Chemical Science

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: H. Wu, C. Margarita, J. Jongcharoenkamol, M. D. Nolan, T. Singh and P. Andersson, *Chem. Sci.*, 2021, DOI: 10.1039/D0SC05276K.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/chemical-science

View Article Online
DOI: 10.1039/D0SC05276K

ARTICLE

Kinetic Resolution of Racemic Allylic Alcohols via Iridium-Catalyzed Asymmetric Hydrogenation: Scope, Synthetic Applications and Insight into the Origin of Selectivity†

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

Haibo Wu,[a] Cristiana Margarita,[a] Jira Jongcharoenkamol,[a‡] Mark D. Nolan,[a] Thishana Singh[b] and Pher G. Andersson*[ab]

Asymmetric hydrogenation is one of the most commonly used tools in organic synthesis, whereas, kinetic resolution via asymmetric hydrogenation was less developed. Herein, we describe the first iridium catalyzed kinetic resolution of a wide range of trisubstituted secondary and tertiary allylic alcohols. Large selectivity factors were observed in most cases (*s* up to 211), providing the unreacted starting materials in good yield with high levels of enantiopurity (*ee* up to >99%). The utility of the method is highlighted by the enantioselective formal synthesis of some bioactive natural products including pumiliotoxin A , inthomycin A and B. DFT studies and selectivity model concerning the origin of selectivity are presented.

Introduction

The demand for enantiomerically pure alcohols is steadily increasing. In particular, chiral allylic alcohols have tremendous synthetic relevance to natural products, pharmaceuticals, agricultural chemicals and specialty materials.[1] Kinetic resolution (KR) is a useful and direct approach to access such compounds, in a manner where they are obtained in high enantiopurity, from inexpensive racemic starting material.[1c] Notably, KR is also one of the most common methods that is used to prepare optically active alcohols on an industrial scale.[2]

Transition-metal catalyzed asymmetric hydrogenation[3] is one of the most efficient and well-established transformations in asymmetric catalysis. Owing to its perfect atom economy and excellent enantioselectivity, this process was frequently used in the preparation of enantiomericially enriched compounds in both academia and industry. However, when compared with other fundamental transformations such as epoxidation[4] and acylation,[5] its application in kinetic resolution is still a far less explored and challenging task. Pioneering work in this field was described by Noyori et al. in 1988 using the Ru-BINAP catalyst system (Fig.1a), which was initially found to be efficient for few aliphatic cyclic substrates.[6] In 2015, Zhou et al. reported an impressive KR of saturated aliphatic alcohols via iridium catalyzed asymmetric hydrogenation of ester (Fig.1b),[7] showing excellent selectivity and high efficiency without the need to convert the OH group to other functionalities. By using rhodium catalysts, Vidal-Ferran et al. developed the KR of racemic vinyl sulfoxides and vinyl phosphane oxides via hydrogenation of terminal olefin (Fig.1c).[8] Despite these progresses, there is still no general hydrogenation protocol available for KR of a wide range of allylic alcohols.

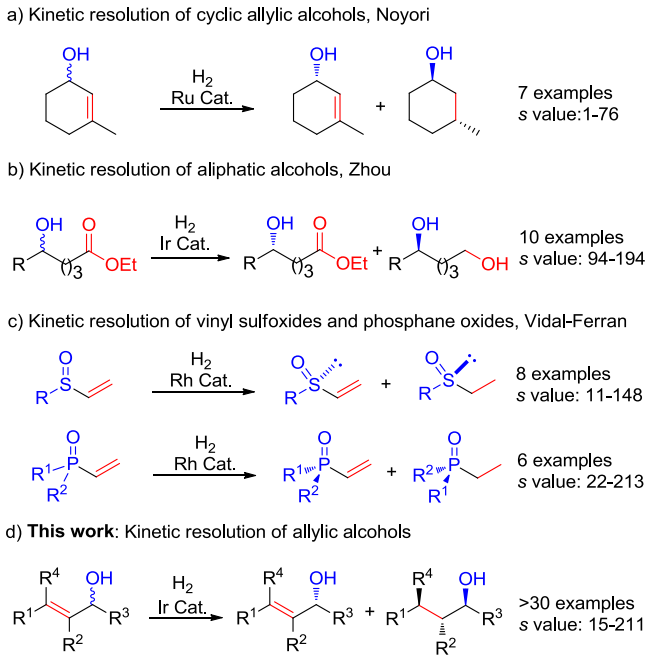


Fig.1 Kinetic resolution via asymmetric hydrogenation

[a] Department of Organic Chemistry, Stockholm University, Arrhenius Laboratory, 106 91, Stockholm, Sweden. Email: pher.andersson@su.se
[b] School of Chemistry and Physics, University of Kwazulu-Natal, Private Bag X54001, Durban, 4000, South Africa.

†Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

‡ Present address: Chulabhorn Graduate Institute, Chulabhorn Royal Academy, 54 Kamphaeng Phet 6 Road, Laksi, Bangkok 10210, Thailand

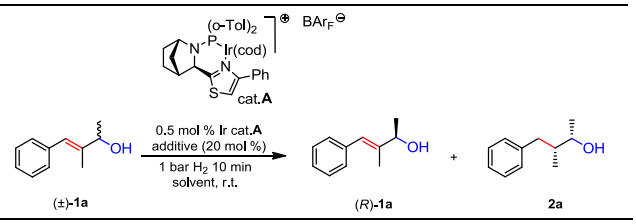
DOI: 10.1039/D0SC05276K

Over the past two decades, our group has developed a variety of iridium N,P complexes, which were successfully employed in asymmetric hydrogenation of different types of olefins with different functionalities.[9] As a continuous interest, further application of asymmetric hydrogenation in kinetic resolution of allylic substrates is highly desired. Iridium catalyzed asymmetric hydrogenation of primary allylic alcohols has been well developed.[10] In contrast, the secondary or tertiary allylic alcohols were found to be challenging substrates[10] for iridium catalyzed asymmetric hydrogenation due to the Lewis or Brønsted acidity of transition-metal-hydride complexes[11] whereas these alcohols are relatively acid-sensitive. There are several known competing transformations such as allylic substitution,[12] elimination,[13] and isomerization[14] that likely occur when iridium hydride species are involved. Additionally, the selective hydrogenation of one olefin in the presence of another olefin is still a generally unsolved but useful task.[15] Herein, we disclose the first iridium-catalyzed KR of racemic secondary and tertiary allylic alcohols via asymmetric hydrogenation.

Results and discussion

We began our investigation using racemic allylic alcohol **1a** and the Ir-N,P thiazole-based catalyst **A** in the screening (Table 1). Preliminary results obtained without an additive (entry 1) showed the allylic alcohol was hydrogenated in high conversion (89%) under 1 bar of H_2 and 0.5% catalyst loading and the remaining starting material had very low *ee* (11%). When AcOH was used as the additive (entry 2), the conversion was similar (91%), and the remaining alcohol **1a** did not show any enantiomeric enrichment. These results indicated that, even in absence of an acid, the acidity of the Ir-N,P catalyst under hydrogenation conditions was sufficient to enable the process of carbocation formation. To our delight, upon addition of a small amount of base the reaction proceeded cleanly and only hydrogenated product and remaining starting material could be observed in the reaction mixture. A number of different bases were screened, either at 10 or 20 mol% loading. The use of K_3PO_4 (entry 3) provided 43% conversion and 63% *ee* of **1a**, which corresponded to kinetic resolution with a good level of selectivity (Table 1). Then KOAc was evaluated (entry 4) and even at a lower loading, it afforded a slightly better result than the previous one, increasing the selectivity of the reaction to s = 24. The use of K_2CO_3 had a significant effect and enhanced the KR performance (entry 5). With 20 mol% base a conversion slightly higher than ideal (55%) was observed, and **1a** was resolved to an excellent *ee*. This corresponded to the highest selectivity factor for this substrate (s = 26). Two other bases were screened (entries 6 and 7) and good results were obtained with regard to conversion and the s factor, however they did not outperform K_2CO_3. With the best basic additive chosen, a screening of a number of different solvents was carried out. When the reaction was run

Table.1 Development of kinetic resolution of allylic alcohol via asymmetric hydrogenation[a]



Entry	Solvent	Additive	Conv.(%)[b]	*ee* of **1a** (%)[c]	s[d]
1	Toluene	None	89(81)	11.0	1.1
2[ef]	Toluene	HOAc	91(78)	0.5	1.0
3	Toluene	K_3PO_4	43	62.5	20.5
4[f]	Toluene	KOAc	44	65.7	23.6
5	Toluene	K_2CO_3	56	94.6	25.9
6	Toluene	$KHCO_3$	54	85.5	17.2
7	Toluene	Na_2CO_3	54	89.7	21.4
8	Benzene	K_2CO_3	58	97.7	24.6
9[e]	CH_2Cl_2	K_2CO_3	55(75)	37.9	2.6
10	$PhCF_3$	K_2CO_3	50	79.0	21.4
11[fg]	Toluene	K_2CO_3	60	99.0	24.2

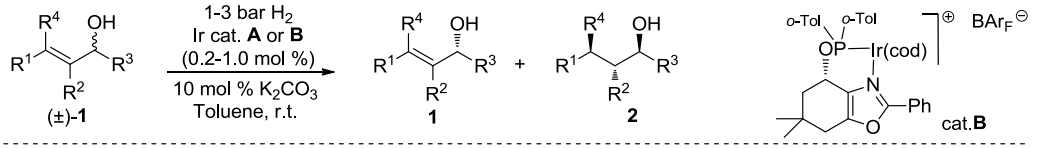
[a] Reaction conditions: (±)-**1a** (0.05 mol), 0.5 mol% catalyst and 20 mol% additive in the solvent (1.0 mL) under 1 bar H_2 at room temperature for 10 min, unless otherwise specified. [b] Conversion was determined by ^{1}H NMR spectroscopy, the combined recovery ratio of **1a** and **2a** >99%, unless specified in parentheses. [c] Enantiomeric excesses were determined by SFC analysis. [d] The selectivity factors: s = ln[(1 – conv.)(1 - *ee*)]/ln[(1 – conv.)(1 + *ee*)]. [e] 3 min reaction time. [f] 10 mol% additive. [g] 0.2 mmol scale reaction.

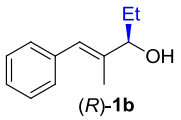
in benzene (entry 8) it gave a comparable outcome to that in toluene but the overall selectivity was not improved. The use of CH_2Cl_2 was completely detrimental to the process (entry 9): even when the reaction was stopped at 55% conversion, the remaining alcohol **1a** was present only in 38% *ee*. When α,α,α-trifluorotoluene was tested (entry 10), the system gave good selectivity (s = 21), but with lower conversion and enantiopurity of **1a** (79% *ee*). Eventually, the reaction was carried out on a preparative scale (0.2 mmol) with 10 mol% K_2CO_3 (entry 11), and gave similar selectivity to that of the smaller scale (entry 5).

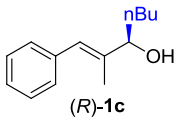
We then evaluated the allylic alcohol scope (Table 2), with a systematic study on the substitution covering a range of different functionalities. The substrates that have different substituents on the allylic position were found to be suitable candidates for the Ir-catalyzed hydrogenation/KR, and excellent *ee*s and high s values were obtained in most cases (**1b**-**f**).

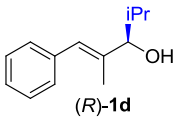
View Article Online
DOI: 10.1039/D0SC05276K

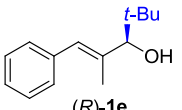
Table.2 Substrate scope[a]

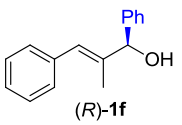


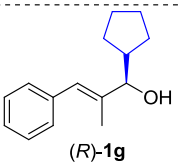

(*R*)-**1b**
99% *ee*, 41% yield
55% conv, *s* = 49

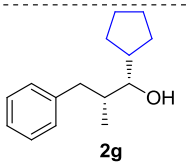

(*R*)-**1c**
99% *ee*, 40% yield
57% conv, *s* = 35

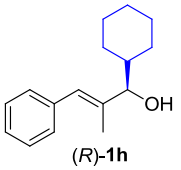

(*R*)-**1d**
99% *ee*, 41% yield
54% conv, *s* = 61

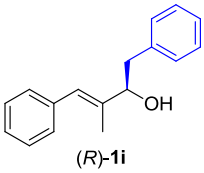

(*R*)-**1e**
99% *ee*, 47% yield[b]
52% conv, *s* = 116

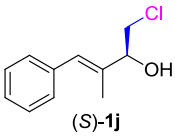

(*R*)-**1f**
99% *ee*, 37% yield
61% conv, *s* = 19

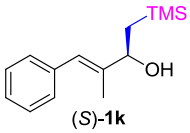

(*R*)-**1g**
89% *ee*, 47% yield
49% conv, *s* = 67

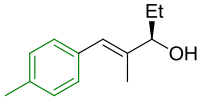

2g
46% yield
99:1 *d.r.*, 98% *ee*

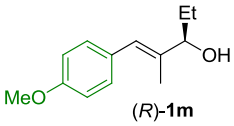

(*R*)-**1h**
99% *ee*, 45% yield
53% conv, *s* = 80

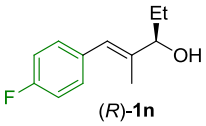

(*R*)-**1i**
98% *ee*, 46% yield
52% conv, *s* = 91

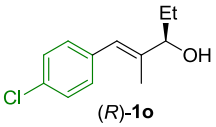

(*S*)-**1j**
99% *ee*, 40% yield
56% conv, *s* = 41

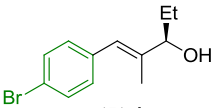

(*S*)-**1k**
87% *ee*, 45% yield[b]
49% conv, *s* = 45

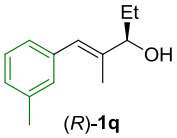

(*R*)-**1l**
99% *ee*, 40% yield
55% conv, *s* = 49

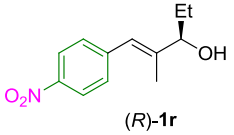

(*R*)-**1m**
99% *ee*, 39% yield
55% conv, *s* = 49

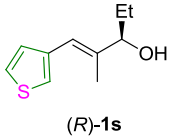

(*R*)-**1n**
99% *ee*, 40% yield
57% conv, *s* = 35

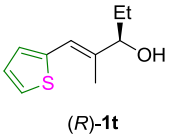

(*R*)-**1o**
99% *ee*, 44% yield
53% conv, *s* = 80

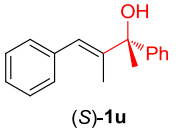

(*R*)-**1p**
99% *ee*, 44% yield
54% conv, *s* = 61

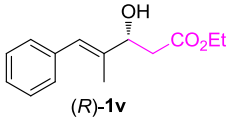

(*R*)-**1q**
99% *ee*, 43% yield
54% conv, *s* = 61

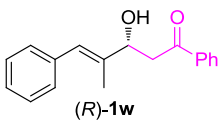

(*R*)-**1r**
95% *ee*, 40% yield
54% conv, *s* = 35

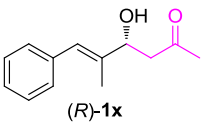

(*R*)-**1s**
99% *ee*, 44% yield
54% conv, *s* = 61

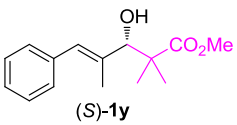

(*R*)-**1t**
94% *ee*, 45% yield
52% conv, *s* = 50

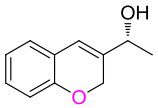

(*S*)-**1u**
98% *ee*, 35% yield[b]
63% conv, *s* = 16

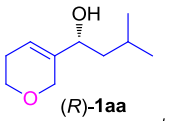

(*R*)-**1v**
99% *ee*, 40% yield
56% conv, *s* =41

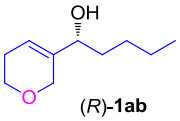

(*R*)-**1w**
93% *ee*, 42% yield
54% conv, *s* = 29

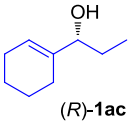

(*R*)-**1x**
89% *ee*, 45% yield
51% conv, *s* = 38

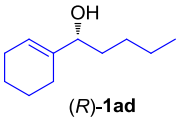

(*S*)-**1y**
99% *ee*, 47% yield
51% conv, *s* = 211

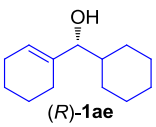

(*R*)-**1z**
89% *ee*, 42% yield[b]
56% conv, *s* = 16

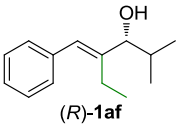

(*R*)-**1aa**
89% *ee*, 45% yield[b]
53% conv, *s* = 25

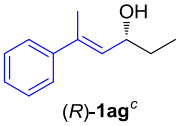

(*R*)-**1ab**
90% *ee*, 44% yield[b]
53% conv, *s* = 27

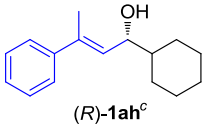

(*R*)-**1ac**
96% *ee*, 41% yield
55% conv, *s* = 32

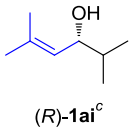

(*R*)-**1ad**
99% *ee*, 40% yield
58% conv, *s* = 31

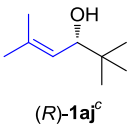

(*R*)-**1ae**
99% *ee*, 39% yield
58% conv, *s* = 31

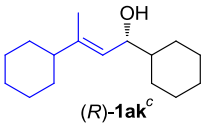

(*R*)-**1af**
96% *ee*, 35% yield
61% conv, *s* = 15


(*R*)-**1ag**[c]
92% *ee*, 40% yield
57% conv, *s* = 17


(*R*)-**1ah**[c]
99% *ee*, 30% yield
64% conv, *s* = 17


(*R*)-**1ai**[c]
91% *ee*, 42% yield
53% conv, *s* = 29


(*R*)-**1aj**[c]
96% *ee*, 43% yield
50% conv, *s* = 194


(*R*)-**1ak**[c]
96% *ee*, 36% yield
58% conv, *s* = 21

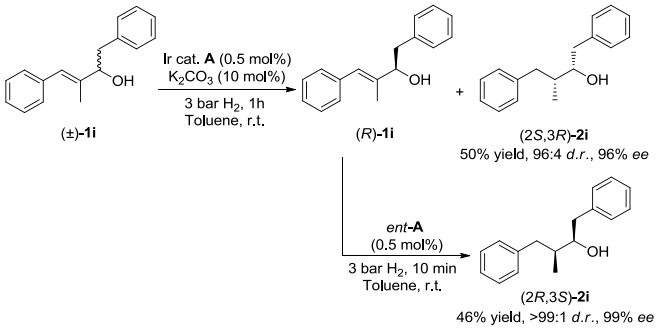
[a] Reaction conditions: (±)-substrate **1** (0.2 mmol), 0.2-1.0 mol% catalyst **A** and 10 mol% K_2CO_3 in Toluene (1.0 mL) under 1-3 bar H_2 at room temperature for 10 min-1 h, unless otherwise specified in the Supporting Information. Isolated yield. Conversion was determined by ^{1}H NMR spectroscopy. The selectivity factors: $s = \ln[(1 - \text{conv.})(1 - ee)]/\ln[(1 - \text{conv.})(1 + ee)]$. Enantiomeric excesses were determined by SFC or GC analysis. [b] Isolated as a mixture with hydrogenated product. [c] Catalyst **B** was used.

These results also indicate how steric bulk influences the catalyst in discriminating between the two enantiomers of the alcohol. The current method could be also applied in the synthesis of saturated alcohols with excellent diastereo- and

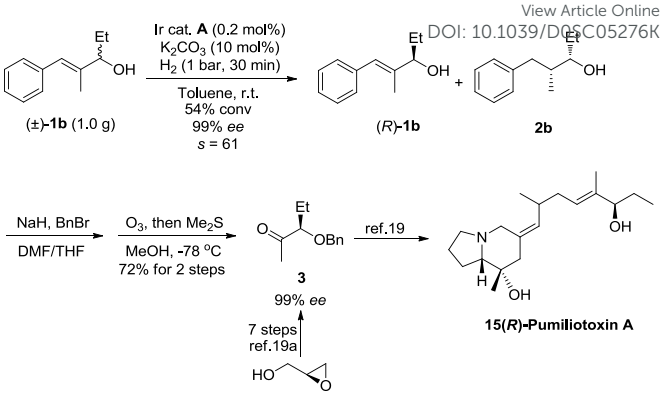
enantio-selectivity. As an illustrative example, substrate **1g** was resolved with slightly lower conversion affording the hydrogenated product **2g** in 46% isolated yield with excellent *d.r.* (99:1) and *ee* (98%). From the measurement of the optical rotation of an isolated sample of resolved compound **1b** and by comparison with literature values[16], the assigned absolute configuration for the alcohol was determined to be (*R*). The stereochemistry of the other resolved alcohols was assigned by analogy. The investigation continued with the evaluation of different functionalities (**1j**, **1k**) such as -CH_2Cl, -CH_2TMS,[17] which were well tolerated by the system and gave good selectivity.

The substrates (**1l**-**r**) bearing an electron-withdrawing group or electron-donating group at the *para* or *meta* position of phenyl ring could be successfully resolved, affording excellent *ee* for the remaining starting material. However, the *ortho*-substituted analogue of **1l** cannot be kinetically resolved, probably due to the unfavorable steric effect. Good results were also achieved for the heteroaromatic compounds **1s** and **1t** containing a thiophene ring. Surprisingly, the challenging tertiary alcohol **1u**, which was a sensitive substrate under hydrogenation conditions, could still be resolved (98% *ee*) even if at higher conversion (63%).

Next, a set of allylic alcohols with a β-carbonyl functionality were also evaluated in our KR system, given their high synthetic utility. The first substrate in this class was ethyl ester **1v**, for which the Ir-N,P catalyst accomplished efficient kinetic resolution (99% *ee*) at 56% conversion, corresponding to a high selectivity (*s* = 41). Good results were also observed in the KR of ketones **1w** and **1x**, with relatively high s factors. When the bulky alcohol **1y** was applied in this hydrogenation/KR strategy, excellent selectivity (s = 211) was obtained. Cyclic substrate **1z** with a methyl group on the allylic position also proceeded with lower selectivity (*s* = 16). Lower selectivity was encountered when manipulating the substitution on the olefin (**1af**). Several fully aliphatic allylic alcohols (**1aa**-**ae**) were tested in the method as well. To our delight, good selectivity was achieved for these substrates and good to excellent *ee* could be reached when the reaction conversion was controlled to a range of 55% to 60%. Finally, a set of β,β-substituted allylic alcohols (**1ag-1ak**) including both aromatic and pure aliphatic substrates were tested using the oxazole-type catalyst **B**, high to excellent selectivities (*s* factor up to 194) were obtained.



Scheme.1 Double stereo-differentiation.



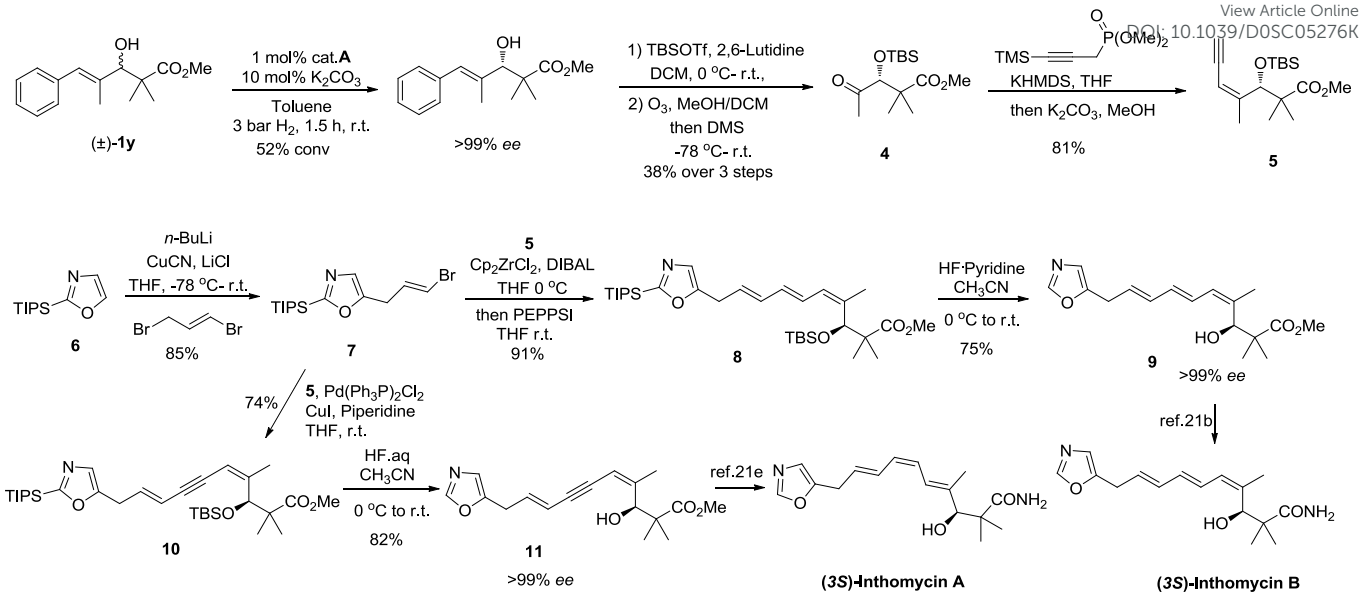
Scheme.2 Gram-scale kinetic resolution and concise synthesis of the chiral building block of 15(*R*)-Pumiliotoxin A

Different stereoisomers of a biologically active molecule can cause completely different effects in biological systems.[18] Meanwhile, the inherent problem of KR processed is the 50% maximum isolated yield. Considering the excellent enantio-discriminating ability of our catalytic system in hydrogenation of racemic allylic alcohols, to make full use of the starting materials we continued to explore its double stereo-differentiation potential, which could provide both enantiomers of saturated secondary alcohol **2i** bearing two contiguous chiral centers (Scheme 1). The resolved alcohol *(R)*-**1i** was subjected to the secondary hydrogenation using the catalyst *ent*-**A** without any additive under 3 bar of hydrogen for 10 minutes, affording the saturated alcohol *(2R,3S)*-**2i** with excellent diastereo- and enantioselectivity (> 99:1 *d.r.*, 99% *ee*). Starting from racemic allylic alcohol **1i**, the combined hydrogenations afforded clean reactions with 96% overall yield of the two separated enantiomers.

In order to demonstrate the utility of this approach, we have performed a gram-scale kinetic resolution of allylic alcohol **1b** with 0.2 mol% catalyst loading under 1 bar hydrogen pressure for 30 minutes, and the resolved allylic alcohol was obtained with 99% *ee* at 54% conversion (Scheme 2). The reaction mixture was benzylated and underwent ozonolysis to yield methyl ketone **3**, which was previously synthesized in 7 steps from glycidol[19a] and is a key intermediate for the total synthesis of pharmacologically active dendrobatid alkaloid pumiliotoxin A.[19b]

Encouraged by the above success, we then turned our attention to the synthesis of the natural products inthomycin A and B with our new method as a key step (Scheme 3). The inthomycins, a small family of polyene natural products were first isolated from *Streptomyces sp.*[20] have attracted considerable attention from synthetic chemists[21] due to their unique structural features and interesting bioactivities.[22] Our synthesis began with KR of racemic alcohol **1y**, which already showed excellent level of selectivity in small scale affording the resolved alcohol with over 99% *ee* at 52% conversion (*s*> 100). Subsequent TBS protection and ozonolysis delivered the enantioenriched ketone **4** in 38% overall yield from the beginning. Surprisingly, the Horner-Wadsworth-Emmons

View Article Online
DOI: 10.1039/D0SC05276K



Scheme.3 Enantioselective formal total synthesis of Inthomycin A and B.

reaction of methyl ketone **4** with dimethyl 3-trimethylsilylpropynyl phosphonate[23] followed by a deprotection of TMS afforded the *Z*-enyne **5** in an 81% yield with an unprecedented exclusive stereoselectivity.

Separately, lithiation of TIPS protected oxazole **6**[21g] followed by allylation at *C*-5 position to give the vinyl bromide **7** in high yield. With **5** and **7** in hand, then we turned to the coupling of two fragments according to the the geometry of the target inthomycins. Firstly, by using of a modification of Negishi's method,[24] enyne **5** was subjected to hydrozirconation and then coupling with **7** to give the triene **8** in good yield with excellent stereoselectivity. After the desilylation of **8**, we achieved the formal total synthesis of (*3S*)-inthomycin B by obtaining the reported alcohol **9**[21b,c] with over 99% *ee*. On the other hand, fragments **5** and **7** can be directly conected by a Sonogashira cross-coupling to afford intermediate **10**, which was further converted to alcohol **11**[21e] after deprotection. Over 99% *ee* was also achieved for alcohol **11** and this constitutes a formal enantioselective synthesis of inthomycin A. This synthetic sequence provides one of the most efficent routes to the inthomycins, with remarkable selectivity.

To rationalize the origin of the enantio-discrimination, the

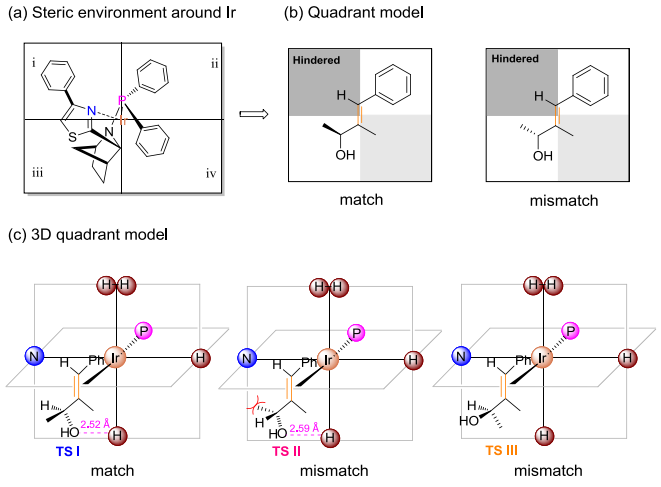


Fig. 2 Origin of selectivity depicting: (a) Steric environment around Ir. (b) Quadrant model illustrating the matched and mismatched allylic alcohol. (c) 3D quadrant model.

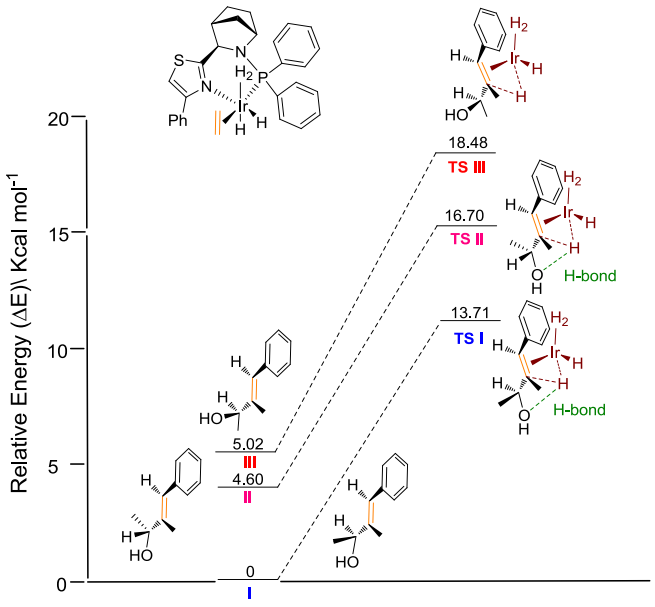


Fig. 3 Calculated relative energy profile

quadrant model analysis correlated with preliminary density functional theory (DFT) studies were performed (Fig. 2).[25,10] According to the previously developed quadrant model, the iridium coordination sphere was divided into four planar quadrants basing on the calculated catalyst structure. When the olefin substrate was fitted into this model (Fig. 2b), the smallest substituent (H atom) always occupies the most hindered quadrant, resulting a fixed conformation for the transition state. As shown in the three-dimensional quadrant model (Fig. 2c), a possible hydrogen bonding interaction between the hydroxyl group and the axial iridium hydride may facilitate the enantio-discrimination, since the corresponding calculated distance is around 2.5 Å for both enantiomers.

Further relative energy calculations for the possible transition states were conducted (Fig. 3). For transition state **TS I** of the matched enantiomer (*S*)-**1a**, the hydrogen bonding interaction leads to a conformation with the methyl group at the carbinol pointing away from the ligand backbone. In contrast, the hydrogen bonding in transition state **TS II** of the matched enantiomer (*R*)-**1a** resulting in the methyl group pointing forward to the ligand backbone, which is not favored for steric reason. The cost of this steric clash resulted in a 3.0 Kcal/mol difference in energy for the two transition states. This result also indicates that substrate with bulkier substituent would give better selectivity, which is consistent with the experimental finding. Another possible transition state **TS III** for the mismatched enantiomer, which adopts a less steric hindered manner of coordination with the catalyst by breaking the hydrogen bond, resulting in an even higher energy barrier. Additionally, absolute configurations of the recovered allylic alcohols obtained are in agreement with the theoretical prediction.

Conclusions

To summarize, we have developed an efficient kinetic resolution protocol for a variety of trisubstituted allylic alcohols by means of Ir-N,P-catalyzed asymmetric hydrogenation. High selectivity factors were observed with this methodology, and they compare well with those reported for other KR systems, especially taking into consideration the mild reaction conditions, short reaction times and operational simplicity. The utility of this strategy is illustrated by the concise formal synthesis of bioactive 15(*R*)-Pumiliotoxin A, (3*R*)-Inthomycin A and B. DFT calculations and quadrant model analysis indicated that a medium strong hydrogen bonding between the alcohol and the iridium center being responsible for the selectivity. This kinetic resolution of diverse allylic alcohols via asymmetric hydrogenation provides new and exciting opportunities for enantioselective synthesis.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

View Article Online
DOI: 10.1039/D0SC05276K

The authors are grateful to the Swedish Research Council (VR), the Knut och Alice Wallenberg Stiftelsen for funding this research. J.J. thanks the Chulabhorn Graduate Institute, Chulabhorn Royal Academy, Thailand for an exchange scholarship to Stockholm University. T.S. acknowledges the NRF South Africa for the Post-PhD Track Thuthuka Grant. All computations were carried out using the computational cluster resources at the National Supercomputer Centre based at Linkoping University, Sweden and at the Center for High Performance Computing, South Africa.

Notes and references

1 For recent reviews, see: (a) E. Skucas, M.-Y. Ngai, V. Komanduri, M. J. Krische, *Acc. Chem. Res.* 2007, **40**, 1394. (b) H. Jiang, N. Holub, K. Anker Jørgensen, *Proc. Natl. Acad. Sci. U. S. A.* 2010, 107, 20630. (c) A. Lumbroso, M. L. Cooke, B. Breit, *Angew. Chem. Int. Ed.* 2013, ***52***, 1890.

2 M. Breuer, K. Ditrich, T. Habicher, B. Hauer, M. Keßeler, R. Stürmer, T. Zelinski, *Angew. Chem. Int. Ed.* 2004, **43**, 788.

3 For reviews, see: (a) T. Ayad, P. Phansavath and V. Ratovelomanana-Vidal, *Chem. Rec.* 2016, **16**, 2754. (b) X. Cui, K. Burgess, *Chem. Rev.* 2005, **105**, 3272. (c) C. Margarita, P. G. Andersson, *J. Am. Chem. Soc.* 2017, **139**, 1346. (d) J. J. Verendel, O. Pàmies, M. Diéguez, P. G. Andersson, *Chem. Rev.* 2014, **114**, 2130. (e) W. Tang, X. Zhang, *Chem. Rev.* 2003, **103**, 3029. (f) J.-H. Xie, S.-F. Zhu, Q.-L. Zhou, *Chem. Rev.* 2011, **111**, 1713. (g) S. J. Roseblade, A. Pfaltz, *Acc. Chem. Res.* 2007, **40**, 1402.

4 For a review, see (a) M. M. Heravi, T. B. Lashaki, N. Poorahmad, *Tetrahedron: Asymmetry* 2015, **26**, 405. For some recent synthetic examples, see: (b) H. Li, S.-J. Shen, C.-L. Zhu, H. Xu, *J. Am. Chem. Soc.* 2018, **140**, 10619. (c) D. Katsumi, K. Nakasone, N. Terayama, E. Yasui, M. Mizukami, M. Miyashita, S. Nagumo, *J. Org. Chem.* 2019, **84**, 1553. (d) L. Jeanne-Julien, G. Masson, E. Astier, G. Genta-Jouve, V. Servajean, J.-M. Beau, S. Norsikian, E. Roulland, *Org. Lett.* 2017, **19**, 4006. (e) M. Kanto, M. Sasaki, *Org. Lett.* 2016, **18**, 112. (f) B. Seetharamsingh, P. R. Rajamohanan, D. S. Reddy, *Org. Lett.* 2015, **17**, 1652. (g) S. Tang, Y.-L. Deng, J. Li, W.-X. Wang, G.-L. Ding, M.-W. Wang, Z.-P. Xiao, Y.-C. Wang, R.-L. Sheng, *J. Org. Chem.* 2015, **80**, 12599. (h) Y.-G. Wang, R. Takeyama, Y. Kobayashi, *Angew. Chem. Int. Ed.* 2006, **45**, 3320.

5 (a) J. C. Ruble, H. A. Latham, G. C. Fu, *J. Am. Chem. Soc.* 1997, **119**, 1492. (b) E. Vedejs, X. Chen, *J. Am. Chem. Soc.* 1996, **118**, 1809. (c) S. Bellemin-Laponnaz, J. Tweddell, J. C. Ruble, F. M. Breitling, G. C. Fu, *Chem. Comm.* 2000, **12**, 1009.

6 M. Kitamura, I. Kasahara, K. Manabe, R. Noyori, H. Takaya, *J. Org. Chem.* 1988, **53**, 708.

7 X.-H. Yang, K. Wang, S.-F. Zhu, J.-H. Xie, Q.-L. Zhou, *J. Am. Chem. Soc.* 2014, **136**, 17426.

8 (a) H. Fernández-Pérez, A. Vidal-Ferran, *Org. Lett.* 2019, **21**, 7019. (b) J. R. Lao, H. Fernández-Pérez, A. Vidal-Ferran, *Org. Lett.* 2015, **17**, 4114.

9 For selected examples, see: (a) K. Källström, C. Hedberg, P. Brandt, A. Bayer, P. G. Andersson, *J. Am. Chem. Soc.* 2004, **126**, 14308. (b) P. Cheruku, J. Diesen, P. G. Andersson, *J. Am. Chem. Soc.* 2008, **130**, 5595. (c) A. Paptchikhine, P. Cheruku, M. Engman, P. G. Andersson, *Chem. Comm.* 2009, **40**, 5996. (d) J. J. Verendel, T. Zhou, J.-Q. Li, A. Paptchikhine, O. Lebedev, P. G. Andersson, *J. Am. Chem. Soc.* 2010, **132**, 8880.

(e) B. K. Peters, J. Liu, C. Margarita, W. Rabten, S. Kerdphon, A. Orebom, T. Morsch, P. G. Andersson, *J. Am. Chem. Soc.* 2016, **138**, 11930. (f) J. Liu, S. Krajangsri, J. Yang, J.-Q. Li, P. G. Andersson, *Nat. Catal.* 2018, **1**, 438. (g) S. Ponra, W. Rabten, J. Yang, H. Wu, S. Kerdphon, P. G. Andersson, *J. Am. Chem. Soc.* 2018, **140**, 13878. (h) S. Kerdphon, S. Ponra, J. Yang, H. Wu, L. Eriksson, P. G. Andersson, *ACS Catal.* 2019, **9**, 6169.

10 J.-Q. Li, J. Liu, S. Krajangsri, N. Chumnanvej, T. Singh and P. G. Andersson, *ACS Catal.* 2016, **6**, 8342.

11 (a) R. G. Pearson, *Chem. Rev.* 1985, **85**, 41. (b) G. Jia, C.-P. Lau, *Coord. Chem. Rev.* 1999, **190-192**, 83. (c) Y. Zhu, Y. Fan, K. Burgess, *J. Am. Chem. Soc.* 2010, **132**, 6249. (d) Y. Zhu, K. Burgess, *Adv. Syn. Catal.* 2008, **350**, 979. (e) Y. Zhu, K. Burgess, *RSC Adv.* 2012, **2**, 4728.

12 For some reviews, see: (a) J. F. Hartwig, M. J. Pouy, in *Iridium Catalysis* (Ed.: P. G. Andersson), Springer Berlin Heidelberg, Berlin, Heidelberg, 2011, pp. 169-208. (b) J. Qu, G. Helmchen, *Acc. Chem. Res.* 2017, **50**, 2539. (c) Q. Cheng, H.-F. Tu, C. Zheng, J.-P. Qu, G. Helmchen, S.-L. You, *Chem. Rev.* 2019, **119**, 1855.

13 H. Li, D. Fiorito, C. Mazet, *ACS Catal.* 2017, **7**, 1554.

14 (a) E. Erbing, A. Vázquez-Romero, A. Bermejo Gómez, A. E. Platero-Prats, F. Carson, X. Zou, P. Tolstoy, B. Martín-Matute, *Chem. Eur. J.* 2016, **22**, 15659. (b) H. Li, C. Mazet, *Acc. Chem. Res.* 2016, **49**, 1232. (c) J.-Q. Li, B. Peters, P. G. Andersson, *Chem. Eur. J.* 2011, **17**, 11143.

15 (a) J. Liu, S. Krajangsri, T. Singh, G. De Seriis, N. Chumnanvej, H. Wu, P. G. Andersson, J *J. Am. Chem. Soc.* 2017, **139**, 14470. (b) C. Margarita, W. Rabten, P. G. Andersson, *Chem. Eur. J.* 2018, **24**, 8022.

16 (a) S. Duce, M. Jorge, I. Alonso, J. L. G. Ruano, M. B. Cid, *Eur. J. Org. Chem.* 2013, **2013**, 7067. (b) L. Pisani, S. Superchi, A. D'Elia, P. Scafato, C. Rosini, *Tetrahedron* 2012, **68**, 5779.

17 S. Krajangsri, H. Wu, J. Liu, W. Rabten, T. Singh and P. G. Andersson, *Chem. Sci.* 2019, **10**, 3649.

18 S.-L. Shi, Z. L. Wong, S. L. Buchwald, *Nature* 2016, **532**, 353.

19 (a) S. Aoyagi, S. Hirashima, K. Saito, C. Kibayashi, *J. Org. Chem.* 2002, **67**, 5517. (b) N.-H. Lin, L. E. Overman, M. H. Rabinowitz, L. A. Robinson, M. J. Sharp, J. Zablocki, *J. Am. Chem. Soc.* 1996, **118**, 9062.

20 T. Henkel, A. Zeeck, *Liebigs Ann. Chem.* 1991, **1991**, 367.

21 Two racemic and two enantioselective reported routes for synthesis of inthomycin A, three reported enantioselective routes for synthesis of inthomycin B, for details see: (a) N. Hénaff, A. Whiting, *Org. Lett.* 1999, **1**, 1137. (b) M. Yoshino, K. Eto, K. Takahashi, J. Ishihara, S. Hatakeyama, *Org. Bio. Chem.* 2012, **10**, 8164. (c) M. R. Webb, C. Donald, R. J. K. Taylor, *Tetrahedron Lett.* 2006, **47**, 549. (d) M. R. Webb, M. S. Addie, C. M. Crawforth, J. W. Dale, X. Franci, M. Pizzonero, C. Donald, R. J. K. Taylor, *Tetrahedron* 2008, **64**, 4778. (e) M. Kumar, L. Bromhead, Z. Anderson, A. Overy, J. W. Burton, *Chem. Eur. J.* 2018, **24**, 16753. (f) B. K. Senapati, L. Gao, S. I. Lee, G.-S. Hwang, D. H. Ryu, *Org. Lett.* 2010, **12**, 5088. (g) S. Balcells, M. B. Haughey, J. C. L. Walker, L. Josa-Culleré, C. Towers, T. J. Donohoe, *Org. Lett.* 2018, **20**, 3583. (h) K. J. Hale, M. Grabski, S. Manaviazar, M. Maczka, *Org. Lett.* 2014, **16**, 1164.

22 (a) Y. Tanaka, I. Kanaya, Y. Takahashi, M. Shinose, H. Tanaka, S. Omura, *J. Antibiot.* 1993, **46**, 1208. (b) S.Omura, *Gene* 1992, **115**, 141. (c) M. Kawada, H. Inoue, I. Usami, D. Ikeda, *Cancer Sci*. 2009, **100**, 150. (d) M. Kawada, Y. Yoshimoto, K. Minamiguchi, H. Kumagai, T. Someno; T. Masuda, M. Ishizuka, D. Ikeda, *Anticancer Res.* 2004, **24**, 1561.

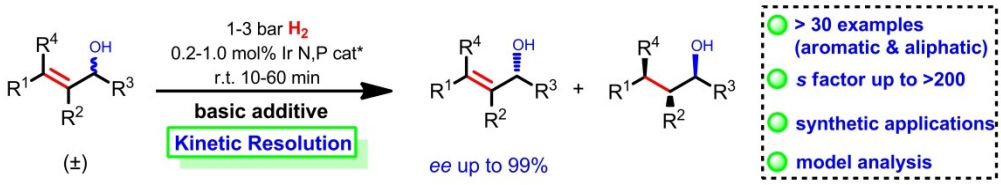
23 A. W. Gibson, G. R. Humphrey, D. J. Kennedy, S. H. B. Wright, *Synthesis* 1991, **1991**, 414.

24 G. Wang, S. Mohan, E.-i. Negishi, *Proc. Natl. Acad. Sci. U. S. A.* 2011, **108**, 11344.

25 T. L. Church, T. Rasmussen, P. G. Andersson, *Organometallics* 2010, **29**, 6769.

View Article Online
DOI: 10.1039/D0SC05276K

View Article Online
DOI: 10.1039/D0SC05276K



1275x235mm (96 x 96 DPI)