Article

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Ruthenium-Catalyzed Dynamic Kinetic Resolution Asymmetric Transfer Hydrogenation of β-Chromanones by an Elimination-Induced Racemization Mechanism

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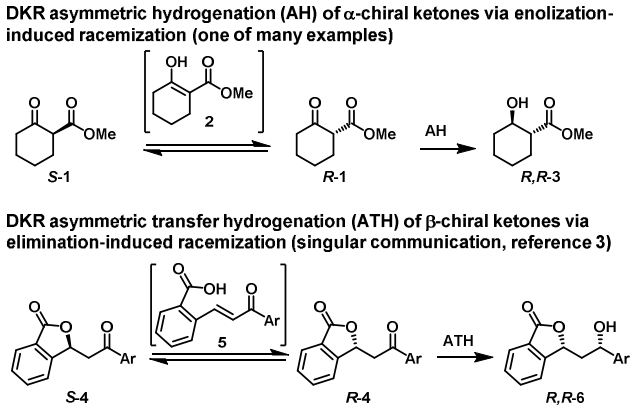
ABSTRACT: Chiral chroman derivatives are important pharmacophores in natural and synthetic bioactive molecules. The discovery of catalytic asymmetric methods for the synthesis of these compounds is an important goal. Ruthenium-catalyzed asymmetric transfer hydrogenation under strongly basic conditions has been found to induce dynamic kinetic resolution of β-substituted chromanones, producing valuable chromanols in high yields and with high levels of stereocontrol. The reaction proceeds by base-catalyzed racemization of the β-stereocenter through a conjugate elimination/conjugate addition pathway in concert with a highly selective ketone transfer hydrogenation step. Computational analysis of the catalyst, substrate, and transition state structures has revealed the driving interactions for diastereoselectivity as well as

unexpected CH-O stabilizing interactions between the catalyst sulfonamide and the reacting substrate.

KEYWORDS: Dynamic kinetic resolution • asymmetric transfer hydrogenation • chroman • β-epimerization • ruthenium

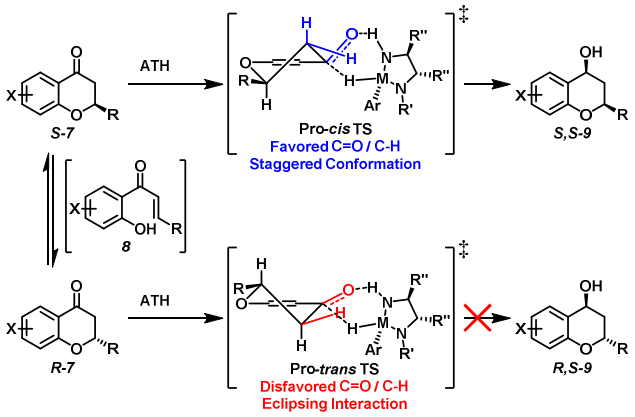
1. Introduction

Dynamic kinetic resolution (DKR) has become a powerful class of reactions for the synthesis of complex chiral molecules, allowing multiple stereocenters to be set in a single transformation from readily available racemic starting materials.[1] Well-known examples include DKR reductions of α-chiral ketones, which proceed through enolization-induced substrate racemization (e.g. ***rac*-1** to ***R,R*-3**, Scheme 1).[2] DKR reductions of β-chiral ketones (e.g. ***rac*-4** to ***R,R*-6**), however, are rare and have required elimination-induced epimerization of a stereocenter distal to the activating carbonyl moiety in order to achieve substrate racemization.[3,4]



Scheme 1. Prior art of DKR ketone reductions.

In the context of our ongoing interest in the synthesis of valuable chroman pharmacophores, we envisioned extending the DKR ketone reduction strategy to an important class of β-chiral chromanones (**7**, Scheme 2). Inspired by Liu's dynamic asymmetric phthalide reduction[3] as well as several related β-DKR examples,[4] we hypothesized that chromanone epimerization could be achieved under basic conditions via β-elimination to form achiral enone **8**, which could convert back to either enantiomer of the starting material by conjugate addition.[5]Further inspired by Metz's rhodium-catalyzed kinetic resolution of flavanones,[6] we expected that an appropriate asymmetric transfer hydrogenation (ATH) catalyst would reduce chromanone enantiomer ***S*-7** to cis-chromanol ***S,S*-9** while leaving ***R*-7** untouched.We hypothesized that torsional strain[7] in the pro-trans transition state, as well as possible steric clash between the catalyst and the substrate's β-substituent, would inhibit reduction of the mismatched enantiomer ***R*-7** and allow both substrate enantiomers to funnel to a single product stereoisomer.

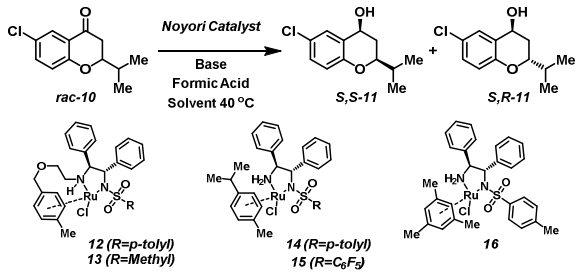


Scheme 2. Design of a DKR-ATH of β-chiral chromanones via elimination-induced racemization and torsional diastereocontrol.

2. Results and Discussion

To investigate the proposed DKR-ATH, we subjected racemic chromanone **10** to modified Noyori transfer hydrogenation conditions using ruthenium catalyst **12**,[8] 13 equivalents of triethylamine, and 10 equivalents of formic acid (Table 1, entry 1).[9] The reduction was efficient and highly enantioselective; however, chromanol **11** was isolated as a 1:1 *cis:trans* mixture, indicating that no racemization had occurred under these conditions. After screening a variety of bases, we were delighted to find that simply replacing triethylamine with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) allowed facile racemization[10] (entry 2), and the desired isomer ***S,S*-11** was generated in 89% yield, 19:1 dr, and near perfect ee. The reaction proved tolerant of a variety of solvents (entries 2 to 5) and the quantity of DBU and formic acid could be reduced (entry 6). Moreover, the *cis*:*trans* ratio could be improved by reducing catalyst loading to 1 mol% (entry 7); the slower reduction rate at lower catalyst loading allowed for racemization to out-compete reduction of the mismatched enantiomer. Lastly, a variety of Noyori-type ruthenium catalysts performed well with TsDENEB complex **12** and TsDPEN-mesitylene complex **16** giving the best results (entries 7 and 13).

Table 1. DKR optimization studies.



Entry	Solvent	B[a]	B:FA[b]	Catalyst	Assay yield	*cis:trans*	cis ee
1	*i*-PrOH	Et_3N	13:10	**12** (2.5)	89%	1:1	99%[c]
2	*i*-PrOH	DBU	13:10	**12** (2.5)	89%	19:1	99%
3	ACN	DBU	13:10	**12** (2.5)	86%	21:1	99%
4	MeOH	DBU	13:10	**12** (2.5)	87%	24:1	99%
5	DMF	DBU	13:10	**12** (2.5)	89%	26:1	99%
6	ACN	DBU	5:2	**12** (2.5)	90%	19:1	99%
7	*ACN*	*DBU*	*5:2*	***12** (1.0)*	*94%*	*30:1*	*99%*
8	ACN	DBU	4:2	**12** (1.0)	90%	24:1	99%
9	ACN	DBU	4:2	**13** (1.0)	77%	25:1	99%
10	ACN	DBU	4:2	**14** (1.0)	77%	10:1	99%
11	ACN	DBU	4:2	**15** (1.0)	72%	11:1	99%
12	ACN	DBU	4:2	**16** (1.0)	85%	14:1	99%
13	*ACN*	*DBU*	*5:2*	***16** (1.0)*	*93%*	*16:1*	*99%*

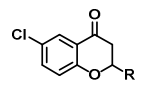
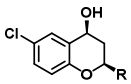
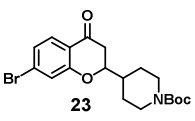
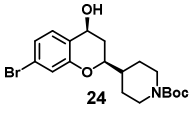
[a] Base. [b] Ratio of base to formic acid in equivalents. [c] ***Cis*-11** 99% ee, ***trans*-11** 98% ee.

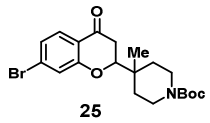
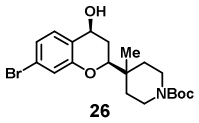
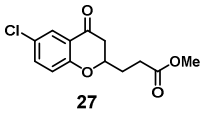
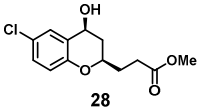
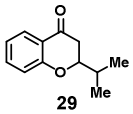
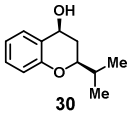
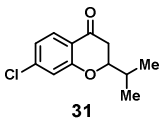
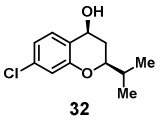
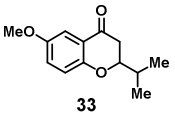
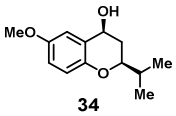
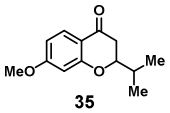
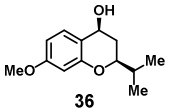
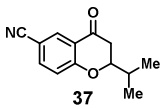
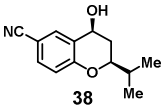
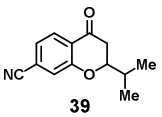
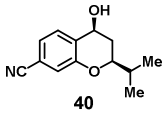
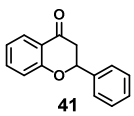
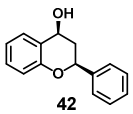
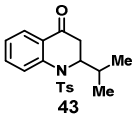
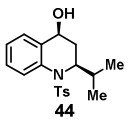
We then investigated the scope of substrates that could be utilized in this novel DKR transformation (Table 2). A wide range of alkyl substituents are viable at the chromanone 2-position, including the full steric range from methyl to *tert*-butyl (**17**, **19**, **10**, and **21**) as well as potentially reactive carbamates **23** and **25** and methyl ester **27**. Excellent results were also obtained with a wide range of arene substitution. Halogens are well-tolerated at the chromanone

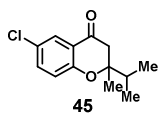
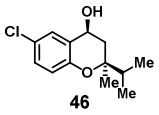
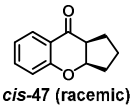
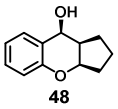
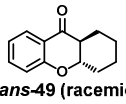
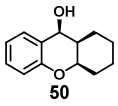
6 and 7 positions. Substitution with highly electron withdrawing nitriles or strongly donating methoxy groups also produced useful substrates (**33**, **35**, **37**, and **39**), although modifications of the base and base:formic acid ratio were necessary to balance the rates of racemization and reduction.

Importantly, the reaction was not limited to 2-alkyl chromanones. Both flavanone **41** and *N*-tosyl tetrahydroquinolone **43** could be reduced to highly enantioenriched products.[11] The scope also could be extended to disubstituted systems. β,β-Disubstituted chromanone **45** was reduced to chromanol **46** with excellent enantioselectivity and modest diastereoselectivity. Moreover, tricyclic chromanones **47** and **49** were exemplary substrates, forming all-*cis* chromanols **48** and **50** with excellent selectivity. Notably, these reactions set three contiguous stereocenters in a single transformation.

Table 2. Substrate scope.

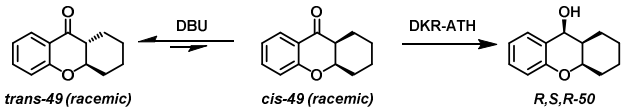
Substrate	Product[a]	Cat	DBU: FA	Isolated Yield	dr	ee
						
17 (R=Me)	**18** (R=Me)	**16**[b]	5:2	89%	17:1	>99%
19 (R=*i*-Bu)	**20** (R=*i*-Bu)	**16**[b]	5:2	86%	23:1	>99%
10 (R=*i*-Pr)	**11** (R=*i*-Pr)	**12**[b]	5:2	88%	30:1	>99%
21 (R=*t*-Bu)	**22** (R=*t*-Bu)	**16**[b]	5:2	96%	16:1	96%
 **23**	 **24**	**16**[b]	5:2	86%	>50:1	>99%

 25	 26	**16**[b]	5:2	85%	25:1	>99%
 27	 28	**16**[b]	5:2	79%	18:1	>99%
 29	 30	**12**[c]	8:2	83%	12:1	>99%
 31	 32	**12**[b]	5:2	78%	28:1	98%
 33	 34	**12**[c,d]	12:4[h]	84%	14:1	>99%
 35	 36	**12**[c]	12:4	80%	19:1	93%
 37	 38	**12**[b]	3:3	96%	>50:1	>99%
 39	 40	**12**[b]	4:3	84%	28:1	94%
 41	 42	**16**[b,f]	3:3	82%	16:1	>99%
 43	 44	**16**[c,e]	5:2	71%	10:1	95%

 45	 46	**12**[b,g]	8:5	90%	2.3:1	>99%[i]
 *cis*-47 (racemic)	 48	**16**[c]	5:2	93%	>50:1	>99%
 *trans*-49 (racemic)	 50	**16**[c,e]	5:2	79%	10:1	96%

[a] Substrate (1.0 mmol) and catalyst (1.0 mol%) were warmed with DBU and formic acid in either ACN or DMF (4 mL) at 40 ^{o}C for 24 h. [b] ACN. [c] DMF. [d] 70 ^{o}C. [e] 2.0 mol% catalyst. [f] 0.5 mol% catalyst. [g] 2.5 mol% catalyst. [h] 7-Methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD) as base. [i] Both diastereomers >99% ee.

We were surprised by the observation of all-*cis*-chromanol **50** from the DKR-ATH of substrate **49**, given that the synthesis of substrate**49** had yielded exclusively the *trans* isomer.[12]Mechanistically, one can envision **50** arising via Curtin-Hammett kinetics with rapid reduction of minor quantities of *cis*-**49** formed under the epimerizing conditions (Scheme 3). However, the chemo-, diastereo-, and enantioselective reduction of a single enantiomer of a minor substrate diastereomer is remarkable and inspired us to further investigate the stereochemical control elements of this reaction.



Scheme 3. Formation of all *cis* chromanol **50** under Curtin-Hammett kinetics.

To better understand the diastereoselectivity of these reactions we undertook a computational investigation of the transition state architectures. We built our understanding with substrate **17** by analyzing transition states of the optimal catalyst geometry with four versions of the substrate, specifically pseudoequatorial and pseudoaxial conformers of the *R* and *S* enantiomers (Figure 1).[13]For this reaction the lowest energy transition state **17A-*R*** proceeds from the *R*-pseudoequatorial chromanone toward the experimentally observed 2*R*,4*S*-chromanol **18**. **17A-*R*** exhibits a low energy staggered conformation around the reacting carbonyl and positions the β-methyl group in an open area away from the catalyst. The structure further shows a stabilizing CH-π interaction from the benzylic protons of the catalyst η^6-mesityl group to the substrate aryl ring,[14] a hydrogen bond from the forming alkoxide to the ruthenium-bound amine,[15,16] and two CH-O hydrogen bonds from the substrate C2 and C3 positions to the sulfonamide oxygens. These CH-O hydrogen bonds appear important for proper substrate orientation and stabilization.[17]

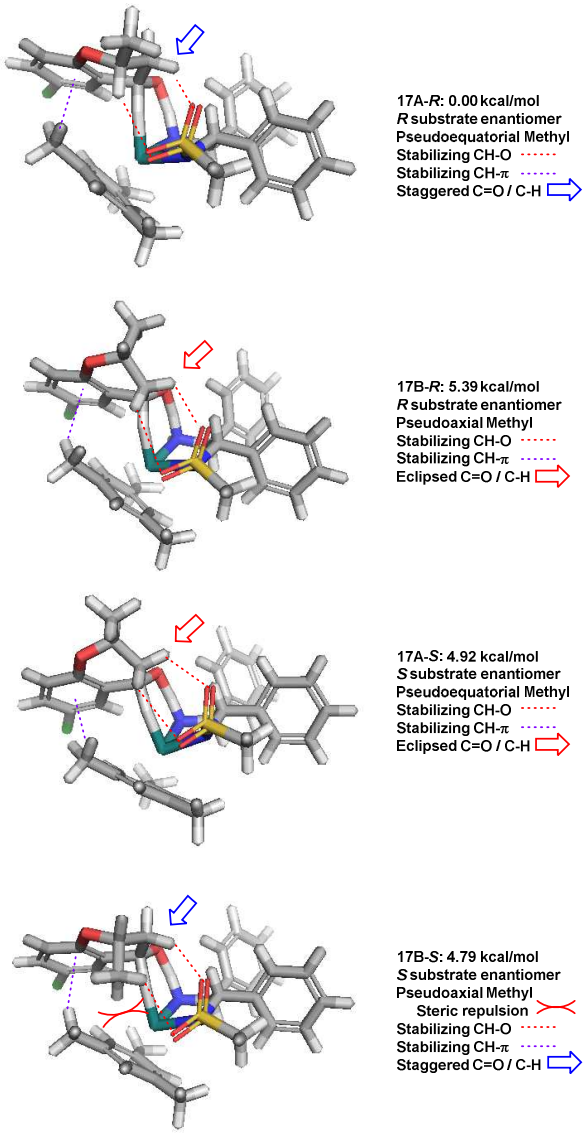


Figure 1. Transition states for the DKR-ATH of chromanone **17** (H = white, C = grey, N = blue, O = red, S = yellow, Ru = green, Cl = lime).

The remaining transitions states for the ATH of **17** are markedly higher in energy than **17A-*R***. **17B-*R*** and **17A-*S*** are destabilized by torsional strain around the reducing CO bond. **17B-*S*** has a low energy staggered conformation around the reducing carbonyl, but the pseudoaxial β-methyl group clashes with the catalyst. Taken together, the correlation of these conformations and

transition state energies supports the hypothesis that torsional strain is an important driver of diastereoselectivity. Interaction of the catalyst with the pseudoaxial group at C2, either a stabilizing CH-O hydrogen bond or a destabilizing alkyl steric clash, also appears important for high selectivity.

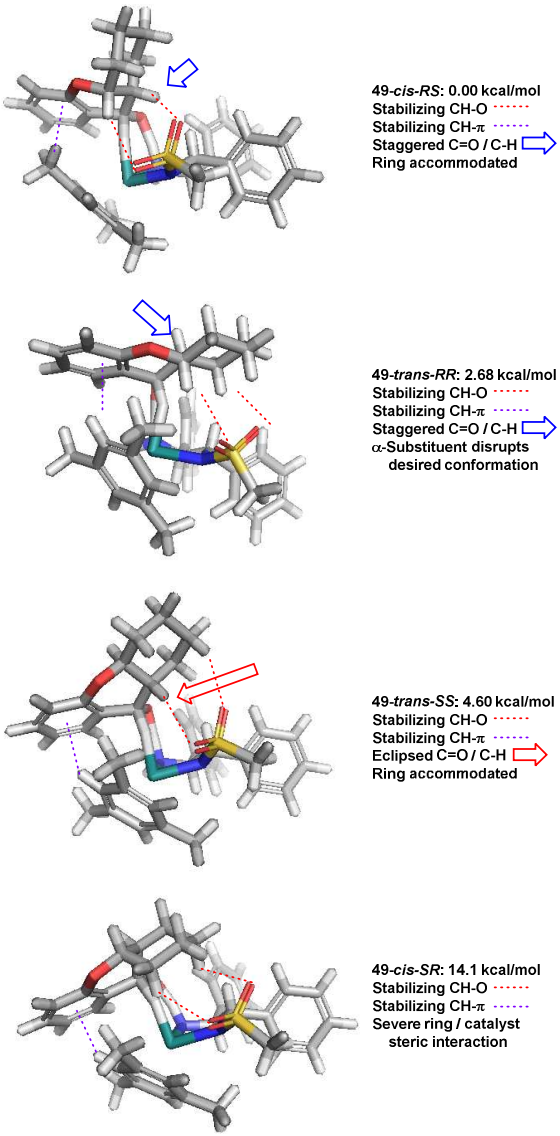
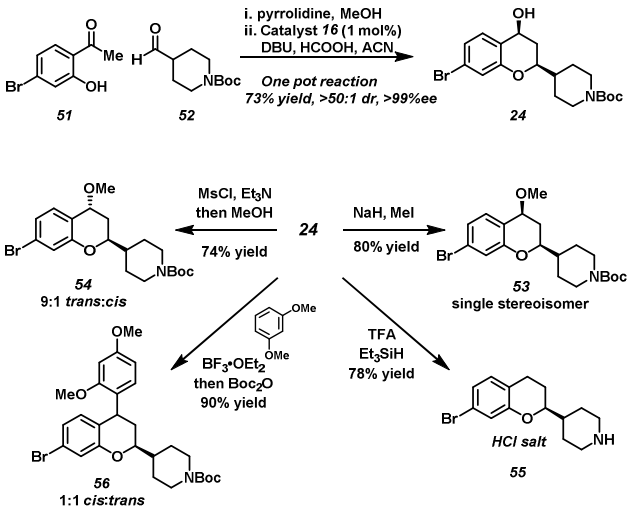


Figure 2. Transition states for the DKR-ATH of chromanone **49** (H = white, C = grey, N = blue, O = oxygen, S = yellow, Ru = green).

We then turned to the intriguing case of substrate *trans*-**49**, which produced all-*cis*-product **50** in the DKR-ATH. Transition state **49-*cis*-*RS***(Figure 2)is favored by 2.68 kcal/mol over **49-*trans*-*RR***, while the remaining transition states are dramatically higher in energy. **49-*cis*-*RS*** is essentially identical in structure to the low energy transition state **17A-*R*** and exhibits the same stabilizing interactions. Comparatively, in **49-*trans*-*RR*** the orientation of the extra ring α-carbon forces the substrate to tilt away from the catalyst sulfonamide and the sulfonamide to rotate toward the η^6-mesitylene. In order to accommodate this shift, the common CH-π interaction from the substrate arene to the benzylic proton of the catalyst mesitylene is disrupted and replaced by an interaction with the mesitylene aromatic proton, allowing overall lesser stabilization of **49-*trans*-*RR*** relative to **49-*cis*-*RS***. The alternative *trans* structure **49-*trans*-*SS*** is destabilized by torsional strain, while transition state **49-*cis*-*SR***, in which the added ring projects directly into the catalyst architecture, is least favorable and exhibited strain in stationary point searches.

Having developed a thorough understanding of the stereochemical underpinnings of the DKR-ATH, we investigated the practical aspects of this reaction. We first developed a one-pot through process for the cyclocondensation DKR-ATH of acetophenone ***51*** and aldehyde ***52***, which converted these simple starting materials directly to chromanol ***24*** with high yield and exquisite stereocontrol (Scheme 4). Chromanol ***24*** was advanced to *cis* methyl ether ***53*** by alkylation with iodomethane and to *trans* ether ***54*** by mesylation followed by displacement with methanol. The free chroman ***55*** was generated by reduction with triethylsilane in the presence of TFA via the intermediacy of a benzylic carbocation. Similarly, generation of the benzylic

carbocation followed by trapping with dimethoxybenzene formed arylated chroman ***56***, a structure reminiscent of the Myristin class of natural products.[18]



Scheme 4. Practical aspects of the chromanone DKR-ATH.

3. Conclusions

We have discovered and developed a unique combination of base-catalyzedβ-epimerization and ruthenium-catalyzed asymmetric transfer hydrogenation that enables facile reductive dynamic kinetic resolution of β-substituted chromanones. Torsional strain and novel CH-O sulfonamide hydrogen bonds have been shown to be important drivers of substrate preference and stereoselectivity. These efficient and practical reactions provide access to a wide range of synthetically useful chromanols and constitute a substantial advance in the nascent field of β–DKR methods.

ASSOCIATED CONTENT

Supporting Information.

Supporting Information Available: Experimental details, analytical data, and supporting calculations (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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[9] Typical Noyori transfer hydrogenation uses a 2:5 ratio of triethylamine to formic acid; see Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.***1997**, *30*, 97–102.

[10] See supporting information for an investigation of chroman racemization.

[11] For the DKR-ATH of flavanone the use of equimolar amounts of DBU and formic acid is necessary to limit conjugate reduction of the hydroxychalcone intermediate.

[12] DFT calculations indicate that *cis*-**49** is approximately 0.51 kcal/mol higher in energy than *trans*-**49**. See supporting information.

[13] See supporting information for catalyst and substrate ground states and a discussion of computational methods.

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[17] To our knowledge this is the first identification of these CH-O interactions in an ATH transition state.

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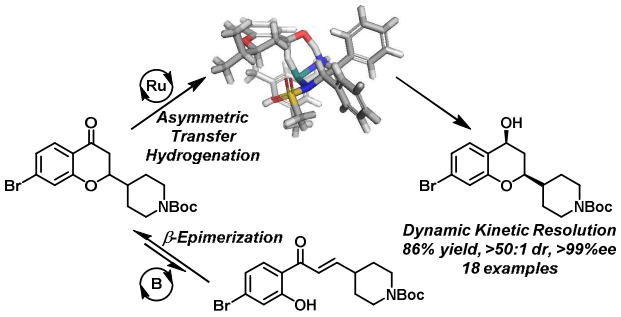
TOC Graphic


Ru
Asymmetric
Transfer
Hydrogenation
Br
O
NBoc
OH
Dynamic Kinetic Resolution
86% yield, >50:1 dr, >99%ee
18 examples
β-Epimerization
B
Br
OH
NBoc