



**HAL**  
open science

# Recent Progress and Applications of Transition-Metal-Catalyzed Asymmetric Hydrogenation and Transfer Hydrogenation of Ketones and Imines through Dynamic Kinetic Resolution

Ricardo Molina Betancourt, Pierre-Georges Echeverria, Tahar Ayad,  
Phannarath Phansavath, Virginie Ratovelomanana-Vidal

## ► To cite this version:

Ricardo Molina Betancourt, Pierre-Georges Echeverria, Tahar Ayad, Phannarath Phansavath, Virginie Ratovelomanana-Vidal. Recent Progress and Applications of Transition-Metal-Catalyzed Asymmetric Hydrogenation and Transfer Hydrogenation of Ketones and Imines through Dynamic Kinetic Resolution. *Synthesis: Journal of Synthetic Organic Chemistry*, 2020, 53, pp.30 - 50. 10.1055/s-0040-1705918 . hal-04351621

**HAL Id: hal-04351621**

**<https://hal.science/hal-04351621>**

Submitted on 18 Dec 2023

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

# Recent Progress and Applications of Transition-Metal-Catalyzed Asymmetric Hydrogenation and Transfer Hydrogenation of Ketones and Imines through Dynamic Kinetic Resolution

Ricardo Molina Betancourt<sup>a</sup>

Pierre-Georges Echeverria<sup>b</sup>

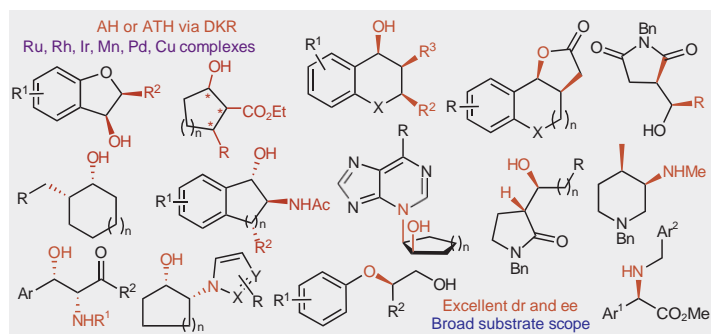
Tahar Ayad<sup>a</sup>

Phannarath Phansavath<sup>\*a</sup>

Virginie Ratovelomanana-Vidal<sup>\*a</sup>

<sup>a</sup> CSB2D Team, Institute of Chemistry for Life & Health Sciences, Chimie ParisTech-CNRS, PSL University, 11 Rue Pierre et Marie Curie, 75005 Paris, France  
phannarath.phansavath@chimieparistech.psl.eu  
virginie.vidal@chimieparistech.psl.eu

<sup>b</sup> Minakem Recherche, 145 Chemin des Lilas, 59310 Beuvry-la-Forêt, France



Received: 19.06.2020

Accepted after revision: 22.07.2020

Published online: 06.10.2020

DOI: 10.1055/s-0040-1705918; Art ID: ss-2020-z0335-r

**Abstract** Based on the ever-increasing demand for enantiomerically pure compounds, the development of efficient, atom-economical, and sustainable methods to produce chiral alcohols and amines is a major concern. Homogeneous asymmetric catalysis with transition-metal complexes including asymmetric hydrogenation (AH) and transfer hydrogenation (ATH) of ketones and imines through dynamic kinetic resolution (DKR) allowing the construction of up to three stereogenic centers is the main focus of the present short review, emphasizing the development of new catalytic systems combined to new classes of substrates and their applications as well.

- 1 Introduction
- 2 Asymmetric Hydrogenation via Dynamic Kinetic Resolution
  - 2.1  $\alpha$ -Substituted Ketones
  - 2.2  $\alpha$ -Substituted  $\beta$ -Keto Esters and Amides
  - 2.3  $\alpha$ -Substituted Esters
  - 2.4 Imine Derivatives
- 3 Asymmetric Transfer Hydrogenation via Dynamic Kinetic Resolution
  - 3.1  $\alpha$ -Substituted Ketones
  - 3.2  $\alpha$ -Substituted  $\beta$ -Keto Esters, Amides, and Sulfonamides
  - 3.3  $\alpha,\beta$ -Disubstituted Cyclic Ketones
  - 3.4  $\beta$ -Substituted Ketones
  - 3.5 Imine Derivatives
- 4 Conclusion

**Key words** asymmetric hydrogenation, asymmetric transfer hydrogenation, dynamic kinetic resolution, chiral alcohols, chiral amines, enantioselectivity, diastereoselectivity

## 1 Introduction

Enantiomerically pure alcohols and amines are structural motifs of central importance for the manufacture of chemical products such as organic materials, agrochemicals, flavors, fragrances, and pharmaceuticals. Therefore, it is not surprising that the development of truly efficient methods to prepare such structures remains a paramount goal of practical significance in both academia and industry. Among the plethora of transformations available in the organic chemistry toolbox, homogeneous late-transition-metal-catalyzed asymmetric hydrogenation (AH)<sup>1</sup> and asymmetric transfer hydrogenation (ATH)<sup>1n,2</sup> are undoubtedly regarded as two of the most efficient, environmentally benign and straightforward approaches to build up diastereomerically and enantiomerically pure alcohols and amines in high yields and selectivities from their prochiral carbonyl and imine starting materials. In the meantime, dynamic kinetic resolution (DKR),<sup>3</sup> an effective alternative to traditional kinetic resolution, has emerged as increasingly fruitful, with many applications in asymmetric synthesis and catalysis over the past decades. In a DKR process, the kinetic resolution step is initiated with an in situ racemization. As a result, the substrate can be fully converted into a single product with a 100% theoretical yield. Consequently, under DKR conditions the AH or ATH of a homochiral substrate bearing a labile stereocenter allows the synthesis of a single, enantiomerically pure diastereomer. To succeed in obtaining an efficient DKR, the rate of racemization ( $k_{\text{rac}}$ ) of the ketone or imine must be faster than the rate of the asymmetric reduction ( $k_1$  and  $k_2$ ) and one enantiomer must

react faster than the other one ( $k_1 > k_2$  or  $k_2 > k_1$ ). Moreover, the asymmetric transformation has to be irreversible, i.e. the product formed during the reaction must be stable to avoid any racemization (Figure 1).

In this regard, the first examples of homogeneous catalytic AH of  $\beta$ -keto esters with a configurationally labile a-

stereocenter using dynamic stereomutation were independently reported in 1989 by the groups of Noyori<sup>4</sup> and Genêt.<sup>5</sup> More precisely, these authors demonstrated that Ru(II) complexes bearing either BINAP or CHIRAPHOS ligands were highly efficient catalysts for the stereoselective hydrogenation of 2-(acylamino)-3-oxobutanone giving the

## Biographical Sketches



**Virginie Vidal** was born in Paris. She received her Ph.D. from Paris-Sud University under the supervision of Prof. H. P. Husson and Dr. J. Royer (Gif, France). She then pursued post-doctoral appointments with Prof. S. Hnessian (Montreal University, Canada, 1989–1990), Prof. P. Potier and Dr. R. H. Dodd (Gif,

1991). She was appointed as a CNRS Associate Researcher with Prof. J. P. Genêt at Ecole Nationale Supérieure de Chimie de Paris. She is currently CNRS Research Director at Chimie Paris-Tech (Paris, France). Her research interests focus on transition-metal catalysis for atom- and step-economical reactions

and the design of atropisomeric ligands (Synphos and Difluorophos) 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** was born in Vientiane (Laos). She received her Ph.D. from Pierre and Marie Curie University in 1997 under the supervision of Prof. M. Malacria and Dr C. Aubert. After postdoctoral studies in the

group of Prof. C. Bolm at the Institut für Organische Chemie, RWTH Aachen (Germany), she was appointed assistant professor in 1999 in the group of Prof. J.-P. Genêt at Ecole Nationale Supérieure de Chimie de Paris

(ChimieParisTech). Her current research interests include total synthesis of biologically relevant natural products and transition-metal-catalyzed asymmetric reactions.



**Tahar Ayad** 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 total synthesis of imino sugars that exhibit antituberculosis activity. After his Ph.D., he was engaged in a

post-doctoral position with Professor Robert S. Coleman at Ohio State University working on total synthesis of oximidine I and II. After a brief period spent in 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 ligands synthesis, transition-metal-catalyzed asymmetric reactions and, the synthesis of biologically relevant active compounds.



**Pierre-Georges Echeverria** 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

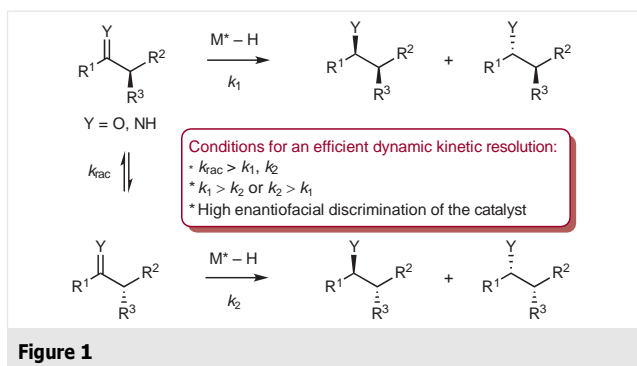
2015 he joined the group of Prof. Alois Fürstner at the Max-Planck-Institut für Kohlenforschung as a postdoctoral fellow working on iron catalysis. He is R&D scientist at Minakem since 2016.



**Ricardo Molina Betancourt** was born in 1995 in Guatemala. He graduated from the National Graduate School of Chemistry of Montpellier (ENSCM; Montpellier, France) in 2019. He

moved to ENSCP Chimie Paris-Tech to continue his education as a Ph.D. student under the supervision of Dr. Phannarath Phansavath and Dr. Virginie Vidal focusing on the develop-

ment of catalytic methodologies to synthesize enantioenriched building blocks.



corresponding *syn* L- and D-threonine derivatives, respectively, in high yields and with excellent levels of stereocontrol depending on the reaction conditions. In the late 1990s, the groups of Knochel<sup>6</sup> and Noyori and Ikariya<sup>7</sup> published the first reports dealing with ATH via DKR of benzil derivatives using well-defined Ru(II) arene complexes that featured either *C*<sub>2</sub>-symmetrical ferrocenyl diamines or *N*-tosyl-1,2-diphenylethylenediamine (TsDPEN) as chiral ligands in *i*-PrOH or in a mixture of formic acid and triethylamine as hydrogen donors, respectively. These pioneering studies have inspired intense work to further expand the concept of AH and ATH combined with DKR of functionalized unsaturated compounds. Since 2000, efforts in this direction have witnessed a significant improvement in the design of new late-transition-metal catalysts with increased performance regarding reactivity, selectivity, and productivity.

This (update)<sup>3a</sup> review covers the period from January 2016 to May 2020 and intends to summarize the latest developments in the rapidly expanding area of late-transition-metal-catalyzed AH and ATH of substituted ketones and imines under cooperative DKR that simultaneously create two or more stereogenic centers in a single synthetic step. Excellent overviews of the topics cited in sections of this current short review have been recently published.<sup>1v,w,2z-ac,3r</sup> The structures of the ligands and complexes reported in this review are depicted in Figure 2 and Figure 3.

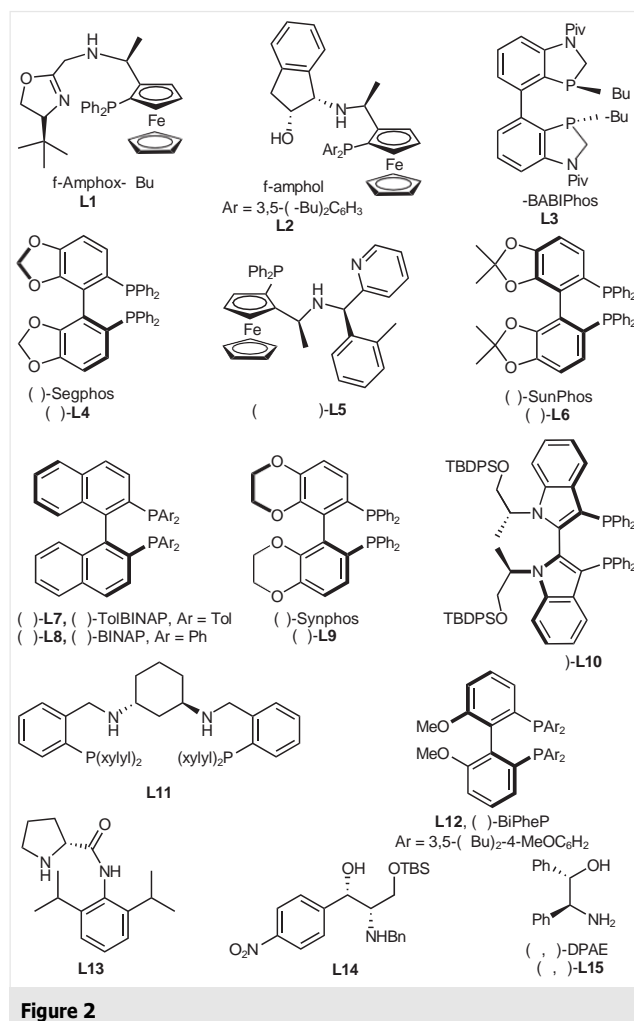
## 2 Asymmetric Hydrogenation via Dynamic Kinetic Resolution

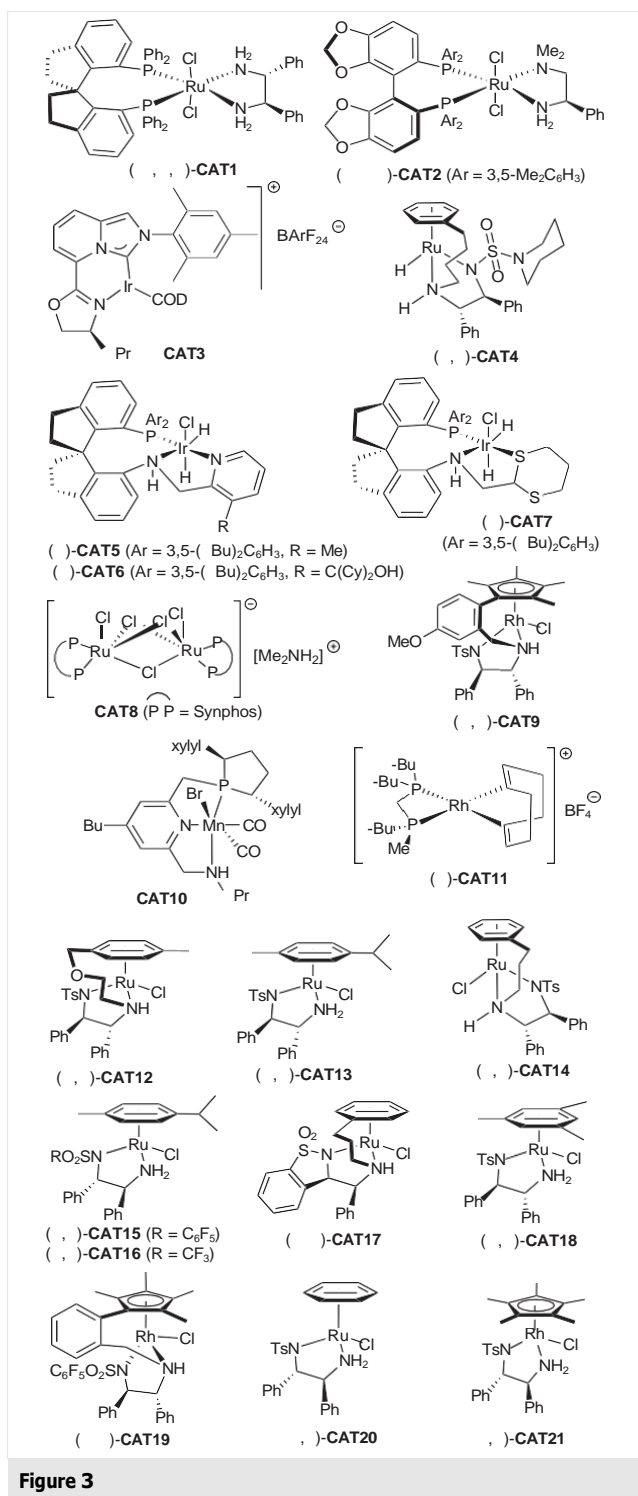
### 2.1 $\alpha$ -Substituted Ketones

In 2016, Zhou and co-workers succeeded in developing a new strategy to access chiral 2,3-*cis*-dimethyldihydrobenzofurans through a scalable Ru-catalyzed AH of racemic 3-(aryloxy)butan-2-ones employing a dynamic kinetic resolution (DKR) as the enantioselective step (Scheme 1).<sup>8</sup> The hydrogenation was performed using 0.02 mol% of chiral spiro ruthenium catalyst (*Sa,R,R*)-CAT1 under 50 atm of hydro-

gen in *i*-PrOH in the presence of *t*-BuOK at room temperature for 2.5 h to provide the targeted chiral alcohols in 99% yield with a high diastereoselectivity (*anti/syn* 95:5) and up to 97% ee. This protocol allowed the development of the first total synthesis of (+)-PI-220 and (+)-3-*epi*-furaquinocin C.

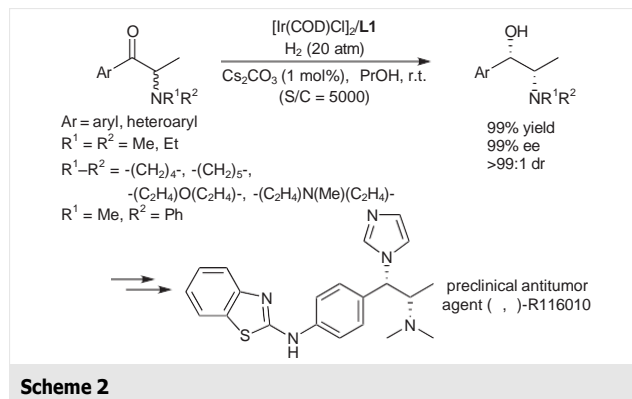
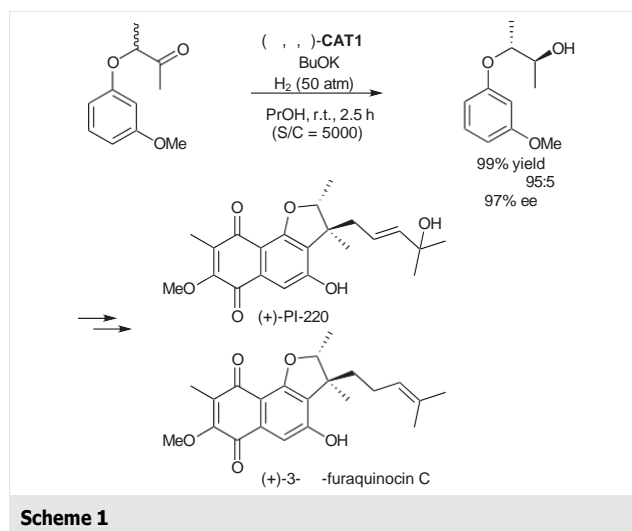
Chiral amino alcohols are important structural features that are present in numerous biologically active natural products, drugs, and pharmaceuticals. In 2017, Zhang, Dong, and co-workers demonstrated that the combination of an iridium complex with the chiral f-Amphox-*t*-Bu ligand (**L1**) in the presence of Cs<sub>2</sub>CO<sub>3</sub> could be efficiently used for the synthesis of chiral *N,N*-disubstituted  $\alpha$ -amino  $\beta$ -unfunctionalized alcohols (Scheme 2).<sup>9</sup> Indeed, under the cooperative dynamic kinetic AH, a broad range of racemic  $\alpha$ -amino  $\beta$ -unfunctionalized ketones were smoothly converted into the corresponding amino alcohols in almost quantitative yields and high levels of stereoselectivity. Worthy of note is that this reaction can be performed under low catalyst loading (up to S/C 5000) with high TON (up to 100000)





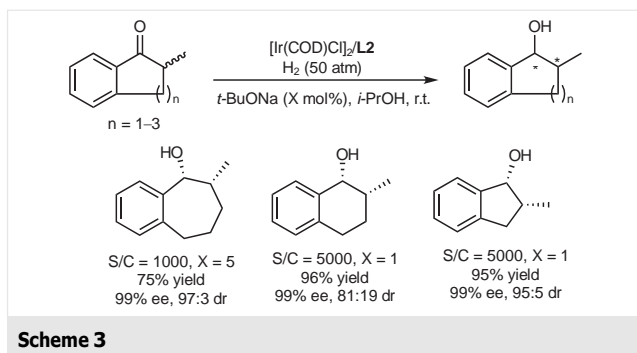
and more importantly, proved to be applicable for the preparation of a key intermediate of the preclinical antitumor agent (*S,S*)-R116010.

In 2018, Zhang, Dong, and co-workers investigated the stereoselective hydrogenation of Ir-mediated AH of racemic

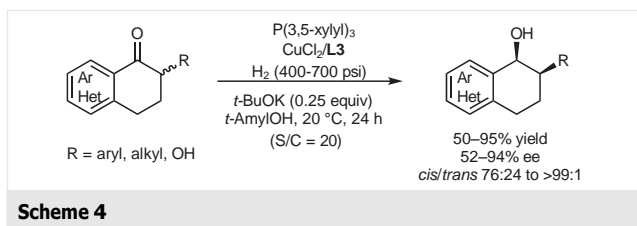


benzo-fused cyclic ketones via a DKR process using a new family of chiral ferrocene-based amino phosphine alcohol (*f*-Amphol) ligands.<sup>10</sup> The *f*-Amphol ligand **L2** with a 3,5-di-*tert*-butylphenyl group was identified as the optimal ligand, giving the targeted chiral benzo-fused cyclic alcohols in 75–96% yields and consistently excellent 99% ee. However, and as depicted in Scheme 3, the diastereomeric ratios of the reaction proved to be highly dependent on the size of the benzo-fused ring. The synthetic utility of the methodology was demonstrated by preparing a key intermediate of an anticonvulsant drug eslicarbazepine acetate (BIA 2-093, not shown).

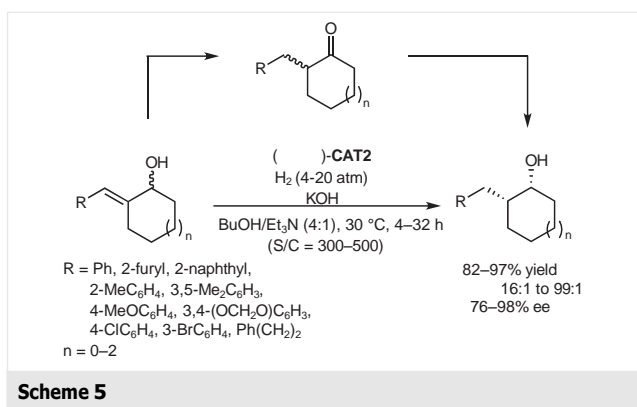
Kozłowski and co-workers designed, in 2018, a new series of highly modular and tunable heterophosphole dimeric ligands that proved to be effective chiral inducers in the first copper-catalyzed AH of racemic 2-substituted 1-tetralones and related heteroaryl ketones through DKR that furnished the corresponding optically enriched 2-substituted 1-tetralols (Scheme 4).<sup>11</sup> Optimization of the reaction parameters revealed that the catalytic system composed of CuCl<sub>2</sub>, electron-rich P(3,5-xylyl)<sub>3</sub> as ancillary phosphine, and the electron-poor azaphosphole *N*-BABIPhos **L3** was



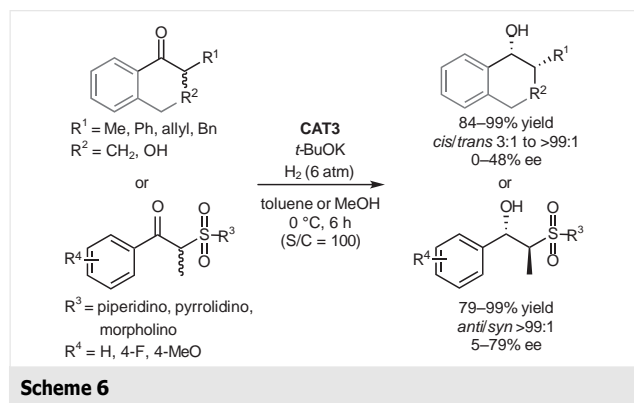
the most efficient, offering a unique combination of high reactivities and selectivities at room temperature in *t*-AmylOH. From a mechanistic point of view, DFT computational methods clearly revealed that this process involves the formation of a reactive heteroligated dimeric copper hydride intermediate incorporating two Cu atoms generated in situ where different ligands are coordinated to each Cu.



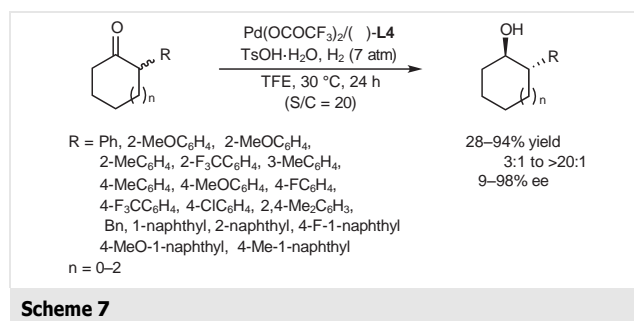
In 2019, Ohkuma and co-workers described the preparation of *cis*-2-substituted cycloalkan-1-ols from racemic 2-alkylidenecycloalkan-1-ols via an isomerization/AH sequence through a DKR (Scheme 5). The use of  $[RuCl_2\{(S)\text{-xylyl-Segphos}\}\{(R)\text{-DMAPEN}\}]$  complex ( $S_p,R_N$ )-CAT2 in the presence of a mixture of *t*-BuOH/*Et*<sub>3</sub>N and KOH under 4–20 atm of hydrogen afforded the corresponding *cis*-alcohols in 82–97% yields with *cis/trans* selectivities up to 99:1 dr and up to 98% ee. The reaction proceeded through isomerization of the allylic alcohol into the racemic  $\alpha$ -substituted ketone which was reduced by AH through DKR.<sup>12</sup>



In 2020, de Ruyter and co-workers reported the AH/DKR of  $\alpha$ -substituted ketones catalyzed by a new chiral iridium carbene-oxazoline complex **CAT3** based on an imidazo[1,5-*a*]pyridine backbone (Scheme 6).<sup>13</sup> The hydrogenation of  $\alpha$ -substituted cyclohexanones, acetophenones, and tetralones and  $\beta$ -keto sulfonamides under 6 atm of hydrogen in the presence of *t*-BuOK proceeded with up to >99:1 dr and up to 79% ee via DKR of the in situ formed enolate.



Zhou, Yu, and co-workers reported the first efficient Pd-catalyzed AH of 2-arylcycloalkanones through DKR under acidic conditions.<sup>14</sup> The reaction was performed with Pd(OCOCF<sub>3</sub>)<sub>2</sub> with (*R*)-Segphos [(*R*)-L4] as a ligand in the presence of TsOH·H<sub>2</sub>O providing a facile access to chiral *trans*-2-arylcycloalkan-1-ols in 28–94% yield, up to 98% ee, and *trans* selectivities for cyclohexanones up to >20:1 dr, whereas cyclopentanones and cycloheptanones gave lower yields (Scheme 7). The role of the Brønsted acid was essential in accelerating the racemization of the 2-arylcycloalkanones via the enol intermediate.

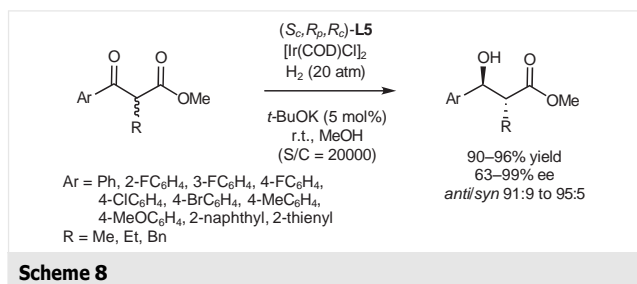


## 2.2 $\alpha$ -Substituted $\beta$ -Keto Esters and Amides

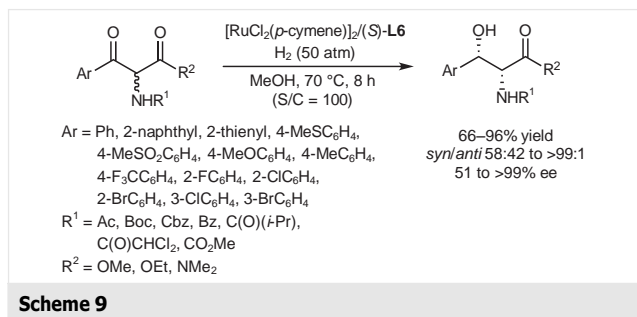
A new class of chiral ferrocenyl *P,N,N*-ligands was designed by Hu and Hou in 2016 for the AH of numerous  $\alpha$ -alkyl-substituted acyclic  $\beta$ -aryl- $\beta$ -keto esters containing diversely substituted aryl groups via DKR.<sup>15</sup> Various ketone substrates were reacted in the presence of 0.005 mol% of  $[Ir(COD)Cl]_2$  and 0.011 mol% of the ligand (*S<sub>c</sub>R<sub>p</sub>R<sub>c</sub>*)-L5 under 20 atm of H<sub>2</sub> in the presence of 5 mol% of *t*-BuOK to de-



liver enantioenriched *anti*- $\beta$ -hydroxy esters in 90–96% yield with up to 95:5 dr and 63–99% ee (Scheme 8). The effectiveness of this new ligand stems from the introduction of a second stereogenic center which increases the structural rigidity and steric hindrance.

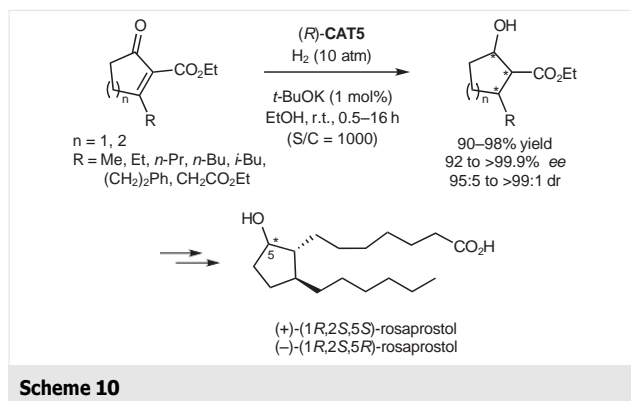


Zhang and co-workers described the synthesis of *syn*- $\alpha$ -amido- $\beta$ -hydroxy esters through AH/DKR of the corresponding  $\alpha$ -amido- $\beta$ -keto esters using the preformed complex [RuCl(*p*-cymene)(*S*)-SunPhos]Cl obtained from [RuCl(*p*-cymene)]<sub>2</sub> and (*S*)-SunPhos [(*S*)-L6] (Scheme 9).<sup>16</sup> This study revealed the importance of the steric and electronic effects of the substituents on the aryl moiety and that the stereoselectivities were also deeply influenced by the nature of the amino protecting group. The hydrogenation proceeded in 66–96% yields with high reactivity (TON up to 940), 58:42 to >99:1 dr, and 51 to >99% ee.

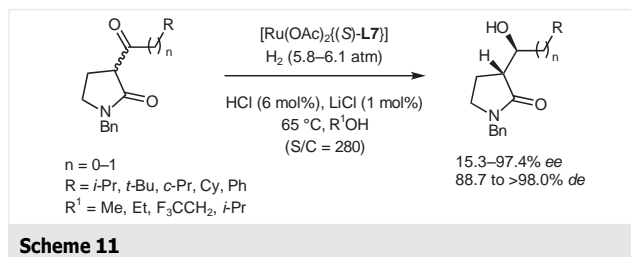


Zhou, Xie, and co-workers displayed a highly enantioselective preparation of chiral cyclopentanols allowing control of three contiguous stereocenters (Scheme 10).<sup>17</sup> The reaction was performed using (*R*)-Ir-SpiroPAP complex (*R*)-CAT5 (0.1 mol%) and *t*-BuOK under 10 atm of H<sub>2</sub> in EtOH giving enantioselectivities ranging from 92 to >99.9% ee and 95:5 to >99:1 dr. The key feature of this reaction is a one-pot, two-step sequential reduction of the C=C bond followed by AH of the C=O bond of the resulting  $\beta$ -keto esters upon DKR. The utility of this methodology was shown by the synthesis of all stereoisomers of the antiulcer drug rospirostol.

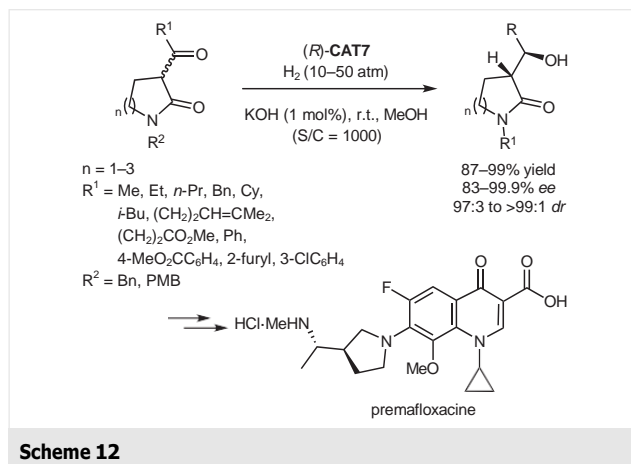
$\beta$ -Hydroxy- $\eta$ -lactam is a common skeleton found in numerous bioactive compounds. As such, in 2016 Maguire and co-workers developed a highly stereoselective synthesis us-



ing Ru-catalyzed AH of  $\beta$ -keto- $\eta$ -lactams through DKR (Scheme 11).<sup>18</sup> Using [Ru(OAc)<sub>2</sub>(*S*)-TolBINAP] complex [with (*S*)-TolBINAP = (*S*)-L7] and HCl/LiCl as additives to enhance the reactivity, under 5.8–6.1 atm of H<sub>2</sub>, a wide range of substrates were reduced with up to >98% de and up to 97.4% ee.

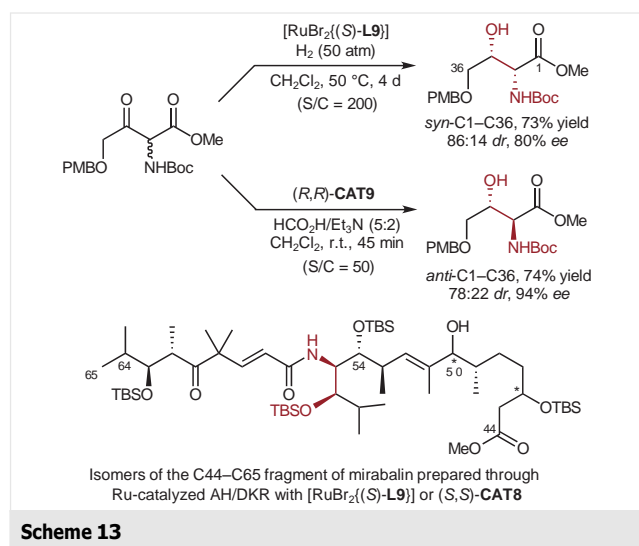


In 2017, Zhou, Xie, and co-workers explored the same transformation<sup>19</sup> using (*R*)-Ir-SpiroSAP complex (*R*)-CAT7 (Scheme 12). Under optimized conditions, racemic  $\beta$ -keto-lactams were reduced using 0.1 mol% of the Ir catalyst with KOH as a base under 10–50 atm of H<sub>2</sub> in methanol to furnish chiral  $\beta$ -hydroxy-lactams in 87–99% yield, 97:3 to >99:1 dr and 83–99.9% ee. Reaction conditions are tolerant



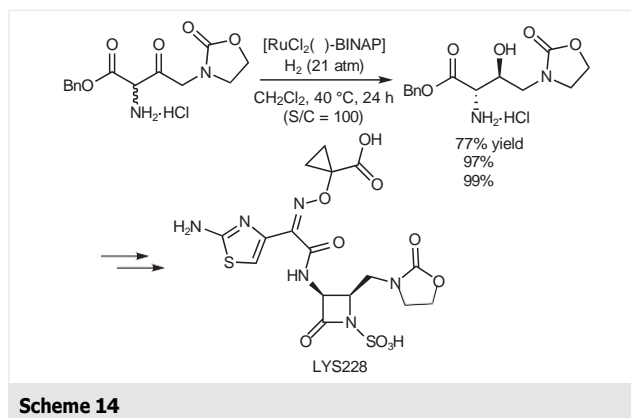
to different ring sizes as well as different ketone substituents (alkyl or aryl). Furthermore, the synthetic utility of this method was successfully demonstrated by the preparation of optically pure (*S*)-*N*-methyl-1-[(*R*)-pyrrolidin-3-yl]ethan-1-amine, a key intermediate en route to the antibiotic premafloxacin.

Continuing a long-established interest in transition-metal-catalyzed asymmetric reductions,<sup>3f,20</sup> our group prepared several key fragments of the cytotoxic macrolide mirabalin through a flexible strategy based on either Ru-catalyzed AH or Rh-promoted ATH (Scheme 13).<sup>21</sup> The *syn*-isomer of the C1–C36 subunit and two isomers of the C44–C65 side chain of mirabalin were thus prepared by using an AH/DKR approach with either the ruthenium complex [RuBr<sub>2</sub>{(*S*)-Synphos}] [i.e. [RuBr<sub>2</sub>(*S*)-**L9**] bearing the in-house developed **L9** ligand<sup>22</sup> or catalyst **CAT8**<sup>23</sup> which afforded good levels of diastereo- and enantioselectivities. On the other hand, the *anti*-isomer of the C1–C36 fragment was obtained by performing an ATH reaction with the rhodium complex (*R,R*)-**CAT9**.<sup>24</sup>

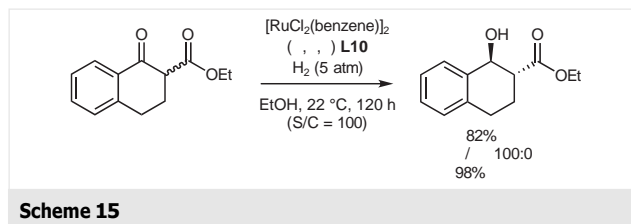


Cheung and co-workers reported a synthesis of the monobactam antibiotic LYS228 based on an AH/DKR of a racemic  $\alpha$ -amino- $\beta$ -keto ester to introduce the *anti*- $\beta$ -amino alcohol moiety (Scheme 14). The hydrogenation was carried out with Noyori's catalyst [RuCl<sub>2</sub>{(*S*)-BINAP}] [with BINAP = (*S*)-**L8**] under 21 atm and delivered the *anti*- $\alpha$ -amino- $\beta$ -hydroxy ester with 97% de and 99% ee.<sup>25</sup>

In 2019, Brückner and Baumann developed a novel route to atropisomerically pure biindolyldiphosphane ligands that did not rely on the resolution of a racemic mixture (Scheme 15).<sup>26</sup> The new ligands (*R,R,M*)-**L10** and (*R,R,P*)-**L10** were remarkably efficient in the Ru(II)-cata-

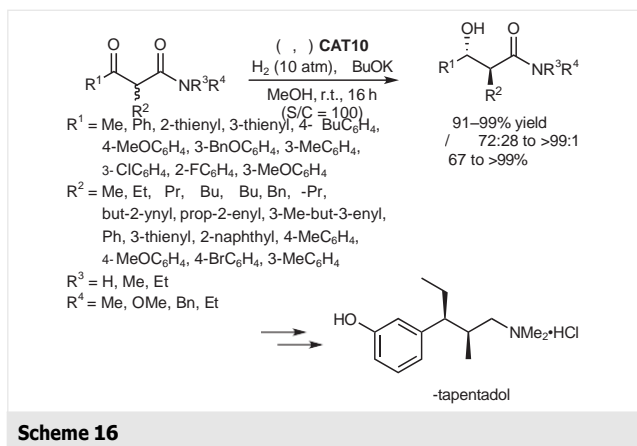


lyzed AH of ethyl 1-oxo-2,3,4-tetrahydronaphthalene-2-carboxylate, affording the corresponding reduced compound with perfect *trans* selectivity and excellent enantioinduction, outperforming BINAP (**L8**) in this case in terms of enantioselectivity.



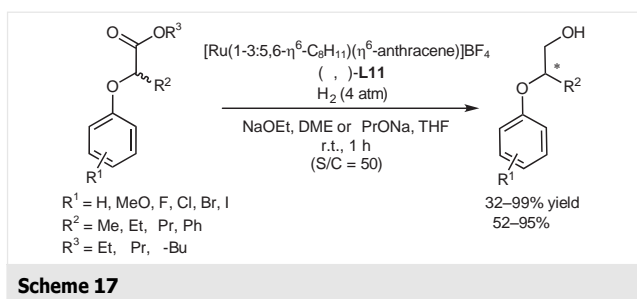
Considering the importance of exploring alternative synthetic methods using non-precious metal complexes for long-term sustainability and because  $\alpha$ -substituted  $\beta$ -hydroxy amides are useful building blocks to access bioactive molecules and chiral drugs, Ding and co-workers succeeded in developing, in 2020, the first application of Mn catalysts in the AH of racemic  $\alpha$ -substituted  $\beta$ -keto amides through DKR (Scheme 16).<sup>27</sup> A screening of the reaction parameters demonstrated that the reaction proceeded smoothly in MeOH at room temperature for 16 h in the presence of *t*-BuOK under 10 atm of hydrogen by using 1 mol% of the complex (*R,R*)-**CAT10** incorporating a lutidine-based chiral *P,N,N*-ligand. The reaction tolerated a broad scope of substrates and the *anti*- $\alpha$ -alkyl- or  $\alpha$ -aryl-substituted  $\beta$ -hydroxy amides were produced in 91–99% yield and TON up to 10000, with up to >99% dr and up to >99% ee. The origin of high stereoselectivities has been detailed by DFT calculation study. The synthetic utility of the method was showcased in the enantioselective formal synthesis of the opioid drug tapentadol. The hydrogenation was efficiently scaled on 10 mmol in the presence of 0.01 mol% of (*R,R*)-**CAT10** and *t*-BuOK under 50 atm of hydrogen at 70 °C for 48 h in MeOH to provide the key intermediate to access the chiral drug tapentadol in 99% yield with 97:3 dr and 90% ee.





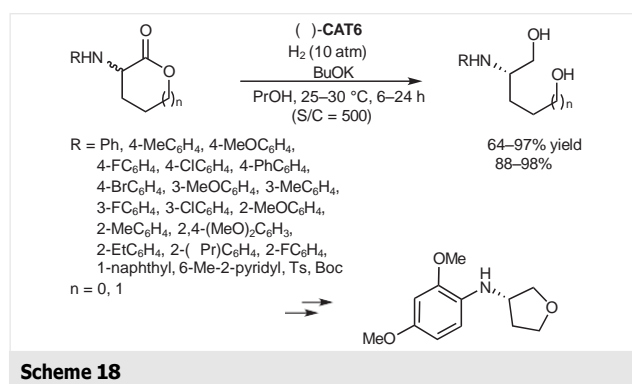
### 2.3 $\alpha$ -Substituted Esters

In 2019, Bergens and co-workers outlined the first highly active and enantioselective hydrogenation of  $\alpha$ -substituted acyclic esters through a DKR process by using an in situ prepared ruthenium complex obtained from  $[\text{Ru}(1\text{-}3\text{-}5,6\text{-}\eta^6\text{-C}_8\text{H}_{11})(\eta^6\text{-anthracene})]\text{BF}_4$  and (*R,R*)-**L11** under 4 atm of hydrogen in the presence of NaOEt or *i*-PrONa as a base (Scheme 17).<sup>28</sup> In this case, the ATH/DKR reaction led to  $\beta$ -chiral primary alcohols, with only one stereocenter present in the reduced compound. Under the optimized conditions, the reaction proceeded with up to 100% conversion, up to 95% ee, and 1000 turnovers to afford the corresponding alcohols.



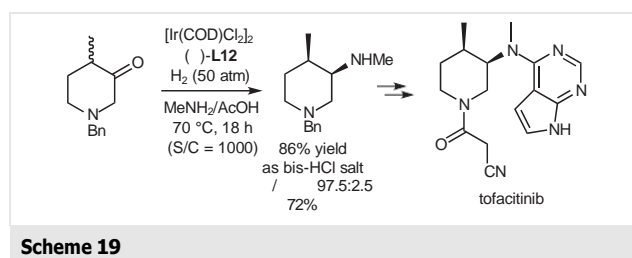
In 2019, Xie and co-workers reported the first Ir-catalyzed enantioselective hydrogenation of racemic  $\alpha$ -(aryl-amino)  $\delta$ - and  $\eta$ -lactones through DKR pattern to provide a novel route to chiral 2-(aryl-amino)alkane-1,4- and -1,5-diols, respectively (Scheme 18).<sup>29</sup> A wide range of  $\alpha$ -(aryl-amino)- $\eta$ -butyrolactones and  $\alpha$ -(aryl-amino)- $\delta$ -valerolactones were hydrogenated under mild conditions in the presence of 0.2 mol% of site-specifically modified chiral spiro iridium complex (*R*)-**CAT6** in *n*-PrOH at 25–30 °C in the presence of *t*-BuOK to deliver the corresponding chiral 2-(aryl-amino)butane-1,4-diols in up to 97% yields with 88–98% ee as well as 2-(aryl-amino)pentane-1,5-diols in 85–96% yields with 90–97% ee. This AH reaction could be performed on a

gram scale using a lower catalyst loading: hydrogenation of racemic  $\alpha$ -(aryl-amino)- $\eta$ -butyrolactone was conducted in the presence of 0.05 mol% of (*R*)-**CAT6** (S/C = 2000) producing the useful building block (*S*)-2-(aryl-amino)butane-1,4-diol in 90% yield with 97% ee allowing access to chiral 3-(aryl-amino)-1-aza/oxocycloalkane derivatives present in numerous pharmaceuticals.

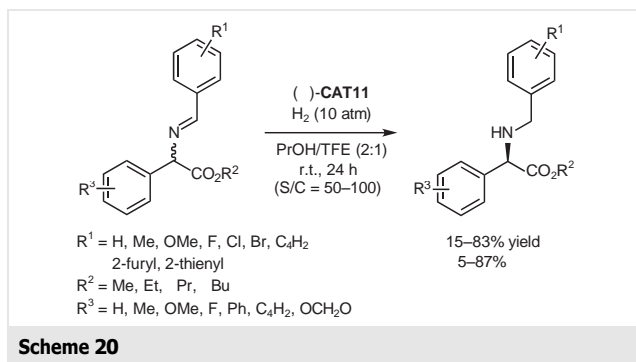


### 2.4 Imine Derivatives

In 2018, Lefort and co-workers developed an efficient catalytic asymmetric reductive amination under DKR conditions for the preparation of a key intermediate in the total synthesis of tofacitinib, a drug used for the treatment of rheumatoid arthritis.<sup>30</sup> A high-throughput screening showed that the best catalytic system for this transformation was the combination of an iridium complex with (*S*)-BiPheP [(*S*)-**L12**] as a ligand (Scheme 19). The use of acidic conditions for the imine formation and the racemization was found to be essential for the success of this protocol.



Zhang, Zhang, and co-workers described the AH of aldimines through DKR catalyzed by the rhodium complex (*R*)-**CAT11** of P-stereogenic diphosphine ligand trichickenfootphos (Scheme 20).<sup>31</sup> When subjected to the optimized reaction conditions using 2 mol% of the Rh complex in *i*-PrOH/TFE at room temperature for 24 h, a series of enantio-enriched arylglycines were prepared in 15–83% yield and up to 87% ee. The proposed mechanism involved a racemization of the substrate via an unstable intermediate in acidic medium. One of the enantiomers is reduced at a faster rate to deliver the main product in the preferred configuration.



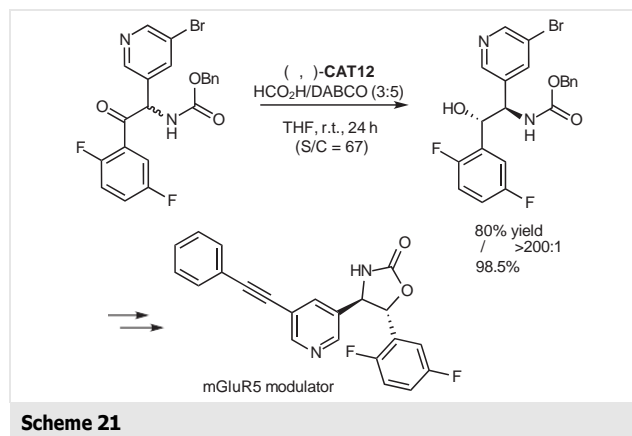
### 3 Asymmetric Transfer Hydrogenation via Dynamic Kinetic Resolution

In 1950, Doering and Young<sup>32</sup> reported the pioneer example of a catalytic ATH highlighting an asymmetric version of the Meerwein–Ponndorf–Verley (MPV) reduction of ketone derivatives catalyzed with *rac*-aluminum alkoxides using (*S*)-butan-2-ol as the hydrogen source to produce chiral alcohols with enantioselectivities ranging from 5.9 to 22%. In 1995, Noyori, Ikariya, and co-workers<sup>33</sup> designed novel Ru(II)-arene catalysts combined with *N*-sulfonylated 1,2-diamines or amino alcohols as chiral ligands which were successfully used in the ATH of ketones and imines and represented a major breakthrough in the field. After this discovery, intense efforts have been devoted to the development of novel efficient catalysts in both academia and industry. Consequently, ATH is now recognized as one of the most effective and practical methods to access enantiomerically pure compounds because of its practicality, broad substrate scope, and high stereoselectivities. Of particular interest is the application of ATH through DKR conditions that offers a challenging route for the enantioselective preparation of enantioenriched alcohols and amines and whose pioneer examples were reported by the groups of Knochel<sup>6</sup> and Noyori and Ikariya.<sup>7</sup> In this section, we will focus our attention on the ATH of carbonyl compounds and imines.

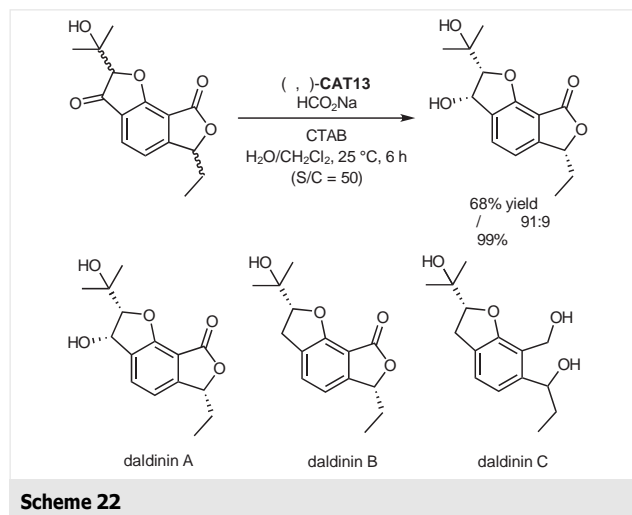
#### 3.1 $\alpha$ -Substituted Ketones

Because the mGluR5 receptor has attracted interest for a few therapeutic indications, in 2016 González-Bobes and co-workers reported the enantioselective preparation of a pharmaceutical candidate mGluR5 modulator via the ATH of an  $\alpha$ -amino ketone derivative (Scheme 21).<sup>34</sup> The key reactions to access the chiral core of the targeted molecule involved an aza-benzoin condensation and a transfer hydrogenation through a DKR process. The ATH was performed at room temperature in THF using 1.5 mol% of (*S,S*)-Ts-DENEB [(*S,S*)-CAT12] with HCO<sub>2</sub>H/DABCO (3:5) as the hydrogen

donor for 24 h to provide the corresponding *anti*- $\beta$ -amino alcohol intermediate in 80% yield with >200:1 dr and 98.5% ee. Considering the relatively low catalyst turnovers of the ketoreductases (80% yield, 41 h, 30 °C), this transition-metal-catalyzed process compared favorably with the biocatalytic method.

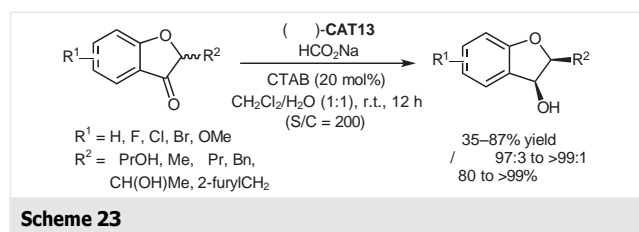


In 2016, Fang and co-workers achieved a practical access to a series of *cis*-benzoannulated compounds using ATH, via DKR.<sup>35</sup> This novel, mild and general synthetic route allowed access to a novel structural class of significance in medicinal chemistry, including daldinins A, B, and C natural products (10.1%, 7.6%, 6.8% overall yields, respectively). Transfer hydrogenation of the racemic lactone derivative was conducted at 25 °C for 6 h using [RuCl(*p*-cymene)][(*R,R*)-TsDPEN] [(*R,R*)-CAT13], HCO<sub>2</sub>Na as the hydrogen source, and cetyltrimethylammonium bromide (CTAB) as a phase-transfer agent in H<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub> delivering the expected *cis*-dihydrobenzofuran motif in 68% yield with 91:9 dr and 99% ee (Scheme 22). The absolute configuration was assigned by X-ray diffraction analysis. Based on previous re-

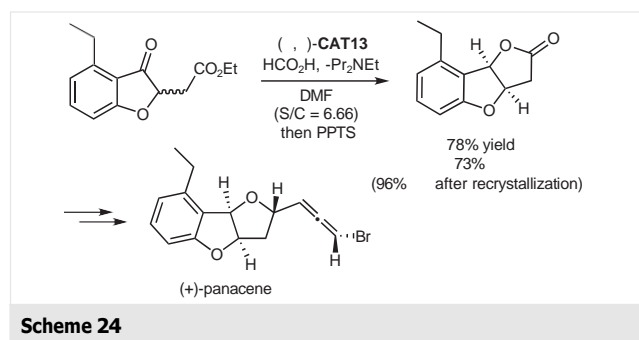


ports, it was proposed that the racemization might occur through retro-oxo-Michael/oxo-Michael reaction and keto-enol tautomerism.

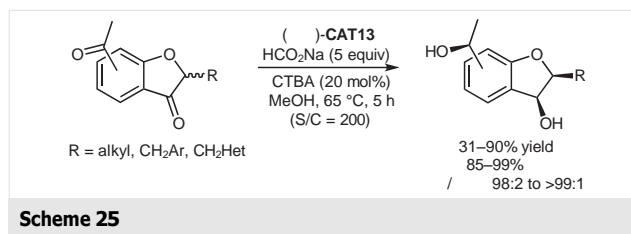
In 2017, Fang and co-workers reported the Ru-catalyzed synthesis of *cis*-2,3-dihydrobenzofuran-3-ols by aqueous transfer hydrogenation via DKR by using complex (*R,R*)-**CAT13**, HCO<sub>2</sub>Na as a hydrogen source, and CTAB as a phase-transfer catalyst in a CH<sub>2</sub>Cl<sub>2</sub>/H<sub>2</sub>O (1:1) mixture at room temperature (Scheme 23).<sup>36</sup> A variety of 2-alkylbenzofuran-3(2*H*)-ones were thus converted under mild conditions into *cis*-2-alkyl-2,3-dihydrobenzofuran-3-ols with 97:3 to >99:1 dr and 80 to >99% ee.



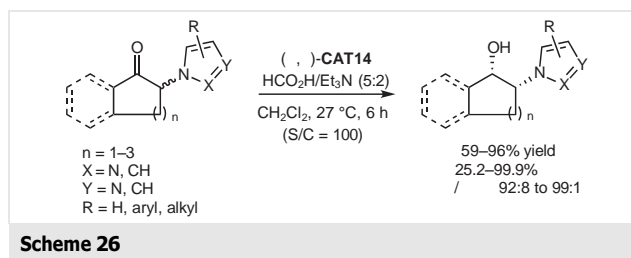
In 2016, McErlean and co-workers accomplished the first total synthesis of the natural marine product (+)-panacene in 17% overall yield (Scheme 24).<sup>37</sup> The racemic 3-oxo-2,3-dihydrobenzofuran-2-acetate was subjected to ATH/DKR using (*S,S*)-**CAT13** in DMF in the presence of HCO<sub>2</sub>H as the hydrogen source and *i*-Pr<sub>2</sub>N<sub>2</sub>Et as a base to furnish the desired enantioenriched tricyclic lactone in 78% yield with 73% ee, which could be upgraded to 96% after recrystallization. This spontaneous lactonization enabled efficient generation of the tricyclic core of (+)-panacene.



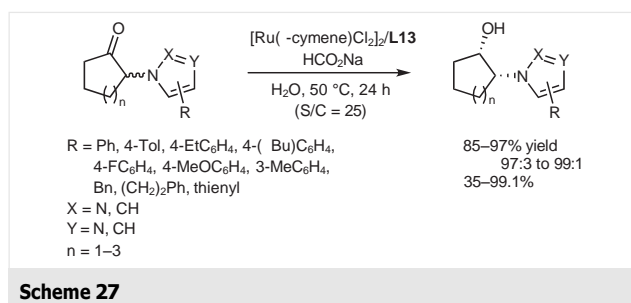
In 2018, Fang and co-workers succeeded in developing a DKR of racemic benzofuran-3(2*H*)-one derivatives through Ru-promoted ATH (Scheme 25).<sup>38</sup> The optimized conditions established for this reaction employed 0.5 mol% of [RuCl(*p*-cymene)][(*R,R*)-TsDPEN] [(*R,R*)-**CAT13**] as catalyst in MeOH at 65 °C in combination with HCO<sub>2</sub>Na as the hydrogen source and CTAB as phase-transfer catalyst. Accordingly, and even if the scope of this transformation is rather limited, a number of benzofuran-3(2*H*)-ones were efficiently reduced to give the corresponding *cis*-2,3-dihydrobenzofuranols in 31–90% yield with up to >99:1 dr and 85–99% ee.



An efficient synthetic route for the construction of biologically relevant *cis*-2-(azaheteroaryl)cycloalkan-1-ols based on the DKR of racemic 2-substituted cycloalkan-1-ones via ATH was reported by Bhanage and Vyas in 2016.<sup>39</sup> The reaction, performed in dichloromethane at 27 °C, was best catalyzed by a Ru-(*R,R*)-TsDPEN tethered complex (*R,R*)-**CAT14** as a catalyst in combination with a HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) mixture as the hydrogen source to afford β-(azaheteroaryl)cycloalkanols containing two adjacent stereocenters. The reaction tolerated a broad substrate scope and gave 59–96% yield, up to 99:1 dr, and 25–99.9% ee depending on the substitution pattern on the azaheteroaryl groups as well as the cycloalkanone ring size (Scheme 26). Interestingly, the usefulness of the method was demonstrated through the efficient asymmetric synthesis of an antileishmanial agent and the preparation of a chiral ionic liquid (not shown).

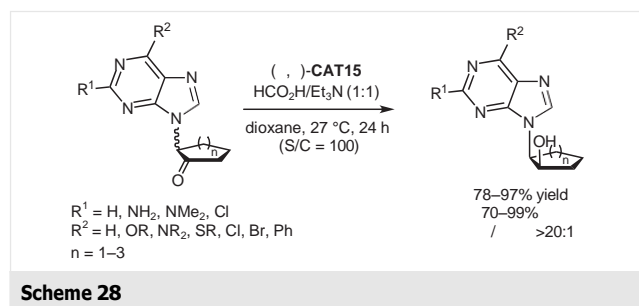


In 2018, Bhanage and Vyas reported the efficient Ru-prolinamide-catalyzed ATH of 2-(azaheteroaryl)- and 2-(phenylsulfonyl)cycloalkan-1-ones through a DKR process (Scheme 27).<sup>40</sup> The reaction was performed in aqueous medium as a surfactant by using [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> and a prolinamide ligand **L13** with bulky *ortho*-isopropyl substituents in the presence of HCO<sub>2</sub>Na as a hydrogen source, de-

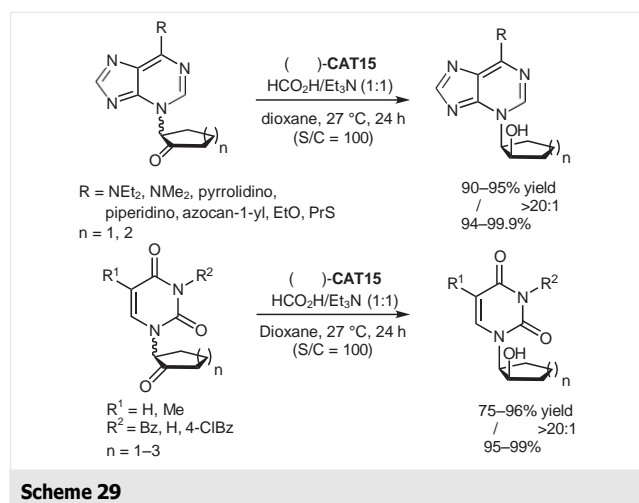


livering *cis*-2-(azaheteroaryl)cycloalkan-1-ols and *cis*-2-(phenylsulfonyl)cycloalkan-1-ols in up to 99:1 dr and 99% ee.

Zhang, Guo, and co-workers devised a synthetic approach that allows an efficient access to valuable chiral carbocyclic nucleosides through Ru-catalyzed ATH relying upon the kinetic conversion of stereolabile 2-(purin-9-yl)cyclopentones (Scheme 28).<sup>41</sup> Under the best operating conditions, which used *N*-(pentafluorophenylsulfonyl)-(*R,R*)-DPEN and [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> as the catalytic system [affording complex (*R,R*)-**CAT15**] and a 1:1 azeotropic HCO<sub>2</sub>H/Et<sub>3</sub>N mixture as the hydrogen donor in dioxane at room temperature, a wide variety of enantioenriched *cis*-2-(purin-9-yl)cyclopentanols were isolated in 78–97% yield, >20:1 *cis/trans* dr, and 70–99% ee.

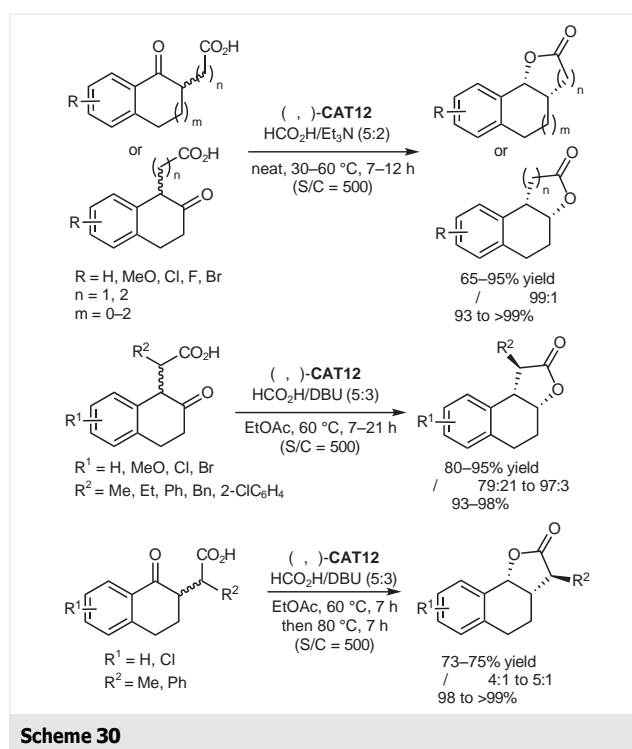


Zhang, Guo, and co-workers extended their work to the ATH/DKR of 2-(purin-3-yl)cyclopentanones catalyzed by (*R,R*)-**CAT15** to access a wide range of *N*<sup>3</sup>-purine nucleosides in 75–96% yield, >20:1 dr and 94–99.9% ee (Scheme 29).<sup>42</sup> Moreover, the catalytic system was suitable for 2-(pyrimidinyl)cyclopentanones, cyclohexanones and cycloheptanones as well.

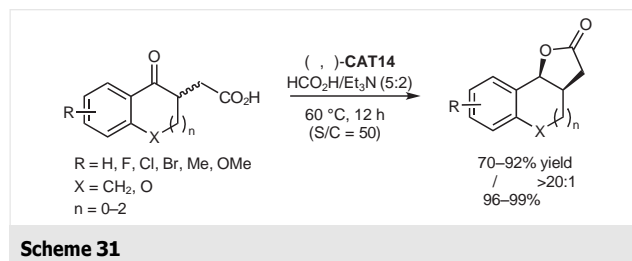


Touge, Kayaki, and co-workers developed a straightforward and versatile methodology for the asymmetric synthesis of chiral fused  $\eta$ - and  $\delta$ -lactones containing multiple

contiguous stereocenters in a single step from racemic 1- or 2-tetralone derivatives through a DKR-ATH/lactonization sequence (Scheme 30). They used oxo-tethered Ru(II) complex (*R,R*)-**CAT12** with HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) as the hydrogen source to perform the asymmetric tandem lactone synthesis which proceeded in 65–95% yield with up to >99:1 dr for the *cis* products and excellent enantioselectivities (93 to >99% ee).<sup>43</sup> Notably, this approach features an ATH/DKR transformation catalyzed by oxo-tethered Ru(II) complex (*R,R*)-**CAT12** and the subsequent *syn*-selective lactonization. These efficient methods were successfully used in the enantioselective synthesis of chiral fused lactones including natural wine lactone (not shown).

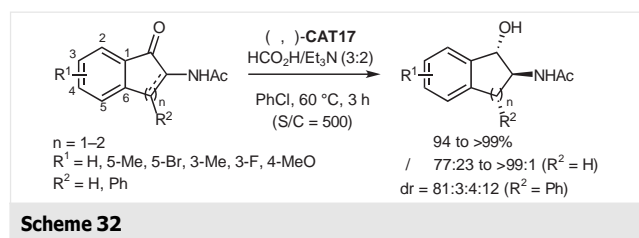


In a similar fashion, in 2020 Lv and co-workers developed the Ru-catalyzed ATH/DKR of benzo-fused  $\eta$ -keto carboxylic acids that led to spontaneous lactonization (Scheme 31).<sup>44</sup> A series of chiral tricyclic  $\eta$ -lactones were thus prepared in 70–92% yield, >20:1 dr, and 96–99% ee, by using the tethered Ru(II) complex (*S,S*)-**CAT14** with the

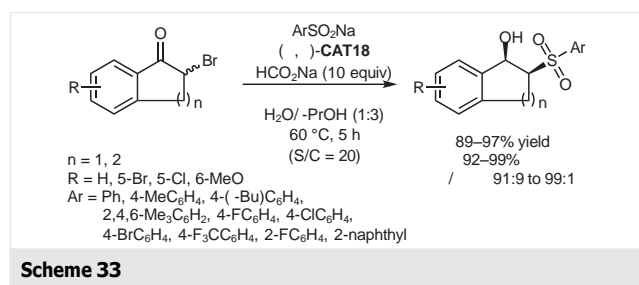


HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) azeotrope as both the hydrogen donor and the solvent.

Efforts by Mohar and co-workers established DKR/ATH as an efficient process to access valuable *trans*- $\beta$ -amido alcohols. They introduced a new enantiomerically pure *ansa*-RuCl[*syn*-ULTAM-(CH<sub>2</sub>)<sub>3</sub>Ph] (*R,S*)-**CAT17** complex to successfully deliver the targeted products in 94 to >99% ee and 77:23 to >99:1 dr, using HCO<sub>2</sub>H/Et<sub>3</sub>N (3:2) mixture at 60 °C in chlorobenzene (Scheme 32).<sup>45</sup> In addition, a reversal of diastereoselectivity (from *trans* to *cis*) was observed by changing the protecting group on the nitrogen atom from acetyl to phthalimide. More interestingly, they showed by DFT calculations that the *trans*-diastereoselectivity was favored due to the existence of two attractive stabilizations: classical CH/ $\pi$  electrostatic interaction and atypical O=S=O...H-NAc H-bond.

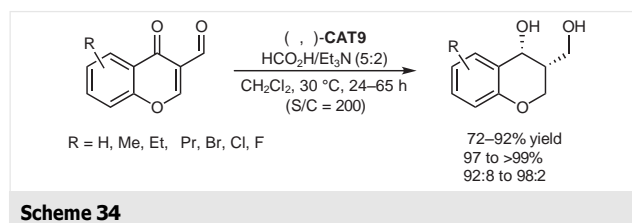


In 2018, Cheng, Liu, and co-workers described a tandem procedure involving a substitution reaction and subsequent DKR/ATH for the synthesis of enantiopure *cis*- $\beta$ -hydroxy sulfones starting from racemic 2-bromoindan-1-ones.<sup>46</sup> Bromide substitution with sodium arylsulfinate led to racemic 2-(arylsulfonyl)indan-1-ones that underwent in situ ATH via DKR using Noyori-type catalyst [RuCl(mesitylene)][(*S,S*)-TsDPEN] [(*S,S*)-**CAT18**] and HCO<sub>2</sub>Na as a hydrogen source in a mixture of H<sub>2</sub>O/*i*-PrOH (1:3) at 60 °C (Scheme 33). Under the best operating conditions, several 2-bromoindan-1-ones or 2-bromo-1-tetralones bearing different groups on the aryl ring were converted into the corresponding  $\beta$ -hydroxy sulfones in 89–97% yield, 92–99% ee, and 91:9–99:1 dr.

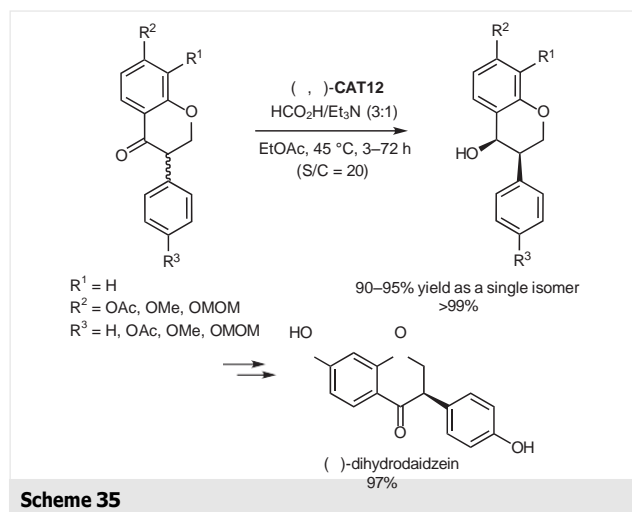


In 2019, our group achieved, under mild reaction conditions, the Rh(III)-mediated enantioselective transfer hydrogenation of diversely substituted 3-formyl-4*H*-chromen-4-one derivatives, providing a range of enantioenriched *cis*-3-

(hydroxymethyl)chroman-4-ols under DKR process (Scheme 34).<sup>47</sup> The optimal reaction conditions used 0.5 mol% of TsDPEN-based tethered Rh(III) complex (*R,R*)-**CAT9** as the catalyst and a HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) mixture as the hydrogen source in CH<sub>2</sub>Cl<sub>2</sub> at 30 °C. This ATH/DKR reaction delivered the corresponding 3-(hydroxymethyl)chroman-4-ols in 72–92% yield with up to 98:2 dr (*cis/trans*) and up to >99% ee, irrespective of the nature and position of the substituents on the aryl group.



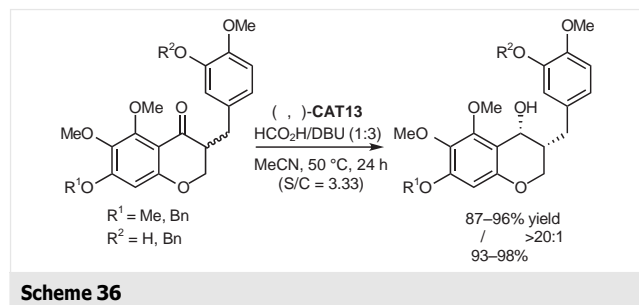
In 2017, Metz and Quin studied the Ru-catalyzed ATH/DKR of racemic isoflavanones using complex (*R,R*)-**CAT12** and HCO<sub>2</sub>H/Et<sub>3</sub>N (3:1) to access enantioenriched isoflavanols with *cis* diastereoselectivities and enantioselectivities >99% ee. Oxidation of the resulting isoflavanols enabled an efficient synthesis of the cardioprotective isoflavone (*R*)-dihydrodaidzein (Scheme 35) and a formal synthesis of the bioactive isoflavan (*R*)-equol (not shown).<sup>48</sup>



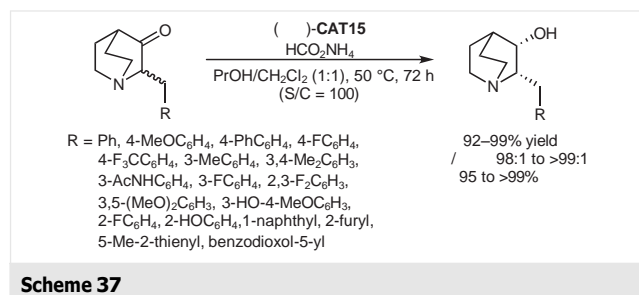
Following their report on the therapeutic potential of anti-angiogenic homoisoflavanone derivatives in retinal and choroidal neovascularization models, Seo, Corson, and co-workers described an enantioselective synthesis of cremastranone and its homoisoflavanone derivatives through Ru-catalyzed ATH/DKR of 5,6,7-substituted homoisoflavanones (Scheme 36).<sup>49</sup> The reaction was performed with [RuCl(*p*-cymene)][(*R,R*)-TsDPEN] [(*R,R*)-**CAT13**] in acetonitrile in the presence of HCO<sub>2</sub>H as the hydrogen source and



DBU as a base. The reaction yielded the corresponding 3-benzylchroman-4-ols in 87–96% yield, >20:1 dr, and 93–98% ee.

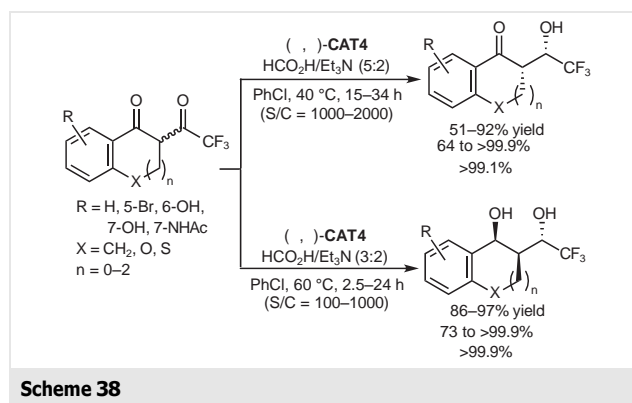


Chiral 2-substituted quinuclidin-3-ols represent key synthetic intermediates of numerous biologically active compounds. In 2020, Zhang, Wang, and co-workers reported the Ru-catalyzed ATH through DKR for the enantioselective synthesis of *cis*-2-[(het)arylmethyl]quinuclidin-3-ols (Scheme 37).<sup>50</sup> After an extensive screening of the reaction parameters, the reaction proceeded in the presence of 1 mol% of (*R,R*)-**CAT15** with HCO<sub>2</sub>NH<sub>4</sub> as the hydrogen source in *i*-PrOH/CH<sub>2</sub>Cl<sub>2</sub> at 50 °C for 72 h providing the corresponding *cis*-2-[(het)arylmethyl]quinuclidin-3-ols in 92–99% yield with diastereoselectivities up to >99:1 dr and 95 to >99% ee. The position of the substitution on the aryl ring or the electronic properties of the quinuclidin-3-ones did not have a significant influence on the reactivity and stereoselectivity of the ATH transformation. Compounds having electron-withdrawing substituents displayed relatively lower enantioselectivities compared to those bearing electron-donating groups at the aryl ring. This operationally simple protocol offered an alternative route to *cis*-2-[(het)arylmethyl]quinuclidin-3-ols and enlarged the scope for the ATH of bicyclic ketones. Moreover, the practicality of this method was confirmed by the gram-scale experiment leading to perfect enantioinduction using a simple recrystallization.



In 2016, Mohar and co-workers published a divergent and efficient stereoselective approach for the preparation of varied carbinols that possess either two of three contiguous stereogenic centers depending on the operating conditions

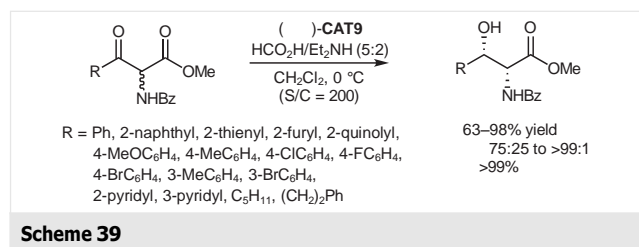
through Ru-catalyzed ATH of  $\alpha$ -trifluoroacetyl-substituted benzofused five- to seven-membered cyclic ketones coupled with either one or two consecutive DKR processes.<sup>51</sup> As outlined in Scheme 38, when the reaction was carried out in chlorobenzene at 40 °C using the *ansa*-Ru(II) complex (*S,S*)-**CAT4** ligated with the enantiopure piperidino-SO<sub>2</sub>DPEN(CH<sub>2</sub>)<sub>4</sub>( $\eta^6$ -Ph) ligand and HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) azeotropic mixture as the hydrogen source, under DKR, diverse carbinols with two adjacent stereocenters were isolated in 51–92% yield, >99% de, and up to >99.9% ee. Interestingly, when the reaction was performed with the same catalytic system at 60 °C and with a higher catalyst loading with HCO<sub>2</sub>H/Et<sub>3</sub>N (3:2), an unprecedented double DKR process occurred, providing various  $\alpha$ -CF<sub>3</sub>-substituted 1,3-diols that bear three contiguous stereocenters with similar results in terms of reactivity and selectivity.



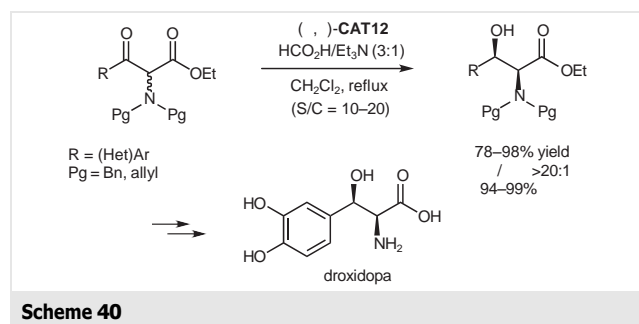
## 3.2 $\alpha$ -Substituted $\beta$ -Keto Esters, Amides, and Sulfonamides

In 2018, our group reported an unprecedented Rh-catalyzed ATH of  $\alpha$ -benzamido- $\beta$ -keto esters via DKR to produce the corresponding *syn*- $\alpha$ -benzamido- $\beta$ -hydroxy esters, which had not previously been directly attained through ATH (Scheme 39).<sup>52</sup> The reaction proceeded using 0.5 mol% of tethered Rh(III) complex (*R,R*)-**CAT9** in the presence of HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) azeotropic mixture as the hydrogen donor in CH<sub>2</sub>Cl<sub>2</sub> at 0 °C. Compounds bearing substituted aryl groups (R) on the ketone functional group delivered the corresponding reduced *syn*-products in 63–98% yield irrespective of the electron-donating or electron-withdrawing character of the substituents. Thus, a series of  $\alpha$ -benzamido- $\beta$ -keto esters were efficiently converted under mild conditions into the corresponding *syn*- $\alpha$ -benzamido- $\beta$ -hydroxy esters with up to >99:1 dr (*syn/anti*) and >99% ee for a broad range of substrates with tolerance for a diverse set of functional groups. Furthermore, this method can be scaled to gram-scale. Of note, preliminary ATH experiments were conducted in CH<sub>2</sub>Cl<sub>2</sub> at 30 °C employing tethered and untethered Ru-complexes with HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) as the hydrogen source, producing the corresponding *anti*-1,2-ami-

no alcohols as the major isomers albeit with low enantioselectivities. To our knowledge, this reversal of diastereoselectivity from *anti* to *syn* provided by switching from Ru complexes to the use of a Rh catalyst had not previously been observed for the ATH of *N*-monoprotected  $\alpha$ -amino- $\beta$ -keto esters.

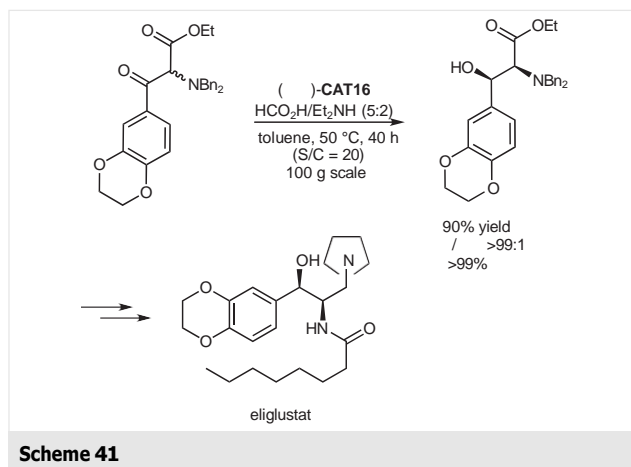


In 2017, Wang and co-workers described the ATH/DKR of  $\beta$ -aryl- $\alpha$ -dibenzylamino- $\beta$ -keto esters using  $(R,R)$ -**CAT12** to access *syn*- $\beta$ -aryl- $\alpha$ -dibenzylamino- $\beta$ -hydroxy esters in up to 98% yield with >20:1 (*syn/anti*) dr and 94–99% ee (Scheme 40).<sup>53</sup> This reaction was used in a gram-scale synthesis of droxidopa.

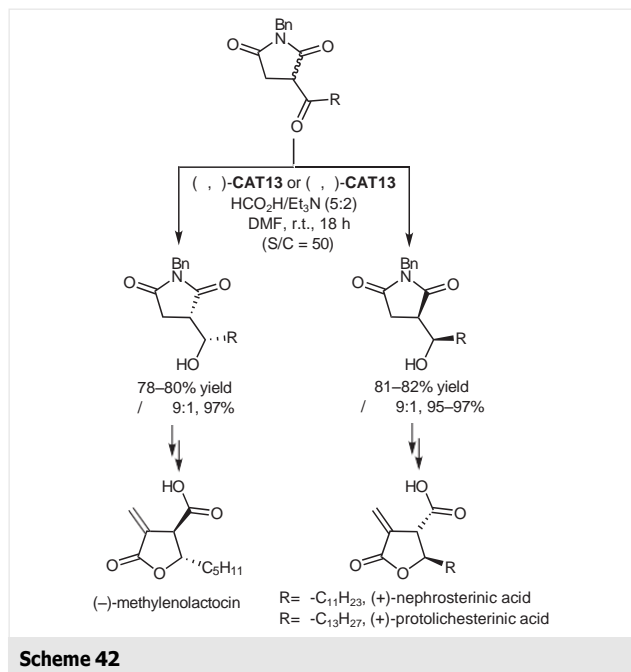


In 2019, Zhang, Wang, and co-workers developed an efficient and scalable synthesis of eliglustat, a specific and potent inhibitor of glucosylceramide synthase, via a Ru-catalyzed ATH/DKR approach (Scheme 41).<sup>54</sup> The required two contiguous stereocenters were installed by ATH in the presence of the  $[\text{RuCl}(p\text{-cymene})((R,R)\text{-TfDPEN})]$  complex  $[(R,R)\text{-CAT16}]$ , generated from  $(R,R)$ -TfDPEN and  $[\text{Ru}(p\text{-cymene})\text{Cl}]_2$ , and the  $\text{HCO}_2\text{H}/\text{Et}_3\text{N}$  (5:2) azeotrope as the hydrogen source. Slow addition of  $\text{HCO}_2\text{H}$  was crucial to ensure high conversion and selectivity. The desired *syn*-product was obtained on a 100-g scale in 90% yield and an excellent >99% ee.

Paraconic acid natural products exhibit antimicrobial, antibiotic, and anti-HIV-1 biological properties and represent an important class of compound in medicinal chemistry. In 2019, Appayee and co-workers accomplished the first ATH/DKR of 3-acylsuccinimides and developed a stereodivergent method to successfully access the synthesis of several bioactive paraconic acid derivatives such as  $(-)$ -methylenolactocin,  $(+)$ -nephrosterinic acid, and  $(+)$ -protolichestirinic acid, as well as  $(-)$ -phaseolinic acid,  $(-)$ -nephro-

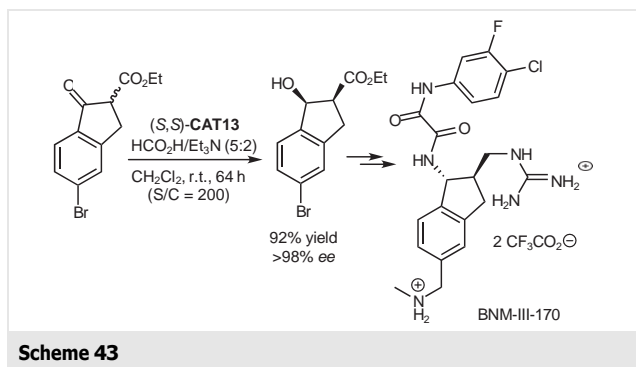


mopsinic acid,  $(+)$ -nephrosterinic acid, and  $(+)$ -roccellaric acid (not shown) (Scheme 42).<sup>55</sup> Under the optimized reaction conditions, the ATH was realized using  $(R,R)$ - or  $(S,S)$ - $[\text{RuCl}(p\text{-cymene})(\text{TSDPEN})]$  complexes  $[(R,R)$ - or  $(S,S)$ -**CAT13**] with  $\text{HCO}_2\text{H}/\text{Et}_3\text{N}$  (5:2) in DMF at room temperature for 18 h in yields up to 82% with up to 9:1 dr and up to 97% ee.

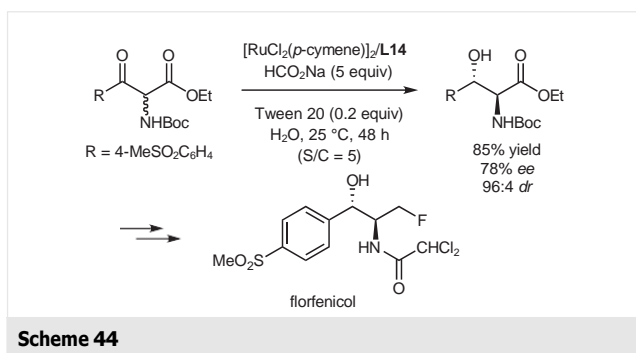


Smith and co-workers reported the development of an effective enantioselective process scale synthesis of the HIV-1 inhibitor BNM-III-170 using an ATH/DKR approach to set the two stereocenters of the molecule.<sup>56</sup> They used  $[\text{RuCl}(p\text{-cymene})((S,S)\text{-TsDPEN})]$   $[(S,S)\text{-CAT13}]$  and  $\text{HCO}_2\text{H}/\text{Et}_3\text{N}$  (5:2) as the catalytic system and managed to produce the desired product in 92% yield and >98% ee

(Scheme 43). The overall efficiency of their new synthesis of BNM-III-170 was significantly improved compared to their first-generation synthesis and required only a single chromatographic purification for the 16 steps.

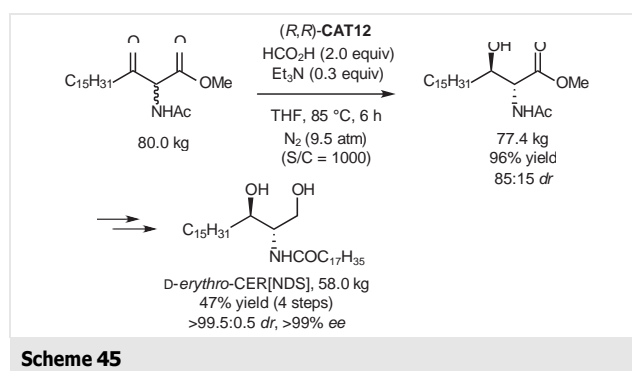


Chen, Wu, and co-workers devised an efficient method for the stereoselective synthesis of florfenicol, an antibiotic with broad spectrum of activity which is a 3'-fluorinated derivative of thiamphenicol.<sup>57</sup> The key step of the synthesis relied on ATH via DKR of an  $\alpha$ -Boc-amino- $\beta$ -keto ester using in situ generated Ru catalyst bearing a chloramphenicol-based ligand **L14** in the presence of the polysorbate-type nonionic surfactant Tween 20 and HCO<sub>2</sub>Na as the hydrogen source (Scheme 44). The reaction proceeded smoothly at 25 °C in water to provide the *anti*-(2*S*,3*S*)- $\alpha$ -Boc-amino- $\beta$ -hydroxy ester in 85% yield, 96:4 dr, and 78% ee; the latter could be improved to 85% ee after one recrystallization from ethyl acetate. The chloramphenicol-based ligand **L14** was recovered in 94% yield after addition of 20% citric acid followed by neutralization with saturated NaHCO<sub>3</sub> and back extraction with dichloromethane.

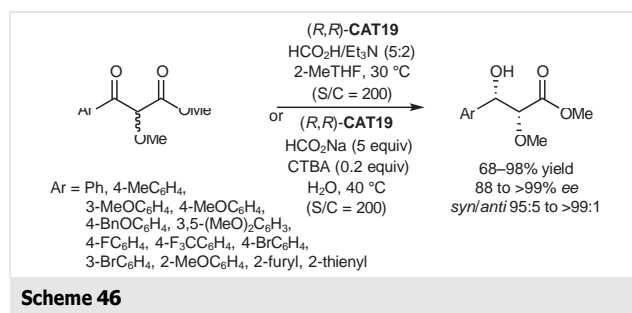


In 2019, Touge and co-workers reported a robust and efficient synthesis of ceramide *D-erythro*-CER[NDS], a drug used for the treatment of skin disease, employing ATH combined with DKR process as a pivotal step (Scheme 45).<sup>58</sup> The reaction was performed on 80.0 kg scale of methyl 2-acetamido-3-oxooctadecanoate using 0.1 mol% of the oxo-tethered Ru(II) complex (*R,R*)-**CAT12** as a catalyst under 9.5 atm N<sub>2</sub> at 85 °C in the presence of 2 equiv of HCO<sub>2</sub>H and 0.3

equiv of Et<sub>3</sub>N affording 77.4 kg of the corresponding *anti*- $\alpha$ -acetamido- $\beta$ -hydroxy ester with an excellent yield (96.2%) and 85:15 dr. This optimal process was carried out using vertical 100-L pipes-in-series reactor and a residence time of 6 h. After 3 chemical steps, 58.0 kg of the targeted ceramide were obtained in optically pure form (>99.5:0.5 dr, >99% ee).

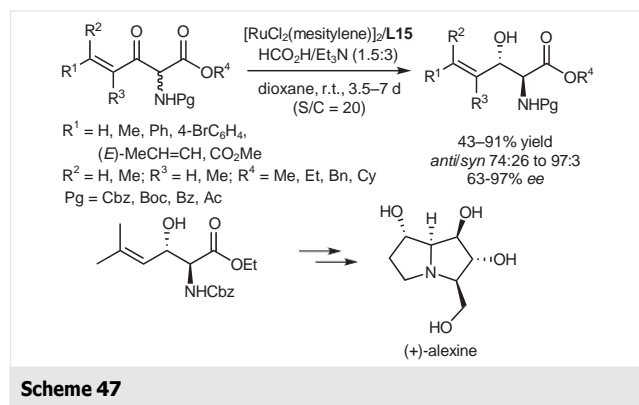


A sustainable enantioselective route to access *syn*- $\beta$ -hydroxy- $\alpha$ -methoxy esters was developed in 2019 by our group. The key step relied on using tethered Rh(III) complex (*R,R*)-**CAT19** to perform ATH through DKR of racemic  $\beta$ -keto- $\alpha$ -methoxy esters (Scheme 46).<sup>59</sup> The reaction was carried out in an open flask in 2-MeTHF with an azeotropic mixture of HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) at 30 °C or in water with HCO<sub>2</sub>Na (5.0 equiv) and CTBA (0.2 equiv) as surfactant at 40 °C. These optimized reaction conditions were applied to the preparation of a wide variety of  $\beta$ -hydroxy- $\alpha$ -methoxy ester derivatives adorned with either electron-donating or electron-withdrawing groups on the aromatic ring in up to 98% yield, *syn* diastereoselectivity up to >99:1 dr, and up to >99% ee.

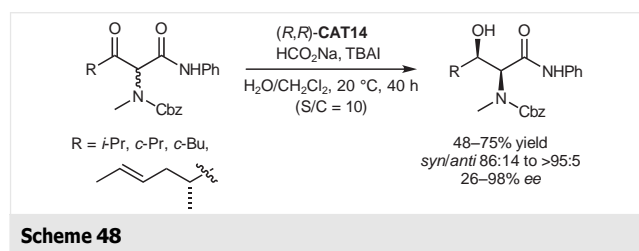


In 2019, Somfai and Yu reported ATH combined with DKR of  $\eta,\delta$ -unsaturated  $\alpha$ -amido- $\beta$ -keto esters, and explored the ability of Ru complexes to perform preferentially a chemoselective 1,2-reduction of the carbonyl function (Scheme 47).<sup>60</sup> The ATH/DKR protocol catalyzed with [RuCl<sub>2</sub>(mesitylene)]<sub>2</sub> combined with (*S,S*)-DPAE [(*S,S*)-**L15**] was performed in dioxane at room temperature using HCO<sub>2</sub>H/Et<sub>3</sub>N (1.5:3) as the hydrogen source to access the

corresponding  $\eta,\delta$ -unsaturated *anti*- $\alpha$ -amido- $\beta$ -hydroxy esters in 43–91% yield, 74:26 to 97:3 (*anti/syn*) dr, and 63–97% ee. The scope of the reaction demonstrated that the substitution of the alkene moiety as well as the *N*-protecting groups played a crucial role on the outcome of the reduction. The method was applied to the asymmetric total synthesis of the polyhydroxylated pyrrolizidine alkaloid (+)-alexine.

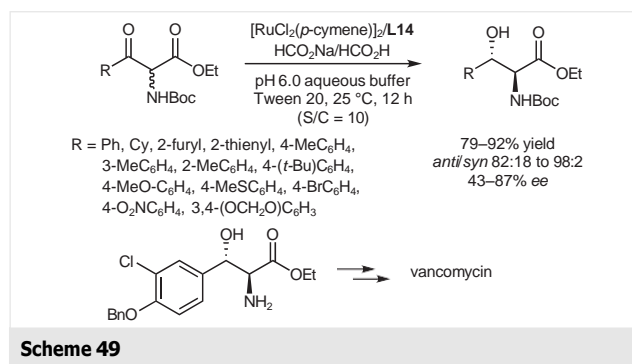


In 2019, Stachulski and co-workers accomplished the ATH of  $\beta$ -keto anilides catalyzed by the Ru-tethered complex (*R,R*)-**CAT14** at 20 °C for 40 h with HCO<sub>2</sub>Na as the hydrogen donor and TBAI in H<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub> mixture (Scheme 48).<sup>61</sup> Under these reaction conditions, the reaction led to the *syn*-products in 48–75% yield, diastereoselectivities up to >95:5 (*syn/anti*) dr, and 26–98% ee. This method allowed the scope of the ATH/DKR leading to relevant  $\eta$ -alkyl- $\beta$ -hydroxy-*N*-Me-amino acids to be expanded. This strategy was used to access a convergent synthesis of the unusual  $\alpha$ -amino- $\beta$ -hydroxy acid MeBmt.

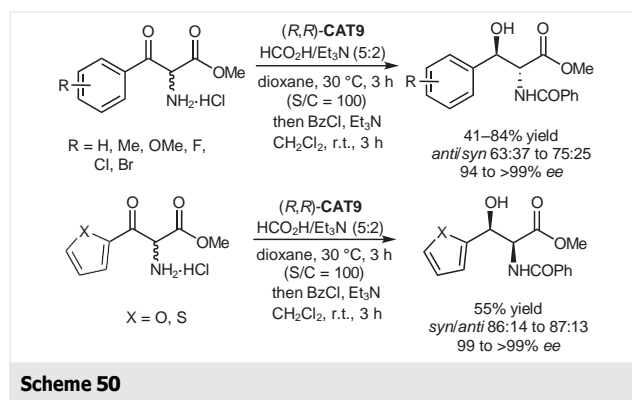


In 2016, Chen and co-workers described the Ru-catalyzed synthesis of *anti*- $\alpha$ -Boc-amino- $\beta$ -hydroxy esters using transfer hydrogenation of racemic  $\alpha$ -Boc-amino- $\beta$ -keto esters via DKR process employing a series of readily available and cost-effective Ru-chloramphenicol **L14** complexes as catalysts (Scheme 49).<sup>62</sup> The results demonstrated that the stereochemical outcome of the transformation was affected by the nature of the chiral ligands. Several phase-transfer catalysts (PTC) were investigated for this transfor-

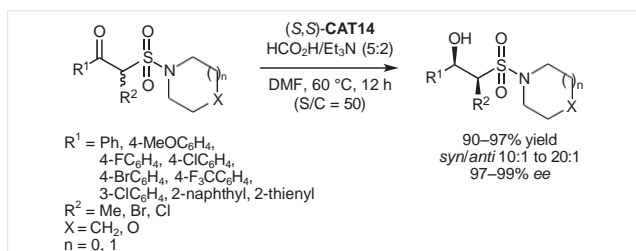
mation and the pH values of the solution showed a crucial role on the reaction rate. Consequently, the ATH was carried out under mild conditions at 25 °C with 10% of Ru catalyst in the presence of HCO<sub>2</sub>Na/HCO<sub>2</sub>H buffer (pH 6.0) and Tween 20 for 12 h. This method showed good functional group tolerance toward a range of aryl- and alkyl-substituted  $\alpha$ -Boc-amino- $\beta$ -keto esters, although hetaryl-substituted compounds led to lower diastereoselectivities; 79–92% yield, up to 96% de, and up to 87% ee were achieved. This method was applied to the stereoselective synthesis of a key intermediate for the preparation of the antibiotic vancomycin.



Our group reported a mild catalytic ATH of a range of  $\alpha$ -amino- $\beta$ -aryl- $\beta$ -keto ester hydrochlorides catalyzed by a Rh(III) complex (*R,R*)-**CAT9** (Scheme 50).<sup>63</sup> The reduction was carried out using HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) as the hydrogen donor source to provide the corresponding *anti*- $\alpha$ -amino- $\beta$ -aryl- $\beta$ -hydroxy esters in good yields, up to 97:3 dr, and up to >99% ee. An interesting reversal of the diastereoselection was observed for  $\alpha$ -amino- $\beta$ -hetaryl- $\beta$ -keto ester hydrochlorides, which under the standard reaction conditions gave the unexpected *syn* products. This transformation served as an atom-economical and stereoselective method to access *anti*- and *syn*- $\alpha$ -amino- $\beta$ -hydroxy ester derivatives found in natural products and bioactive molecules with a high level of enantioinduction (up to >99% ee).



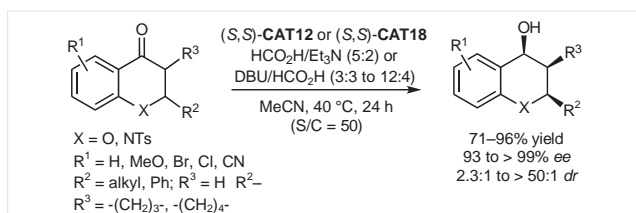
In 2018, Lv, Zhang, and co-workers described an efficient ATH/DKR of  $\alpha$ -aryl- $\beta$ -keto sulfonamides by using 2 mol% of the Ru(II) complex (*S,S*)-**CAT14** with HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) as the hydrogen donor in DMF at 60 °C to produce the corresponding  $\alpha$ -aryl- $\beta$ -hydroxy sulfonamides in high yields (90–97%) with up to 20:1 dr and up to 99% ee (Scheme 51).<sup>64</sup> The electronic properties and the position of the substituent groups on the aryl ring had no significant influence on the ATH. When the aryl group was replaced by a polycyclic aromatic or a hetaryl group, such as 2-naphthyl or 2-thienyl, the  $\beta$ -keto sulfonamides were still hydrogenated efficiently. Switching from the piperidino group (X = CH<sub>2</sub>, n = 1) of the sulfonamide to a pyrrolidino (X = CH<sub>2</sub>, n = 0), morpholino (X = O, n = 1), or dimethylamino group did not affect the stereochemical course of the transformation. Additionally, this practical operationally simple method accommodated a broad substrate scope and the reduction proceeded smoothly on a gram scale as well at 60 °C in the presence of 0.5 mol% of the Ru complex delivering the  $\alpha$ -substituted  $\beta$ -hydroxy sulfonamide core in 95% yield with the same diastereo- and enantioinduction (up to 20:1 dr, 99% ee).



Scheme 51

### 3.3 $\alpha,\beta$ -Disubstituted Cyclic Ketones

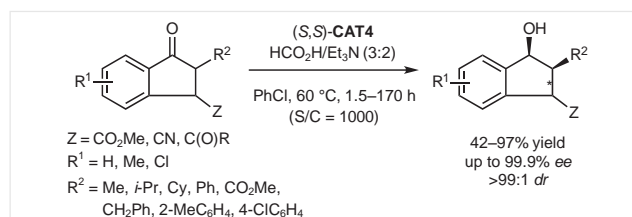
Ashley, Sherer, and co-workers disclosed in 2017, an efficient Ru-catalyzed ATH under DKR of substituted chroman-4-ones possessing  $\beta$ -stereolabile centers (Scheme 52).<sup>65</sup> Under strongly basic conditions, a wide range of valuable chroman-4-ols were produced in 71–96% yield with up to >99% ee and up to >50:1 dr using 2 mol% of either (*S,S*)-**CAT12** or [RuCl(mesitylene)][(*S,S*)-TsDPEN] [(*S,S*)-**CAT18**] in combination with HCO<sub>2</sub>H as a hydrogen source and either Et<sub>3</sub>N or DBU as a base at 40 °C in acetonitrile. From a mechanistic point of view, this cooperative DKR/ATH transforma-



Scheme 52

tion occurs via racemization of the stereocenter distal to the activating ketone group through a  $\beta$ -elimination process to deliver the corresponding achiral enone, which could then be converted back into either enantiomer of the starting  $\beta$ -substituted chromanone by conjugate addition.

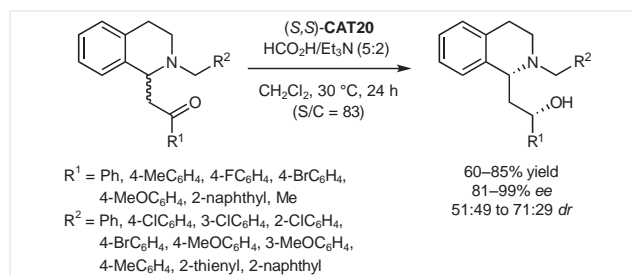
In 2018, Mohar and co-workers described the synthesis of indanol derivatives using the tethered Ru(II) complex (*S,S*)-**CAT4** via a DKR/ATH process (Scheme 53).<sup>66</sup> This reaction was conducted at 60 °C with a low catalyst loading (S/C = 1000) in the presence of HCO<sub>2</sub>H/Et<sub>3</sub>N (3:2) mixture as a hydrogen donor to furnish 2,3-disubstituted indan-1-ols in 42–97% yield, >99:1 dr, and up to 99.9% ee.



Scheme 53

### 3.4 $\beta$ -Substituted Ketones

An enantioselective synthesis of *syn*-1,3-amino alcohols was reported in 2018 by our group based on Ru-catalyzed ATH of ring-substituted  $\beta$ -amino ketones via DKR.<sup>67</sup> The key feature of this approach relied on epimerization of the  $\beta$ -stereocenter by an intermolecular elimination (retro-Manich)/addition sequence. This transformation was carried out using [RuCl(*S,S*)-TsDPEN(benzene)] [(*S,S*)-**CAT20**] in dichloromethane in the presence of HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) as the hydrogen source at 30 °C (Scheme 54). With these reaction conditions, various *syn*-1,3-amino alcohols were obtained in 60–85% yield, up to 71:29 dr, and 81–99% ee.

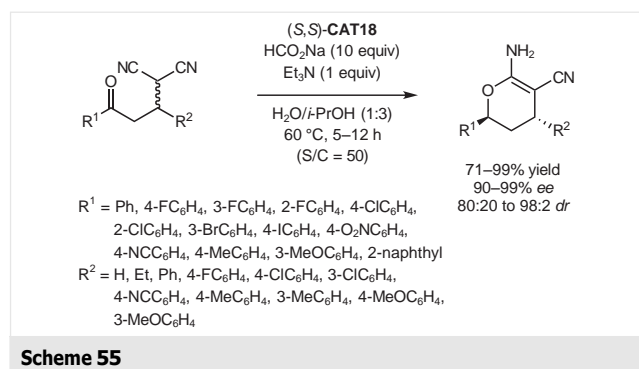


Scheme 54

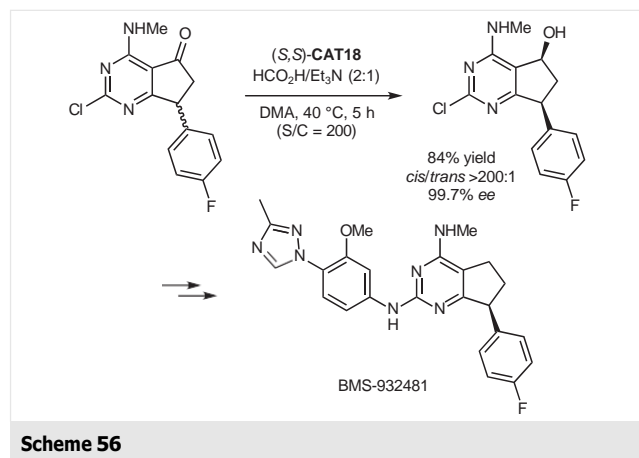
Wang, Liu, and co-workers developed a DKR/ATH methodology for the asymmetric reduction of racemic  $\eta$ -aryl- $\eta$ -keto malononitriles leading to convenient 2-aryl-3,4-dihydro-2H-pyran-5-carbonitrile intermediates in a one-pot operation (Scheme 55).<sup>68</sup> Under optimized conditions employing [RuCl(mesitylene)][(*S,S*)-TsDPEN] [(*S,S*)-**CAT18**] in combination with HCO<sub>2</sub>Na in *i*-PrOH/H<sub>2</sub>O (3:1) at 60 °C, several 2-aryl-3,4-dihydro-2H-pyran-5-carbonitriles were



synthesized in 71–99% yield with 90–99% ee and 80:20 to 98:2 dr. A striking feature of this reaction was a complex reaction sequence involving retro-Michael addition, followed by an ATH upon DKR and a subsequent spontaneous diastereoselective cyclization reaction.



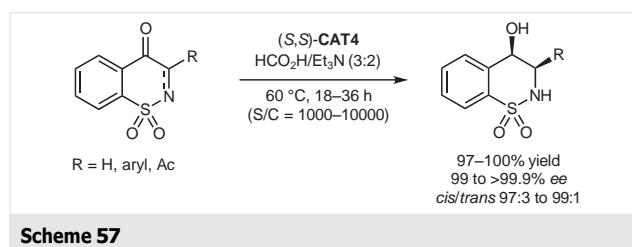
In 2018, Strotman and co-workers developed efficient asymmetric routes to  $\eta$ -secretase modulator BMS-932481, as a potential candidate for the treatment of Alzheimer's disease (Scheme 56).<sup>69</sup> The first strategy involved a challenging enantioselective hydrogenation of an unfunctionalized trisubstituted alkene to install the benzylic stereocenter through a combination of high throughput experimentation and process optimization. The second route showed a unique vinylogous dynamic kinetic resolution (VDKR) ketone reduction, with a racemizable stereocenter conjugated with a pyrimidine ring. The ATH was carried out in the presence of 0.5 mol% of [RuCl(mesitylene)][(*S,S*)-TsDPEN] [(*S,S*)-CAT18] which was selected for further development, in HCO<sub>2</sub>H/Et<sub>3</sub>N (2:1) as the hydrogen source in DMA at 40 °C for 5 h providing the expected (*S,S*)-*cis*-alcohol in high yield with excellent diastereo- and enantioselectivities. Moreover, the ATH was scaled-up to 400 g with 146:1 dr and 99.4% ee observed for the reduction. After work-up and isolation, the (*S,S*)-*cis*-alcohol was obtained in 84% yield with >200:1 dr and 99.7% ee. This transformation required



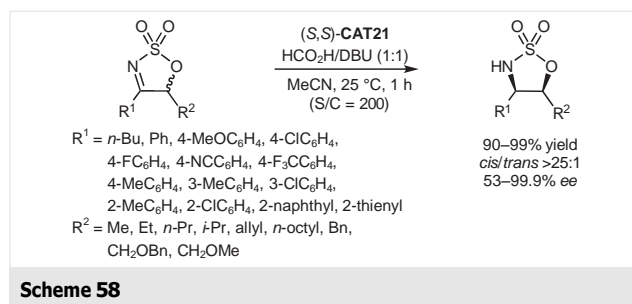
catalyst and substrate control and the non-adjacent benzylic center of the ketone substrate to be more acidic than that of the alcohol product. DFT computations allowed prediction of the relative acidities of the intermediates involved in the transformation. These results enabled the development of a sustainable and scalable route toward  $\eta$ -secretase modulator BMS-932481.

### 3.5 Imine Derivatives

Mohar and co-workers showed that the chiral *ansa*-Ru(II) complex (*S,S*)-CAT4 was an effective catalyst for the ATH of  $\alpha$ -(sulfonylimino) and  $\alpha$ -(sulfonylamino) aryl ketones under DKR conditions (Scheme 57).<sup>70</sup> Notably, this protocol was performed at 60 °C in a HCO<sub>2</sub>H/Et<sub>3</sub>N (3:2) binary mixture under a low catalyst loading of S/C = 10000, giving optically active 4-hydroxy-1,2,3,4-tetrahydro-1,2-benzothiazine *S,S*-dioxides with two contiguous stereogenic centers in 97–100% isolated yield with up to >99.9% ee and consistently high levels of *cis* diastereofacial selectivity.

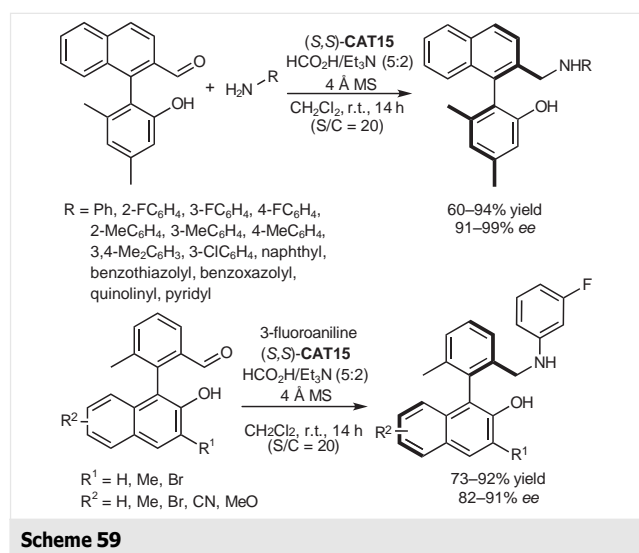


In 2018, Lee and co-workers reported a convenient and highly stereoselective ATH to access cyclic sulfamidates, *cis*-4-aryl-5-alkyl-1,2,3-oxathiazolidine *S,S*-dioxides (Scheme 58).<sup>71</sup> Attempts to increase the stereoselectivity of ATH reactions of 5-alkyl-substituted cyclic sulfamidates showed that stronger bases than Et<sub>3</sub>N, such as DBU, facilitated rapid racemization of the configurationally labile cyclic imine substrates and led to better stereoselectivities. Consequently, the Rh-catalyzed ATH/DKR was conducted in combination with HCO<sub>2</sub>H/DBU (1:1) as the hydrogen source employing (*S,S*)- or (*R,R*)-[RhClCp\*(TsDPEN)] [(*S,S*)- or (*R,R*)-CAT21] in acetonitrile within 1 h at room temperature in 90–99% yield, *cis* diastereoselectivities of >25:1 dr, and 53–99.9% ee.



The reduced products are potentially valuable intermediates for the preparation of chiral 1,2-functionalized amines and 1,2-amino alcohols.

Wang and co-workers described the Ru-catalyzed reductive amination of 2-formyl-2'-hydroxybiphenyls with arylamines to access chiral 2-(arylamino)-2'-hydroxybiphenyls under mild conditions and with a wide substrate scope (Scheme 59).<sup>72</sup> The enantiomerically enriched 2-(arylamino)-2'-hydroxybiphenyls were obtained in 60–94% yield by using (*S,S*)-**CAT15** and HCO<sub>2</sub>H/Et<sub>3</sub>N (5:2) as the hydrogen donor at room temperature, with 91–99% ee through a DKR process.



## 4 Conclusion

Undoubtedly, transition-metal-catalyzed asymmetric reduction reactions (AH and ATH) are still widely used and considered as cornerstone reactions in the toolbox of medicinal and process chemists endowed with a powerful retrosynthetic disconnection strategy.<sup>73</sup> Furthermore, by introducing chirality and resolution processes (such as DKR), it allows the control of several stereocenters starting from racemic substrates. As highlighted in this review, the development of more stereodiscriminant ligands and catalysts as well as the use of continuous chemistry partake to the construction of complex reaction sequences with high stereoselectivities granting rapid access to biological active molecules.

## Funding Information

We thank the CNRS (Centre National de la Recherche Scientifique) and the MENESR (Ministère de l'Éducation Nationale, de l'Enseignement Supérieur et de la Recherche) for financial support. R.M.B. is grateful to the MENESR for a grant (2019-2022).

## Acknowledgment

We gratefully acknowledge financial support from our industrial partners.

## References

- (1) (a) *The Handbook of Homogeneous Hydrogenation, Vol. 1*; de Vries, J. G.; Elsevier, C. J., Ed.; Wiley-VCH: Weinheim, **2007**. (b) *Modern Reduction Methods*; Andersson, P. G.; Munslow, I. J., Ed.; Wiley-VCH: Weinheim, **2008**. For comprehensive reviews and chapters on asymmetric hydrogenation (AH), see: (c) Knowles, W. S. *Angew. Chem. Int. Ed.* **2002**, *41*, 1998. (d) Noyori, R. *Angew. Chem. Int. Ed.* **2002**, *41*, 2008. (e) Genêt, J.-P. *Acc. Chem. Res.* **2003**, *36*, 908. (f) Blaser, H.-U.; Malan, C.; Pugin, B.; Spindler, F.; Steiner, H.; Studer, M. *Adv. Synth. Catal.* **2003**, *345*, 103. (g) Zhou, Y.-G. *Acc. Chem. Res.* **2007**, *40*, 1357. (h) Shang, G.; Li, W.; Zhang, X. *Catalytic Asymmetric Synthesis, 3rd ed*; Ojima, I., Ed.; John Wiley & Sons: New York, **2010**, 343. (i) Xie, J. H.; Zhu, S. F.; Zhou, Q. L. *Chem. Rev.* **2011**, *111*, 1713. (j) Gopalaiah, K.; Kagan, H. B. *Chem. Rev.* **2011**, *111*, 4599. (k) Wang, D.-S.; Chen, Q.-A.; Lu, S.-M.; Zhou, Y.-G. *Chem. Rev.* **2012**, *112*, 2557. (l) Chen, Q.-A.; Ye, Z.-S.; Duan, Y.; Zhou, Y.-G. *Chem. Soc. Rev.* **2013**, *42*, 497. (m) Hamada, Y. *Chem. Rec.* **2014**, *14*, 235. (n) Li, Y.-Y.; Yu, S.-L.; Shen, W.-Y.; Gao, J.-X. *Acc. Chem. Res.* **2015**, *48*, 2587. (o) Xie, J.-H.; Bao, D.-H.; Zhou, Q.-L. *Synthesis* **2015**, *47*, 460. (p) Zhang, Z.; Butt, N. A.; Zhang, W. *Chem. Rev.* **2016**, *116*, 14769. (q) Li, W.; Lu, B.; Zhang, Z. *Chem. Rec.* **2016**, *16*, 2506. (r) Mashima, K.; Higashida, K.; Iimuro, A.; Nagae, H.; Kita, Y. *Chem. Rec.* **2016**, *16*, 2585. (s) Luo, Y.-E.; He, Y.-M.; Fan, Q.-H. *Chem. Rec.* **2016**, *16*, 2697. (t) Ohkuma, T.; Arai, N. *Chem. Rec.* **2016**, *16*, 2801. (u) Imamoto, T. *Chem. Rev.* **2016**, *16*, 2659. (v) Xie, X.; Lu, B.; Li, W.; Zhang, Z. *Coord. Chem. Rev.* **2018**, *355*, 39. (w) Seo, C. S. G.; Morris, R. H. *Organometallics* **2019**, *38*, 47.
- (2) For comprehensive reviews and chapters on asymmetric transfer hydrogenation (ATH), see: (a) Zassinovich, G.; Mestroni, G.; Gladiali, S. *Chem. Rev.* **1992**, *92*, 1051. (b) de Graauw, C. F.; Peters, J. A.; van Bekkum, H.; Huskens, J. *Synthesis* **1994**, 1007. (c) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97. (d) Palmer, M. J.; Wills, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2045. (e) Pàmies, O.; Bäckvall, J.-E. *Chem. Eur. J.* **2001**, *7*, 5052. (f) Everaere, K.; Mortreux, A.; Carpentier, J.-F. *Adv. Synth. Catal.* **2003**, *345*, 67. (g) Gladiali, S.; Alberico, E. *Chem. Soc. Rev.* **2006**, *35*, 226. (h) Samec, J. S. M.; Bäckvall, J.-E.; Andersson, P. G.; Brandt, P. *Chem. Soc. Rev.* **2006**, *35*, 237. (i) Ikariya, T.; Blacker, A. J. *Acc. Chem. Res.* **2007**, *40*, 1300. (j) Blacker, A. J. *The Handbook of Homogeneous Hydrogenation*; de Vries, J. G.; Elsevier, C. J., Ed.; Wiley-VCH: Weinheim, **2007**, 1215. (k) Wang, C.; Wu, X.; Xiao, J. *Chem. Asian J.* **2008**, *3*, 1750. (l) Ikariya, T. *Bull. Chem. Soc. Jpn.* **2011**, *84*, 1. (m) Zheng, C.; You, S.-L. *Chem. Soc. Rev.* **2012**, *41*, 2498. (n) Bartoszewicz, A.; Ahlsten, N.; Martín-Matute, B. *Chem. Eur. J.* **2013**, *19*, 7274. (o) Slagbrand, T.; Lundberg, H.; Adolfsson, H. *Chem. Eur. J.* **2014**, *20*, 16102. (p) Štefane, B.; Požgan, F. *Catal. Rev.* **2014**, *56*, 82. (q) Ito, J.-I.; Nishiyama, H. *Tetrahedron Lett.* **2014**, *55*, 3133. (r) Gotarca, L.; Verzini, M.; Volpicelli, R. *Chim. Oggi* **2014**, *32*, 36. (s) Wang, D.; Astruc, D. *Chem. Rev.* **2015**, *115*, 6621. (t) Foubelo, F.; Nájera, C.; Yus, M. *Tetrahedron: Asymmetry* **2015**, *26*, 769. (u) Nedden, H. G.; Zanotti-Gerosa, A.; Wills, M. *Chem. Rec.* **2016**, *16*, 2623. (v) Štefane, B.; Požgan, F. *Top. Curr. Chem.* **2016**, *18*, 374. (w) Ayad, T.; Phansavath, P.; Ratovelomanana-Vidal, V. *Chem. Rec.* **2016**, *16*, 2754. (x) Matuška, O.; Kindl, M.; Kačer, P. *New Advances in Hydroge-*

- nation Process; Ravanchi, T. M., Ed.; InTech: Croatia, **2017**, 37.
- (y) Milner, L.; Talavera, G.; Nedden, H. G. *Chim. Oggi* **2017**, *35*, 37. (z) Matsunami, A.; Kayaki, Y. *Tetrahedron Lett.* **2018**, *59*, 504.
- (aa) Whittlesey, M. K. *Science of Synthesis: N-Heterocyclic Carbenes in Catalytic Organic Synthesis 1*; Nolan, S. P.; Cazin, C. S. J., Ed.; Georg Thieme Verlag: Stuttgart, **2018**, 285. (ab) Zhang, Z.; Butt, N. A.; Zhou, M.; Liu, D.; Zhang, W. *Chin. J. Chem.* **2018**, *36*, 443. (ac) Talavera, G.; Santana Fariña, A.; Zanotti-Gerosa, A.; Nedden, H. G. *Top. Organomet. Chem.* **2019**, *65*, 73.
- (3) For previous comprehensive reviews covering this topic, see: (a) Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36. (b) Caddick, S.; Jenkins, K. *Chem. Soc. Rev.* **1996**, *25*, 447. (c) Ward, R. S. *Tetrahedron: Asymmetry* **1995**, *6*, 1475. (d) Sturmer, R. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1173. (e) El Gihani, M. T.; Williams, J. M. J. *Curr. Opin. Chem. Biol.* **1999**, *3*, 11. (f) Ratovelomanana-Vidal, V.; Genêt, J.-P. *Can. J. Chem.* **2000**, *78*, 846. (g) Huerta, F. F.; Minidis, A. B. E.; Bäckvall, J.-E. *Chem. Soc. Rev.* **2001**, *30*, 321. (h) Faber, K. *Chem. Eur. J.* **2001**, *7*, 5005. (i) Pàmies, O.; Bäckvall, J.-E. *Chem. Rev.* **2003**, *103*, 3247. (j) Pellissier, H. *Tetrahedron* **2003**, *59*, 8291. (k) Turner, N. J. *Curr. Opin. Chem. Biol.* **2004**, *8*, 114. (l) Vedejs, E.; Jure, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 3974. (m) Martín-Matute, B.; Bäckvall, J.-E. *Curr. Opin. Chem. Biol.* **2007**, *11*, 226. (n) Pellissier, H. *Tetrahedron* **2008**, *64*, 1563. (o) Pellissier, H. *Tetrahedron* **2011**, *67*, 3769. (p) Xie, J.-H.; Zhou, Q.-L. *Aldrichimica Acta* **2015**, *48*, 33. (q) Echeverria, P.-G.; Ayad, T.; Phansavath, P.; Ratovelomanana-Vidal, V. *Synthesis* **2016**, *48*, 2523. (r) Bhat, V.; Welin, E. R.; Guo, X.; Stoltz, B. M. *Chem. Rev.* **2017**, *117*, 4528.
- (4) Noyori, R.; Ikeda, T.; Ohkuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Akutagawa, S.; Sayo, N.; Saito, T. *J. Am. Chem. Soc.* **1989**, *111*, 9134.
- (5) Jugé, S.; Genêt, J.-P.; Mallard, S. EP 0489071A1, **1992**; the original French patent application FP 19890011159 was filed in 1989.
- (6) Schwink, L.; Ireland, T.; Püntener, K.; Knochel, P. *Tetrahedron: Asymmetry* **1998**, *9*, 1143.
- (7) Murata, K.; Okano, K.; Miyagi, M.; Iwane, H.; Noyori, R.; Ikariya, T. *Org. Lett.* **1999**, *1*, 1119.
- (8) Pu, L. Y.; Chen, J. Q.; Li, M. L.; Li, Y.; Xie, J. H.; Zhou, Q. L. *Adv. Synth. Catal.* **2016**, *358*, 1229.
- (9) Wu, W.; You, C.; Yin, C.; Liu, Y.; Dong, X.-Q.; Zhang, X. *Org. Lett.* **2017**, *19*, 2548.
- (10) Yin, C.; Dong, X.-Q.; Zhang, X. *Adv. Synth. Catal.* **2018**, *360*, 4319.
- (11) Zatochnaya, O. V.; Rodriguez, S.; Zhang, Y.; Lao, K. S.; Tcyrulnikov, S.; Li, G.; Wang, X.-J.; Qu, B.; Biswas, S.; Mangunuru, H. P. R.; Rivalti, D.; Sieber, J. D.; Desrosiers, J.-N.; Leung, J. C.; Grinberg, N.; Lee, H.; Haddad, N.; Yee, N. K.; Song, J. J.; Kozlowski, M. C.; Senanayake, C. H. *Chem. Sci.* **2018**, *9*, 4505.
- (12) Arai, N.; Okabe, Y.; Ohkuma, T. *Adv. Synth. Catal.* **2019**, *361*, 5540.
- (13) Swamy, P. C.; Varenikov, A.; de Ruyter, G. *Chem. Eur. J.* **2020**, *26*, 2333.
- (14) Li, X.; Zhao, Z.-B.; Chen, M.-W.; Wu, B.; Wang, H.; Yu, C.-B.; Zhou, Y.-G. *Chem. Commun.* **2020**, *56*, 5815.
- (15) Hou, C.-J.; Hu, X.-P. *Org. Lett.* **2016**, *18*, 5592.
- (16) Lu, B.; Wu, X.; Li, C.; Ding, G.; Li, W.; Xie, X.; Zhang, Z. *J. Org. Chem.* **2019**, *84*, 3201.
- (17) Liu, Y.-T.; Chen, J.-Q.; Li, L.-P.; Shao, X.-Y.; Xie, J.-H.; Zhou, Q.-L. *Org. Lett.* **2017**, *19*, 3231.
- (18) Lynch, D.; Deasy, R. E.; Clarke, L.-A.; Slattery, C. N.; Khandavilli, U. B. R.; Lawrence, S. E.; Maguire, A. R.; Magnus, N. A.; Moynihan, H. A. *Org. Lett.* **2016**, *18*, 4978.
- (19) Bao, D.-H.; Gu, X.-S.; Xie, J.-H.; Zhou, Q.-L. *Org. Lett.* **2017**, *19*, 118.
- (20) (a) Phansavath, P.; Duprat de Paule, S.; Ratovelomanana-Vidal, V.; Genêt, J.-P. *Eur. J. Org. Chem.* **2000**, 3903. (b) Lavergne, D.; Mordant, C.; Ratovelomanana-Vidal, V.; Genêt, J.-P. *Org. Lett.* **2001**, *3*, 1909. (c) Mordant, C.; Caño de Andrade, M. C.; Touati, R.; Ben Hassine, B.; Ratovelomanana-Vidal, V.; Genêt, J.-P. *Synthesis* **2003**, 2405. (d) Mordant, C.; Dunkelmann, P.; Ratovelomanana-Vidal, V.; Genêt, J.-P. *Chem. Commun.* **2004**, 1296. (e) Mordant, C.; Dunkelmann, P.; Ratovelomanana-Vidal, V.; Genêt, J.-P. *Eur. J. Org. Chem.* **2004**, 3017. (f) Mordant, C.; Reymond, S.; Ratovelomanana-Vidal, V.; Genêt, J.-P. *Tetrahedron* **2004**, *60*, 9715. (g) Labeeuw, O.; Phansavath, P.; Genêt, J.-P. *Tetrahedron: Asymmetry* **2004**, *15*, 1899. (h) Mordant, C.; Reymond, S.; Tone, H.; Lavergne, D.; Touati, R.; Ben Hassine, B.; Ratovelomanana-Vidal, V.; Genêt, J.-P. *Tetrahedron* **2007**, *63*, 6115. (i) Tone, H.; Buchotte, M.; Mordant, C.; Guittet, E.; Ayad, T.; Ratovelomanana-Vidal, V. *Org. Lett.* **2009**, *11*, 1995. (j) Prevost, S.; Gauthier, S.; Caño de Andrade, M. C.; Mordant, C.; Touati, R.; Lesot, P.; Savignac, P.; Ayad, T.; Phansavath, P.; Ratovelomanana-Vidal, V.; Genêt, J.-P. *Tetrahedron: Asymmetry* **2010**, *21*, 1436. (k) Cartigny, D.; Püntener, K.; Ayad, T.; Scalone, M.; Ratovelomanana-Vidal, V. *Org. Lett.* **2010**, *12*, 3788. (l) Prévost, S.; Ayad, T.; Phansavath, P.; Ratovelomanana-Vidal, V. *Adv. Synth. Catal.* **2011**, *353*, 3213. (m) Echeverria, P. G.; Féraud, C.; Cornil, J.; Guérinot, A.; Cossy, J.; Phansavath, P.; Ratovelomanana-Vidal, V. *Synlett* **2014**, 2761. (n) Echeverria, P.-G.; Prévost, S.; Cornil, J.; Féraud, C.; Reymond, S.; Guérinot, A.; Cossy, J.; Ratovelomanana-Vidal, V.; Phansavath, P. *Org. Lett.* **2014**, *16*, 2390. (o) Perez, M.; Echeverria, P. G.; Martínez-Arribe, E.; Ez Zoubir, M.; Touati, R.; Zhang, Z.; Genêt, J. P.; Phansavath, P.; Ayad, T.; Ratovelomanana-Vidal, V. *Eur. J. Org. Chem.* **2015**, 5949. (p) Echeverria, P. G.; Cornil, J.; Féraud, C.; Guérinot, A.; Cossy, J.; Phansavath, P.; Ratovelomanana-Vidal, V. *RSC Adv.* **2015**, *5*, 56815.
- (21) (a) Cornil, J.; Echeverria, P.-G.; Reymond, S.; Phansavath, P.; Ratovelomanana-Vidal, V.; Guérinot, A.; Cossy, J. *Org. Lett.* **2016**, *18*, 4534. (b) Echeverria, P.-G.; Pons, A.; Prévost, S.; Féraud, C.; Cornil, J.; Guérinot, A.; Cossy, J.; Phansavath, P.; Ratovelomanana-Vidal, V. *ARKIVOC* **2019**, (iv), 44.
- (22) (a) Duprat de Paule, S.; Champion, N.; Ratovelomanana-Vidal, V.; Genêt, J.-P.; Dellis, P. WO 03029259A1, **2003**. (b) Duprat de Paule, S.; Jeulin, S.; Ratovelomanana-Vidal, V.; Genêt, J.-P.; Champion, N.; Dellis, P. *Eur. J. Org. Chem.* **2003**, 1931. (c) Duprat de Paule, S.; Jeulin, S.; Ratovelomanana-Vidal, V.; Genêt, J.-P.; Champion, N.; Deschaux, G.; Dellis, P. *Org. Process Res. Dev.* **2003**, *7*, 399. (d) Jeulin, S.; Duprat de Paule, S.; Ratovelomanana-Vidal, V.; Genêt, J.-P.; Champion, N.; Dellis, P. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5799. (e) Jeulin, S.; Champion, N.; Dellis, P.; Ratovelomanana-Vidal, V.; Genêt, J.-P. *Synthesis* **2005**, 3666.
- (23) Yamagata, T.; Tadaoka, H.; Nagata, M.; Hirao, T.; Kataoka, Y.; Ratovelomanana-Vidal, V.; Genêt, J.-P.; Mashima, K. *Organometallics* **2006**, *25*, 2505.
- (24) (a) Echeverria, P.; Féraud, C.; Phansavath, P.; Ratovelomanana-Vidal, V. *Catal. Commun.* **2015**, *62*, 95. (b) Zheng, L.-S.; Llopis, Q.; Echeverria, P.-G.; Féraud, C.; Guillamot, G.; Phansavath, P.; Ratovelomanana-Vidal, V. *J. Org. Chem.* **2017**, *82*, 5607.
- (25) Fei, Z.; Wu, Q.; Li, L.; Jiang, Q.; Li, B.; Chen, L.; Wang, H.; Wu, B.; Wang, X.; Gao, F.; Qiu, W.; Guo, J.; Cheung, C. M. J. *Org. Chem.* **2020**, *85*, 6854.
- (26) Baumann, T.; Brückner, R. *Angew. Chem. Int. Ed.* **2019**, *58*, 4714.
- (27) Zhang, L.; Wang, Z.; Han, Z.; Ding, K. *Angew. Chem. Int. Ed.* **2020**, *59*, 15565.

- (28) Endean, R. T.; Rasu, L.; Bergens, S. H. *ACS Catal.* **2019**, *9*, 6111.
- (29) Gu, X. S.; Yu, N.; Yang, X. H.; Zhu, A.-T.; Xie, J. H.; Zhou, Q. L. *Org. Lett.* **2019**, *21*, 4111.
- (30) Verzijl, G. K. M.; Schuster, C.; Dax, T.; de Vries, A. H. M.; Lefort, L. *Org. Process Res. Dev.* **2018**, *22*, 1817.
- (31) Fan, D.; Lu, J.; Liu, Y.; Zhang, Z.; Liu, Y.; Zhang, W. *Tetrahedron* **2016**, *72*, 5541.
- (32) Doering, W. E.; Young, R. W. *J. Am. Chem. Soc.* **1950**, *72*, 631.
- (33) Hashiguchi, S.; Fujii, A.; Takehara, J.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 7562.
- (34) González-Bobes, F.; Hanson, R.; Strotman, N.; Guo, Z.; Goswami, A. *Adv. Synth. Catal.* **2016**, *358*, 2077.
- (35) Fang, L.; Lyu, Q.; Lu, C.; Li, H.; Liu, S.; Han, L. *Adv. Synth. Catal.* **2016**, *358*, 3196.
- (36) Fang, L.; Liu, S.; Han, L.; Li, H.; Zhao, F. *Organometallics* **2017**, *36*, 1217.
- (37) Alnafta, N.; Schmidt, J. P.; Nesbitt, C. L.; McErlean, C. S. P. *Org. Lett.* **2016**, *18*, 6520.
- (38) Fang, L.; Zhao, F.; Hu, S.; Han, L.; Hu, X.; Wang, M.; Sun, Q. *J. Org. Chem.* **2018**, *83*, 12213.
- (39) Vyas, V. K.; Bhanage, B. M. *Org. Lett.* **2016**, *18*, 6436.
- (40) Vyas, V. K.; Bhanage, B. M. *Asian J. Org. Chem.* **2018**, *7*, 346.
- (41) Zhang, Y.-M.; Zhang, Q.-Y.; Wang, D.-C.; Xie, M.-S.; Qu, G.-R.; Guo, H.-M. *Org. Lett.* **2019**, *21*, 2998.
- (42) Zhang, Q.; Zhang, Y.; Hao, E.; Bai, J.; Qu, G.; Guo, H. *Chin. J. Org. Chem.* **2020**, *40*, 376.
- (43) Touge, T.; Sakaguchi, K.; Tamaki, N.; Nara, H.; Yokozawa, T.; Matsumura, K.; Kayaki, Y. *J. Am. Chem. Soc.* **2019**, *141*, 16354.
- (44) Xiong, Z.; Tian, J.; Xue, P.; Zhang, X.; Lv, H. *Org. Chem. Front.* **2020**, *7*, 104.
- (45) Cotman, A. E.; Lozinšek, M.; Wang, B.; Stephan, M.; Mohar, B. *Org. Lett.* **2019**, *21*, 3644.
- (46) Hu, X.; Zhang, K.; Chang, F.; Liu, R.; Liu, G.; Cheng, T. *Mol. Catal.* **2018**, *452*, 271.
- (47) He, B.; Phansavath, P.; Ratovelomanana-Vidal, V. *Org. Lett.* **2019**, *21*, 3276.
- (48) Qin, T.; Metz, P. *Org. Lett.* **2017**, *19*, 2981.
- (49) Heo, M.; Lee, B.; Sishtla, K.; Fei, X.; Lee, S.; Park, S.; Yuan, Y.; Lee, S.; Kwon, S.; Lee, J.; Kim, S.; Corson, T. W.; Seo, S.-Y. *J. Org. Chem.* **2019**, *84*, 9995.
- (50) Luo, Z.; Wang, Z.; Sun, G.; Jian, W.; Jiang, F.; Luan, B.; Li, R.; Zhang, L. *Org. Lett.* **2020**, *22*, 4322.
- (51) Cotman, A. E.; Cahard, D.; Mohar, B. *Angew. Chem. Int. Ed.* **2016**, *55*, 5294.
- (52) Zheng, L.-S.; Férard, C.; Phansavath, P.; Ratovelomanana-Vidal, V. *Chem. Commun.* **2018**, *54*, 283.
- (53) Sun, G.; Zhou, Z.; Luo, Z.; Wang, H.; Chen, L.; Xu, Y.; Li, S.; Jian, W.; Zeng, J.; Hu, B.; Han, X.; Lin, Y.; Wang, Z. *Org. Lett.* **2017**, *19*, 4339.
- (54) Sun, G.; Jian, W.; Luo, Z.; Sun, T.; Li, C.; Zhang, J.; Wang, Z. *Org. Process Res. Dev.* **2019**, *23*, 1204.
- (55) Sarkale, A. M.; Maurya, V.; Giri, S.; Appayee, C. *Org. Lett.* **2019**, *21*, 4266.
- (56) Chen, J.; Park, J.; Kirk, S. M.; Chen, H.-C.; Li, X.; Lippincott, D. J.; Melillo, B.; Smith, A. B. III. *Org. Process Res. Dev.* **2019**, *23*, 2464.
- (57) Wang, X.; Xu, L.; Yan, L.; Wang, H.; Han, S.; Wu, Y.; Chen, F. *Tetrahedron* **2016**, *72*, 1787.
- (58) Touge, T.; Kuwana, M.; Komatsuki, Y.; Tanaka, S.; Nara, H.; Matsumura, K.; Sayo, N.; Kashibuchi, Y.; Saito, T. *Org. Process Res. Dev.* **2019**, *23*, 452.
- (59) He, B.; Zheng, L.-S.; Phansavath, P.; Ratovelomanana-Vidal, V. *ChemSusChem* **2019**, *12*, 3032.
- (60) Yu, L.; Somfai, P. *RSC Adv.* **2019**, *9*, 2799.
- (61) Rolt, A.; O'Neill, P. M.; Liang, T. J.; Stachulski, A. V. *RSC Adv.* **2019**, *9*, 40336.
- (62) Wang, X.; Xu, L.; Xiong, F.; Wu, Y.; Chen, F. *RSC Adv.* **2016**, *6*, 37701.
- (63) Llopis, Q.; Férard, C.; Guillamot, G.; Phansavath, P.; Ratovelomanana-Vidal, V. *Synthesis* **2016**, *48*, 3357.
- (64) Xiong, Z.; Pei, C.; Xue, P.; Lv, H.; Zhang, X. *Chem. Commun.* **2018**, *54*, 3883.
- (65) Ashley, E. R.; Sherer, E. C.; Pio, B.; Orr, R. K.; Ruck, R. T. *ACS Catal.* **2017**, *7*, 1446.
- (66) Cotman, A. E.; Modéc, B.; Mohar, B. *Org. Lett.* **2018**, *20*, 2921.
- (67) Zheng, L.-S.; Phansavath, P.; Ratovelomanana-Vidal, V. *Org. Chem. Front.* **2018**, *5*, 1366.
- (68) Zheng, D.; Zhao, Q.; Hu, X.; Cheng, T.; Liu, G.; Wang, W. *Chem. Commun.* **2017**, *53*, 6113.
- (69) Strotman, N. A.; Ramirez, A.; Simmons, E. M.; Soltani, O.; Parsons, A. T.; Fan, Y.; Sawyer, J. R.; Rosner, T.; Janey, J. M.; Tran, K.; Li, J.; La Cruz, T. E.; Pathirana, C.; Ng, A. T.; Deerberg, J. J. *J. Org. Chem.* **2018**, *83*, 11133.
- (70) Jeran, M.; Cotman, A. E.; Stephan, M.; Mohar, B. *Org. Lett.* **2017**, *19*, 2042.
- (71) Kim, H. R.; Achary, R.; Lee, H. K. *J. Org. Chem.* **2018**, *83*, 11987.
- (72) Zhang, B.; Liu, L.; Guo, D.; Wang, J. *ChemistrySelect* **2019**, *4*, 1195.
- (73) Schneider, N.; Lowe, D. M.; Sayle, R. A.; Tarselli, M. A.; Landrum, G. A. *J. Med. Chem.* **2016**, *59*, 4385.