities. Generally, the reaction was not affected by the substitution pattern and the electronic properties of the aryl group, giving target products with 99% yield and 99% ee (**2a–2l**). Heteroaryl substituted substrates (**2m–2o**) were also well tolerated. Changing the position and the electronic properties of the R group didn't cause any changes in reactivity and in stereocontrol, affording target products with high yields and excellent diastereo- and enantioselectivities (**2p–2s**). When the O atom on the ring was replaced by a methylene group, the reactivity dropped, it required 0.5–1 mol% catalyst loading to achieve this transformation, delivering **2t–2v** with good yields and high stereoselectivities. Interestingly, when the ring size was changed from a 6-membered to a 5-membered ring, the reaction proceeded smoothly, offering chiral 3-hydroxyl-2,3-dihydrobenzofurans, the core structure of several natural products,[11] in 99% yield with 93% ee (**2w**).

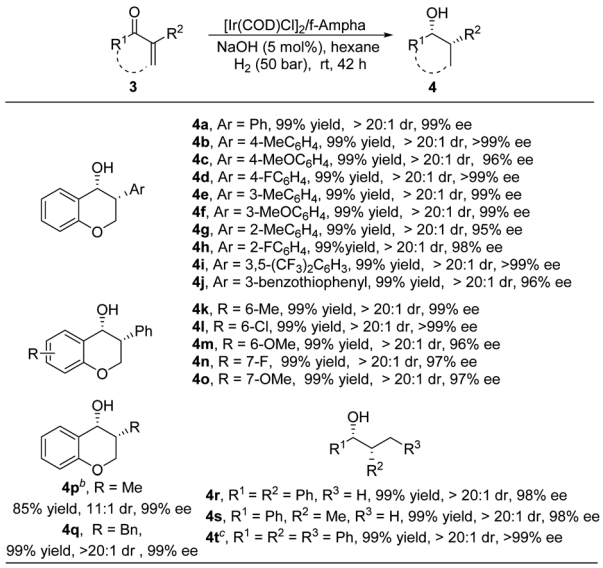
To further explore the substrate scope of this methodology, other types of enones, such as endocyclic enones and acyclic enones, were also examined under standard conditions. As

Table 3 Substrate scope of the Ir-catalyzed asymmetric hydrogenation of exocyclic α,β-unsaturated ketones[a]



[a] Unless otherwise mentioned, all reactions were carried out with a [Ir(COD)Cl]$_2$/f-Ampha/**1** (0.5 mmol) ratio of 0.5 : 1.1 : 1000 in 2.0 mL of hexane. The dr was determined by ^{1}H NMR. The yield was an isolated yield. The ee was determined by HPLC analysis using a chiral stationary phase. [b] 24 h, S/C = 200. [c] 36 h, S/C = 100, NaOMe was used instead of NaOH.

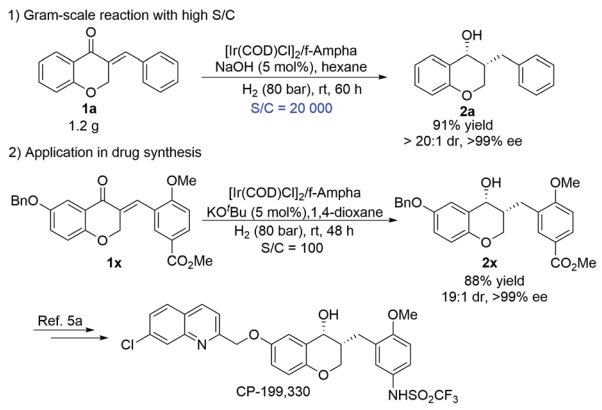
Table 4 Substrate scope of Ir-catalyzed asymmetric hydrogenation of endocyclic α,β-unsaturated ketones and acyclic enones[a]



[a] Unless otherwise mentioned, all reactions were carried out with an $[Ir(COD)Cl]_2$/f-Ampha/**3** (0.2 mmol) ratio of 0.5 : 1.1 : 1000 in 2.0 mL of hexane. The dr was determined by ^1H NMR. The yield was an isolated yield. The ee was determined by HPLC analysis using a chiral stationary phase. [b] 5 mol% KO^{t}Bu, 16% TBAOH (tetrabutylammonium hydroxide). [c] S/C = 100, 4 days.

shown in Table 4, various 3-aryl substituted endocyclic enones, regardless of the electronic properties and the position of the substituents on the benzene ring, were well tolerated in this transformation, furnishing 3-arylchroman-4-ones **4a–4o** with high yields and excellent enantioselectivities. Alkyl substituted endocyclic enones were also compatible in this reaction, delivering target products **4p–4q** in high yields with good diastereo- and enantioselectivities. Moreover, acyclic enones also proved to be good substrates for this transformation, affording corresponding alcohols **4r–4t** in 99% yield with 98–99% ee.

To demonstrate the potential utility of this catalytic system, the gram-scale reaction with 0.005 mol% catalyst loading (S/C = 20 000) was conducted, and it proceeded very smoothly, affording **2a** in high yield and excellent diastereo- and enantioselectivity (Scheme 2-1, 91% yield, >99% ee, >20 : 1 dr), which indicated that the Ir/f-Ampha complex is very efficient for the sequential asymmetric hydrogenation of enones, and has a practical application prospect. In addition, a highly efficient and concise synthetic route to the antiasthmatic drug CP-199,330 was developed. As shown in Scheme 2-2, **1x** can be sequentially hydrogenated efficiently to afford **2x** in 88% yield and 99% ee, which can be transformed into the antiasthmatic drug CP-199,330 according to the reported procedure.[5a] Compared with the previous method through racemic resolution,[12] the sequential asymmetric hydrogenation strategy is more cost-effective and more environmentally friendly.



Scheme 2 Gram-scale experiment with high TON and asymmetric synthesis of the antiasthmatic drug CP-199,330.

The change of product distribution with reaction time was investigated to shed light on the reaction mechanism. As shown in Fig. 1, most of **1a** was quickly transformed into **2a′** within 0.17 hours by selective reduction of C=C bonds, without any **2a″** and **2a** being detected. Prolonging the reaction time to one hour, the starting material **1a** was completely consumed, affording target product **2a** in 82% yield along with **2a′** in 18% yield. On further increasing the reaction time, the amount of **2a′** decreased gradually until it was totally transformed into **2a**. It was noteworthy that no **2a″** was detected in these experiments. In order to further identify the reaction pathway, the possible intermediates **2a′** and **2a″** were synthesized and then hydrogenated under the standard reaction conditions. The results show that the intermediate **2a′** was hydrogenated smoothly, affording chiral 3-benzylchroman-4-ol **2a** in a quantitative yield with excellent enantioselectivity and diastereoselectivity (Scheme 3-1), which demonstrated that a dynamic kinetic resolution (DKR) was involved in the reaction process. **2a″** can't be hydrogenated under standard conditions, which indicated that the reaction pathway involving the asymmetric hydrogenation of a ketone

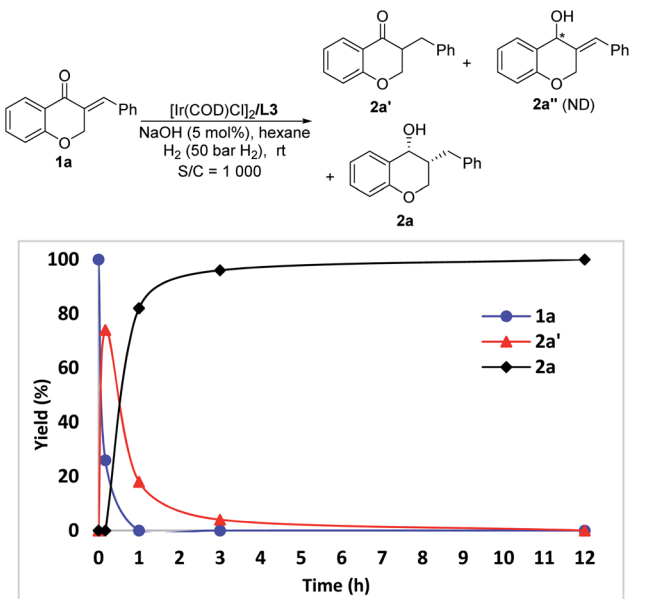
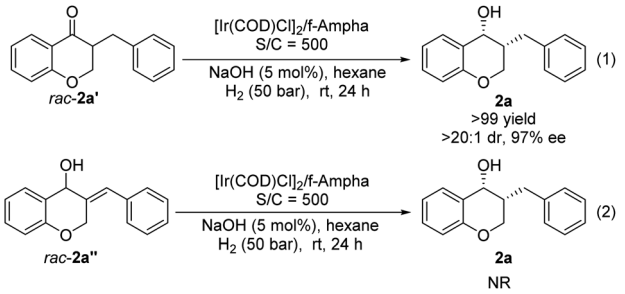


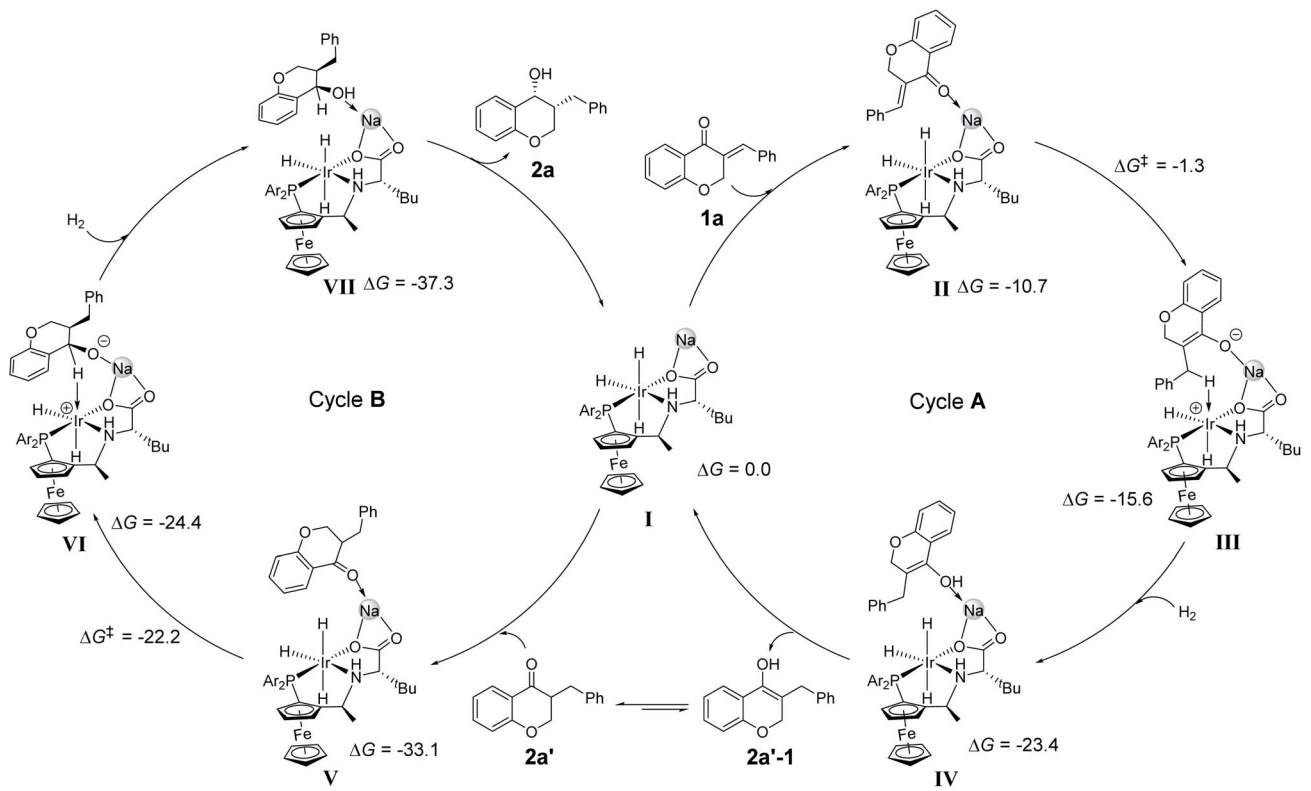
Fig. 1 Plots of product distribution with reaction time.



Scheme 3 The hydrogenation of the possible intermediates **2a′** and **2a″**.

followed by the reduction of C=C double bonds was excluded (Scheme 3-2). Taking together, these results clearly demonstrated that the hydrogenation of **1a** proceeded through the hydrogenation of the C=C double bonds of **2a** to form **2a′**, then asymmetric hydrogenation of **2a′** *via* DKR to afford the desired product **2a**.

DFT calculations were also conducted to understand the reaction pathway and the enantioselectivity in the DKR process. The hydrogenation of **1a** to **2a** was considered in our DFT calculations. Referring to the above mechanistic discussion and our related work,[13] an outer sphere pathway for 1,4-addition to produce **2a′**, followed by hydrogenation of C=O is proposed (Scheme 4). The role of alkali cation in hydrogenation reactions has been demonstrated in recent publications[14] and our previous study.[9] The trihydride IrH_3(f-Ampha) complex **I** involving an alkali cation Na^+ was proposed as the starting point in our DFT study. Complex **I** attracts **1a** and gives complex **II**, and the reaction is exothermic by 10.7 kcal mol^{-1}. The Ir(III)-hydride can make a nucleophilic attack on the carbonyl carbon or the β-carbon on the Re/Si face of **1a**. DFT calculations indicate that hydride transfer to the β-carbon of the **1a** Re face gives the most favorable transition state ($\mathbf{TS_{II-III}}$) with a barrier of 9.4 kcal mol^{-1} (with respect to complex **II**) (see the ESI, Fig. S1 and S2†). It is understandable that the carbonyl as a π withdrawing group increases the contribution of the β-carbon to the LUMO, thus promoting the hydride transfer to the β-carbon. A similar mechanism of nucleophilic attack of the Cu–B σ bond on α,β-unsaturated carbonyl compounds was well studied.[15] After hydride transfer, molecular H_2 coordinates to the Ir(III) and forms a dihydrogen Ir(III)(η^2-H_2) complex **III+H_2**. The H_2 activation between the Ir(III) and the enolate anion (formed by hydride transfer to **1a**) is barrierless and gives an enol compound **2a′–1**. The compound **2a′–1** undergoes a keto-to-enol isomerization to the more stable keto **2a′**. Compound **2a′** enters the cycle B. The hydrogenation of **2a′** to the β-benzyl cyclic alcohol **2a** is also achieved through hydride transfer and H_2 activation processes (see the ESI, Fig. S3†). The hydride transfer to the carbonyl carbon is the enantio-determining step. The energy barrier leading to the major product **2a**(*R*,*R*) is 10.9 kcal mol^{-1} from complex **V**, which is lower than the barriers to **2a**(*S*,*R*), **2a**(*S*,*S*) and **2a**(*R*,*S*) by 2.2, 4.3 and 7 kcal mol^{-1}, respectively (see the ESI, Fig. S4†). The DFT-calculated ee and dr values are 99.9% and 40 : 1, which are



Scheme 4 Proposed catalytic cycles. Cycle A: 1,4-addition of **1a**; cycle B: DKR to form **2a**. Relative free energies are given in kcal mol^{-1}.

well consistent with the experimental results (ee 99%, dr > 20 : 1). The unique chair pocket of the Ir(III)/f-Ampha catalyst can account for the excellent enantioselectivities and diastereoselectivities in the DKR process.

Conclusions

In summary, we have developed a highly efficient asymmetric sequential hydrogenation of α,β-unsaturated ketones *via* an Ir/f-ampha complex catalyzed DKR process, which provides a general and practical access to chiral alcohols with two contiguous stereocenters. Remarkably, this method not only exhibited excellent stereo-control (up to >99% ee and >20 : 1 dr, TON up to 18 200), but also showed excellent substrate compatibility with various enones, including exocyclic α,β-unsaturated ketones, endocyclic α,β-unsaturated ketones and acyclic enones, which make this method particularly valuable in organic synthesis. In addition, the experimental and theoretical calculation investigations of the mechanism revealed that the C=C and C=O double bonds of the enones were hydrogenated sequentially through an outer sphere pathway. Furthermore, the synthetic utility of this protocol was demonstrated by a concise synthetic route to a key chiral intermediate of the antiasthmatic drug CP-199,330. Further studies on the extension of this novel catalytic system are currently underway in our laboratory.

Data availability

All experimental procedures, characterization data, computational methods and detailed energy profiles in this article are available in the ESI.†

Author contributions

H. L. conceived the project. W. L., N. S., R. L. and J. L. performed the experiments. T. Y. performed DFT calculations. W. L. and H. L. wrote the manuscript, H. L and X. Z. provided useful suggestions for this work. All the authors discussed the results and contributed to the preparation of the final manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

1 Selected reviews for recent advances on transition-metal catalyzed asymmetric hydrogenation, see: (*a*) W. Zhang, Y. Chi and X. Zhang, *Acc. Chem. Res.*, 2007, **40**, 1278–1290; (*b*) J.-H. Xie, S.-F. Zhu and Q.-L. Zhou, *Chem. Rev.*, 2011, **111**, 1713–1760; (*c*) D.-S. Wang, Q.-A. Chen, S.-M. Lu and Y.-G. Zhou, *Chem. Rev.*, 2012, **112**, 2557–2590; (*d*) G. Xu, C. H. Senanayake and W. Tang, *Acc. Chem. Res.*, 2019, **52**, 1101–1112; (*e*) Z. Zhang, N. A. Butt, M. Zhou, D. Liu and W. Zhang, *Chin. J. Chem.*, 2018, **36**, 443–454; (*f*) J. J. Verendel, O. Pàmies, M. Diéguez and P. G. Andersson, *Chem. Rev.*, 2014, **114**, 2130–2169; (*g*) Q.-A. Chen, Z.-S. Ye, Y. Duan and Y.-G. Zhou, *Chem. Soc. Rev.*, 2013, **42**, 497–511; (*h*) Z. Zhang, N. A. Butt and W. Zhang, *Chem. Rev.*, 2016, **116**, 14769–14827; (*i*) J.-H. Xie and Q.-L. Zhou, *Acta Chim. Sin.*, 2012, **70**, 1427–1438; (*j*) Y. Liu, Z. Wang and K. Ding, *Acta Chim. Sin.*, 2012, **70**, 1464–1470; (*k*) S. Kraft, K. Ryan and R. B. Kargbo, *J. Am. Chem. Soc.*, 2017, **139**, 11630–11641; (*l*) S.-F. Zhu and Q.-L. Zhou, *Acc. Chem. Res.*, 2017, **50**, 988–1001; (*m*) F. Meemken and A. Baiker, *Chem. Rev.*, 2017, **117**, 11522–11569; (*n*) C. Margarita and P. G. Andersson, *J. Am. Chem. Soc.*, 2017, **139**, 1346–1356; (*o*) P. Tang, H. Wang, W. Zhang and F.-E. Chen, *Green Synth. Catal.*, 2020, **1**, 26–41.

2 (*a*) J. Li, Y. Zhu, Y. Lu, Y. Wang, Y. Liu, D. Liu and W. Zhang, *Organometallics*, 2019, **38**, 3970–3978; (*b*) J. Li, Y. Lu, Y. Zhu, Y. Nie, J. Shen, Y. Liu, D. Liu and W. Zhang, *Org. Lett.*, 2019, **21**, 4331–4335; (*c*) J.-B. Xie, J.-H. Xie, X.-Y. Liu, W.-L. Kong, S. Li and Q.-L. Zhou, *J. Am. Chem. Soc.*, 2010, **132**, 4538–4539; (*d*) F. Chen, Y. Zhang, L. Yu and S. Zhu, *Angew. Chem., Int. Ed.*, 2017, **56**, 2022–2025; (*e*) R. Moser, Ž. V. Bošković, C. S. Crowe and B. H. Lipshutz, *J. Am. Chem. Soc.*, 2010, **132**, 7852–7853; (*f*) J. Kim, J. Bruning, K. E. Park, D. J. Lee and B. Singaram, *Org. Lett.*, 2009, **11**, 4358–4361; (*g*) Y. Wang, G. Yang, F. Xie and W. Zhang, *Org. Lett.*, 2018, **20**, 6135–6139.

3 (*a*) S.-M. Lu and C. Bolm, *Angew. Chem., Int. Ed.*, 2008, **47**, 8920–8923; (*b*) W.-J. Lu, Y.-W. Chen and X.-L. Hou, *Angew. Chem., Int. Ed.*, 2008, **47**, 10133–10136; (*c*) F. Tian, D. Yao, Y. Liu, F. Xie and W. Zhang, *Adv. Synth. Catal.*, 2010, **352**, 1841–1845; (*d*) X. Wang, Z. Han, Z. Wang and K. Ding, *Angew. Chem., Int. Ed.*, 2012, **51**, 936–940; (*e*) X. Liu, Z. Han, Z. Wang and K. Ding, *Angew. Chem., Int. Ed.*, 2014, **53**, 1978–1982; (*f*) Q. Li, P. Wan, Y. He, Y. Zhou, L. Li, B. Chen, K. Duan, R. Cao, Z. Zhou and L. Qiu, *Asian J. Org. Chem.*, 2014, **3**, 774–783; (*g*) J. Xia, Y. Nie, G. Yang, Y. Liu, I. D. Gridnev and W. Zhang, *Chin. J. Chem.*, 2018, **36**, 612–618; (*h*) B. Gao, X. Feng, W. Meng and H. Du, *Angew. Chem., Int. Ed.*, 2020, **59**, 4498–4504; (*i*) J. Yang, X. Li, C. You, S. Li, Y.-Q. Guan, H. Lv and X. Zhang, *Org. Biomol. Chem.*, 2020, **18**, 856–859; (*j*) J. Xia, Y. Nie, G. Yang, Y. Liu, I. D. Gridnev and W. Zhang, *Chin. J. Chem.*, 2018, **36**, 612–618; (*k*) B. B. C. Peters, J. Jongcharoenkamol, S. Krajangsri and P. G. Andersson, *Org. Lett.*, 2021, **23**, 242–246.

4 (*a*) L. Tang, Z. Lin, Q. Wang, X. Wang, L. Cun, W. Yuan, J. Zhu and J. Deng, *Tetrahedron Lett.*, 2012, **53**, 3828–3830; (*b*) D. Zhao, B. Beiring and F. Glorius, *Angew. Chem., Int. Ed.*, 2013, **52**, 8454–8458; (*c*) Q. Hu, J. Chen, Z. Zhang, Y. Liu and W. Zhang, *Org. Lett.*, 2016, **18**, 1290–1293; (*d*) Y.-T. Liu, J.-Q. Chen, L.-P. Li, X.-Y. Shao, J.-H. Xie and Q.-L. Zhou,

Org. Lett., 2017, **19**, 3231–3234; (*e*) Y. Ma, J. Li, J. Ye, D. Liu and W. Zhang, *Chem. Commun.*, 2018, **54**, 13571–13574; (*f*) N. Arai, H. Satoh, R. Komatsu and T. Ohkuma, *Chem.–Eur. J.*, 2017, **23**, 8806–8809.

5 (*a*) R. J. Chambers, A. Marfat, G. W. Antognoli, J. B. Cheng, D. B. Damon, A. V. Kuperman, T. C. Liston, C. Mebus, J. S. Pillar, J. T. Shirley and J. W. Watson, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 2773–2778; (*b*) P. P. Deshpande, F. Tagliaferri, S. F. Victory, S. Yan and D. C. Baker, *J. Org. Chem.*, 1995, **60**, 2964–2965; (*c*) T. Ma, L. Liu, H. Xue, L. Li, C. Han, L. Wang, Z. Chen and G. Liu, *J. Med. Chem.*, 2008, **51**, 1432–1446; (*d*) C. Conti and N. Desideri, *Bioorg. Med. Chem.*, 2009, **17**, 3720–3727; (*e*) K. Koch, L. S. Melvin, L. A. Reiter, M. S. Biggers, H. J. Showell, R. J. Griffiths, E. R. Pettipher, J. B. Cheng and A. J. Milici, *J. Med. Chem.*, 1994, **37**, 3197–3199; (*f*) E. G. Andrews, G. W. Antognoli, R. Breslow, M. P. Carta, T. J. Carty, R. J. Chambers, J. B. Cheng, V. L. Cohan, J. L. Collins, D. B. Damon, J. Delehunt, J. F. Eggler, J. D. Eskra, K. W. Freiert, W. A. Hada, A. Marfat, H. Masamune, L. S. Melvin, C. J. Mularski, B. A. Naclerio, C. J. Pazoles, J. S. Pillar, L. A. Rappach, P. Reiche, F. W. Rusek, H. Sherman, J. T. Shirley, F. J. Sweeney, J. E. Tickner, J. W. Watson and C. F. Wright, *Bioorg. Med. Chem. Lett.*, 1995, **5**, 1365–1370; (*g*) R. J. Chambers, G. W. Antognoli, J. B. Cheng, A. Marfat, J. S. Pillar, J. T. Shirley and J. W. Watson, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 1791–1796; (*h*) L.-G. Lin, H. Xie, H.-L. Li, L.-J. Tong, C.-P. Tang, C.-Q. Ke, Q.-F. Liu, L.-P. Lin, M.-Y. Geng, H. Jiang, W.-M. Zhao, J. Ding and Y. Ye, *J. Med. Chem.*, 2008, **51**, 4419–4429; (*i*) T. Janeczko, J. Dmochowska-Gładysz, A. Szumny and E. Kostrzewa-Susłow, *J. Mol. Catal. B: Enzym.*, 2013, **97**, 278–282.

6 W. Chiang, Y. Lin, C. Chung and H. Chen, *US Pat.*, 2013/0158107A1, 2013.

7 In the preparation of this manuscript, asymmetric sequential reduction of enones using transfer hydrogenation was reported, see: (*a*) R. Molina Betancourt, P. Phansavath and V. Ratovelomanana-Vidal, *Org. Lett.*, 2021, **23**, 1621–1625; (*b*) G. S. Caleffi, J. d. O. C. Brum, A. T. Costa, J. L. O. Domingos and P. R. R. Costa, *J. Org. Chem.*, 2021, **86**, 4849–4858.

8 (*a*) W. Wu, S. Liu, M. Duan, X. Tan, C. Chen, Y. Xie, Y. Lan, X.-Q. Dong and X. Zhang, *Org. Lett.*, 2016, **18**, 2938–2941; (*b*) Y. Zheng, X. Zhang, R. Zhang and B. Ma, *Green Synth. Catal.*, 2021, **2**, 393–396.

9 J. Yu, J. Long, Y. Yang, W. Wu, P. Xue, L. W. Chung, X.-Q. Dong and X. Zhang, *Org. Lett.*, 2017, **19**, 690–693.

10 J. Yu, M. Duan, W. Wu, X. Qi, P. Xue, Y. Lan, X.-Q. Dong and X. Zhang, *Chem.–Eur. J.*, 2017, **23**, 970–975.

11 (*a*) F. Thuaud, Y. Bernard, G. Türkeri, R. Dirr, G. Aubert, T. Cresteil, A. Baguet, C. Tomasetto, Y. Svitkin, N. Sonenberg, C. G. Nebigil and L. Désaubry, *J. Med. Chem.*, 2009, **52**, 5176–5187; (*b*) M. Itoigawa, C. Ito, H. T. W. Tan, M. Okuda, H. Tokuda, H. Nishino and H. Furukawa, *Cancer Lett.*, 2001, **174**, 135–139.

12 R. J. Chambers, A. Marfat, G. W. Antognoli, J. B. Cheng, D. B. Damon, A. V. Kuperman, T. C. Liston, C. Mebus, J. S. Pillar, J. T. Shirley and J. W. Watson, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 2773–2778.

13 (*a*) G. Gu, T. Yang, J. Lu, J. Wen, L. Dang and X. Zhang, *Org. Chem. Front.*, 2018, **5**, 1209–1212; (*b*) Z. Liang, T. Yang, G. Gu, L. Dang and X. Zhang, *Chin. J. Chem.*, 2018, **36**, 851–856.

14 (*a*) P. A. Dub and J. C. Gordon, *Nat. Rev. Chem.*, 2018, **2**, 396–408; (*b*) P. A. Dub, *Eur. J. Inorg. Chem.*, 2021, **2021**, 4884–4889; (*c*) P. A. Dub, N. J. Henson, R. L. Martin and J. C. Gordon, *J. Am. Chem. Soc.*, 2014, **136**, 3505–3521.

15 L. Dang, Z. Lin and T. B. Marder, *Organometallics*, 2008, **27**, 4443–4454.