

Recent Developments in Asymmetric Hydrogenation and Transfer Hydrogenation of Ketones and Imines through Dynamic Kinetic Resolution

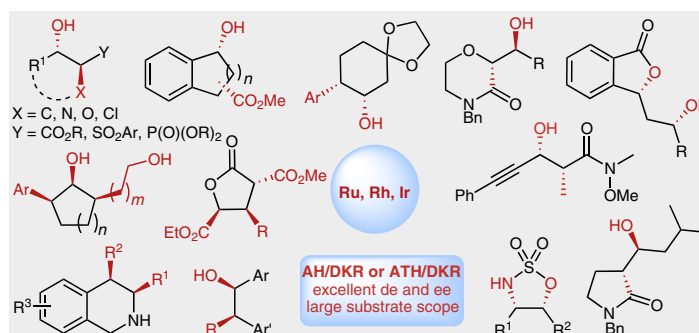
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Abstract The transition-metal-catalyzed asymmetric transfer hydrogenation (ATH) and asymmetric hydrogenation (AH) of α - and β -substituted ketone or imine derivatives are efficient methods for accessing chiral alcohols or amines bearing up to three stereogenic centers through a dynamic kinetic resolution (DKR) process. This review provides a summary of recent work in this field, focusing on the development of new catalytic systems and on the extension of these asymmetric reductions to new classes of substrates.

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Key words asymmetric hydrogenation, asymmetric transfer hydrogenation, dynamic kinetic resolution, chiral alcohols, chiral amines, stereoselectivity, ketones, imines

1 Introduction

Because chirality is present in many natural products, the importance of asymmetric synthesis is now indubitable. Moreover, this concept of chirality is directly linked to the biological activity of drugs. Therefore, discovering and de-

veloping new asymmetric reactions is of critical importance to organic synthesis.¹

Amongst stereoselective reactions, the asymmetric reduction of unsaturated compounds is the most fundamental means of introducing chirality in organic compounds.² Two of these transformations, transition-metal-catalyzed asymmetric hydrogenation (AH)³ and asymmetric transfer hydrogenation (ATH),⁴ are powerful methods of producing optically enriched compounds, and have been shown to be useful in large-scale applications for the synthesis of fine chemicals and pharmaceuticals.⁵ Furthermore, the combination of both methods with a dynamic kinetic resolution (DKR) process allows a highly efficient route to chiral compounds bearing two or more stereogenic centers.

In a DKR process, the kinetic resolution step proceeds with an in situ racemization and consequently the substrate can be totally converted into a single product with a 100% theoretical yield. Therefore, under DKR conditions, the AH or ATH of a substrate possessing a labile stereocenter allows the enantioselective synthesis of one diastereomer. To achieve efficient DKR, Curtin–Hammett kinetic conditions must be fulfilled: the rate of racemization (k_{rac}) of the starting material has to be faster than the rate of the asymmetric transformation (k_1 and k_2) and one enantiomer must react faster than the other one ($k_1 > k_2$ or $k_2 > k_1$). Furthermore, the asymmetric reaction has to be irreversible, i.e., the product formed during the reaction has to be stable to avoid any racemization (Scheme 1).

This review updates major advances from 2011 to February 2016 in the field of transition-metal-catalyzed DKR using AH and ATH applied to ketones and imines. Several comprehensive reviews covering this topic have been previously published.⁶ The structures of the ligands and complexes described in this review are shown in Figure 1 and Figure 2, respectively.



Virginie Vidal (left) received her Ph.D. from Paris-Sud University under the supervision of Professor H. P. Husson and Dr. J. Royer (Gif, France). She then pursued postdoctoral appointments with Professor S. Hanessian (Montreal University, Canada, 1989–1990), and Professor P. Potier and Dr. R. H. Dodd (Gif, 1991). She was appointed as a CNRS Associate Researcher with Professor J.-P. Genêt at Ecole Nationale Supérieure de Chimie de Paris. She is currently CNRS Research Director at Chimie ParisTech (Paris, France). Her research interests focus on transition-metal catalysis and metallo-organocatalysis for atom- and step-economical reactions and the design of atropisomeric ligands (Synphos and Difluorphos) for asymmetric catalysis. The synthesis of biorelevant targets is also a focus in her group. She was Chair of the Division of Organic Chemistry of the French Chemical Society (2009–2012).

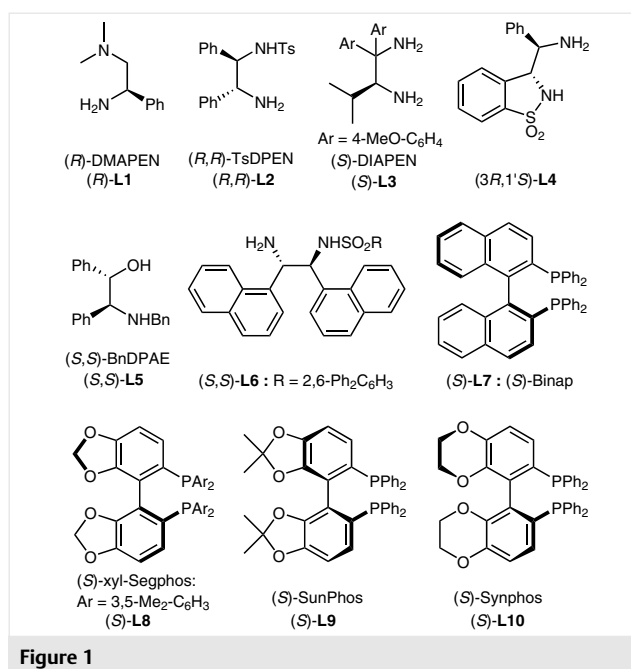
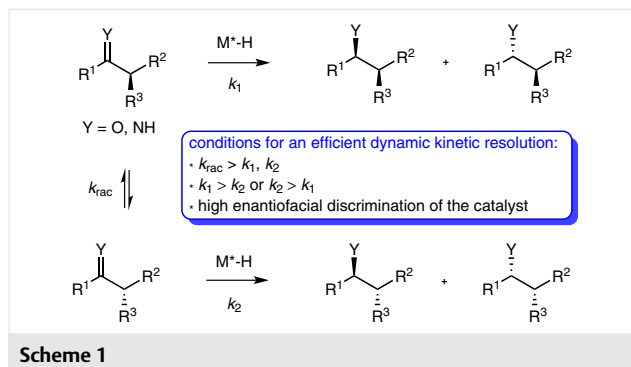
Phannarath Phansavath (second from left) was born in Vientiane (Laos). She received her Ph.D. from Pierre and Marie Curie University in 1997 under the supervision of Professor M. Malacria and Dr C. Aubert. After postdoctoral studies in the group of Professor C. Bolm at the Institut für Organische Chemie, RWTH Aachen (Germany), she was appointed assistant professor in 1999 in the group of Professor J.-P. Genêt at Ecole Nationale Supérieure de Chimie de Paris (Chimie ParisTech). Her current research interests include total synthesis of biologically relevant natural products and transition-metal-catalyzed asymmetric reactions.

Tahar Ayad (second from right) was born in Saint-Etienne (France). He received his Ph.D. degree (2003) from the University of Toulouse under the supervision of Dr. Y. Génisson and Dr. M. Baltas, working on the total synthesis of imino sugars that exhibit antituberculosis activity. After his Ph.D., he was engaged in a postdoctoral position with Professor Robert S. Coleman at The Ohio State University working on the total synthesis of oximidine I and II. After a brief period spent at Toulouse University working as an associate professor in R. Chauvin's group in 2005, he joined the group led by Professor J.-P. Genêt and Dr. V. Vidal at the Ecole Nationale Supérieure de Paris, Chimie ParisTech. His present research fields include ligand synthesis, transition-metal-catalyzed asymmetric reactions and the synthesis of biologically relevant active compounds.

Pierre-Georges Echeverria (right) was born in 1987 in France. He graduated from the engineering school ENSIACET (Toulouse, France) in 2011. He moved to ENSCP Chimie ParisTech to continue his education under the supervision of Dr. Phannarath Phansavath and Dr. Virginie Vidal, earning his Ph.D. in 2014. During this time, his research focused on the total synthesis of mirabalin and the development of different methodologies to control amino alcohol moieties by asymmetric reduction. In 2015, he joined the group of Professor Alois Fürstner at the Max-Planck-Institut für Kohlenforschung as a postdoctoral fellow working on iron catalysis. He is currently an R&D scientist at Minakem.

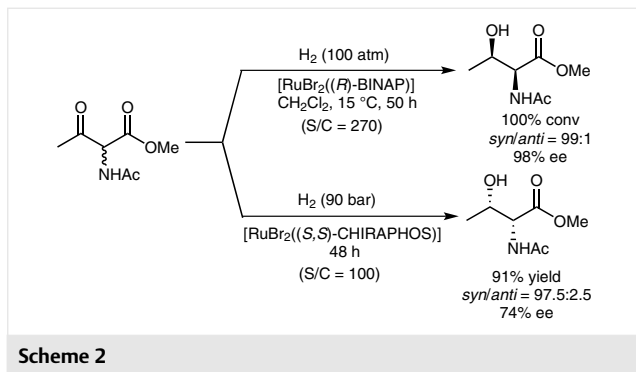
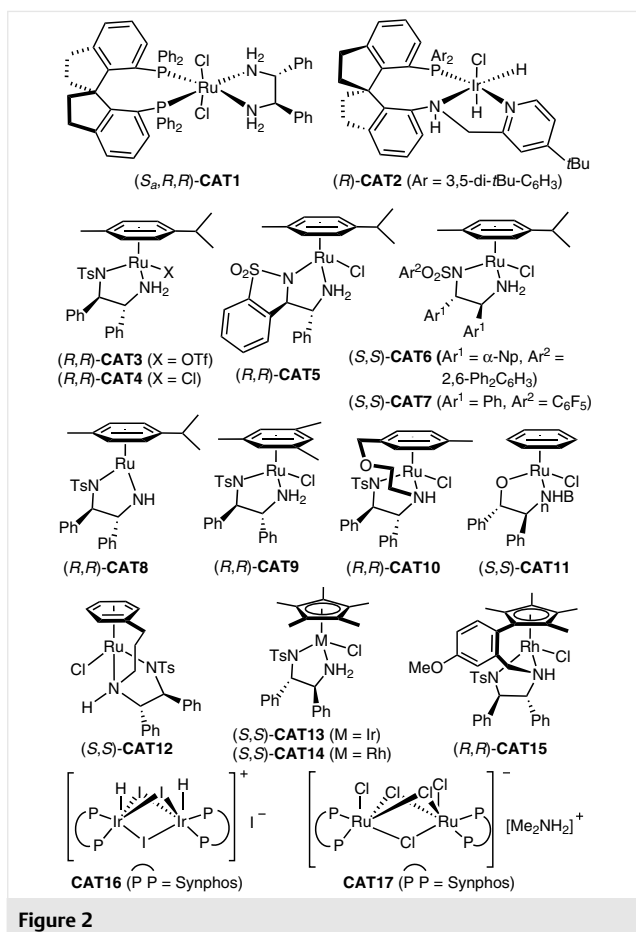
2 Asymmetric Hydrogenation via Dynamic Kinetic Resolution

The first example of asymmetric reduction coupled with a DKR was reported by Tai in 1979 with the heterogeneous hydrogenation of α -substituted- β -keto esters, catalyzed by Raney-Nickel modified by (*R,R*)-tartaric acid, yield-



ing the reduced product as a 78:22 *syn/anti* mixture with a 57% ee for the *syn* isomer.⁷ In 1989, the pioneering work of Noyori⁸ and that of Genêt and co-workers⁹ led to the first examples of homogeneous enantioselective ruthenium-promoted hydrogenations of racemic α -acetamido β -keto esters via dynamic kinetic resolution using, respectively, BINAP-Ru(II) and CHIRAPHOSRu(II) catalysts (Scheme 2). The hydrogenation reaction of racemic 2-acylamino-3-oxobutyrates provided the corresponding *syn* L- and D-threonine derivatives with high levels of enantioselectivity (up to 98% ee) and diastereoselectivity (*syn/anti* up to 99:1).

Thereafter, Noyori and co-workers published extensively on asymmetric hydrogenation via DKR of α -substituted β -keto esters, including stereochemical models^{6a} and a mathematical analysis of the kinetics of the DKR, marking an important breakthrough in this area.^{10,11} Numerous authors have subsequently made important contributions to

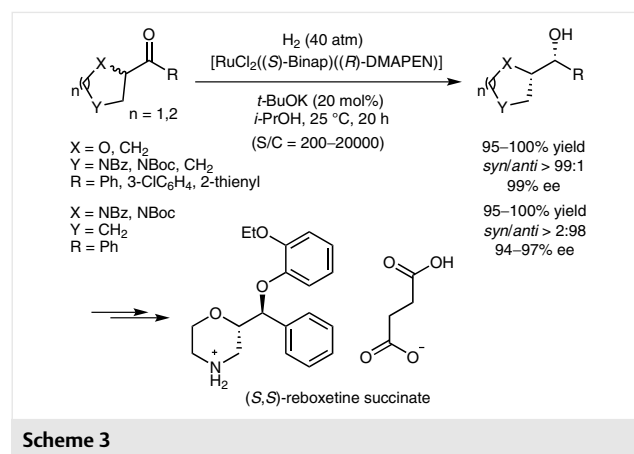


this field of research and they include, but are not limited to, asymmetric hydrogenation via DKR of non-activated ketones,¹² organocatalyzed DKR¹³ and enzymatic DKR.¹⁴

2.1 α -Substituted Ketones

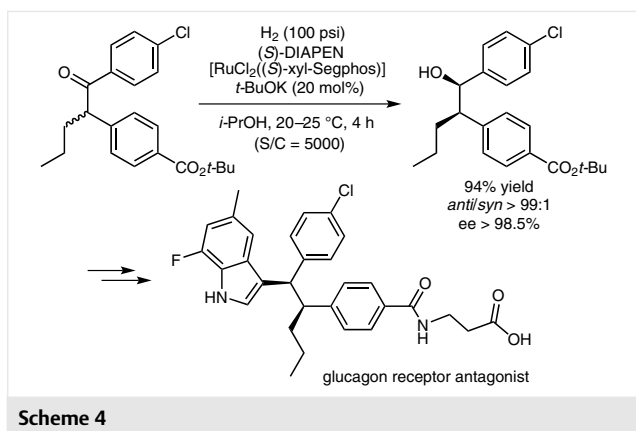
In 2011, Ohkuma and co-workers reported the asymmetric hydrogenation of various aryl heterocycloalkyl ketones through DKR using $[\text{RuCl}_2((S)\text{-Binap})((R)\text{-DMAPEN})]$

as the catalyst (Scheme 3).¹⁵ Under optimized reaction conditions, the corresponding alcohols were efficiently produced in 95–100% yields with good to excellent diastereoselectivities (>99:1) and ee values ranging from 94–99%. The authors noted that the diastereoselectivity of the reaction was essentially controlled by the nature of the X group present on the heterocyclic rings. Specifically, high *syn* selectivities were obtained for the hydrogenation of ketones with X = O or X = CH₂, whereas high *anti* selectivities were observed for substrates having a bulkier NBz or NBoc substituent. The authors also showed that such a reaction could be performed with a very low catalyst loading (S/C = 20000) without affecting the catalytic efficiency. This method was successfully applied to the synthesis of (*S,S*)-reboxetine succinate, a selective norepinephrine uptake inhibitor.

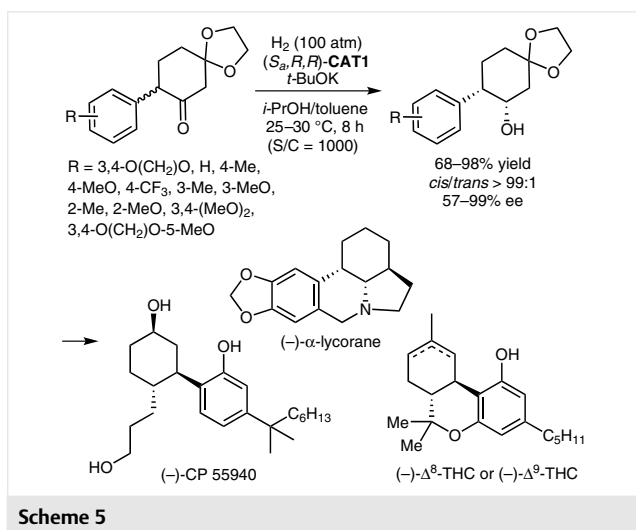


In the course of the synthesis of a new glucagon receptor antagonist drug candidate for the treatment of type 2 diabetes, scientists from Merck Research Laboratories developed, in 2012, a robust and highly efficient route using an asymmetric hydrogenation reaction combined with DKR as a key step to install the two adjacent tertiary stereogenic centers (Scheme 4).¹⁶ After intensive experiments, the $\text{RuCl}_2(S)\text{-xyl-Segphos}/(S)\text{-DIAPEN}$ complex was identified as the optimum catalyst for this transformation giving the targeted reduced alcohol in 94% yield with excellent diastereoselectivity (*anti/syn* >99:1) and high enantioselectivity (>98.5%). Furthermore, this reaction was performed efficiently on a multikilogram scale with a relatively low catalyst loading (S/C = 5000).

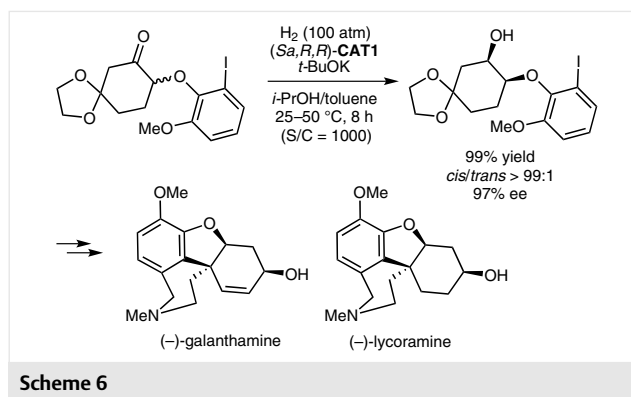
In 2012, Zhou and co-workers described a highly enantio- and diastereoselective ruthenium-catalyzed hydrogenation of racemic α -arylcyclohexanones through DKR by using a chiral (diamine)(spirodiphosphine)ruthenium(II) chloride complex as the catalyst (Scheme 5).¹⁷ Under optimized reaction conditions, a series of enantiomerically enriched α -arylcyclohexanols was obtained in 68–98% yield with excellent *cis* selectivities (*cis/trans* >99:1) and enan-



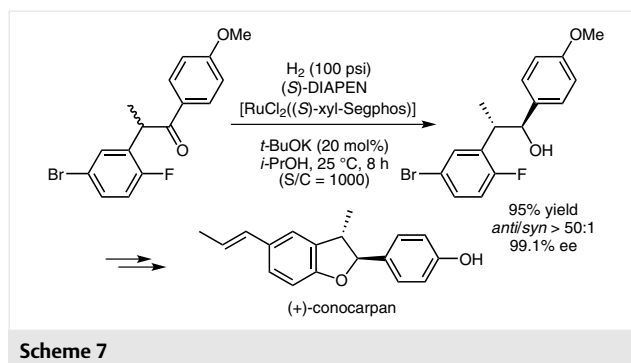
tioselectivities ranging from 57% to 99% by employing (*S_a,R,R*)-**CAT1** as a precatalyst. It must be noted, however, that substrates bearing *ortho*-substituents afforded products in lower yields and ee values. As shown in Scheme 5, the usefulness of these enantiopure α -arylcyclohexanols was also demonstrated by the synthesis of several biologically active molecules such as (–)- α -lycorane, (–)-CP 55940 and tetrahydrocannabinol derivatives.



The same group further extended the above-mentioned method for the enantioselective synthesis of (–)-galanthamine and (–)-lycoramine, two alkaloids that have been used clinically as selective acetylcholinesterase inhibitors for the treatment of Alzheimer's disease (Scheme 6).¹⁸ In this case, the synthetic route featured ruthenium-catalyzed asymmetric hydrogenation via DKR of a racemic α -aryloxy cyclohexanone producing the key chiral β -aryloxy cyclohexanol intermediate in 99% yield with up to 97% ee and >99:1 *cis/trans* selectivity.



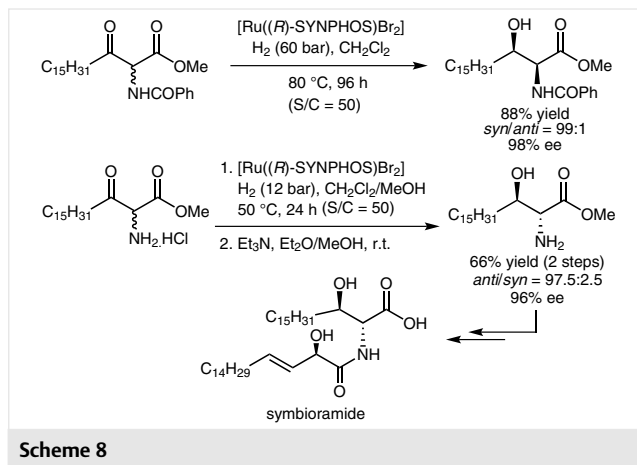
Neolignans are the most abundant natural products found in several families of plants. These molecules exhibit a wide range of biological properties and feature a common 2-aryl-2,3-dihydrobenzofuran skeleton. In 2013, Chen and co-worker developed a concise and straightforward access to this family of compounds based on the asymmetric hydrogenation of racemic ketones under DKR conditions (Scheme 7).¹⁹ A screening of reaction parameters revealed that the use of 0.1 mol% of [RuCl₂((*S*)-xyl-Segphos)((*S*)-DIAPEN)] as the catalyst in the presence of *t*-BuOK facilitated epimerization, resulting in the formation of the chiral carbinol key intermediate with nearly perfect selectivity (99.1% ee, >50:1 dr) and excellent yield (95%). This protocol has been applied to the synthesis of (+)-conocarpan as well as other members of the neolignan family.



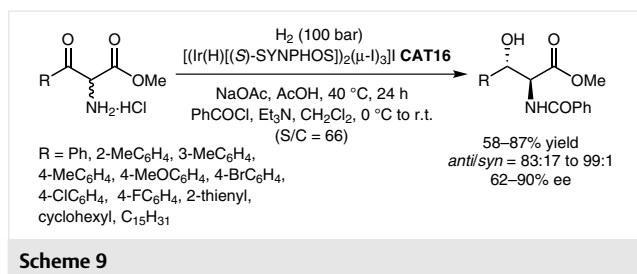
2.2 α -Substituted β -Keto Esters and Amides

Continuing a long-established interest in metal-catalyzed reductions/DKR,^{6f,20} our group used the key step of asymmetric hydrogenation to achieve a short and efficient total synthesis of the naturally occurring bioactive ceramide symbioramide starting from readily accessible racemic α -amino and α -amido β -keto esters (Scheme 8). Application of the Ru(II)-SYNPHOS-catalyzed asymmetric hydrogenation reaction to both racemic α -amino and α -amido β -keto ester derivatives enabled, through a dynamic kinetic resolution process, the preparation of the corresponding

anti and *syn* amino alcohols in high enantio- and diastereoselectivities (up to 98% de and 98% ee). This flexible strategy also provided an efficient access to structural isomers of symbioramide, which were prepared with high asymmetric inductions.²¹

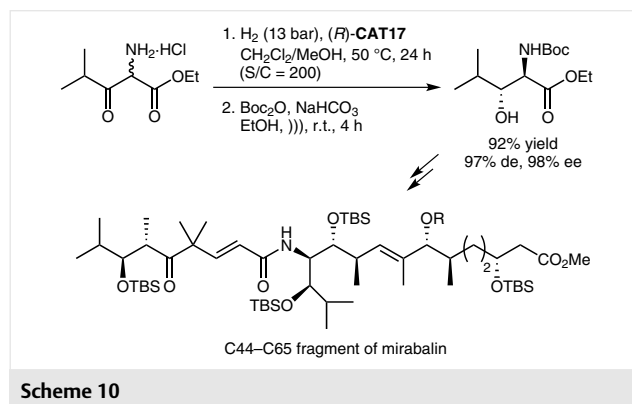


Pioneering work on the hydrogenation of α -amino β -keto ester hydrochlorides associated with a DKR process was reported in 2004 by Hamada²² and our group.^{20d,e,g} In 2014, we accomplished the AH/DKR transformation of α -amino β -keto ester hydrochlorides using a cationic dinuclear iridium(III) complex incorporating an in-house-developed SYNPHOS ligand (Scheme 9).²³ The reaction allowed for the synthesis of a wide range of enantioenriched *anti* α -amino β -hydroxy ester hydrochloride derivatives containing alkyl, and electron-rich and electron-poor aryl groups. When subjected to the optimized hydrogenation conditions using 1.5 mol% of the cationic dinuclear iridium(III) catalyst $[(\text{Ir}(\text{H}))(\text{S})\text{-SYNPHOS}]_2(\mu\text{-I})_3\text{I}$ (**CAT16**)²⁴ and NaOAc in acetic acid under 100 bar of hydrogen pressure at 40 °C, excellent *anti* diastereoselectivities (*anti/syn* up to 99:1) and enantioselectivities (up to 90% ee) were achieved.²⁵

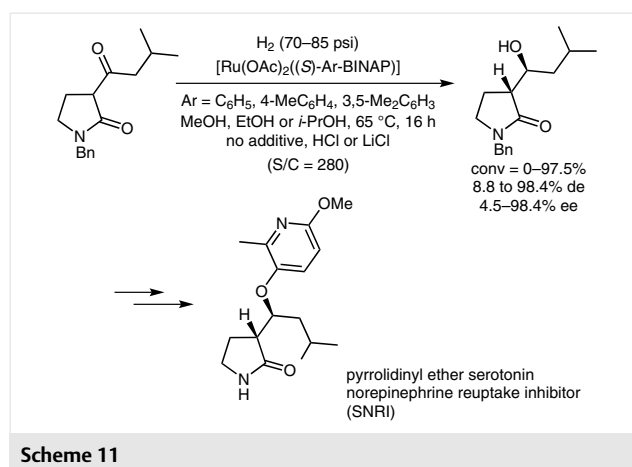


We successfully used the ruthenium-catalyzed dynamic kinetic resolution of racemic α -amino β -keto ester hydrochlorides to access the C44–C65 fragment of mirabalin, a cytotoxic macrolide isolated in 2008 from the marine sponge, *Siliquariaspongia mirabilis* (Scheme 10).²⁶ The hydrogenation reaction was carried out efficiently under mild

conditions at 50 °C in $\text{CH}_2\text{Cl}_2/\text{MeOH}$ using 13 bar of hydrogen pressure and 1 mol% of the Ru-SYNPHOS catalyst (**R-CAT17**) developed in our group.^{23e} This operationally facile process, scaled to 25 g, provided a ready access to the N-protected *anti* amino alcohol in 92% yield and with high levels of diastereo- and enantioinduction (97% de, 98% ee).

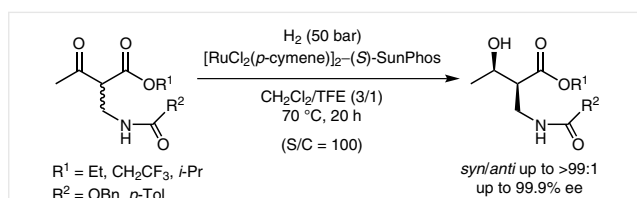


Because serotonin norepinephrine reuptake inhibitors (SNRIs) have demonstrated efficiency in the treatment of pain, researchers from Eli Lilly established a stereoselective route to access pyrrolidine ether SNRIs based on enantio- and diastereoselective DKR/hydrogenation of a β -keto- γ -lactam derivative (Scheme 11).²⁷ A catalyst structure evaluation showed that high stereoselectivities (96% ee, 94% de) were obtained using the $[\text{Ru}(\text{OAc})_2((\text{S})\text{-tol-BINAP})]$ complex in isopropanol compared to ethanol or methanol with catalytic amounts of HCl (6 mol%) and LiCl (1 mol%) to increase the reactivity of the catalytic system. Interestingly, studies using online NMR and HPLC revealed that one enantiomer of the racemic β -keto- γ -lactam was hydrogenated faster than the interconversion between the enantiomers.



Zhang and co-workers described the enantio- and diastereoselective synthesis of β' -hydroxy- β -amino acids using in situ generated $[\text{RuCl}_2(p\text{-cymene})]_2(\text{S})\text{-SunPhos}$ as the

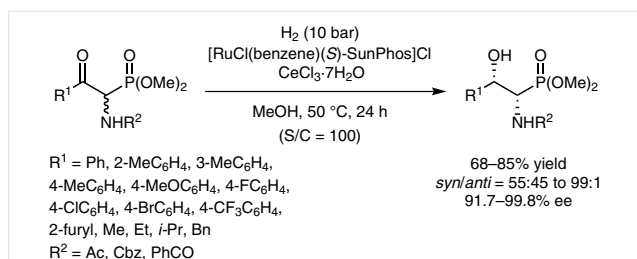
catalyst for the asymmetric hydrogenation of β' -keto- β -amino esters through DKR (Scheme 12).²⁸ The highest levels of diastereo- (up to 98% de) and enantioinduction (up to 99.9% ee) were obtained using dichloromethane/2,2,2-trifluoroethanol (TFE) or 1,2-dichloroethane/TFE combinations as solvents. The authors showed that the use of $[\text{RuCl}_2(p\text{-cymene})]_2\text{-(S)-SunPhos}$ in these solvent mixtures was more efficient than $[\text{RuCl}_2(p\text{-cymene})]_2$ associated with common diphosphine ligands in $\text{CH}_2\text{Cl}_2/\text{MeOH}$ or $\text{CH}_2\text{Cl}_2/\text{EtOH}$.



Scheme 12

2.3 α -Substituted β -Keto Phosphonates and Sulfones

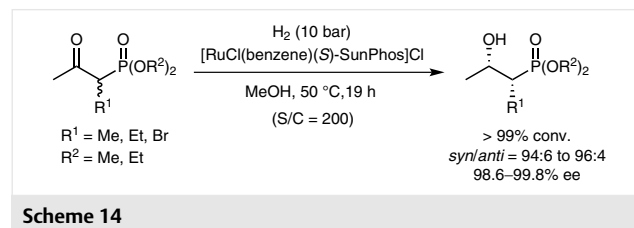
Because of their prevalence in bioorganic and medicinal chemistry, and owing to their unique biological activities as well as their potential uses as peptide mimics, chiral β -hydroxy α -amino phosphonates have received considerable attention in recent years. In 2013, Zhang and co-workers reported a convenient and general protocol for the synthesis of these compounds through Ru-catalyzed hydrogenation of α -amido β -keto phosphonates via DKR (Scheme 13).²⁹ By using $[\text{RuCl}(\text{benzene})(\text{S})\text{-SunPhos}]\text{Cl}$ as the catalyst, excellent levels of stereoselectivity were observed for the corresponding *syn*- α -amido β -hydroxy phosphonates (up to 99:1 *syn/anti*, up to 99.8% ee). The authors demonstrated the crucial role of additives in the stereochemical outcome of the reaction, because a dramatic increase of both dr and ee was observed after the addition of $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$.



Scheme 13

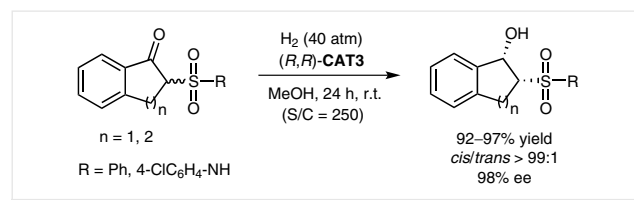
The same group disclosed the asymmetric hydrogenation of α -substituted β -keto phosphonates in the presence of $[\text{RuCl}(\text{benzene})(\text{S})\text{-SunPhos}]\text{Cl}$ as the catalyst (Scheme 14).³⁰ The corresponding *syn*- β -hydroxy phosphonates

were obtained with excellent diastereo- and enantioselectivities (up to 96:4 *syn/anti*, up to >99.8% ee) under optimized reaction conditions.



Scheme 14

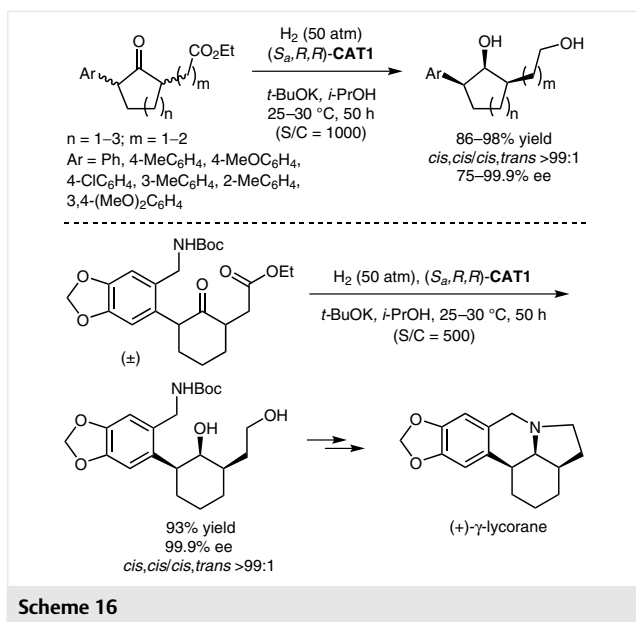
In 2013, Wang and co-workers depicted a cascade asymmetric hydrogenation/DKR of racemic cyclic β -keto sulfonamides and β -keto sulfones derived from α -indanone or α -tetralone (Scheme 15).³¹ The reaction was performed using 0.4 mol% of the cationic complex $[\text{Ru}(\text{OTf})(p\text{-cymene})((R,R)\text{-TsDPEN})]$ [(*R,R*)-CAT3] in methanol at room temperature under 40 atmospheres of hydrogen pressure to deliver the corresponding *cis*- β -hydroxy sulfonamides and β -hydroxy sulfones in high yields (92–97%), with excellent enantioselectivities (98%) and very high diastereoselectivities (*cis/trans* >99:1).



Scheme 15

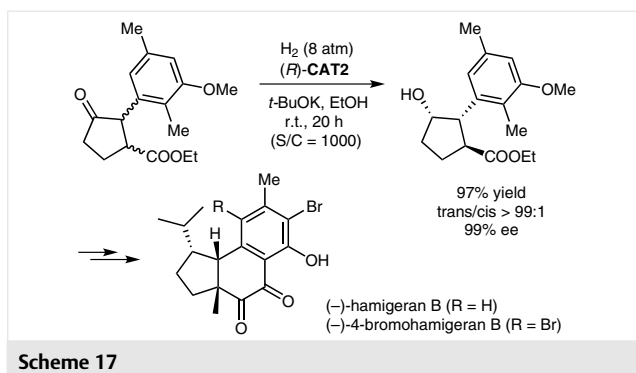
2.4 α,α' -Disubstituted Cyclic Ketones

Zhou, Xie and co-workers developed a strategy for the highly enantioselective ruthenium-catalyzed hydrogenation of racemic α,α' -disubstituted cyclic ketones through DKR for the synthesis of chiral diols bearing three contiguous stereocenters (Scheme 16).³² The reduction of α -ethoxycarbonyl-alkyl- α' -arylcyclic ketones catalyzed by (*S_a*,*R,R*)-CAT1 at room temperature under 50 atmospheres of hydrogen pressure delivered the corresponding chiral diols in high yields with excellent *cis,cis* selectivities (*cis,cis/cis,trans* >99:1) and enantioselectivities (up to 99.9% ee), with the ester group being hydrogenated in the process. The size of the cyclic ketone strongly affected the enantioselectivity of the reaction, because only moderate enantioselectivity (75% ee) was observed with a five-membered ring, whereas six- and seven-membered rings afforded high ee values. The authors showed that both the aryl and ester groups were necessary to achieve high enantioselectivity. In addition, this highly efficient strategy was used for the enantioselective total synthesis of (+)- γ -lycorane.



2.5 α,β -Disubstituted Cyclic Ketones

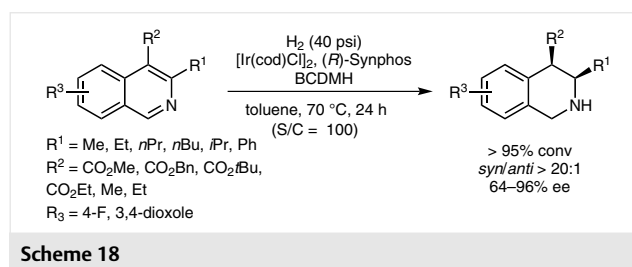
In 2016, Zhou, Xie and co-workers reported the enantioselective total synthesis of (–)-hamigeran B and (–)-4-bromohamigeran B.³³ The key feature of this approach relied on the construction of the chiral cyclopentanol moiety having three contiguous stereocenters by using a highly efficient iridium-catalyzed asymmetric hydrogenation of a racemic ketone via DKR (Scheme 17). Optimization of the reaction conditions revealed that the chiral iridium complex (*R*)-**CAT2**, bearing a spiropyridine–aminophosphine ligand, was the catalyst of choice for the asymmetric hydrogenation of racemic *trans*-2-(3-methoxy-2,5-dimethylphenyl)-3-(ethoxycarbonyl)cyclopentanone, providing the targeted cyclopentanol in excellent yield (97%), and with high enantioselectivity (99% ee) and nearly perfect *trans* selectivity ($trans/cis >99:1$).



2.6 Imine Derivatives

The reduction of heteroarenes³⁴ is still a long-standing challenge in the field of asymmetric reduction and several examples involving DKR can be found in the literature.

In 2012, Zhou and co-workers disclosed the enantioselective hydrogenation of 3,4-disubstituted isoquinolines using $[Ir(cod)Cl]_2/(R)$ -SYNPHOS as the catalyst and 1-bromo-3-chloro-5,5-dimethylhydantoin (BCDMH) as an additive (Scheme 18).³⁵ This method afforded chiral 3,4-disubstituted tetrahydroisoquinolines with excellent diastereoselectivities ($dr >20:1$) and enantioselectivities up to 96%. Different control experiments showed that the reaction proceeded via a DKR process involving an imine–enamine tautomerization.

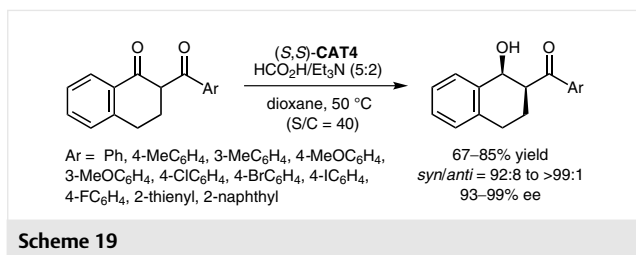


3 Asymmetric Transfer Hydrogenation via Dynamic Kinetic Resolution

Historically, the first example of a catalytic ATH was reported in 1950 by Doering,³⁶ who described an asymmetric version of the Meerwein–Ponndorf–Verley (MPV) reduction of ketones catalyzed by *rac*-aluminum alkoxides in the presence of (*S*)-2-butanol as a hydrogen donor to give the corresponding chiral alcohols with ee values of 5.9–22%. However, a major breakthrough occurred in 1995, when Noyori, Ikariya and co-workers³⁷ designed a conceptually new Ru(II)-arene catalyst bearing *N*-sulfonylated 1,2-diamines or amino alcohols as chiral ligands for highly efficient ATH of ketones and imines. After this milestone discovery, intense efforts were devoted by the synthetic community for the development of new highly efficient catalyst systems in both academia and industry. ATH is now recognized as one of the most powerful and versatile tools for synthesizing chiral alcohols and amines, because of its operational simplicity, wide substrate scope and high selectivity. Of particular interest is the application of ATHs under DKR conditions that allow highly enantioselective syntheses of chiral alcohols and amines containing two or more stereogenic centers, the first examples of which were reported by the groups of Knochel³⁸ and Noyori.³⁹

3.1 α -Substituted β -Diketones and Ketones

In 2011, Zhang and co-workers achieved a practical and highly stereoselective synthesis of 2-aryl-1-tetralones using $[\text{RuCl}_2(p\text{-cymene})]_2$ in combination with (1*S*,2*S*)-TsDPEN and $\text{HCO}_2\text{H}/\text{Et}_3\text{N}$ as the hydrogen source (Scheme 19).⁴⁰ The ATH/DKR reaction using the (*S,S*)-**CAT4** complex was applied to a series of diversely substituted 2-aryl-1-tetralones to provide the corresponding alcohols in good yields (up to 85%) and asymmetric inductions (up to 99% ee, >99:1 dr). No conversion was observed with *ortho*-substituted phenyl groups. The authors showed that the steric effect and the rigidity of the fused ring system played a crucial role in the stereochemical outcome of the reaction because significantly lower stereoselectivities (50% ee, 72:28 dr) were obtained with a cyclohexyl diketone derivative.

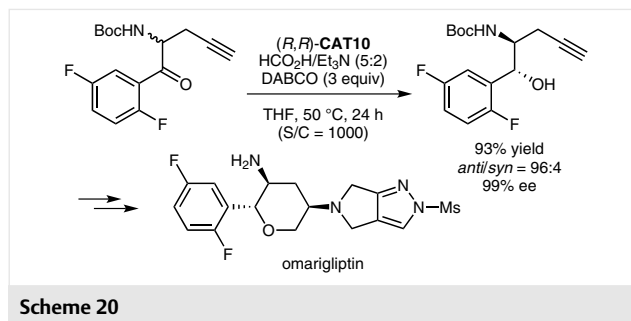


Scheme 19

Omarigliptin is a long-acting DPP-4 inhibitor for the treatment of type 2 diabetes. In 2015, scientists from Merck Research Laboratories developed a synthetic route to this important pharmaceutical drug that was amenable to multikilogram-scale production. One of the reactions featured in this process relied on the use of a Ru-catalyzed DKR reduction of a racemic *N*-Boc- α -substituted ketone to provide the desired *anti*-1,2-amino alcohol bearing two of the three stereogenic centers (Scheme 20).⁴¹ The best results were obtained with 0.1 mol% of the oxo-tethered $[\text{RuCl}((R,R)\text{-TsDENEb})]$ complex $[(R,R)\text{-CAT10}]$ as the catalyst, five equivalents of an azeotropic mixture of formic acid/triethylamine (5:2) as the hydrogen source, and three equivalents of DABCO. Under these optimized reaction conditions, the key chiral 1,2-amino alcohol intermediate was obtained in 93% yield with high *anti* selectivity (*anti*/*syn* = 96:4) and nearly perfect enantioselectivity (99% ee). In this transformation, it was found that removal of generated CO_2 (by purging with N_2) during the course of the reaction was essential for achieving high catalytic efficiency.

3.2 α -Substituted β -Keto Esters, Amides and Phosphonates

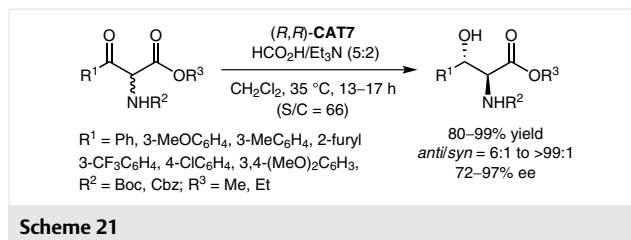
Chiral β -hydroxy- α -amino acid derivatives with an *anti* configuration are important structural motifs found in a wide variety of biologically active and natural products. Many stereoselective approaches to prepare such building blocks have been reported in the literature,⁴² from which



Scheme 20

ATH and ATH of α -substituted- β -keto esters, amides and phosphonates are undoubtedly among the most elegant and powerful methods.

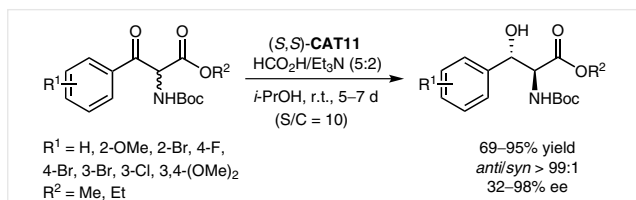
In 2011, Liu, Shultz and co-workers from Merck Research Laboratories succeeded in developing a practical and highly stereoselective synthesis of *anti* aryl β -hydroxy α -amino esters using $[\text{RuCl}(p\text{-cymene})((R,R)\text{-C}_6\text{F}_5\text{SO}_2\text{DPEN})]$ complex $[(R,R)\text{-CAT7}]$ and $\text{HCO}_2\text{H}/\text{Et}_3\text{N}$ (5:2) as the hydrogen source, with slow addition of formic acid (42:1 dr, 91% ee) in dichloromethane for 13–17 hours (Scheme 21).⁴³ Careful investigations demonstrated that the combination of an electron-deficient perfluorinated ligand with slow addition of formic acid over five hours was critical to control the stereochemical outcome of the reaction because a significantly lower enantioselectivity (73% ee) was obtained by using directly the $\text{HCO}_2\text{H}/\text{Et}_3\text{N}$ (5:2) azeotropic mixture. These optimized DKR transfer reaction conditions were applied to a series of diversely substituted aryl β -keto α -amino esters bearing both electron-donating and electron-withdrawing substituents on the aromatic ring. A variety of functional groups were tolerated, and the corresponding *anti* alcohols were obtained in good yields (up to 99%) and high stereoselectivities (up to >97% ee, >99:1 dr). The absolute stereochemistry of the desired *anti* products was assigned unambiguously by chemical derivatization and vibrational circular dichroism spectroscopy.



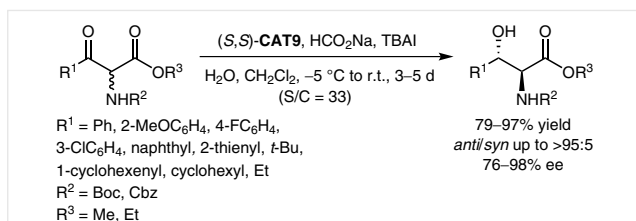
Scheme 21

Somfai and co-workers later described a procedure allowing access to the *anti* diastereomers using complex (*S,S*)-**CAT11** obtained from $[\text{RuCl}_2(\text{benzene})]_2$ and (*S,S*)-BnDPAE **L5** as the ligand, in the presence of $\text{HCO}_2\text{H}/\text{Et}_3\text{N}$ as the hydrogen source. The reaction proceeded mainly in excellent diastereoselectivities (*anti*/*syn* >99:1) and enantio-

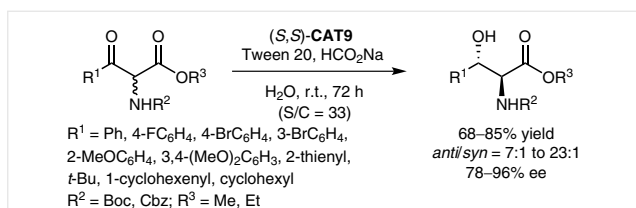
selectivities (up to 98% ee) for aryl ketone derivatives in 5–7 days using 10 mol% of the ruthenium catalyst in isopropanol (Scheme 22).⁴⁴



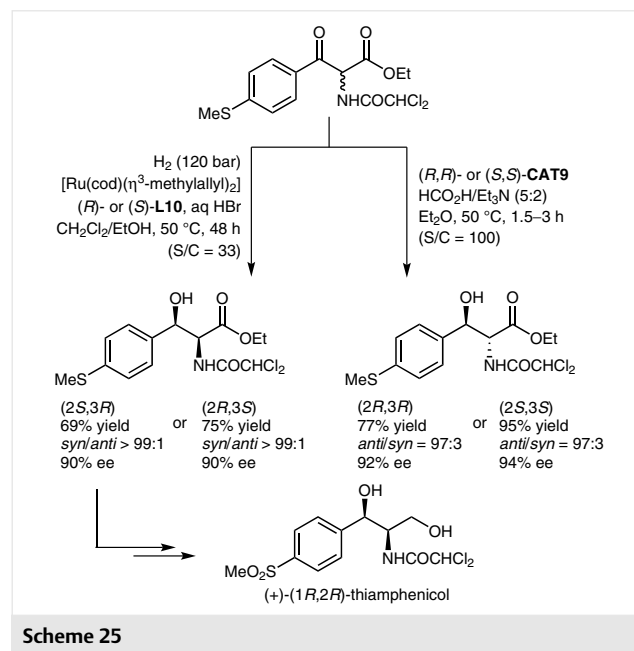
The same group disclosed a water-CH₂Cl₂ emulsion-based method for the construction of *anti*-β-hydroxy α-amido esters through ATH/DKR (Scheme 23).⁴⁵ In the presence of the preformed catalyst, (*S,S*)-**CAT9**, sodium formate as the reducing agent and tetrabutylammonium iodide, the reduction of α-amido β-keto esters proceeded with high diastereo- and enantioselectivities (*anti/syn* up to 95:5, up to 98% ee) using a lower catalyst loading (S/C = 33) than previously, and within shorter reaction times (3–5 days). Moreover, the emulsion conditions provided a significantly broader reaction scope, including aryl-, heteroaryl-, alkyl-, and even alkyl-substituted α-amido β-keto esters.



Somfai and co-workers then investigated the same reaction in water, obviating the need for an organic solvent, by employing a neutral surfactant, Tween 20 [polyoxyethylene (20) sorbitan monolaurate] to overcome solubility issues. The procedure gave generally high yields (68–85%), diastereoselectivities (*anti/syn* up to 23:1) and enantioselectivities (up to 96% ee) for a broad range of substrates (Scheme 24).⁴⁶

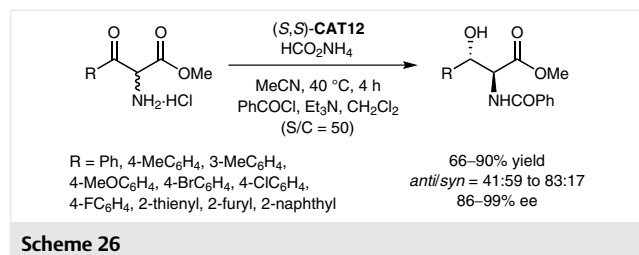


In 2015, our group developed an efficient, flexible and atom-economical synthesis of the four stereoisomers of (+)-(1*R*,2*R*)-thiamphenicol, used for its antibacterial activities against several Gram-positive and Gram-negative microorganisms, through both AH/DKR and ATH/DKR processes using a racemic α-amido β-keto ester (Scheme 25).⁴⁷ The ruthenium-catalyzed asymmetric hydrogenation reaction was carried out under 120 bar of hydrogen pressure at 50 °C using in-house in situ generated Ru(II)-SYNPHOS^{23e} as the best catalyst, furnished the corresponding (2*S*,3*R*)- and (2*R*,3*S*)-*syn*-alcohols in high yields and stereoselectivities (*syn/anti* >99/1, 90% ee). Alternatively, asymmetric transfer hydrogenation employing the [RuCl(η⁶-mesitylene)((*S,S*)-TsDPEN)] complex, (*S,S*)- or (*R,R*)-**CAT9** and HCO₂H/Et₃N (5:2) as the hydrogen source provided, at 50 °C, the *anti*-(2*R*,3*R*)- and (2*S*,3*S*)-isomers, respectively, in 77% and 95% isolated yields and in high diastereo- and enantioselectivities (*anti/syn* = 97:3, up to 94% ee). The complementarity of these reduction methods was demonstrated through the practical access to all the *syn* and *anti* stereoisomers of thiamphenicol.

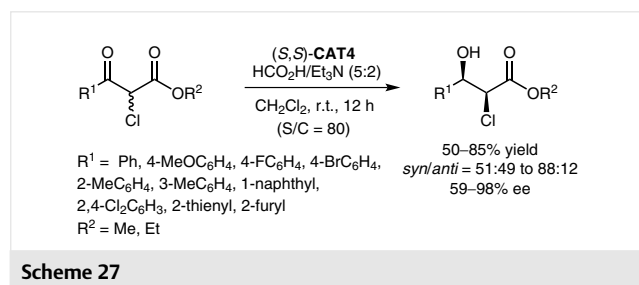


We also focused our attention on the first asymmetric transfer hydrogenation of racemic α-amino β-keto ester hydrochlorides (Scheme 26).⁴⁸ The ruthenium-tethered complex (*S,S*)-**CAT12**, combined with ammonium formate as the hydrogen source, delivered the corresponding *anti* alcohols in good yields (up to 90%), diastereo- and enantioselectivities (*anti/syn* up to 83:17, up to 99% ee) through a DKR process. The operational utility of this ATH was applied to various α-amino β-keto ester hydrochlorides containing both electron-rich and electron-poor aryl groups on the ketone functional group. Interestingly, heteroaromatic com-

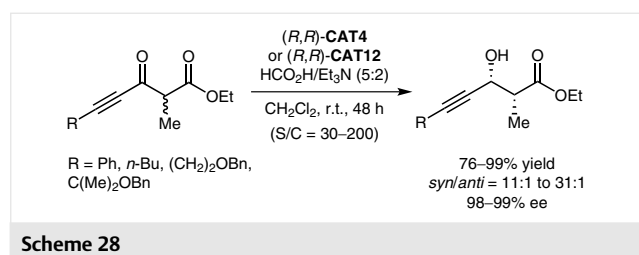
pounds underwent the desired reduction in good yields (up to 79%) affording predominantly the *syn* isomers with excellent enantioselectivities (>98% ee), albeit with moderate diastereoselectivities (*syn/anti* up to 68:32).



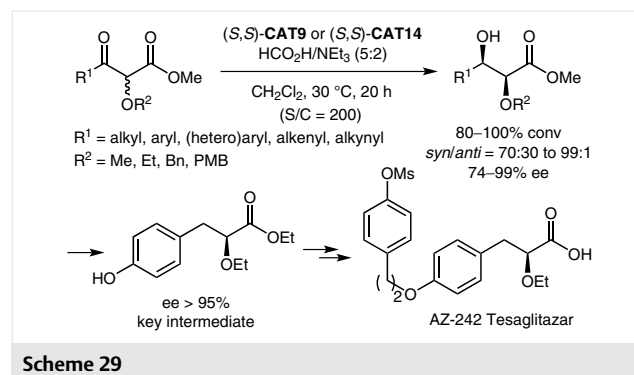
Enantiomerically enriched 2-chloro-3-hydroxy esters are key intermediates of several products of medicinal interest. Zhang and co-workers outlined a new stereoselective route to *syn*-2-chloro-3-hydroxy esters using ATH combined with a DKR process (Scheme 27).⁴⁹ A range of 2-chloro-3-oxo esters was smoothly reduced at room temperature using (*S,S*)-**CAT4** complex and HCO₂H/Et₃N in dichloromethane. Moderate to good yields (up to 85%) were observed with good diastereo- and enantioselectivities (*syn/anti* up to 88:12, 59–98% ee).



In their investigation of the ATH of functionalized acetylenic ketones and diketones using the azeotropic mixture of HCO₂H/Et₃N in combination with complexes (*R,R*)-**CAT4** or (*R,R*)-**CAT12**, Wills and Fang observed an efficient dynamic kinetic resolution with the α -methylated derivatives (Scheme 28).⁵⁰ In all cases, the *syn* product was favored, and the reduction proceeded in high yields (76–99%) with high diastereo- and enantioselectivities (*syn/anti* up to 31:1, 98–99% ee).

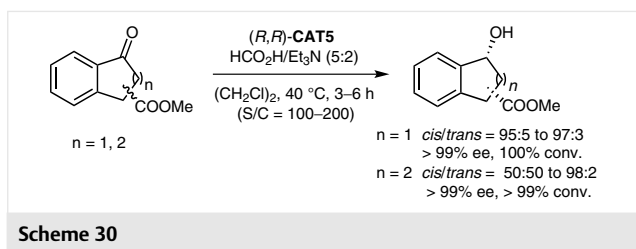


Differentiated *syn*-1,2-diol derivatives are very useful building blocks in organic synthesis and important synthons in natural product synthesis. Our group documented the first direct enantio- and diastereoselective Rh(III)-⁵¹ and Ru(II)-promoted asymmetric hydrogen transfer of racemic α -alkoxy β -keto esters in dichloromethane at 30 °C using HCO₂H/Et₃N (5:2).⁵² This novel strategy had a broad scope and accommodated a wide range of electronically diverse α -alkoxy β -keto esters containing aryl-, alkenyl-, alkynyl- and alkyl-substituted ketones under mild reaction conditions, providing the corresponding α -alkoxy β -hydroxy esters with excellent levels of efficiency and stereocontrol (*syn/anti* up to 99:1, up to 99% ee) (Scheme 29). To highlight the value of this new ATH/DKR transformation, a short synthetic route to a key intermediate of AZ-242 Tesaglitazar, which exhibits type II antidiabetic properties, was developed.

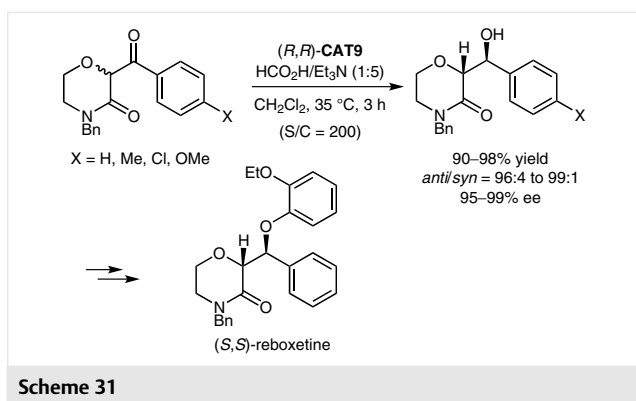


In 2016, Mohar and co-workers achieved the synthesis of several new enantiopure 3-(α -aminobenzyl)-benzo- γ -sultam ligands, which are five-membered cyclic Ts-DPEN analogues. The authors demonstrated that their compounds were excellent ligands in Ru-mediated asymmetric transfer hydrogenation of ketones using triethylammonium formate as a hydride donor (Scheme 30).⁵³ In particular, it was found that the use of the in situ generated catalyst (*R,R*)-**CAT5**, obtained from [RuCl₂(*p*-cymene)]₂ as the ruthenium source, and (*3R,1'S*)-**L4** as the chiral diamine ligand, in dichloroethane at 40 °C, smoothly converted racemic 2- or 3-methoxycarbonyl-1-indanones into the corresponding chiral alcohols with near-perfect enantioselectivities (up to >99% ee) and good to excellent *cis* diastereoselectivities (*cis/trans* ranging from 95:5 to 97:3). Similar results were obtained with 2-methoxycarbonyl- α -tetralone (99% ee, *cis/trans* = 98:2), whereas no diastereoselectivity was observed for the reduction of 3- and 4-methoxycarbonyl- α -tetralones (*cis/trans* = 50:50), while maintaining excellent enantioselectivities (>99% ee).

Lee and co-worker showed that ATH/DKR of 2-benzoylmorpholinones proceeded efficiently to give the corresponding (*2R,3S*)- or (*2S,3R*)-2-(hydroxyphenylmethyl)morpholin-3-ones with an excellent level of diastereo-

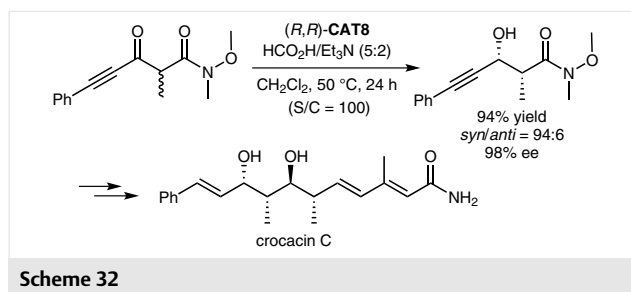


and enantioselectivity (*anti/syn* up to 99:1, 95–99% ee) using 0.5 mol% of the ruthenium complex *(R,R)*-**CAT9** and HCO₂H/Et₃N (5:2) azeotropic mixture as the hydrogen source (Scheme 31).⁵⁴ In addition, this process was employed to prepare all four stereoisomers of the antidepressant, reboxetine.

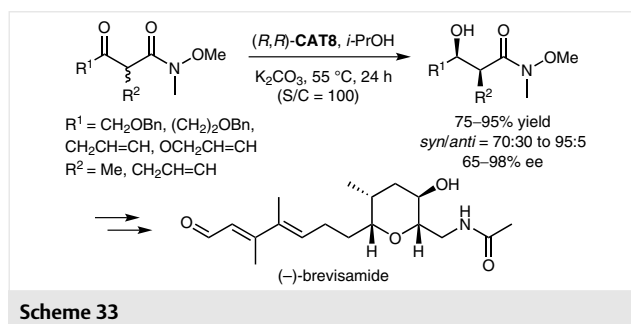


In 2015, Kumaraswamy and co-workers used a Ru(II)-promoted asymmetric transfer hydrogenation of an α -methylated β -keto Weinreb amide coupled with a DKR process in their approach to the potent antifungal and cytotoxic agent (+)-crocacin C. This process provided the key *syn* configuration of the stereotetrad motif (Scheme 32).⁵⁵ Initially, the reaction was performed at 50 °C in dichloromethane using the 18-electron complex [RuCl(*p*-cymene)](*(R,R)*-TsDPEN)] [*(R,R)*-**CAT4**] with a substrate to catalyst ratio of 33 in the presence of HCO₂H/Et₃N (5:2) azeotropic mixture as the hydrogen source. Under these conditions, the enantioenriched acetylenic α -methylated β -hydroxy Weinreb amide was obtained in 60% yield, 92% ee, and good diastereoselectivity (*syn/anti* = 92:8). Interestingly, it was found that a better catalytic activity (94% yield, 98% ee and *syn/anti* = 94:6) could be obtained at a lower catalyst loading (*S/C* = 100) by using the isolated 16-electron Ru-TsDPEN amido complex *(R,R)*-**CAT8**.

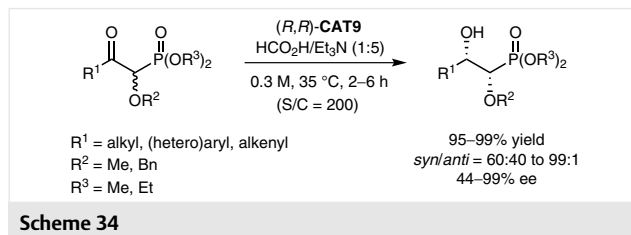
The same group exploited the ATH/DKR reaction for the synthesis of a range of δ/γ -alkoxy- β -hydroxy- α -alkyl-substituted Weinreb amides (Scheme 33).⁵⁶ Careful examinations demonstrated that the presence of δ - or γ -benzyloxy or alkoxy substituents was essential for the reaction to proceed. The reduction was performed employing 1 mol% of



the preformed complex, [Ru(*p*-cymene)](*(R,R)*-TsDPEN)] [*(R,R)*-**CAT8**], in 2-propanol at 55 °C with 10 mol% of K₂CO₃ delivering the expected *syn* alcohols with high stereoselections (*syn/anti* up to 95:5, up to 98% ee). This key transformation could be scaled to 10 g and was applied to the preparation of an advanced intermediate of (–)-brevisamide.

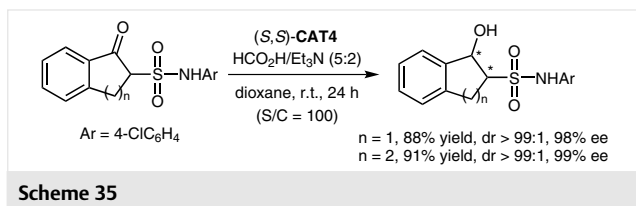


Lee and co-worker described a general protocol for the ATH of a wide range of racemic 2-substituted α -alkoxy β -keto phosphonates employing a HCO₂H/Et₃N (1:5) azeotropic mixture as the hydrogen source and solvent, along with the well-defined chiral catalyst *(R,R)*-**CAT9** (Scheme 34).⁵⁷ The corresponding *syn* monohydroxy-protected 2-aryl-, 2-heteroaryl-, 2-alkyl-, and 2-alkenyl-substituted 1,2-dihydroxy phosphonates were produced in high yields (95–99%) and mainly excellent diastereo- and enantioselectivities (*syn/anti* up to 99:1, up to 99% ee).

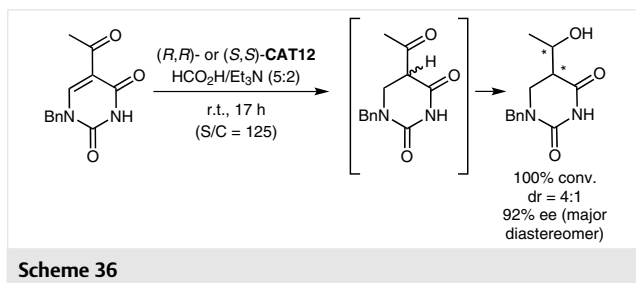


Zhang and co-workers related the DKR of cyclic α -tetralone and α -indanone derivatives (Scheme 35). The ATH of the corresponding β -ketosulfonamides proceeded under mild reaction conditions in dioxane at room temperature with high ee (98%) and dr values (>99:1 dr) using *(S,S)*-**CAT4**

as the catalyst and $\text{HCO}_2\text{H}/\text{Et}_3\text{N}$ (5:2) as the hydrogen donor.⁵⁸



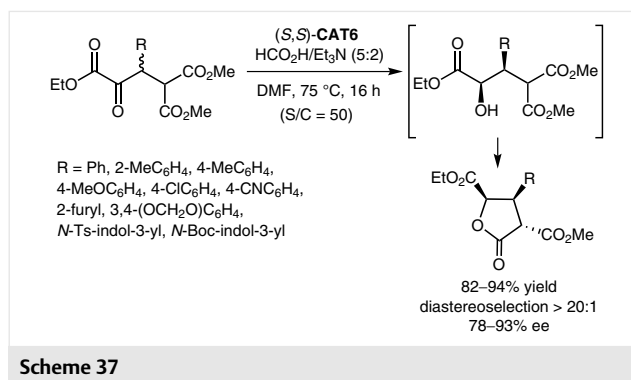
The ATH of *N*-benzyl-5-acetyluracil was investigated by Wills and co-workers with the ruthenium catalysts (*R,R*)-**CAT12** and (*S,S*)-**CAT12** in $\text{HCO}_2\text{H}/\text{Et}_3\text{N}$ (5:2) (Scheme 36).⁵⁹ Interestingly, the use of catalyst (*R,R*)-**CAT12** resulted in the formation of the reduced compound in a 4:1 diastereomeric ratio (the relative configuration of the diastereomers was not determined) in 92% and 33% ee, respectively, whilst catalyst (*S,S*)-**CAT12** gave similar results in terms of stereoselectivity delivering the same major diastereomer. These results suggest that conjugate addition occurred first, resulting in the formation of an enol intermediate, which would tautomerize to give a racemic ketone whose reduction may then proceed via a (dynamic)kinetic resolution.



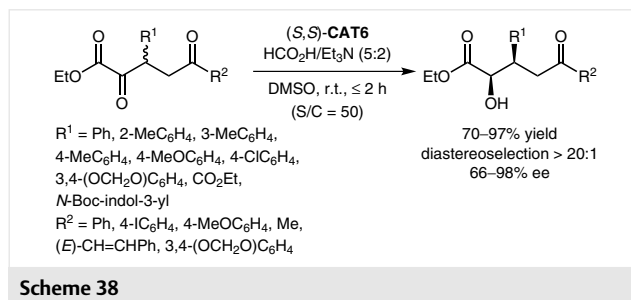
3.3 β -Substituted α -Keto Esters and Phosphonates

The first highly enantioselective ATH/DKR of β -aryl α -keto esters was reported by Johnson and co-workers using a new α -naphthyl/diphenylbenzene sulfonamide catalyst, (*S,S*)-**CAT6**, obtained from $[\text{RuCl}_2(p\text{-cymene})]_2$ and the DPEN-based ligand (*S,S*)-**L6** (Scheme 37).⁶⁰ Because spontaneous diastereoselective lactonization occurred in the process, this transformation allowed direct access to trisubstituted γ -butyrolactones in high yields (up to 94%), establishing three contiguous stereogenic centers with complete diastereocontrol (diastereoselection >20:1) and high enantioselectivities (up to 93% ee).

The chemoselective ATH/DKR of α,δ -diketo esters was also investigated by these authors using the same catalytic system, (*S,S*)-**CAT6** (Scheme 38).⁶¹ The selective reduction of the α -keto ester in the presence of an aryl ketone allowed the exclusive formation of the corresponding δ -keto α -hy-

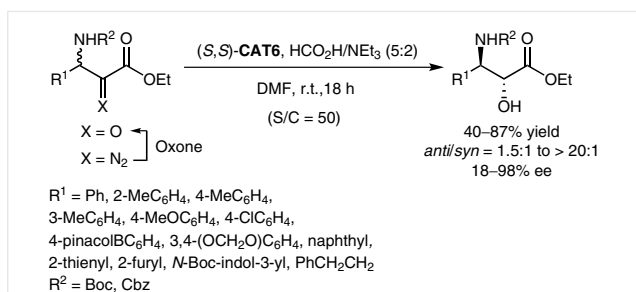


droxy ester as a single diastereomer. High yields (70–97%) and enantioselectivities (up to 98% ee) were obtained for substrates incorporating electron-rich, electron-poor, and heteroaryl substituents at the β -position. Additionally, the ATH/DKR of β -chloro α -keto esters was developed wherein a remarkable ligand-controlled inversion of the preference for the *syn* selectivity to provide *anti*-chlorohydrins was observed. The reaction proceeded with high levels of diastereo- and enantioselectivity for a range of aliphatic and aromatic substrates (*anti/syn* up to >20:1, up to 99% ee).



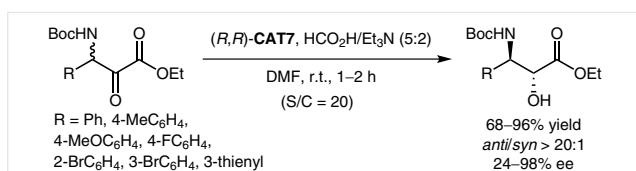
Johnson and co-workers also developed an approach to enantioenriched *anti*- α -hydroxy- β -amino acid derivatives by enantioconvergent reduction of racemic α -keto esters through Ru(II)-catalyzed ATH. The latter were readily prepared from the corresponding α -diazo esters by oxidation with Oxone (Scheme 39).⁶² With the exception of aliphatic β -substituted substrates, high levels of diastereo- and enantioselectivity were attained with heteroaromatic as well as electron-rich and electron-poor aromatic systems (*anti/syn* up to >20:1, up to 98% ee) using (*S,S*)-**CAT6** as the catalyst.

Somfai and co-worker disclosed the ATH/DKR of β -amido α -keto esters to give the corresponding *anti*- β -amido α -hydroxy esters using commercially available or simply prepared chiral ruthenium catalysts (Scheme 40).⁶³ By employing $[\text{RuCl}(p\text{-cymene})((R,R)\text{-FsDPEN})]$ [(*R,R*)-**CAT7**] as the catalyst and $\text{HCO}_2\text{H}/\text{Et}_3\text{N}$ as the reducing agent, the transfer hydrogenation proceeded much faster than on the regioisomeric α -amido β -keto esters and delivered the *anti* aromat-



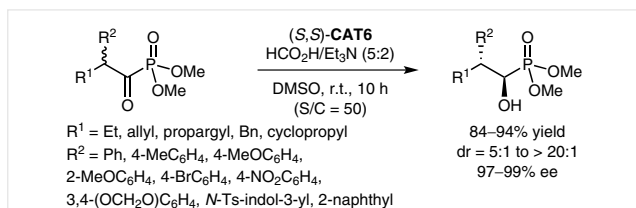
Scheme 39

ic and heteroaromatic compounds as the only detectable diastereomers in good yields and usually with high enantioselectivities (up to 98% ee).



Scheme 40

Johnson and Corbett related the first highly selective dynamic kinetic resolution of acyl phosphonates through ruthenium-mediated ATH with an unexpected reversal in facial selectivity as compared to the analogous reduction of α -keto esters (Scheme 41).⁶⁴ The highest diastereoselectivities (dr up to >20:1) were observed using $[\text{RuCl}_2(p\text{-cymene})_2]$ associated with the bulky α -naphthyl ethylenediamine-derived ligand (*S,S*)-**L6** to generate the corresponding complex (*S,S*)-**CAT6**. A variety of electron-donating and electron-withdrawing groups were tolerated, including heteroaromatic substituents as well as linear and cyclic aliphatic substituents, and the ATH of these substrates provided the reduced products in high yields and enantioselectivities (up to 99% ee).

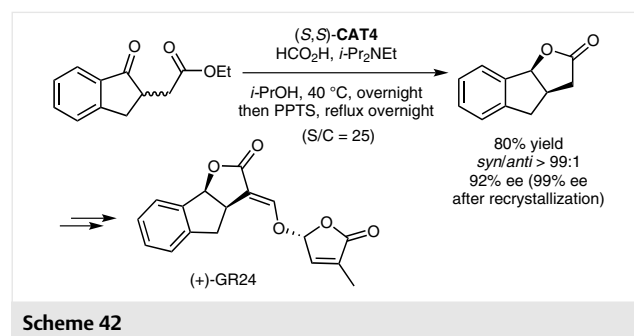


Scheme 41

3.4 β -Substituted γ -Keto Esters

In 2014, a short enantioselective synthesis of the synthetic strigolactone (+)-GR24 was described by McErlean and co-workers (Scheme 42).⁶⁵ One of the key steps in this

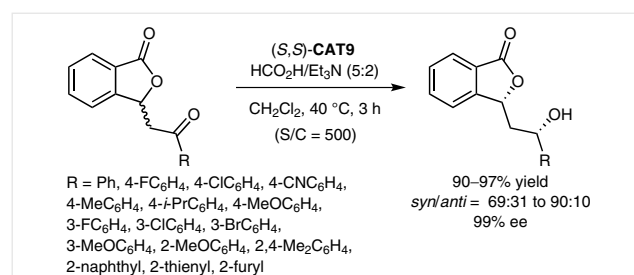
approach relied on the DKR of a racemic indanone via asymmetric transfer hydrogenation. The reaction was performed in the presence of a $\text{HCO}_2\text{H}/i\text{-Pr}_2\text{NEt}$ mixture as the hydrogen source, using 4 mol% of Noyori's (*S,S*)-**CAT4** as the catalyst to afford exclusively, after acid-mediated epimerization, the desired chiral lactone intermediate in 80% yield and 92% ee. This could be improved to >99% ee after a single recrystallization. Interestingly, the use of the (*R,R*)-**CAT4** enantiomer as the catalyst delivered the corresponding (–)-GR24 strigolactone with similar efficiency.



Scheme 42

3.5 β -Alkoxy Ketones

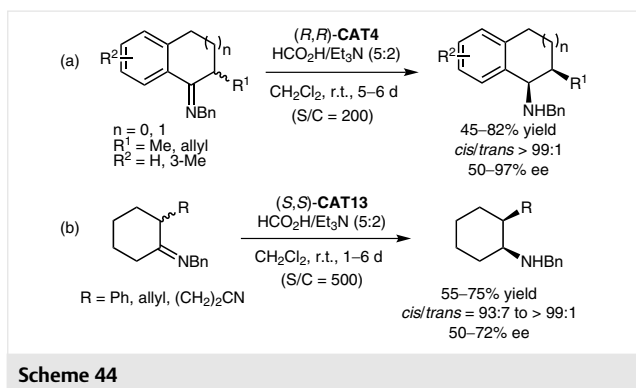
Phthalide frameworks are structural subunits that can be found in a large number of natural products, many of which demonstrate a wide range of biological activity. In 2015, Chen and co-workers showed that by using 0.2 mol% of Noyori's $[\text{RuCl}(\text{mesitylene})(\text{S,S})\text{-TsDPEN}]$ complex [(*S,S*)-**CAT9**] as the catalyst and $\text{HCO}_2\text{H}/\text{Et}_3\text{N}$ as the hydrogen source in dichloromethane at 40 °C, a variety of 3-(2-oxo-arylethyl)isobenzofuran-1(3*H*)-ones could be efficiently reduced to the corresponding optically active phthalide derivatives bearing 1,3-diastereocenters (Scheme 43).⁶⁶ The yield (90–97%) and enantioselectivity (up to 99% ee) of the reaction seemed to be insensitive to both the position and the electronic and steric properties of the substituents on the aryl ring. However, only poor to good diastereomeric ratios ranging from 69:31 to 90:10 were achieved under these conditions.



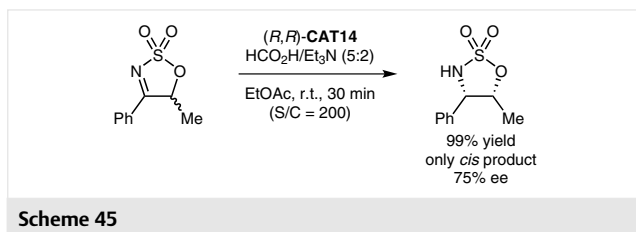
Scheme 43

3.6 Imine Derivatives^{4m,67}

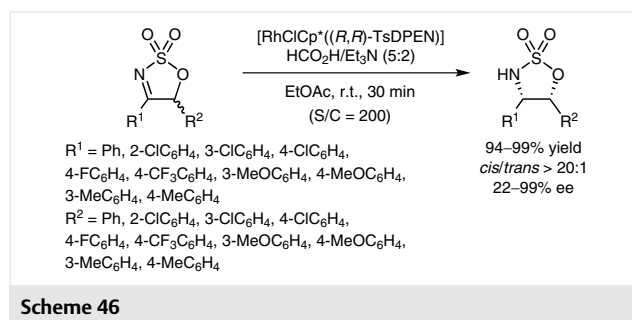
The first report on the ATH of imines associated with a DKR process was published in 2005 by Fernández and co-workers.⁶⁸ The reduction of 2-substituted bicyclic and monocyclic ketimines using a HCO₂H/Et₃N azeotropic mixture as the hydrogen source and [RuCl(*p*-cymene)(*R,R*)-TsDPEN] [(*R,R*)-**CAT4**] or [IrClCp*((*S,S*)-TsDPEN)] [(*S,S*)-**CAT13**] as the catalyst afforded the corresponding cycloalkylamines with excellent *cis* selectivities in all cases (Scheme 44). For the bicyclic substrates, the Ru(II) catalyst (*R,R*)-**CAT4** afforded moderate to good yields with enantioselectivities up to 97%, after extended reaction times (5 to 6 days, Scheme 44, a). On the other hand, the less bulky monocyclic substrates gave better results in Ir(III)-mediated reactions, with high *cis* selectivities and enantioselectivities of up to 72% being observed with (*S,S*)-**CAT13** (Scheme 44, b). Moreover, to overcome the difficulties encountered in some imine syntheses, the authors also described a one-pot procedure starting from the corresponding ketones, with similar overall yields and selectivities. They showed that imines reacted faster than ketones under ATH conditions, as previously reported by the group of Noyori.⁶⁹



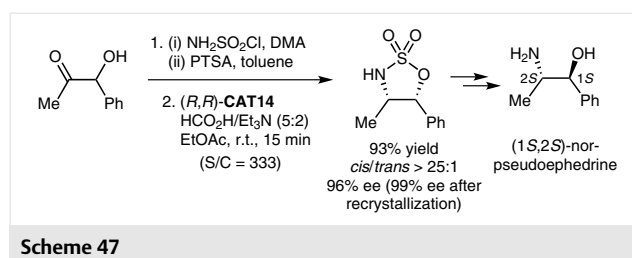
In 2010, Lee and co-workers published the first example of the ATH of racemic 4,5-disubstituted cyclic sulfamidates via DKR, using [RhClCp*((*R,R*)-(TsDPEN))] [(*R,R*)-**CAT14**] as the catalyst and HCO₂H/Et₃N azeotropic mixture as the hydrogen source (Scheme 45).⁷⁰ The reduced compound was obtained in excellent yield, perfect *cis* diastereoselectivity and an enantioselectivity of 75%.



The same authors found that replacing the methyl substituent at the 5-position by an aryl group resulted in a considerable increase in enantioselectivity, from 75% to 99% (Scheme 46).⁷¹ This might be explained by a more rapid racemization at the stereocenter owing to enhancement of the lability of the related hydrogen. A broad scope of aryl substituents showed excellent yields and high stereoselectivities (*cis/trans* >20:1, up to 99% ee). Notably, substrates bearing electron-withdrawing groups at the *ortho*-position displayed low enantioselectivities (22%). Surprisingly, when a cyclic sulfamidate imine possessing an electron-donating group at the *para*-position was subjected to the optimized ATH reaction conditions, only the starting material was recovered.

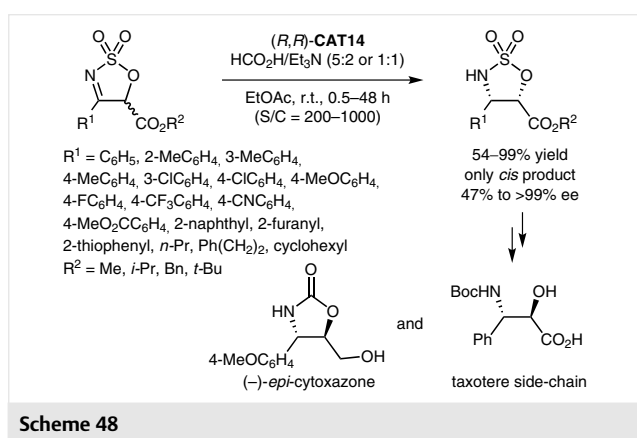


The same group reported the use of this method for a straightforward route to both enantiomers of norpseudoephedrine, an alkaloid possessing psychostimulant activities and showing numerous uses as a ligand in asymmetric synthesis.⁷² Commercially available 1-hydroxy-1-phenylpropan-2-one was easily converted into the cyclic sulfamidate imine, which was subjected to the ATH reaction using 0.3 mol% of the Rh catalyst (*R,R*)-**CAT14** in combination with HCO₂H/Et₃N as the hydrogen source to afford only the *cis* product with excellent yield (93%) and enantioselectivity (96%, improved to 99% after recrystallization). The product was then easily transformed into the desired (1*S*,2*S*)-norpseudoephedrine after four steps including the inversion of configuration at C-1 without loss of optical purity (Scheme 47).

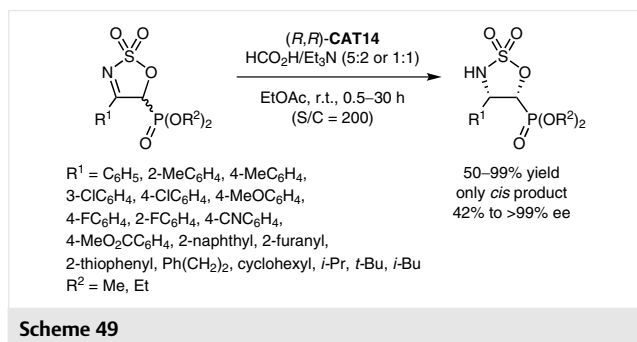


To extend the scope of the reaction and to demonstrate the utility of this transformation, Lee and co-workers applied the Rh-catalyzed ATH/DKR procedure to substrates bearing a carboxylate group at the acidic stereogenic posi-

tion. Several substituted sulfamidates have been reduced under these conditions with excellent yields (54–99%) and stereoselectivity (only *cis* product, up to 99% ee) (Scheme 48).⁷³ It should be pointed out that several substrates bearing alkyl substituents have also been reduced with moderate to high levels of stereoselectivity. The authors observed that changing the HCO₂H/Et₃N ratio from 5:2 to 1:1 had a significant positive effect on both the reactivity and the stereochemical outcome of the reaction.⁷⁴ Moreover, using the aforementioned ATH/DKR process as a key step, convenient and highly stereoselective syntheses of (–)-*epi*-cytoxazone and of the taxotere side-chain were achieved.



Finally, reduction by ATH/DKR of cyclic sulfamidates bearing a phosphonate group was reported in 2015 by Lee and co-workers using the chiral [RhClCp*((*R,R*)-TsDPEN)] [(*R,R*)-CAT14] catalyst and HCO₂H/Et₃N as the hydrogen source (Scheme 49).⁷⁵ Compounds with electron-withdrawing and electron-donating groups as well as heteroaryl and alkyl-bearing substrates have been reduced with high yields (up to 99%) and stereoselectivities (only the *cis* product was obtained, up to >99% ee).



4 Conclusion

Asymmetric reduction of ketone and imine derivatives to access chiral alcohols and amines is a major synthetic organic transformation. In this context, asymmetric hydroge-

nation and transfer hydrogenation reactions based on dynamic kinetic resolution processes using organometallic catalysts enable the transformation of inexpensive, prochiral starting materials into high-value building blocks. These methods allow efficient access to pharmaceutical agents and natural products via a simple one-step procedure, with high diastereo- and enantiocontrol of the target structures. This review demonstrates the utility of such homogeneous catalytic processes, which can be used for the production of high-profile medicinal targets in operationally simple and broadly general protocols.

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