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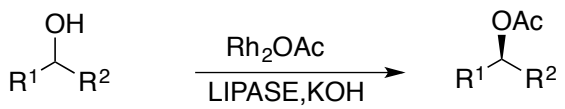
Iridium-Catalyzed Asymmetric Hydrogenation of Allylic Alcohols via Dynamic Kinetic Resolution

Jianguo Liu[1], Suppachai Krajangsri[1], Jianping Yang[1], Jia-Qi Li[2] and Pher G. Andersson[1]*

Dynamic kinetic resolutions (DKRs) allow for the conversion of both enantiomers of starting material into a single enantiomer of product, thereby avoiding the 50% yield limit in traditional kinetic resolutions. As such, transition metal catalysed variants have become an important and useful method in asymmetric synthesis. Here we report an asymmetric hydrogenation of allylic alcohols using an Ir-N, P ligand complex via DKR. In contrast to the many dynamic kinetic resolutions involving carbonyl reduction, this methodology allows for DKR during alkene reduction. Mechanistic studies support the hypothesis that racemization of the substrate is achieved by cleavage and reforming of the oxygen-carbon bond. Under the cooperative dynamic kinetic asymmetric hydrogenation, a broad range of chiral alcohols containing two stereogenic centres were produced in excellent diastereoselectivities (up to 95:5) and enantioselectivities (up to 99% ee).

Dynamic kinetic resolution (DKR) has been established as an extremely valuable method in asymmetric synthesis, because both enantiomers of a racemic substrate are converted into a single enantioenriched product. This strategy thus overcomes the limitation of a maximum theoretical yield of 50% inherent in traditional kinetic resolutions[1-3]. These stereo-convergent processes require either a rapid racemization of the substrate or conversion of the racemic substrate to an achiral intermediate, before the enantio-determining step and, as a result, an efficient DKR can theoretically produce the desired products in quantitative yields [4, 5]. The main challenge however in carrying out an efficient DKR is finding conditions capable of racemizing the substrate that do not adversely affect the resolution or interfere with the chiral integrity of the product[6].

a



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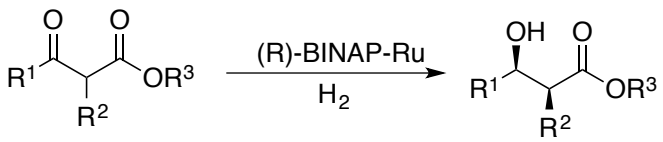

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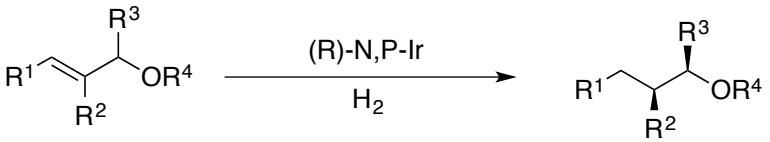

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Fig. 1 Dynamic Kinetic Resolution using catalysts and enzymes. a, DKR of secondary alcohols using combined enzyme and metal catalyst. b, DKR of β -keto ester using asymmetric hydrogenation. c, This work.

In the last few decades, enzymatic [7,8],organocatalyzed[9], and transition metal-catalyzed DKR[10,11], as well as many others [8,12], have been extensively reviewed. Transition metal-catalyzed racemization coupled with enzymatic resolution has become an important method in the DKR process[13]. Initial work in the field was carried out using Shvo's catalyst[14]. In the mid-1990s, the groups of Willams'[15] and Bäckvall[16] separately modified Shvo's catalyst and created efficient racemization pathways for secondary alcohols.

Generally, DKR relies on the combination of a racemization of a stereogenic centre in the substrate with a stereospecific reaction that selectively converts one of the enantiomers of the substrate into an enantiomerically enriched product (Fig. 1a).

There are some examples of DKR where a racemic substrate with one stereogenic centre is deracemized in concert with the construction of an additional chiral centre[4, 17-26]. In theory, this system can transform a starting material containing one prochiral functionality and a racemic, chiral centre into a product containing two chiral, non-racemic centres.

Catalytic asymmetric hydrogenation of configurationally labile substrates, such as β-keto esters, has proven to be a highly efficient method to simultaneously create two or more stereogenic centres in a single synthetic step[17-20].Noyori and co-workers were the first to investigate this phenomenon in a pioneering work in 1989 (Fig. 1b)[4]. They reported on the stereoselective hydrogenation of 2-substituted 3-oxo carboxylic esters *via* DKR using a chiral Ru-BINAP complex. The product was obtained in excellent diastereoselectivity and enantioselectivity. The substrate scope of asymmetric hydrogenation via DKR has been expanded to α-substituted ketones[21] and α-substituted β-keto esters[22], α-substituted β-keto phosphonates[23] and sulfones[24], cyclic ketones [25], and imine derivatives[26]. This interesting and useful method requires the substrate to have an acidic hydrogen at the carbon to be racemized and the racemization is effectuated by addition of relatively strong bases which are compatible with the Ru- and Rh-based hydrogenation catalysts. The stereoselective outcome using Rh- and Ru-catalysts has been explained by using transition-state molecular chelation-controlled model[27-29].

In the last few decades, the use of iridium catalysts in the asymmetric hydrogenation of alkenes has attracted much attention and the substrate scope has also extended to substrates bearing little or no functionality[30]. The coordinating functional group effect in the hydrogenation process has been studied by

several groups[31-33]. Alkenes bearing Lewis basic substituents can coordinate to Ir, and this effect may influence the performance of catalysts in the hydrogenation process. Crabtree's iridium catalyst with monodentate phosphine and pyridine ligands showed a high tendency to coordinate to alcohol groups in the substrate resulting in highly diastereoselective hydrogenations[34]. However, for bulky, bidentate chiral N,P-ligand iridium complexes normally used in asymmetric versions of the reaction, there exists no clear evidence for any stereo-directing coordination in asymmetric hydrogenations. Burgess and co-workers[32] conducted experimental work and computational studies. They found that a 2-substituted allylic alcohol (2-methylbut-2-en-1-ol) did not coordinate to iridium. Recent studies by Pfaltz[33] did not provide any evidence for strong coordination between the hydroxyl group and Ir.

Here, we present an iridium-catalyzed asymmetric hydrogenation of allylic alcohols via a DKR process – a rare example of DKR during alkene reduction. Notably, this protocol is operated under very mild conditions with excellent diastereoselectivity (*dr*) and enantioselectivity (*ee*) being obtained (up to 95/5 *dr*, 99% *ee*). Initial mechanistic studies support a racemization mechanism involving cleavage of the hydroxyl carbon-oxygen bond.

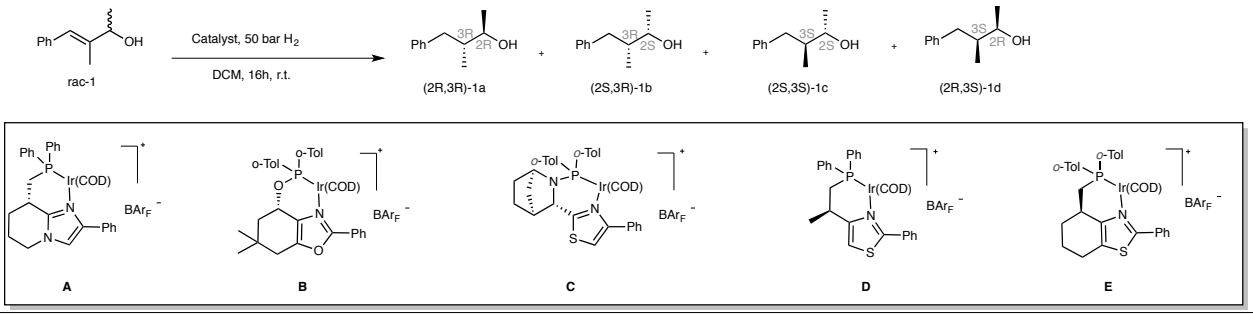
Results

Reaction development and optimization

Our initial study began with secondary allylic alcohol *rac*-**1** (Table 1). Hydrogenation of this alcohol using Pd/C catalyst yielded four diastereomers which were separated by chiral GC and assigned their absolute configuration by independent synthesis and comparison to results reported in literature (entry 1)[35]. *Surprisingly, when substrate **1** was hydrogenated using an iridium catalyst, the product was obtained in both high enantioselectivity and good diastereoselectivity (entry 2).* The starting material (Rac)-**1** (entries 1 and 2) is racemic and contains 50% of (*S*)-**1** and 50% of (*R*)-**1. Hence,** the combined yield of the diastereomeric pairs (**1a** + **1d)** and (**1b** + **1c)** should be 50% ecch. However, in the asymmetric hydrogenation of (*Rac*)-**1** (entry 2), a combined yield of over 70% was obtained for **1b** and **1c**. To understand this observation, we carried out the following experiment: enantiomerically pure (*S*)-**1** and (*R*)-**1** isomers were prepared and then separately hydrogenated using the same reaction conditions. For the (*S*)-**1** isomer only one saturated allylic alcohol **1b** was obtained in excellent yield and enantioselectivity (entry 3). The (*R*)-**1** isomer (entry 4) was had a total yield of

65% for **1a** and **1d** was obtained. Interestingly, we found that over 30% of the stereochemically inverted product, **1b** was also isolated. The most plausible reason for these observations is that the secondary allylic alcohol (*R*)-**1** underwent a certain degree of racemization at the C2 position thus producing (*S*)-**1** during the hydrogenation process. Motivated by these observations, we commenced our investigation by examining the dynamic kinetic resolution hydrogenation (DKRAH) of allylic racemic alcohol **1** using iridium catalysts. The key results of the initial optimization of the reaction conditions are summarized in Table 1. A catalyst screening established complex **C** to be an efficient and stereoselective catalyst for this reaction. A solvent screening verified that toluene was the preferred solvent since it yielded **1d** with an enhanced diastereomeric ratio and enantioselectivity (Table 1, entry 7) when compared to benzene (Table 1, entry 6). The hydrogen pressure also significantly affected the reaction significantly. Decreasing the pressure from 50 bar to 3 bar of H_2 improved both the dr and ee of **1d** (Table 1, entries 7 and 8). Furthermore, addition of a small amount (10 mol%) of acetic acid delivered the best results giving high stereo-selectivity, with a *dr* of 97/3 and an excellent enantioselectivity of 98% (entry 9).

Table 1 Initial study of asymmetric hydrogenation of allylic alcohols via dynamic kinetic resolution [a]



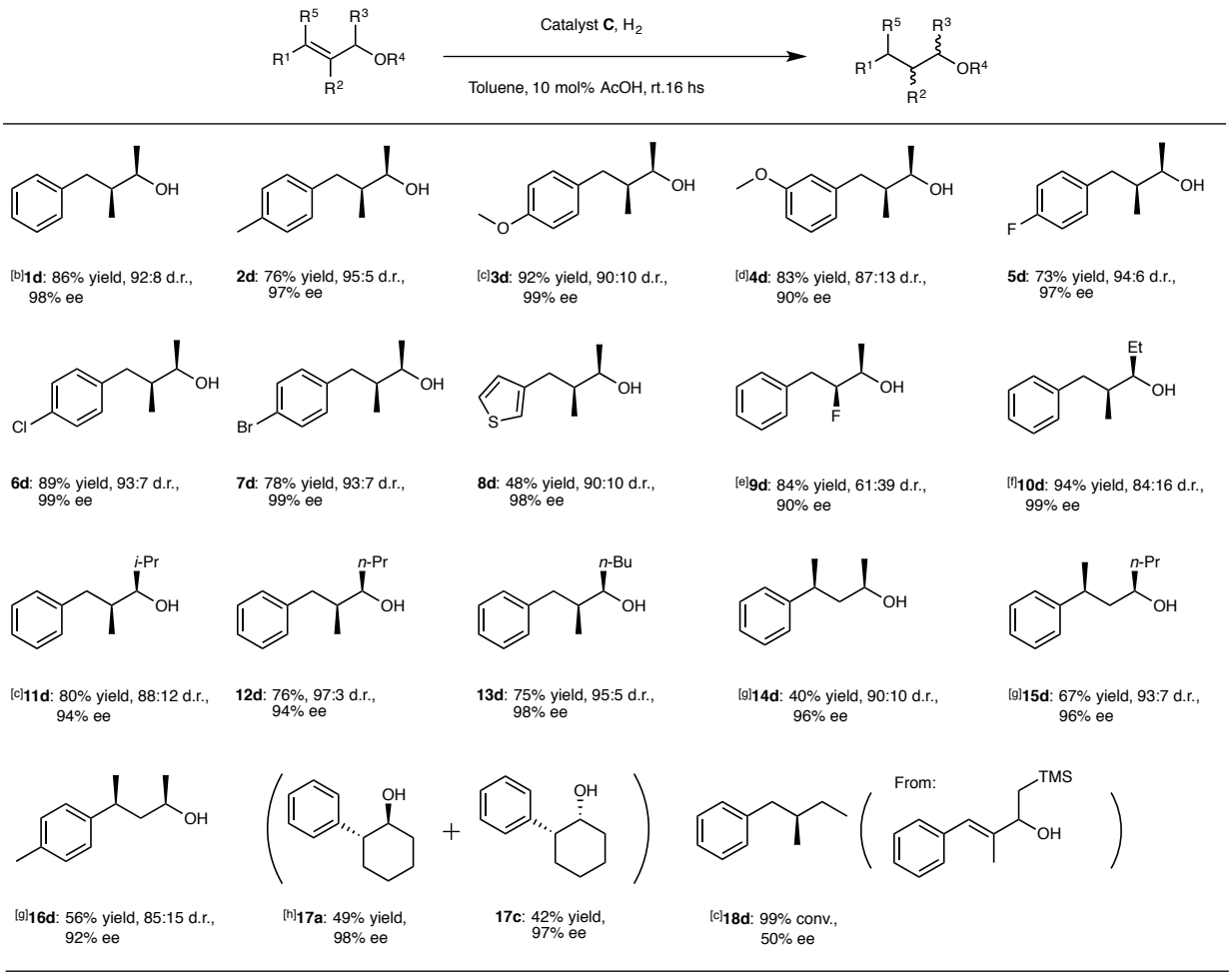
Entry	Substrate	Catalyst	Additive	Solvent	Pressure(bar)	Product distribution[b] %				dr (1b+1d)/(1a+1c)	ee (1b-1d)/(1b+1d)
						(2R,3R)-1a	(2S,3R)-1b	(2S,3S)-1c	(2R,3S)-1d		
1	rac-1	**Pd/C**	—	DCM	50	23	25	26	26	51/49	0
2	rac-1	**A**	--	DCM	50	13	73	0	14	87/13	68
3	(S)-1	**A**	--	DCM	50	0	99	0	0	99/1	99
4	(R)-1	**A**	--	DCM	50	55	35	0	10	45/55	56
5	rac-1	**C**	--	DCM	50	0	5	38	57	62/38	84
6	rac-1	**C**	--	Benzene	50	0	4	35	61	65/35	88
7	rac-1	**C**	--	Toluene	50	0	3	24	73	76/24	92
8	rac-1	**C**	--	Toluene	3	0	1	10	89	90/10	97
9	rac-1	**C**	10 mol% AcOH	Toluene	3	0	1	3	96	97/3	98

[a] Reaction conditions: 0.03 mmol of substrate, 1 mol% catalyst, 1 mL solvent, 16 h, r.t. [b] Determined and calculated by chiral GC/MS using chiral stationary phases, CHIRALDEX B-DM Capillary GC column (see the supporting information for details).

Scope of the reaction

With the optimal reaction conditions established, the scope of the DKRAH of allylic alcohols was investigated. First, the electronic effect of the aromatic ring having different substituents including electron donating and electron withdrawing groups at the *meta* and *para* positions were examined. Good results were obtained for the *p*-methyl substituent product **2d** with an isolated yield of 76% and high *dr* and *ee* of, 95/5 (syn/anti) and 97%, respectively. For the strongly electron donating OMe group, at the *para* position, the yield increased to 92% with high *dr* (90/10) and excellent *ee* (99%) (**3d**). Similar results were obtained for the substrate bearing the OMe substituent at the *m*-position. Substrates containing the *p*-halogenated substituents were converted smoothly to the desired products **5d - 7d** in good yields and excellent *dr*s and *ee*s. Replacement of the phenyl ring with a thiophene moiety, resulted in a decrease in the yield to 48% however the high *dr* (90/10) and *ee* (98%), were maintained (**8d**). The effect of a substituent at the β-position was also investigated. Interestingly, a substrate bearing fluorine at the β-position could tolerate the reaction conditions and gave the desired product **9d** in good yield (84%), moderate *dr* and high *ee*. The effect of changing the substituent at the α-position was also investigated. As the α-substituent changed from ethyl, isopropyl, *n*-propyl to *n*-butyl, the DKR hydrogenation continued to furnish the product in good yields as well as excellent stereoselectivities (**10d** – **13d**).

Table 2 Substrate scope [a]



[a] Reaction conditions: 0.52 mmol of substrate, 1 mol% catalyst, 15 mL Toluene, 3 bar H_2, 10 mol% AcOH, 16 h, r.t., unless stated otherwise in the supporting information; isolated yield; d.r. was determined by ^{1}H NMR spectroscopy of the isolated product; *ee* was determined by chiral GC/MS or SFC using chiral stationary phases (see the supporting information for details). [b] Absolute configuration was assigned based on literature.[36] [c] 0.14 mmol of substrate, no AcOH. [d] 0.14 mmol of substrate. [e] No AcOH. [f] 5 bar H_2, no AcOH. [g] Catalyst **B** was used, 10 bar of H_2, no AcOH. [h] Catalyst **E** was used, 50 bar of H_2, no AcOH.

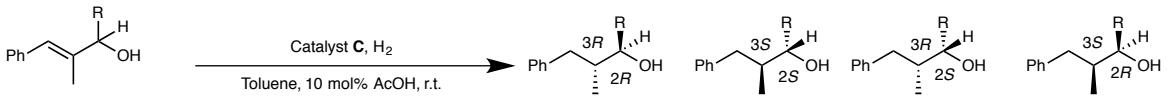
The geometry of the olefin also plays a significant role in the asymmetric hydrogenation in terms of reactivity and stereoselectivity. Asymmetric dynamic kinetic hydrogenation of γ,γ-disubstituted and cyclic allylic alcohols turned out to be more difficult than the β,β disubstituted substrates as presented in Table 2. Catalyst **B** proved to give the best results for γ,γ-disubstituted substrates (**14-16d**). The syn product was obtained in moderate isolated yields but in high dr and ee. The cyclic substrate **17** underwent hydrogenation to give the product in excellent yield. However, with this substrate no racemization was observed. Instead a highly stere-

ospecific hydrogenation took place and both enantiomers of the substrate was hydrogenated from the same prochiral face of the olefin giving a 1:1 ratio of diastereomers in 98 and 97% *ee*. Finally, substrate **18** containing a TMS group was evaluated. This substrate most likely underwent an acid catalyzed Peterson elimination under the hydrogenation conditions to give a 1,3-diene that was further hydrogenated into the alkane **18d**.

Mechanistic study

In order to understand the mechanism of this reaction several experiments were carried out on enantiomerically pure substrates and are presented in Table 3. The isomers (*R*)-**1** and (*R*)-**11** were both hydrogenated with full conversion to give only **1d** and **11d** products in a very fast reaction that was complete in 3 minutes. For the enantiomeres (*S*)-**1** and (*S*)-**11**, a much longer reaction time was required and led to a mixture of products. In these reactions an isomerization took place and the main products **1d** and **11d** were obtained in 89% and 87% respectively (Table 3, column 8, entries 3 and 4). These results suggest that one of the two enantiomeric forms of the alcohol substrate match the catalyst, ((*R*)-**1** and (*R*)-**11**) and results in a clean and fast hydrogenation giving a single stereoisomer of the product. The other enantiomer of the substrate ((*S*)-**1** and (*S*)-**11**) results in a mis-match and does not undergo hydrogenation as easily. In this case the substrate must first isomerize into the matched (*R*)-**1** or (*R*)-**11** before it is hydrogenated. In order to see if the isomerization resulted from a redox mechanism in which the two enantiomeric alcohols are in equilibrium *via* the corresponding ketone or other type of racemization,[37,38] an experiment was attempted using the ketone **19** as starting material. In this reaction the ketone functionality remained in the product and in addition, the stereogenic centre formed had the opposite absolute configuration as observed in the dynamic kinetic resolution of the alcohol.

Table 3 Mechanistic studies

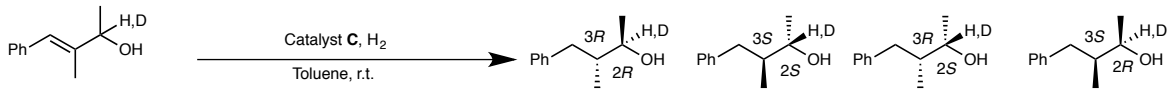


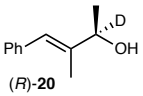
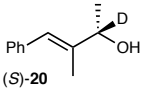
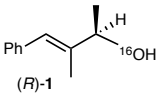
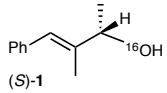
Entry[a]	Substrate	Time	% Conv.[b]	Product distribution[c]				
				(2*R*,3*R*)	(2*S*,3*S*)	(2*S*,3*R*)	(2*R*,3*S*)	
1	(*R*)-**1**	3 min	99	0	0	0	99	--
2[d]	(*R*)-**11**	3 min	99	0	0	0	99	--
3[e]	(*S*)-**1**	16 h	99	1	5	5	89	--
4[d]	(S)-**11**	16 h	99	0	13	0	87	--
5	**19**	16 h	99	0	--	--	--	99(*R*)

[a] Reaction conditions: 0.03 mmol of substrate, 1 mol% catalyst, 1 mL toluene, 3 bar H_2, 10 mol% AcOH, r.t., unless stated otherwise. [b] Conversion was determined by ^{1}H NMR spectroscopy. [c] Determined and calculated by chiral GC/MS using chiral stationary phases (see the supporting information for details). [d] 5 bar H_2.

To further understand the mechanism of the racemization an isotope labelling study was also carried out and is presented in Table 4. Enantiomerically pure deuterated alcohols (*R*)-**20** and (*S*)-**20** was prepared and subjected to the reaction. In both cases the deuterium is fully retained in the product, regardless if a racemization occurred or not. Finally, alcohols (*R*)-**1** and (*S*)-**1** were subjected to the dynamic kinetic resolution in the presence of 5 equivalents of $H_2{}^{18}O$. In the case (*R*)-**1** is used there is a match between the substrate and the catalyst that results in a very fast hydrogenation and no inclusion of ^{18}O is detected. On the other hand, (*S*)-**1** results in a mis-match and during its isomerization a 57% inclusion of ^{18}O could be detected in the product mixture. This suggests that the isomerization that is responsible for the dynamic kinetic resolution results from a cleavage of the carbon-oxygen bond.

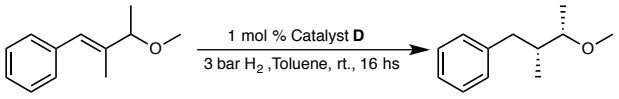
Table 3 Isotope labelling experiments



Entry[a]	Substrate	Additive	Time	% Conv.[b]	Product distribution[c]			
					(2*R*,3*R*)	(2*S*,3*S*)	(2*S*,3*R*)	(2*R*,3*S*)
1	 (*R*)-**20**	10 mol% AcOH	3 min	99	0	0	0	99(100% D)
2	 (*S*)-**20**	10 mol% AcOH	16 h	99	0	13(100% D)	5(100% D)	82(100% D)
3[d]	 (*R*)-**1**	10 mol% AcOH, 5 equiv. $H_2{}^{18}O$	16 h	99	0.8(nd)	1.7(nd)	0.7(nd)	96.8(100% ^{16}O)[e]
4[d]	 (*S*)-**1**	10 mol% AcOH, 5 equiv. $H_2{}^{18}O$	16 h	99	0.1(nd)	19.2(nd)	5.6(nd)	75.1(57% ^{18}O, 43% ^{16}O)[e]

[a] Reaction conditions: 0.03 mmol of substrate, 1 mol% catalyst, 1 mL toluene, 3 bar H_2, 10 mol% AcOH, r.t., unless stated otherwise. [b] Conversion was determined by ^1H NMR spectroscopy. [c] Determined and calculated by chiral GC/MS using chiral stationary phases (see the supporting information for details). [d] 5 equiv of $H_2{}^{18}O$ was added in the reaction. [e] Determined and calculated by LC-MS.

Since the outcome of the mechanistic studies implies that the racemization takes place via cleavage of the oxygen-carbon bond, it also suggests that other oxygen functionalities besides alcohols can be used. To test this hypothesis, an allylic methyl ether was also evaluated. The methyl ether **21** provided 88% yield of **21c** with 85/15 distereoselectivity and 96% ee using catalyst **D**. This result showed that also other allylic oxygen functional group can undergo DKR hydrogenation by the Ir catalyst resulting in a product in high dr and ee.



21 **21c**: 88% yield, 85:15 d.r., 96% ee

Fig. 2 Asymmetric dynamic kinetic resolution hydrogenation of methyl ether protected allylic alcohol. Synthesis of **21c**.

Conclusion

To summarize, we have reported an asymmetric hydrogenation of secondary allylic alcohols *via* dynamic kinetic resolution using highly efficient Ir-N,P-catalysts. Under the cooperative catalysis of N,P-ligated iridium catalysts with AcOH, high yield, excellent diasteroselectivities (up to 95:5) and enantioselectivities (up to 98% ee) were obtained. We are currently exploring this method to access more functionalized molecules and the development of more effective catalysts to promote this dynamic kinetic asymmetric hydrogenation.

Methods

See the Supplementary Methods for experimental details and characterization data in the Supplementary Information. For nuclear magnetic resonance spectra of compounds in this article, see Supplementary Figures 1-31. For GC, HPLC and HRMS traces of the chiral products, see Supplementary Figures 32-59.

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Author contributions

P.G.A. conceived and designed the experiments. J. -G.L., S. K., J. -P. Y. and J. -Q. L. performed experiments and prepared the Supplementary Information. P.G.A. and J. -G.L. wrote the paper. All authors discussed the results and commented on the manuscript.

Additional information

Supplementary information and chemical compound information are available in the online version of the paper.

Competing interests

The authors declare no competing financial interests.

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