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

Pierre-Georges Echeverria
Tahar Ayad
Phannarath Phansavath*
Virginie Ratovelomanana-Vidal*

PSL Research University, Chimie ParisTech - CNRS, Institut de Recherche de Chimie Paris, 75005 Paris, France
virginie.vidal@chimie-paristech.fr

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.

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 developing new asymmetric reactions is of critical importance to organic synthesis.

Amongst stereoselective reactions, the asymmetric reduction of unsaturated compounds is the most fundamental means of introducing chirality in organic compounds. Two of these transformations, transition-metal-catalyzed asymmetric hydrogenation (AH) and asymmetric transfer hydrogenation (ATH), 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. 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 (% rac) of the starting material has to be faster than the rate of the asymmetric transformation (% asym, k asymmetric) and one enantiomer must react faster than the other one (% asym). 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. The structures of the ligands and complexes described in this review are shown in Figure 1 and Figure 2, respectively.
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 \( \alpha \)-substituted-\( \beta \)-keto esters, catalyzed by Raney-Nickel modified by \((RR)\)-tartaric acid, yielding the reduced product as a 78:22 \( \text{syn/anti} \) mixture with a 57% ee for the syn isomer.\(^7\) In 1989, the pioneering work of Noyori\(^8\) and that of Genêt and co-workers\(^9\) led to the first examples of homogeneous enantioselective ruthenium-promoted hydrogenations of racemic \( \alpha \)-acetamido-\( \beta \)-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-oxobutyrate provided the corresponding \( \text{syn-L} \) and \( \text{D-threo} \) derivatives with high levels of enantioselectivity (up to 98\% ee) and diastereoselectivity (\( \text{syn/anti} \) up to 99:1).

Thereafter, Noyori and co-workers published extensively on asymmetric hydrogenation via DKR of \( \alpha \)-substituted-\( \beta \)-keto esters, including stereochemical models\(^{10,11}\) 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
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). After intensive experiments, the RuCl$_2$(S)-xyl-Segphos/(S)-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 $\alpha$-arylcyclohexanones through DKR by using a chiral (diamine)/(spirodiphosphine)ruthenium(II) chloride complex as the catalyst (Scheme 5). Under optimized reaction conditions, a series of enantiomerically enriched $\alpha$-arylcyclohexanols was obtained in 68–98% yield with excellent cis selectivities ($cis/trans >99:1$) and enan-

this field of research and they include, but are not limited to, asymmetric hydrogenation via DKR of non-activated ketones, organocatalyzed DKR and enzymatic DKR. Organocatalyzed DKR has been 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). After intensive experiments, the RuCl$_2$(S)-xyl-Segphos/(S)-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 $\alpha$-arylcyclohexanones through DKR by using a chiral (diamine)/(spirodiphosphine)ruthenium(II) chloride complex as the catalyst (Scheme 5). Under optimized reaction conditions, a series of enantiomerically enriched $\alpha$-arylcyclohexanols was obtained in 68–98% yield with excellent cis selectivities ($cis/trans >99:1$) and enan-

2.1 $\alpha$-Substituted Ketones

In 2011, Ohkuma and co-workers reported the asymmetric hydrogenation of various aryl heterocycloalkyl ketones through DKR using [RuCl$_2$((S)-Binap)((R)-DMAPEN)] as the catalyst (Scheme 3). 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 $X = CH_2$, 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.

As the catalyst (Scheme 3), 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 $X = CH_2$, 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.
tioselectivities ranging from 57% to 99% by employing \((S_r, R_r)-\text{CAT1}\) 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 \(\alpha\)-arylcyclohexanols was also demonstrated by the synthesis of several biologically active molecules such as \((-)\text{-}\text{\textit{\textalpha}}\text{-lycorane}, \text{\textit{\textalpha}}\text{-CP 55940 and tetrahydrocannabinol derivatives.}

The same group further extended the above-mentioned method for the enantioselective synthesis of \((-)\text{-galanthamine and (-)}\text{-lycoramine, two alkaloids that have been used clinically as selective acetylcholinesterase inhibitors for the treatment of Alzheimer's disease (Scheme 6).}^{18}\) In this case, the synthetic route featured ruthenium-catalyzed asymmetric hydrogenation via DKR of a racemic \(\alpha\)-aryloxy cyclic ketone, producing the key chiral \(\beta\)-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 \([\text{RuCl}_2(S\text{-xyl-Segphos})][\text{(S-DIA-PEN)}] 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 \((+)-\text{conocarpan as well as other members of the neolignan family.}

### 2.2 \(\alpha\)-Substituted \(\beta\)-Keto Esters and Amides

Continuing a long-established interest in metal-catalyzed reductions/DKR,^{16,20}\) 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 \(\alpha\)-amino and \(\alpha\)-amido \(\beta\)-keto esters (Scheme 8). Application of the \(\text{Ru(II)}\text{-SYNPHOS}-catalyzed asymmetric hydrogenation reaction to both racemic \(\alpha\)-amino and \(\alpha\)-amido \(\beta\)-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 Hamada and our group.22,23 In 2014, we accomplished the AH/DKR transformation of α-amino β-keto ester hydrochlorides using a catalytic 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 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 [(Ir([H][S]-SYNPHOS)][μ-I])2 (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 CH2Cl2/MeOH using 13 bar of hydrogen pressure and 1 mol% of the Ru-SYNPHOS catalyst (R)-CAT17 developed in our group.23 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 stereoinductions (96% ee, 94% de) were obtained using the [Ru(OAc)2((S)-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 hydrogenating faster than the interconversion between the enantiomers.

Zhang and co-workers described the enantio- and diastereoselective synthesis of β-hydroxy-β-amino acids in situ generated [RuCl2(p-cymene)]2−(S)-SunPhos as the
catalyst for the asymmetric hydrogenation of β'-keto-β- amino esters through DKR (Scheme 12). 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 [RuCl₂(p-cymene)]₂⋅(S)-SunPhos in these solvent mixtures was more efficient than [RuCl₂(p-cymene)]₂ associated with common diphosphine ligands in CH₂Cl₂/MeOH or CH₂Cl₂/EtOH.

**Scheme 12**

![Scheme 12](image)

**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). By using [RuCl₂(benzene)](S)-SunPhos 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 CeCl₃·7H₂O.

**Scheme 13**

![Scheme 13](image)

The same group disclosed the asymmetric hydrogenation of α-substituted β-keto phosphonates in the presence of [RuCl₂(benzene)](S)-SunPhos as the catalyst (Scheme 14). 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**

![Scheme 14](image)

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-iodanone or α-tetralone (Scheme 15). The reaction was performed using 0.4 mol% of the cationic complex [Ru(OTf)₂(p-cymene)][(R,R)-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**

![Scheme 15](image)

**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). The reduction of α-ethoxycarbonyl-alkyl-α’-aryl cyclic ketones catalyzed by (S,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-lycoranone.
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. The key feature of this approach relied on the selective total synthesis of (−)-hamigeran B and (−)-4-bromohamigeran B. The catalyst of choice for the asymmetric hydrogenation of racemic ketones catalyzed by [Ir(cod)Cl]2(R)-CAT2, bearing a spiropropidine–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 heteroarenes 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). 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, 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-workers designed a conceptually new Ru(II)-arene catalyst bearing N-sulfonylated 1,2-di-amines 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 Knochel and Noyori.
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 [(RuCl₂(p-cymene))₂] in combination with (Ts₂S)-TsDPEN and HCO₂H/Et₃N as the hydrogen source (Scheme 19).⁴⁰ The ATH/DKR reaction using the (SS)-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 [(RuCl₂((RR)-Ts-DPEN)] complex [(RR)-CAT₇] and HCO₂H/Et₃N (5:2) as the hydrogen source, 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 HCO₂H/Et₃N (5:2) azeotropic mixture. These optimized DKR transfer reaction conditions were applied to a series of diversely substituted allyl 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 20

AH 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 [(RuCl₂(p-cymene)/(RR)-C₅F₅SO₂DPEN)] complex [(RR)-CAT₆] and HCO₂H/Et₃N (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 HCO₂H/Et₃N (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 α-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 α 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 (SS)-CAT₁₁ obtained from [RuCl₂(benzene)]₂ and (SS)-BnDPAE LS as the ligand, in the presence of HCO₂H/Et₃N 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).

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). 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%), diastereo- and enantioselectivities (anti/syn up to 23:1) and enantioselectivities (up to 96% ee) for a broad range of substrates (Scheme 24). In 2015, our group developed an efficient, flexible and atom-economic synthesis of the four stereoisomers of (+)-(1R,2R)-thiampenicol, 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). 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 as the best catalyst, furnished the corresponding (2S,3R)- and (2R,3S)-syn-alcohols in high yields and stereoselectivities (syn/anti >99:1, 90% ee). Alternatively, asymmetric transfer hydrogenation employing the [RuCl(η⁵-mesitylène)[(S,S)-TsDPEN]] complex, (SS)- or (RR)-CAT9 and HCO₂H/Et₂N (S/C = 33) as the hydrogen source provided, at 50 °C, the anti- (2R,3R)- and (2S,3S)-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 thiampenicol.

We also focused our attention on the first asymmetric transfer hydrogenation of racemic α-amino β-keto ester hydrochlorides (Scheme 26). 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-

Scheme 22

Scheme 23

Scheme 24

Scheme 25
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).

Differentiated syn-1,2-diol derivatives are very useful building blocks in organic synthesis and important synths in natural product synthesis. Our group documented the first direct enantio- and diastereoselective Rh(III)- and Ru(II)-promoted asymmetric hydrogen transfer of racemic α-alkoxy β-keto esters in dichloromethane at 30 °C using HCO2H/NEt3N (5:2). This novel strategy had a broad scope and accommodated a wide range of electronically diverse α-alkoxy β-keto esters containing aryl-, alkenyl-, alkylnyl- 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.

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). A range of 2-chloro-3-oxo esters was smoothly reduced at room temperature using (S,S)-CAT4 complex and HCO2H/NEt3N 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). 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).

In 2016, Mohar and co-workers achieved the synthesis of several new enantiopure 3-(α-aminoaryl)-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). 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-benzoyl morpholinones proceeded efficiently to give the corresponding (2R,3S)- or (2S,3R)-2-(hydroxyphenylmethy) 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) azotropic mixture as the hydrogen source (Scheme 31). 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 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) azotropic mixture as the hydrogen source and solvent, along with the well-defined chiral catalyst [(R,R)-CAT9] (Scheme 34). 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-te-tralone 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 HCO$_2$H/Et$_3$N (5:2) as the hydrogen donor.$^{58}$

Scheme 35

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 HCO$_2$H/Et$_3$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.

Scheme 36

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/diphenyl/benzene sulfonamide catalyst, (S,S)-CAT6, obtained from [RuCl$_2$(p-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-butyro lactones in high yields (up to 94%), establishing three contiguous stereogenic centers with complete diastereoselectivity (diastereoselection > 20:1) and high enantioselectivities (up to 93% ee).

Scheme 37

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 diazo esters by oxidation with Oxone (Scheme 39).$^{62}$ With the exception of aliphatic β-substituted substrates, high levels of diastereore- 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 [RuCl$_2$(p-cymene)(R,R)-FsDPEN] [(R,R)-CAT7] as the catalyst and HCO$_2$H/Et$_3$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-
ic and heteroaromatic compounds as the only detectable diastereomers in good yields and usually with high enantioselectivities (up to 98% ee).

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). The highest diastereoselectivities (dr up to >20:1) were observed using [RuCl₂(α-naphthyl)mesitylene] 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 (RR)-CAT4 enantiomer as the catalyst delivered the corresponding (+)-GR24 strigolactone with similar efficiency.

### 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 ([RuCl₆][P-cymene])₂ complex ([SS]-CAT9) as the catalyst and HCO₂H/Et₃N as the hydrogen source in dichloromethane at 40 °C, a variety of 3-(2-oxo-aryl)isobenzofuran-1(3H)-ones could be efficiently reduced to the corresponding optically active phthalide derivatives bearing 1,3-diastereocenters (Scheme 43). 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 39**

\[
\text{DHCO}_2\text{H}, \text{HNEt}_2 (S/C = 5:2)
\]

\[
\begin{align*}
\text{NH}_2\text{O} & \quad \text{R}^1 \quad \text{O} \\
\text{OH} & \quad \text{R}^2 \quad \text{O}
\end{align*}
\]

**Scheme 40**

**Scheme 41**

**Scheme 42**

**Scheme 43**

---

3.6 Imine Derivatives

The first report on the ATH of imines associated with a DKR process was published in 2005 by Fernández and co-workers. The reduction of 2-substituted bicyclic and monocyclic ketimines using a HCO₂H/Et₃N azeotropic mixture as the hydrogen source and [RuCl₂(p-cymene)][(R,R)-TsDPEN] [(R,R)-CAT₄] or [IrCl₂(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.

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). 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.

In 2010, Lee and co-workers published the first example of the ATH of racemic 4,5-disubstituted cyclic sulfamidates via DKR, using [RhCl₂(Cp*)][(R,R)-(TsDPEN)] [(R,R)-CAT₁₄] as the catalyst and HCO₂H/Et₃N azeotropic mixture as the hydrogen source (Scheme 45). The reduced compound was obtained in excellent yield, perfect cis diastereoselectivity and an enantioselectivity of 75%.

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. Commerically 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 (1S,2S)-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 position.
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). 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 stereochemo- logical outcome of the reaction. Moreover, using the aforementioned ATH/DKR process as a key step, convenient and highly stereoselective syntheses of (–)-epi-cytaxozane 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). 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).

Acknowledgment

The contributions of all current and past group members are gratefully acknowledged. This work was supported by the CNRS (Centre National de la Recherche Scientifique) and the MENESR (Ministère de l’Éducation nationale, de l’Enseignement supérieur et de la Recherche). P.-G.E. is grateful to the Agence Nationale de la Recherche (ANR-11-BS07-017-02) for a grant (2011-2014). We also gratefully acknowledge financial support from our industrial partners.

References

(42) For a recent review, see: Zhang, Y.; Farrant, H.; Li, X. Chem. Asian J. 2014, 9, 1752.