



HAL
open science

Green Synthesis of Biorelevant Scaffolds through Organocatalytic/Enzymatic Dynamic Kinetic Resolution

Hélène Pellissier

► **To cite this version:**

Hélène Pellissier. Green Synthesis of Biorelevant Scaffolds through Organocatalytic/Enzymatic Dynamic Kinetic Resolution. *Current Topics in Medicinal Chemistry*, 2024, 24, 10.2174/0115680266294434240322043536 . hal-04555850

HAL Id: hal-04555850

<https://hal.science/hal-04555850>

Submitted on 23 Apr 2024

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.

Green Synthesis of Biorelevant Scaffolds through Organocatalytic/Enzymatic Dynamic Kinetic Resolution

Hélène Pellissier*

Aix Marseille Univ, CNRS, Centrale Marseille, iSm2, Marseille, France
Email: h.pellissier@univ-amu.fr

Abstract: This review highlights major developments in the application of green organocatalytic and enzymatic dynamic kinetic resolutions (DKRs) in the total synthesis of biorelevant scaffolds. It illustrates the diversity of useful bioactive products and intermediates that can be synthesized under greener and more economic conditions through the combination of the powerful concept of DKR, which allows the resolution of racemic compounds with up to 100% yield, with either asymmetric organocatalysis or enzymatic catalysis, avoiding the use of toxic and expensive metals. With the need of more ecologic synthetic technologies, this field will undoubtedly even more expand its scope in the future with the employment of other organocatalysts/enzymes to even more types of transformations, thus allowing powerful greener and more economic strategies to reach other biologically important molecules.

Keywords: Dynamic kinetic resolution, Asymmetric organocatalysis, Enzymatic catalysis, Biorelevant scaffolds, Green synthesis

1. INTRODUCTION

To this day, the resolution of racemic compounds is still the procedure the mostly used in industry to prepare enantiopure products despite the level of performance achieved in the field of asymmetric synthesis. The oldest and simplest methodology for the resolution of a racemic compound is the kinetic resolution shown in Fig. (1). In this process, one enantiomer (S_R) of a racemic mixture is faster converted into chiral product (P_R) whereas the less reactive enantiomer (S_S) is recovered unaffected [1-4] (Fig. 1).

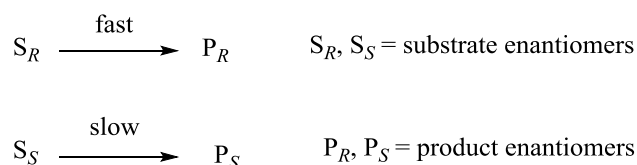


Fig. (1). The kinetic resolution methodology.

The principal disadvantage of this simple methodology is related to the fact that the yield of the reaction is limited to 50%. This major drawback is overcome in dynamic kinetic resolution (DKR), which permits the production of one of the enantiomers with up to 100% yield. The DKR methodology involves the combination of a kinetic resolution step with an *in situ* racemization of the substrate, as illustrated in Fig. (2). The two enantiomers must equilibrate faster than the reaction of the slow-reacting enantiomer with the chiral reagent occurs (Curtin–Hammett kinetics). If the stereoselectivity of the reaction is adequate, then a highly enantioenriched product can be obtained with a yield of 100%. To achieve DKR, the resolution step must be irreversible and the product cannot racemize under the reaction conditions. To reach a high level of enantioselectivity, the selectivity (k_A/k_B) of the step of resolution must be at least of 20. Moreover, the constant rate for the racemization (k_{inv}) must be faster than the constant rate of the resolution step (k_A), otherwise an excellent level of stereoselectivity has to be insured.

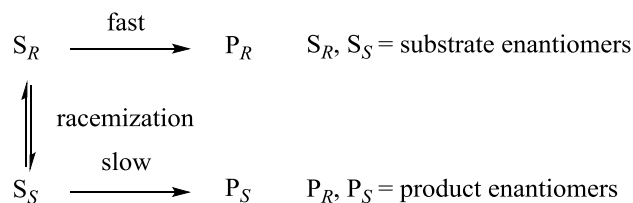


Fig. (2). The DKR methodology.

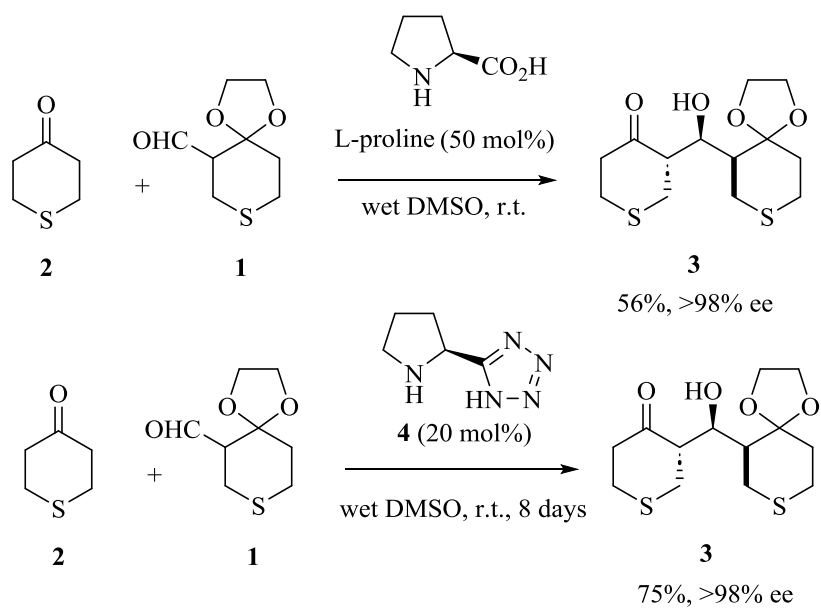
Under optimal DKR conditions, an enantiopure compound can be produced with 100% yield from a racemic mixture. The racemization of the substrate can be achieved chemically, biocatalytically, or even spontaneously. In all cases, the conditions will have to avoid the racemization of the formed

enantioenriched product. The concept of DKR is applicable to enzymatic [5-10], as well as non-enzymatic reactions [11-30]. Along with metal catalysts [31-47], green organocatalysts present advantages to be non-toxic, cheap, and robust [48-63]. Their involvement in the total synthesis of pharmaceuticals is challenging because the products are not contaminated by traces of hazardous metals. The impressive developments of these green catalysts have allowed the first organocatalyzed DKRs to be achieved in the last twenty years, contributing to a wide expansion of the scope of the DKR methodology. Along with organocatalysts, enzymes also represent a green option for DKR in view of the mild conditions generally associated with enzyme-catalyzed racemization processes [16, 18, 25, 64-67]. Furthermore, biocatalytic processes are often remarkably enantio- and regioselective in comparison with more unpredictable chemical reactions. Today, numerous key intermediates for medicinal chemistry are prepared from enzymatic DKR methodologies. This review collects major developments in the total synthesis of biorelevant scaffolds based on the use of green organocatalytic and enzymatic DKRs. It is divided into two sections, dealing successively with organocatalytic processes, and enzymatic ones. It must be noted that methodologies based on the use of enzymes and transition metals in tandem are not included in this review which focusses on green methodologies.

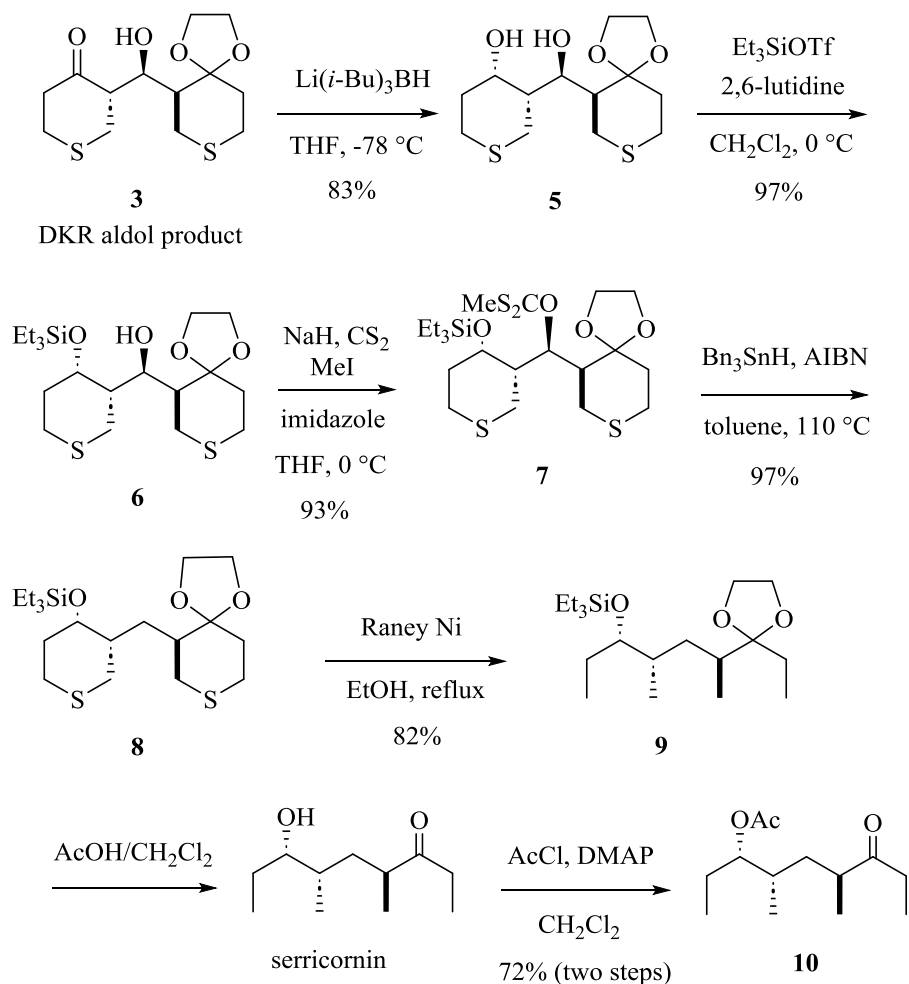
2. ORGANOCATALYTIC DKRS

2.1. Synthesis of Acyclic Products

In 2005, Ward and co-workers disclosed an asymmetric direct aldol reaction between 1,4-dioxo-8-thia-spiro[4.5]decane-6-carboxaldehyde **1** and tetrahydro-4*H*-thiapyranone **2** catalyzed with 50 mol% of L-proline which evolved through DKR (Scheme 1) [68]. It afforded at room temperature in wet DMSO as solvent the corresponding diastereo- and enantiopure (>98% ee) alcohol **3** in 56% yield. Since this reaction was difficult to perform on a large scale, it was reinvestigated in 2006 by using more soluble L-proline-derived catalyst **4** at only 20 mol% of catalyst loading [69]. The process afforded at room temperature within 8 days desired enantiopure (>98% ee) product **3** with a better yield of 75% yield (Scheme 1). This process constituted the key step of an efficient synthesis of serricornin, which is a female sex pheromone from the cigarette beetle. The total synthesis of this acyclic product included seven steps from readily available aldehyde **1**. After the first DKR step, aldol product **3** was submitted to a stereoselective reduction by treatment with Li(*i*-Bu)₃BH in THF at -78 °C, which led diastereoselectively to *anti*-1,3-diol **5** in 83% yield. Then, the latter was treated with Et₃SiOTf at 0 °C in dichloromethane in the presence of 2,6-lutidine as base to give the corresponding chiral mono silyl ether **6** in quantitative yield (97%). Subsequently, a Barton-McCombie deoxygenation of **6** into product **8** was achieved in two steps. The first one furnished product **7** in 93% yield upon treatment with NaH and CS₂ in the presence of imidazole in THF at 0 °C. The second step occurred in the presence of AIBN and tributyl-stannane to provide product **8** with 97% yield. The latter was further submitted to Raney nickel in refluxing ethanol to yield the serricornin derivative **9** in 82% yield. Finally, exposure of **9** to acetic acid delivered expected serricornin that was actually isolated as its acetate derivative **10** obtained with 72% from **9**.



synthesis of serricornin:

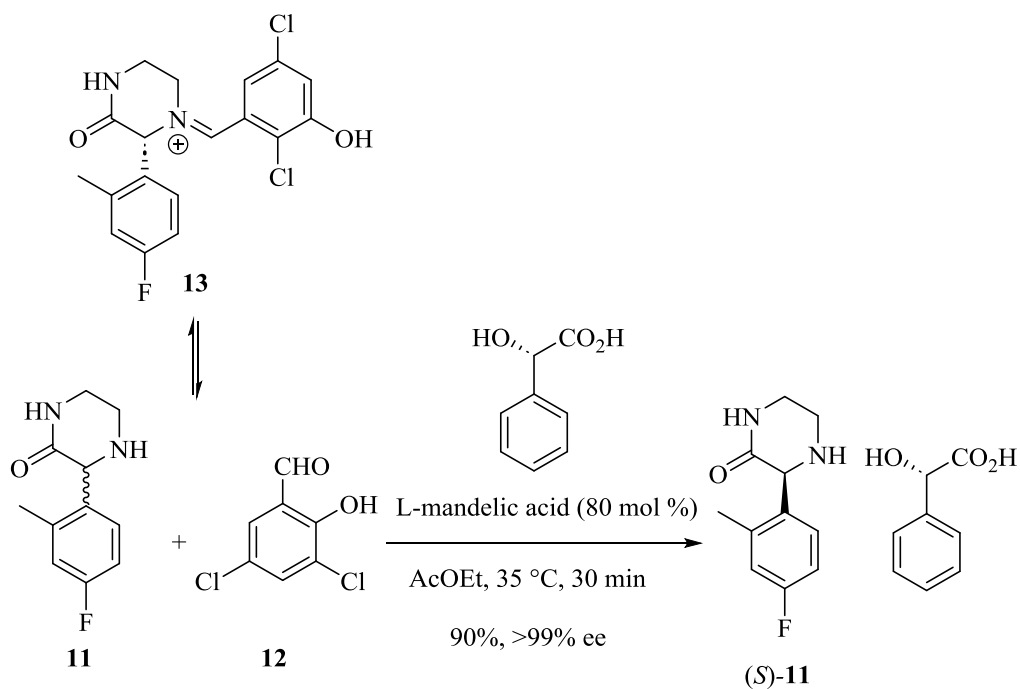


Scheme 1. Synthesis of serricornin.

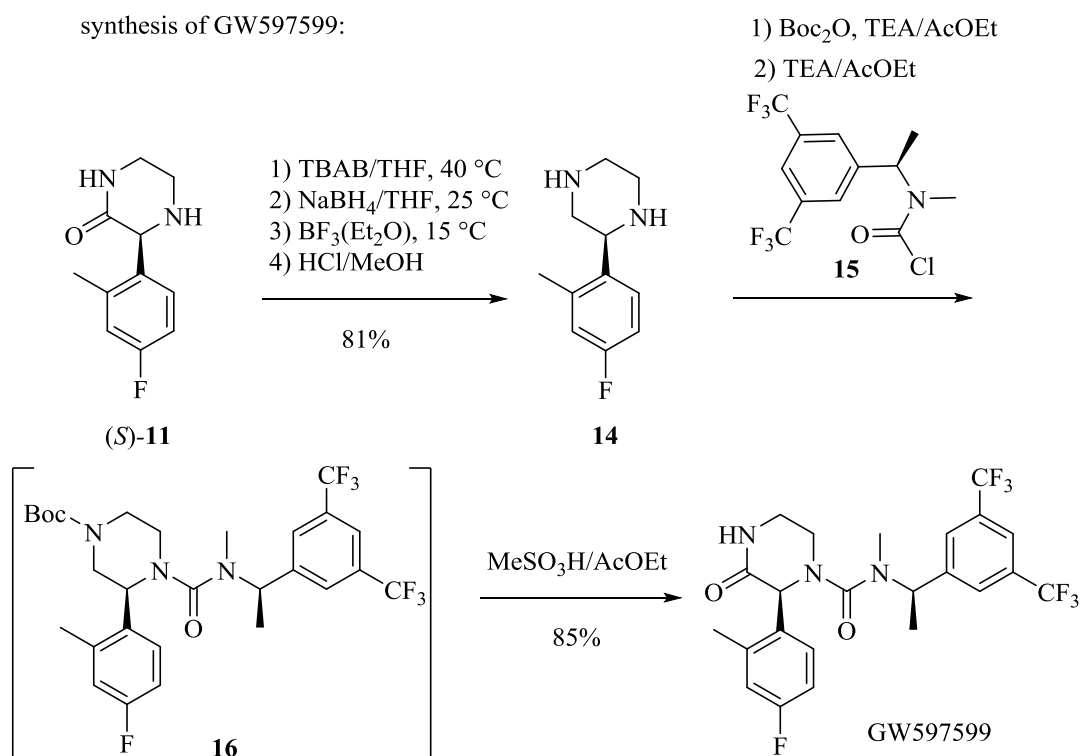
2.2. Synthesis of Monocyclic Products

In 2008, a total synthesis of NK-1 antagonist GW597599 was reported by Guercio and Bacchi [70]. Whereas the previous methodology involved a classic kinetic resolution of a ketopiperazine which was

obtained with 38% yield, these authors proposed a DKR methodology promoted by L-mandelic acid (Scheme 2). Racemic ketopiperazine **11** reacted at 35 °C with dichlorosalicylaldehyde **12** to generate after 30 minutes an iminium derivative, allowing an increased acidity of the benzylic proton. The latter intermediate racemized, resulting in the precipitation of the (*S*)-enantiomer as its mandelate salt, while the undesired enantiomer **13** remained in solution ready to be further racemized. On the basis of this methodology, enantiopure (*S*)-ketopiperazine **11** was isolated with an excellent yield (90% yield). It was used as key intermediate in a total synthesis of GW597599. The reduction of the latter intermediate into the corresponding cyclic diamine **14** was achieved through four steps with 81% overall yield, involving treatments with TBAB in THF, NaBH₄, BF₃·Et₂O, successively and then HCl in methanol [71]. Subsequently, chiral diamine **14** was regioselectively protected by treatment with Boc₂O, and the resulting *N*-Boc protected amine further reacted with carbamoyl chloride **15** in the presence of TEA as base to give urea **16** [72]. Then, deprotection of **16** in the presence of MeSO₃H delivered final GW597599 with 85% overall yield from compound **14**.



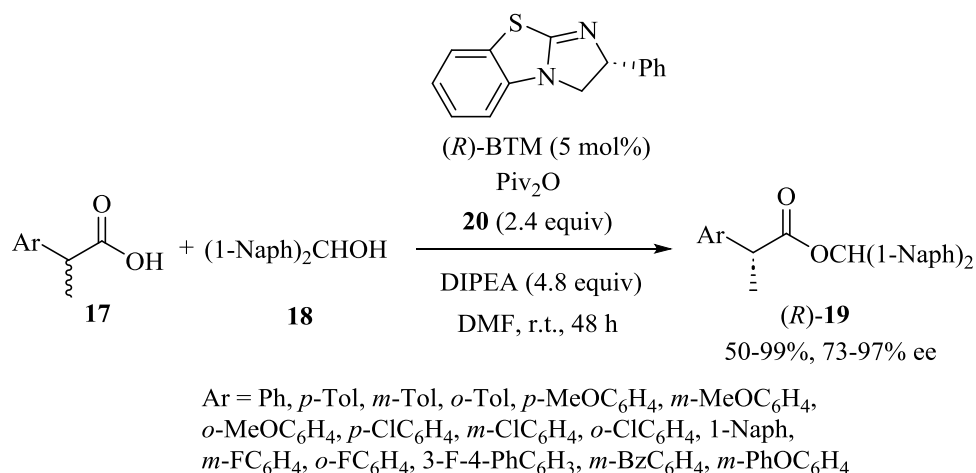
synthesis of GW597599:



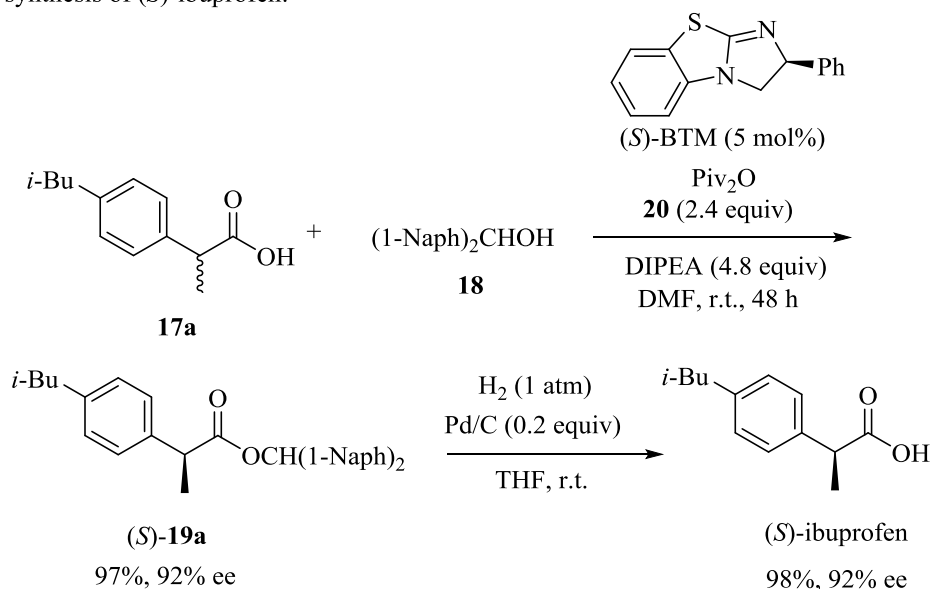
Scheme 2. Synthesis of NK-1 antagonist GW597599.

Chiral carboxylic acids and derivatives constitute potent medicinal molecules and, consequently, their synthesis is challenging [73]. For instance; α -arylalkanoic acids, such as naproxen and ibuprofen, are widely employed as nonsteroidal anti-inflammatory drugs [74]. In order to develop a novel route to ibuprofen, Shiina et al. investigated in 2012 the esterification of α -arylalkanoic acids **17** with bis(α -naphthyl)methanol **18** catalyzed in DMF by only 5 mol% of (*R*)-BTM in the presence of pivalic anhydride as an activator [75]. The DKR process evolved through enantio-discriminating esterification of racemic α -arylalkanoic acids **17** with alcohol **18** and racemization of the chiral α -arylalkanoic acids via the formation of the mixed-anhydrides generated from pivalic anhydride **20** in the presence of a base, such as DIPEA. The nature of the solvent played a major role, since the racemization was found dramatically enhanced in

polar DMF. As shown in Scheme 3, the reaction provided after 48 hours a range of α -arylalkanoic esters (**R**)-**19** in 50-99% yields and 73-97% ee. Especially, substrates exhibiting electron-donating groups, such as methyl and methoxy groups, on the phenyl ring at either *ortho*-, *meta*-, or *para*-positions all provided both high yields (85-96%) and enantioselectivities (84-97% ee). The scope of the methodology was also applicable to 2-arylpropanoic acids including several nonsteroidal anti-inflammatory drugs. All the reactions provided the desired (*R*)-carboxylic esters with excellent yields (88-96%) and ee values (81-93% ee) irrespective of the substitution pattern and the electronic effects on the aromatic rings of the substrates. Moreover, the synthesis of nonsteroidal anti-inflammatory drug (*S*)-ibuprofen was achieved by using (*S*)-BTM as an organocatalyst. Indeed, the esterification of α -arylalkanoic acid **17a** with bis(α -naphthyl)methanol **18** performed in the presence of 5 mol% of (*S*)-BTM in the presence of pivalic anhydride and DIPEA as base in DMF afforded at room temperature expected enantiomeric α -arylalkanoic ester (*S*)-**19a** with 97% yield and 92% ee (Scheme 3). The latter was subsequently submitted at room temperature to hydrogenation on Pd/C in THF to deliver desired (*S*)-ibuprofen in 92% ee and 98% yield (Scheme 3).



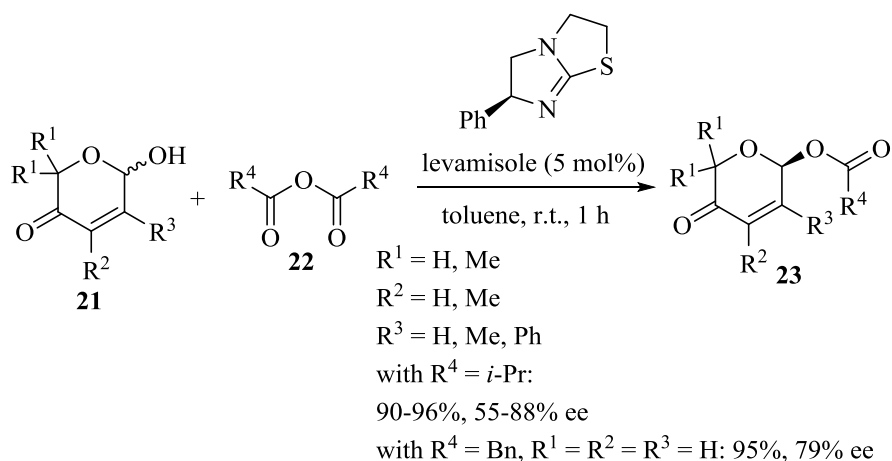
synthesis of (*S*)-ibuprofen:



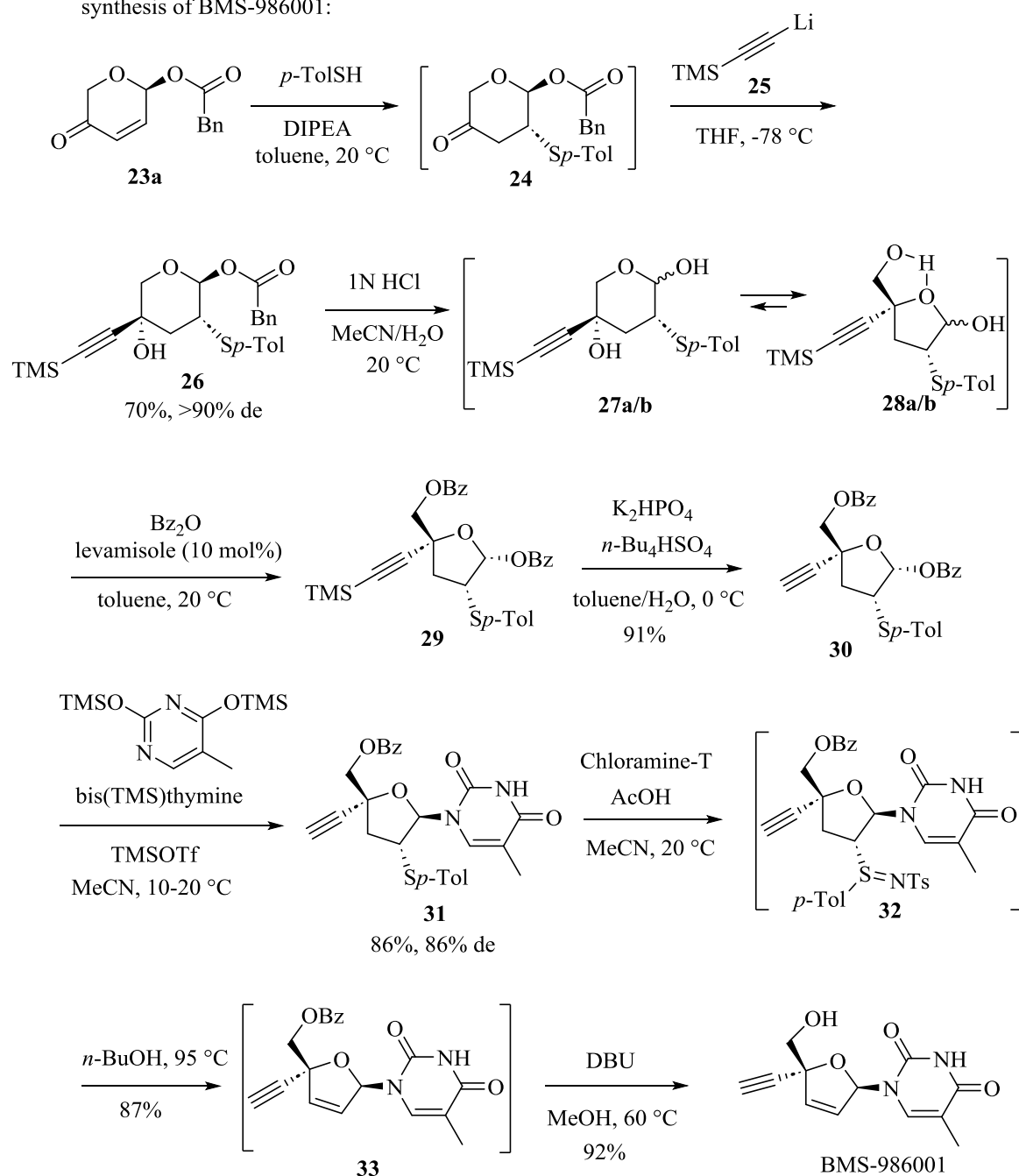
Scheme 3. Synthesis of (*S*)-ibuprofen.

With the aim of developing a novel route to potent HIV inhibitor BMS-986001, Ortiz et al. investigated in 2015 the asymmetric esterification of pyranose lactols **21** with isobutyric anhydride **22** ($R^4 = i\text{-Pr}$) performed in the presence of levamisole as organocatalyst (Scheme 4) [76]. The reaction evolving through DKR afforded after 1 hour at room temperature the corresponding isobutyl esters **23** ($R^4 = i\text{-Bu}$) in 90-96% yields and 55-88% ee. A good tolerance for alkyl substitution at C2 ($R^1 = R^2 = \text{H}$, $R^3 = \text{Me}$: 96%, 72% ee), C3 ($R^1 = R^3 = \text{H}$, $R^2 = \text{Me}$: 90%, 82% ee), and C5 ($R^1 = \text{Me}$, $R^2 = R^3 = \text{H}$: 91%, 96% ee) was observed

while aryl substitution at C2 led to reduced enantioselectivity ($R^1 = R^2 = H$, $R^3 = Ph$: 96%, 55% ee). Applied to benzyl anhydride ($R^4 = Bn$), the reaction of unsubstituted pyranose lactol ($R^1 = R^2 = R^3 = H$) furnished benzyl ester **23a** in 95% yield and 79% ee. This chiral compound was further converted into BMS-986001 through five steps with 44% overall yield. The first step consisted of a diastereoselective aza-Michael addition of *p*-thiocresol to the DKR product **23a** carried out at 20 °C in toluene in the presence of DIPEA as base to give sulfide **24** as an almost single diastereomer (>96% de). The latter was directly submitted in THF at -78 °C to a diastereoselective nucleophilic addition with lithio-TMS-acetylene **25** to afford pyranose **26** in 70% yield and >90% de. Then, hydrolysis of **26** with aqueous HCl in acetonitrile at 20 °C provided access to furanoses **28a/b** through rapid equilibration of pyranoses **27a/b**. When this mixture of four lactol isomers **27a/b** and **28a/b** was treated in toluene at 20 °C with Bz₂O in the presence of chiral levamisole as catalyst, it was found that furanoses **28a/b** could be selectively trapped as their bis(benzoate) derivative **29** (98:2, furanose/pyranose, 50:1 α : β). Then, selective removal of the TMS group in **29** by treatment with K₂HPO₄ in the presence of *n*-Bu₄NHSO₄ in aqueous toluene at 0 °C delivered crystalline α -Bz-furanose **30** with 91% overall yield from **26**. Next, a Vorbrüggen reaction with bis(TMS)thymine occurred in the presence of TMSOTf in acetonitrile to form nucleoside **31** in 86% yield and high β -selectivity (86% de). This nucleoside **31** was then converted with 87% yield into dehydrofuranose **33** through a selective sulfur oxidation mediated by Chloramine-T providing intermediate sulfilimine **32**, followed by a thermolysis at 95 °C. The final step of the synthesis dealt with a DBU-catalyzed transesterification carried out at 60 °C in methanol, which delivered desired HIV-inhibitor BMS-986001 with 92% yield.

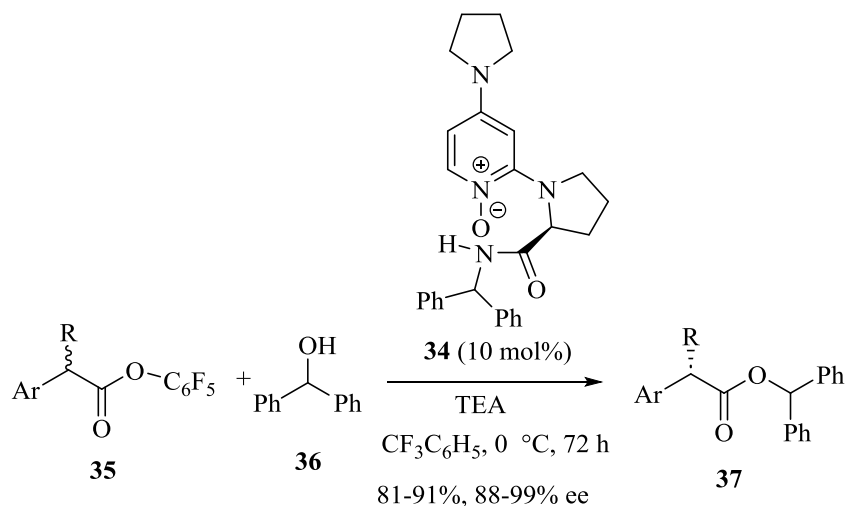


synthesis of BMS-986001:



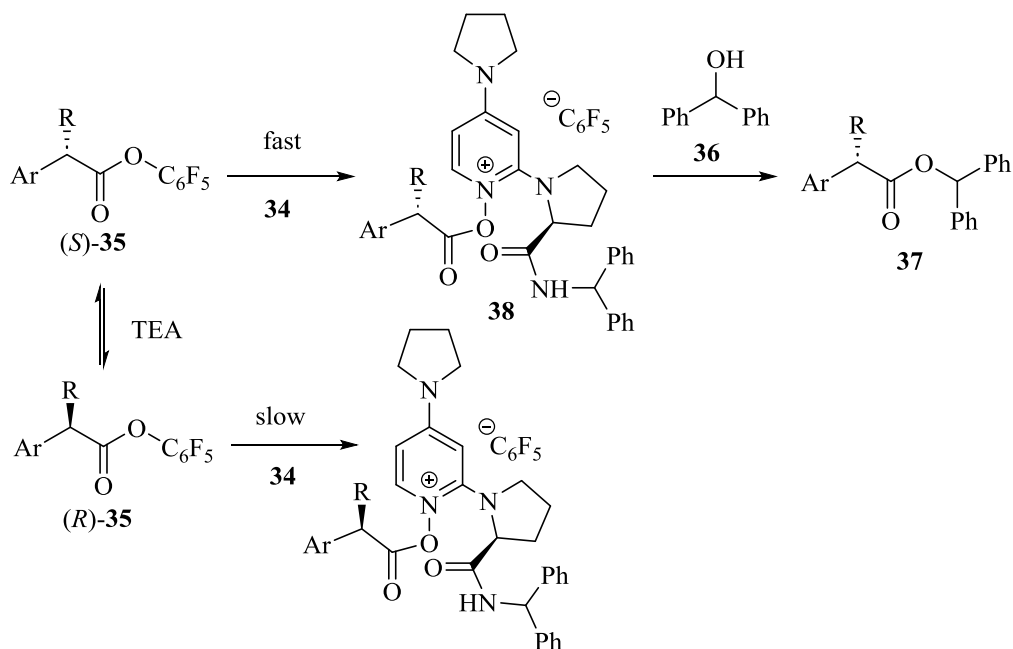
Scheme 4. Synthesis of HIV inhibitor BMS-986001.

In 1996, the first chiral 4-(dialkylamino)pyridine catalysts were introduced by Vedejs [77]. Ever since, these special organocatalysts have been successfully applied as promoters in many types of asymmetric transformations including DKRs [78-81]. In 2021, Guo, Xie and Tian involved chiral 4-pyrrolidinopyridine *N*-oxide catalyst **34** in the transesterification of pentafluorophenol esters **35** with diphenylmethanol **36** evolving through DKR (Scheme 5) [82]. In the presence of a base such as TEA and 10 mol% of catalyst **34** in trifluoromethylbenzene, a range of esters reacted at 0 °C with diphenylmethanol **36** to produce after 72 hours chiral α -aryl α -alkyl carboxylic esters **37** in 81-91% yields and 88-99% ee. The substrate was racemized in the presence of TEA. The (*S*)-enantiomer reacted faster with **34** to form the corresponding intermediate **38**, which further underwent a nucleophilic substitution with diphenylmethanol **36** to furnish the final product. The catalytic system tolerated esters bearing electron-donating or electron-withdrawing substituents on the phenyl ring, thus generating the desired products in both high yields (81-91%) and enantioselectivities (88-99% ee). It was found that the ee values arising from the reaction of *ortho*-substituted esters were higher than those obtained from the corresponding *para*-substituted esters. In the case of 1-naphthyl- and 2-naphthyl-substituted esters, the desired chiral carboxylic esters were obtained in 97% and 86% ee, respectively. Furthermore, changing the α -methyl group (R = Me) into an ethyl or a benzyl substituent (R = Et, Bn) resulted in negligible changes in enantioselectivity (Ar = Ph, R = Et, Bn: 93-94% ee vs Ar = Ph, R = Me: 93% ee). Applying this methodology, four chiral esters of anti-inflammatory drugs, such as (*S*)-ibuprofen ester **37a**, (*S*)-ketoprofen ester **37b**, (*S*)-fenaprofen ester **37c**, and (*S*)-flurbiprofen ester **37d**, could be easily synthesized with 84-89% yields and 88-94% ee, as illustrated in Scheme 5.

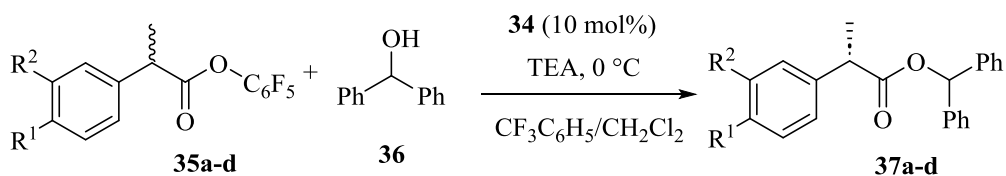


Ar = *p*-MeOC₆H₄, Ph, *o*-Tol, *p*-Tol, *o*-Tol, *o*-MeOC₆H₄,
o-ClC₆H₄, *p*-ClC₆H₄, 1-Naph, 2-Naph
 R = Me, Et, Bn

mechanism:



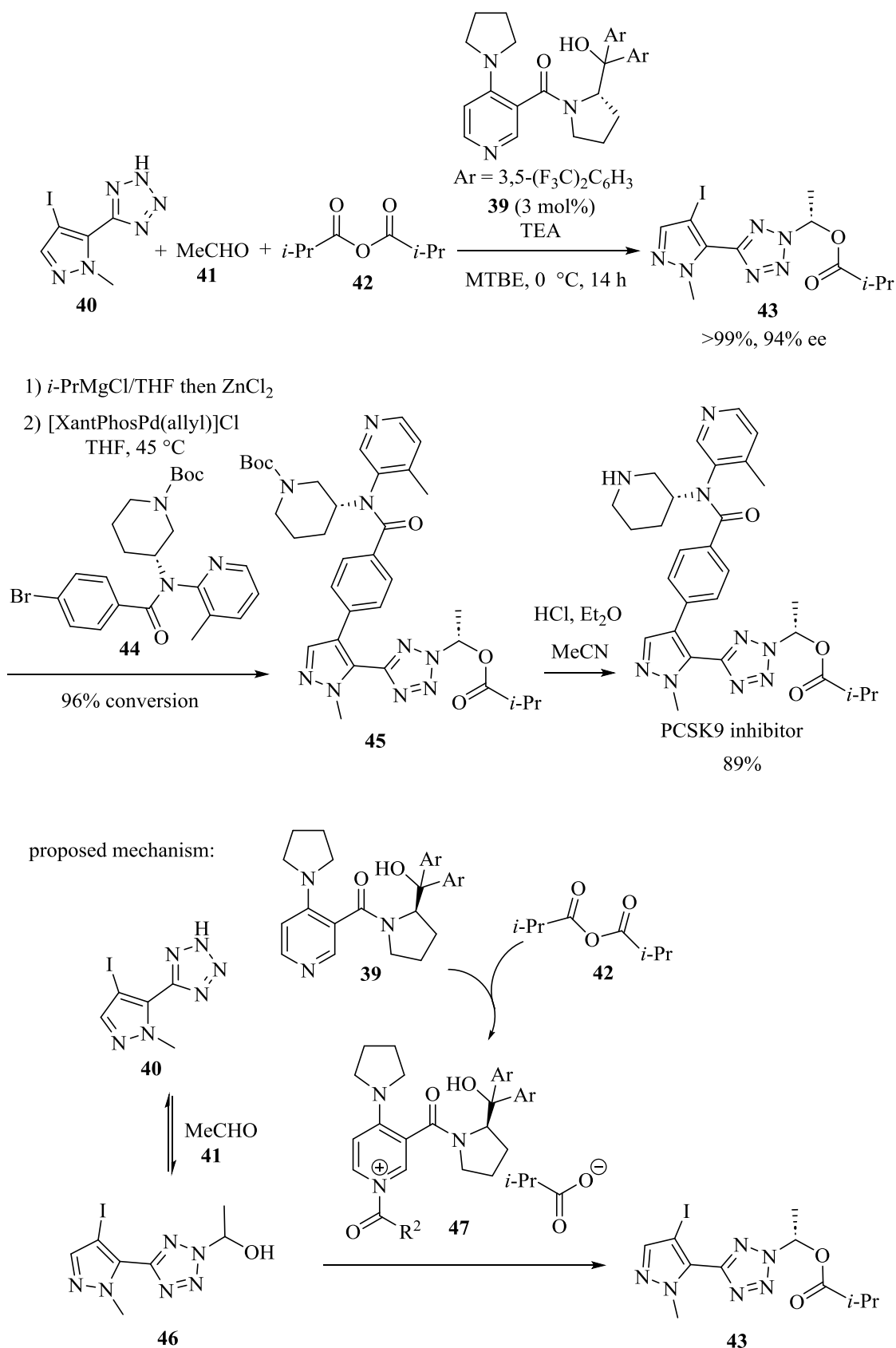
synthesis of nonsteroidal anti-inflammatory drug esters:



(S)-ibuprofen ester **37a** (R¹ = *i*-Bu, R² = H): 89%, 90% ee
(S)-ketoprofen ester **37b** (R¹ = H, R² = Bz): 86%, 88% ee
(S)-fenaprofen ester **37c** (R¹ = H, R² = OPh): 84%, 94% ee
(S)-flurbiprofen ester **37d** (R¹ = OPh, R² = F): 88%, 91% ee

Scheme 5. Synthesis of *(S)*-ibuprofen, *(S)*-ketoprofen, *(S)*-fenaprofen, and *(S)*-flurbiprofen esters.

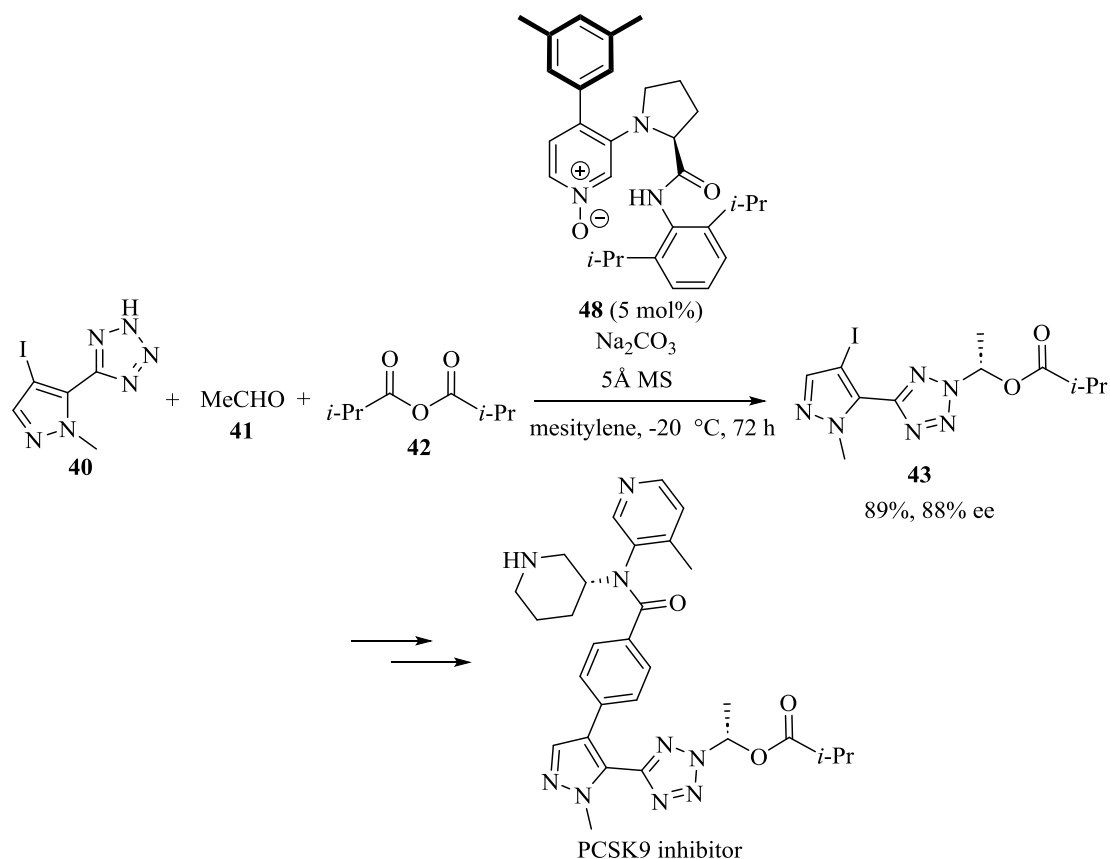
Along with esterifications, other types of transformations have been employed as key DKR steps in total synthesis of bioactive products. For example in 2017, Salan and Piotrowski employed only 3 mol% of chiral 4-(dialkylamino)pyridine catalyst **39** to promote a DKR process based on a three-component reaction [83-84]. The transformation consisted in an enantioselective and regioselective three-component reaction between acetaldehyde **41**, tetrazole **40**, and isobutyric anhydride **42** (Scheme **6**). Carried out at 0 °C in MTBE in the presence of TEA as base, it resulted after 14 hours in the formation of chiral hemiaminal **43** in 94% ee and quantitative yield. As detailed in Scheme **6**, the reaction began with the reversible addition of tetrazole **40** to aldehyde **41**, generating transient hemiaminal species **46**. Alternatively, chiral acylpyridinium cation **47** was generated from anhydride **42** and Lewis base catalyst **39**. The latter reacted with hemiaminal species **46** to give final hemiaminal **43**. An inhibitor of proprotein convertase subtilisin/kexin type 9 (PCSK9) could be prepared from this domino product through four additional steps. Indeed, in a first step, the magnetisation of chiral tetrazole **43** with *i*-PrMgCl was performed at -45 °C in THF. Then, transmetalation to the thus-formed organozinc species was achieved in the presence of ZnCl₂. Subsequently, the addition of bromide **44** and [XantPhosPd(allyl)]Cl at 45 °C underwent coupling which furnished product **45**. After deprotection performed in the presence of HCl, the final product was obtained in 89% yield.



Scheme 6. Synthesis of a PCSK9 inhibitor.

In 2022, Xie, Tian and Guo reinvestigated the same three-component reaction by using chiral 4-aryl-pyridine-*N*-oxide **48** as catalyst [85]. In this case, the reaction of tetrazole **40**, isobutyric anhydride **42**, and acetaldehyde **41** was performed in mesitylene in the presence of 5 mol% of **48** and Na₂CO₃ as base

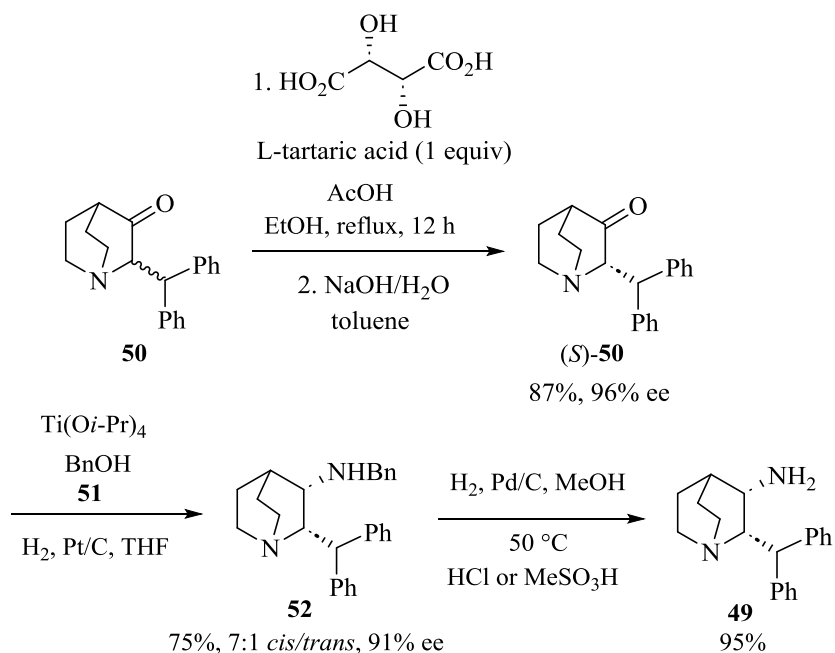
(Scheme 7). Carried out at $-20\text{ }^{\circ}\text{C}$, the DKR led regioselectively ($>20:1$) after 72 hours to the corresponding chiral hemiaminal **43** with 89% yield and 88% ee. The methodology was applied to the same total synthesis of the PCSK9 inhibitor as depicted in Scheme 6.



Scheme 7. Modified synthesis of a PCSK9 inhibitor.

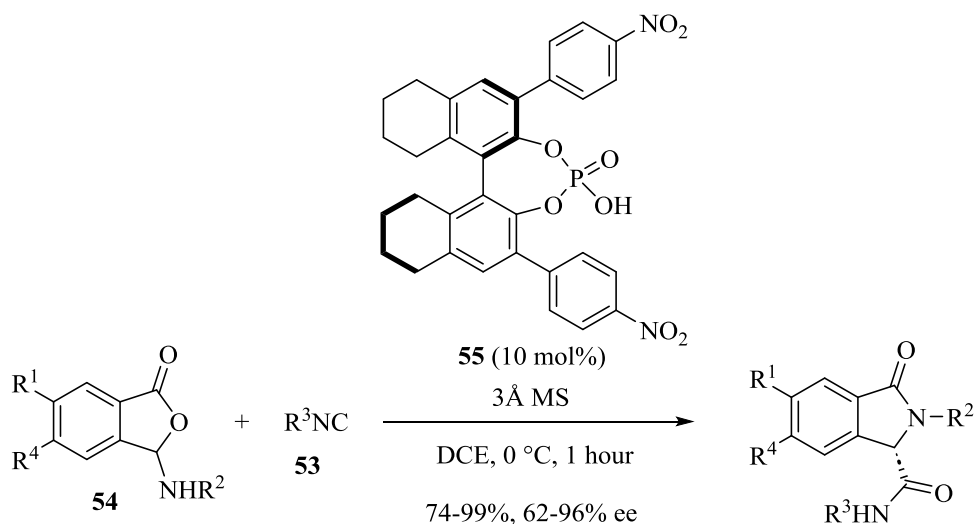
2.3. Synthesis of Bicyclic Products

Antagonists of natural peptidic substance P are pharmaceutical agents employed against central nervous system, gastrointestinal, or inflammatory disorders. In 2006, an efficient synthesis of precursor **49** to substance P antagonists was disclosed by Nugent and Seemayer (Scheme 8) [86]. It was based on the DKR of quinuclidinone **50** achieved by using L-tartaric acid (one equivalent). The almost enantiopure product (*S*)-**50** was obtained with 87% yield within 12 hours. The latter was further submitted to reductive amination with benzylamine **51** to give the corresponding chiral benzylamine **50**. With this aim, chiral benzhydryl quinuclidinone (*S*)-**50** and benzylamine **51** were stirred in THF with $\text{Ti}(\text{O}i\text{-Pr})_4$ and subsequently submitted to hydrogenation at 50 psi with Pt/C to give desired chiral benzylamine **52** in 75% yield and 91% ee as a 7:1 mixture of *cis/trans* diastereomers. Finally, the deprotection of the amine was achieved through hydrogenation on Pd/C performed at $50\text{ }^{\circ}\text{C}$ in the presence of HCl or MeSO_3H to provide expected precursor **49** to substance P antagonists with 95% yield.



Scheme 8. Synthesis of a pivotal precursor to substance P antagonists.

Chiral Brønsted acids are among the most employed organocatalysts in asymmetric catalysis [87-93]. Among them, chiral phosphoric acids derived from BINOL and derivatives have been intensively used as bifunctional catalysts in many types of asymmetric transformations including DKRs [94-99]. An example reported by Wang and Zhu in 2016 dealt with an enantioselective two-component Ugi-type reaction between isonitriles **53** and 3-(arylamino)isobenzofuran-1(3H)-ones **54** (Scheme 9) [100]. The process was carried out at 0 °C by 10 mol% of chiral phosphoric acid **53** in DCE, leading in 1 hour to chiral 3-oxo-2-arylisoindoline-1-carboxamides **56** in 74-99% yields and 62-96% ee. These bicyclic molecules are of great importance in medicinal chemistry, which is illustrated in the skeleton of analgesic drug (*R*)-pazinaclone. The mechanism of the Ugi-type reaction proposed by the authors involved the formation of iminium salt **57** which subsequently added isonitrile **53** to give nitrilium intermediate **58** (step a). The latter was subsequently trapped by the tethered carboxylate to provide intermediate **59**. Then, rearrangement of **59** via the bridged intermediate **60** (step b) afforded final isoindolinone **56**. At the same time, **59** was submitted to an imine/enamine isomerization (steps c/d) to give isocoumarin **61** through prototropic tautomerization. The fact that this equilibrium was faster than step b was responsible for the DKR.



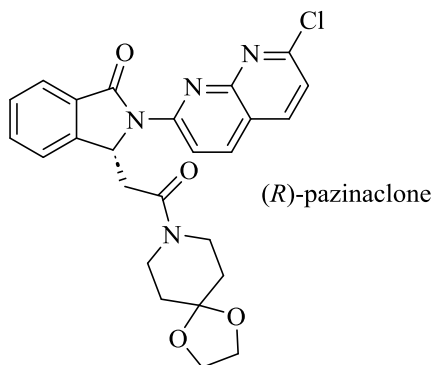
$\text{R}^1 = \text{H, OMe, F}$

$\text{R}^2 = p\text{-ClC}_6\text{H}_4, p\text{-BrC}_6\text{H}_4, p\text{-FC}_6\text{H}_4, p\text{-F}_3\text{CC}_6\text{H}_4, p\text{-MeO}_2\text{CC}_6\text{H}_4,$

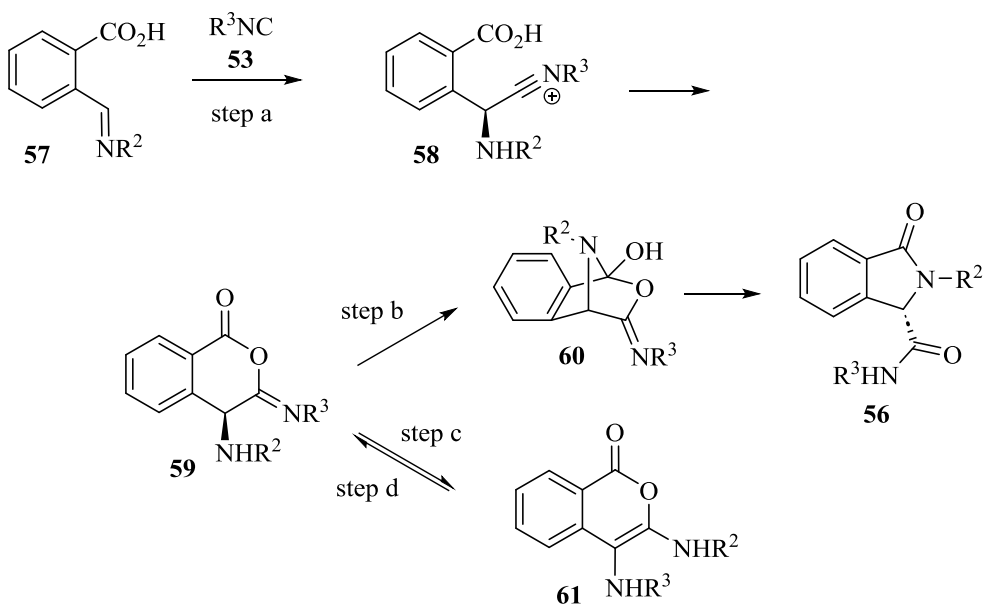
$p\text{-MeOC}_6\text{H}_4, 2\text{-Naph, 1-Naph, } m\text{-BrC}_6\text{H}_4, \text{Ph}$

$\text{R}^3 = t\text{-Bu, Cy, } n\text{-Bu, (Me)}_2\text{C(CO}_2\text{Me)}$

$\text{R}^4 = \text{H, OMe, F}$

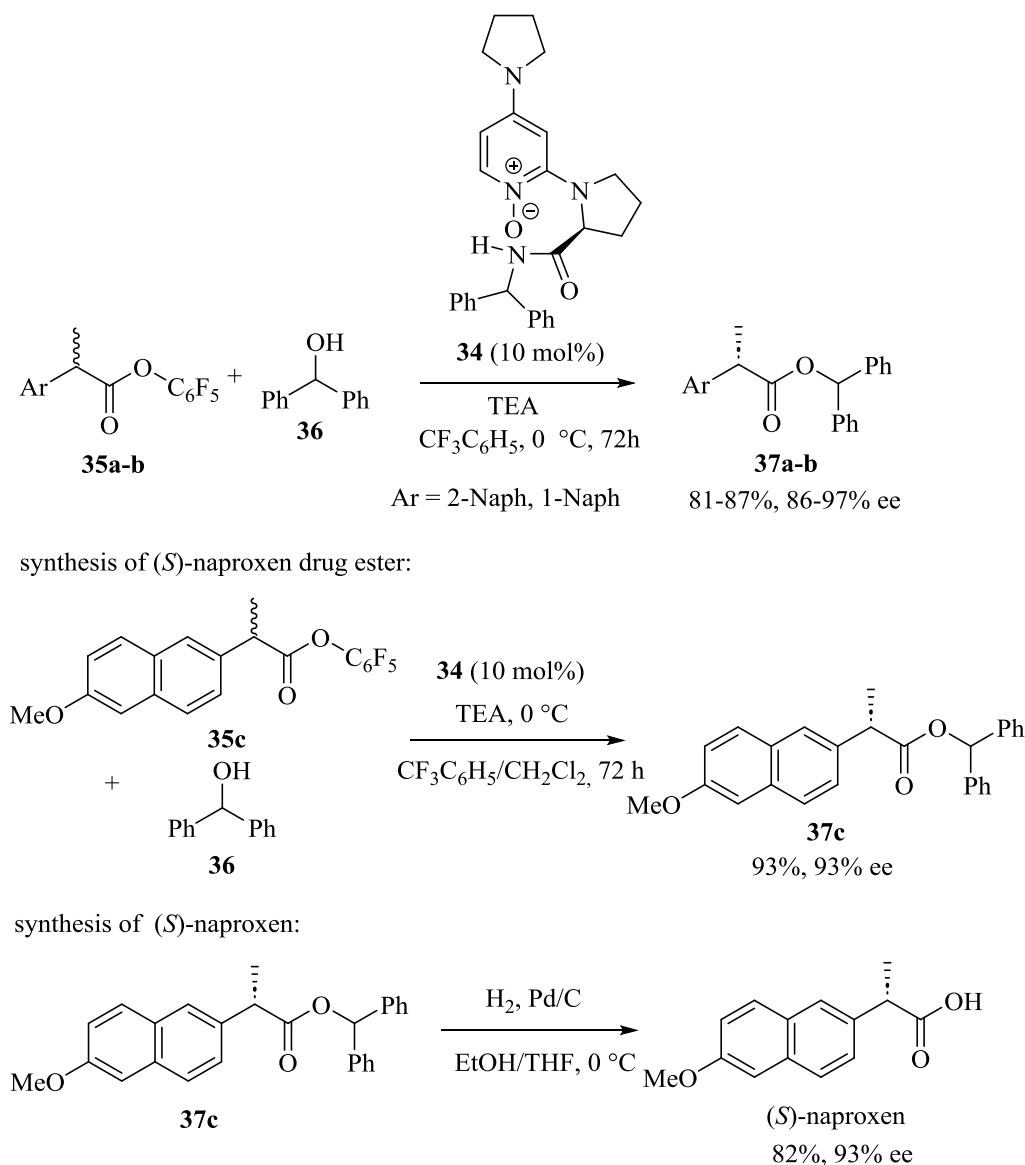


proposed mechanism (with $\text{R}^1 = \text{R}^4 = \text{H}$):



Scheme 9. Synthesis of the skeleton of (*R*)-pazinaclone.

The scope of the DKR methodology reported in 2021 by Guo, Tian and Xie and described in Scheme 5 [82] was also extended to naphthyl-substituted pentafluorophenol esters **35a-b** which reacted with diphenylmethanol **36** in the presence of 10 mol% of chiral 4-pyrrolidinopyridine *N*-oxide catalyst **34** to give within 72 hours through transesterification chiral α -naphthyl α -alkyl carboxylic esters **37ab** with 81-87% yields and 86-97% ee, as presented in Scheme 10 [82]. The racemization of the substrate was achieved in the presence of TEA. This reaction was applied to the synthesis of (*S*)-naproxen ester **37c** with 93% yield and 93% ee. It must be noted that this ester could be prepared on a gram scale with 87% yield and 94% ee with complete recovery of the catalyst which was recyclable and reusable. Furthermore, hydrogenation on Pd/C of (*S*)-naproxen ester **37c** delivered (*S*)-naproxen with 82% yield and 93% ee.

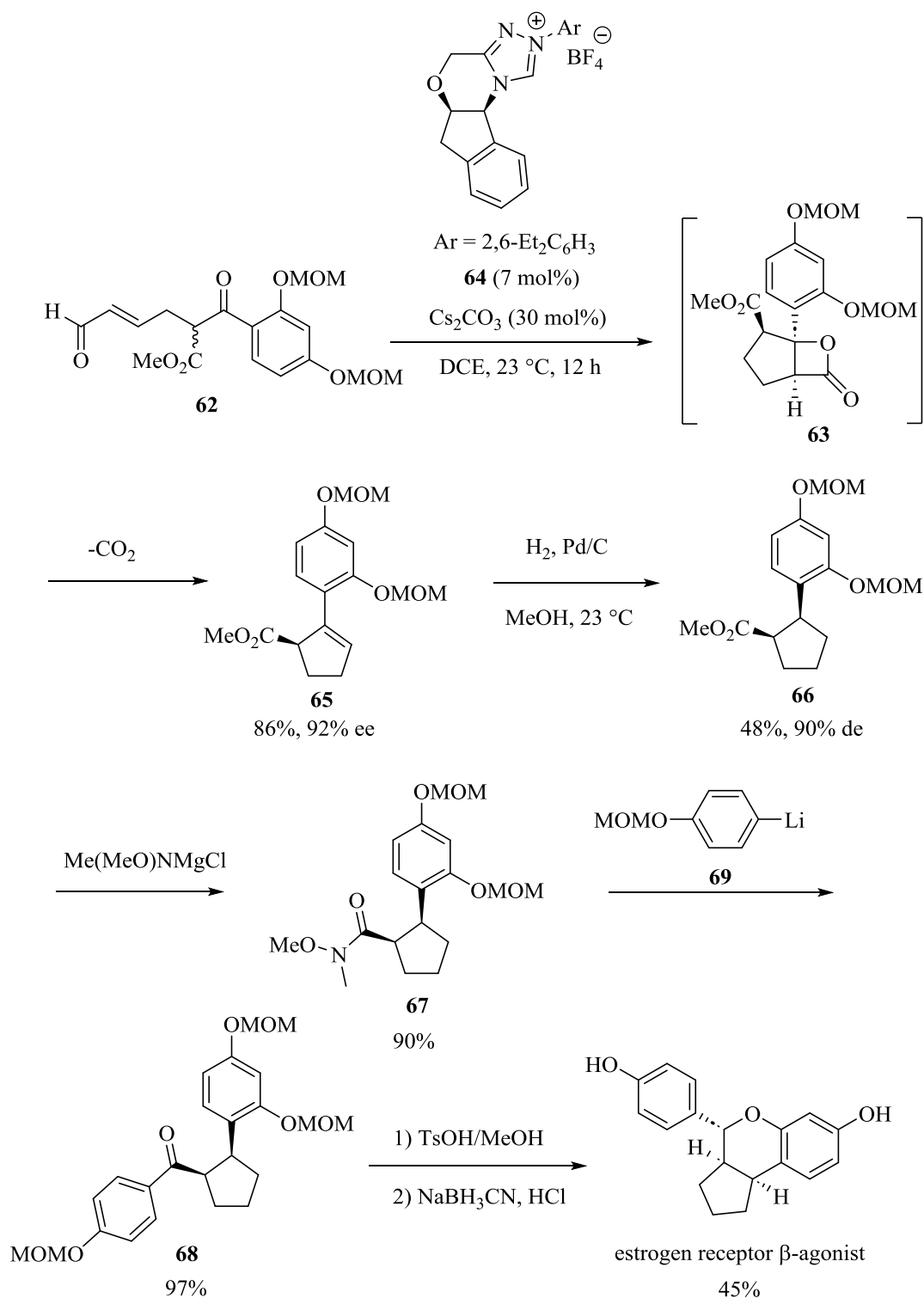


Scheme 10. Synthesis of (*S*)-naproxen (ester).

2.4. Synthesis of Tricyclic Products

N-Heterocyclic carbenes have been widely employed in asymmetric organocatalysis in the last decades [101-104], and more particularly in the area of domino reactions [105-130]. Aldehydes react with these catalysts to generate (homo)enolate equivalents, which can be further trapped by electrophilic species. Imidazolium-, thiazolium-, or triazolylidene stable carbenes [131-132] are synthesized from chiral amino acids. The active carbene species are *in situ* generated through deprotonation in the presence of a base of the precursor salts of the corresponding N-heterocyclic carbenes. It must be noted that examples of DKRs catalyzed by N-heterocyclic carbenes still remain rare and especially their applications to the total synthesis of bioactive products [133-134]. However in 2015, Scheidt and Cheong disclosed a rare example, which

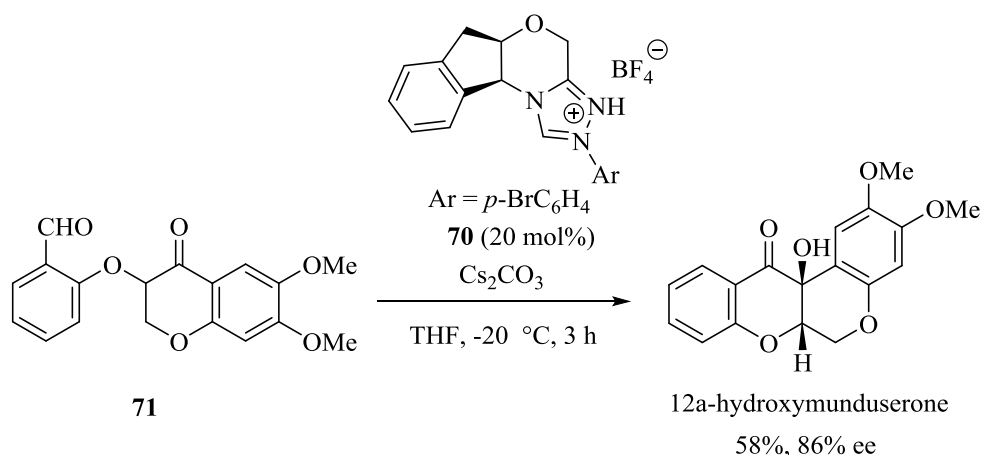
was applied to develop a novel total synthesis of an estrogen receptor β -agonist (Scheme 11) [135] The key DKR step of the sequence dealt with an intramolecular domino aldol/acylation reaction of α -substituted- β -ketoester **62** into chiral bicyclic lactone **63** performed at 23 °C within 12 hours in DCE in the presence of 7 mol% of chiral N-heterocyclic carbene catalyst **64**. The thus-formed lactone **63** was not isolated but directly underwent at room temperature an unusual β -lactone decarboxylation to give chiral cyclopentene product **65** with 92% ee and 86% yield. This domino product was further converted into expected estrogen receptor β -agonist through four additional steps. The first one was the hydrogenation of **65** performed on Pd/C to give cyclopentane **66** with 48% yield and 90% de. Treatment of the latter species with a Grignard reagent furnished Weinreb amide **67** with 90% yield. Then, **67** reacted with aryllithium reagent **69** to give aryl ketone **68**. Finally, successive treatment with TsOH in methanol followed by addition of NaBH₃CN in the presence of HCl allowed deprotection followed by cyclization of **68**, which delivered the final bioactive product with 45% overall yield.



Scheme 11. Synthesis of a benzopyran estrogen receptor β-agonist.

2.5. Synthesis of Tetracyclic Products

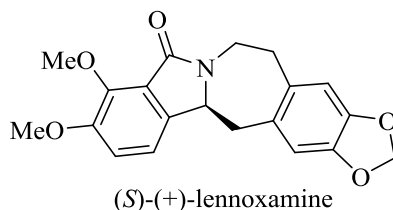
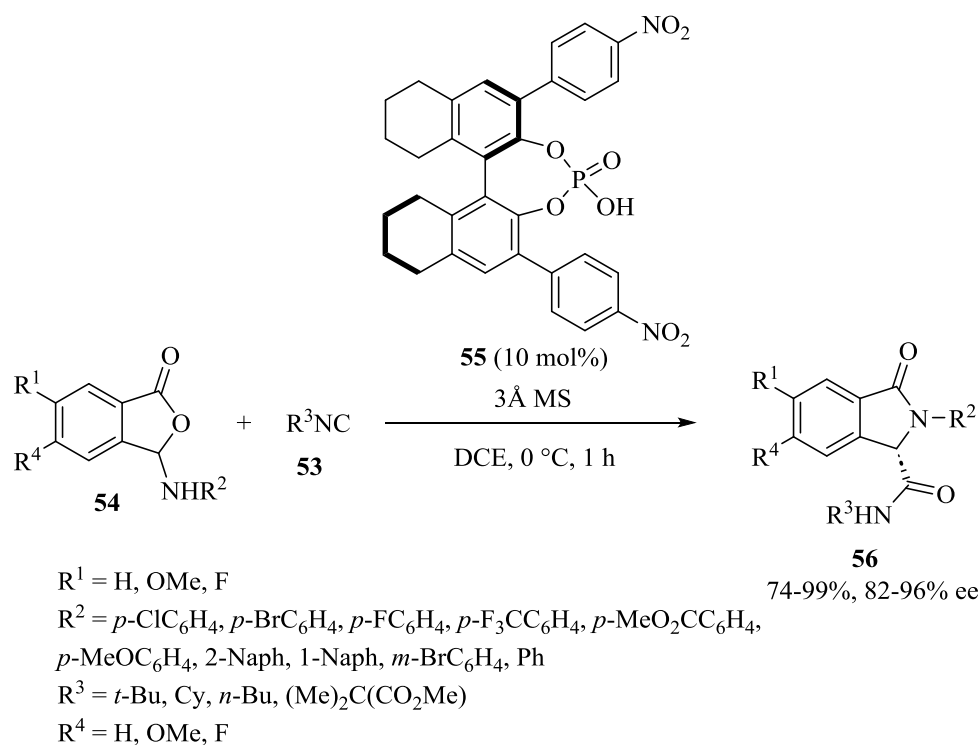
In 2019, Fang et al. employed closely related chiral *N*-heterocyclic carbene catalyst **70** to promote the intramolecular benzoin reaction of ketoaldehyde **71** evolving through DKR [136]. The process was carried out at -20 °C in THF in the presence of 20 mol% of catalyst **70** and Cs₂CO₃ as base. As depicted in Scheme 12, the benzoin reaction of substrate **71** produced within 3 hours natural and bioactive 12a-hydroxymunduserone in 58% yield and 86% ee.



Scheme 12. Synthesis of 12a-hydroxymunduserone.

2.6. Synthesis of Pentacyclic Products

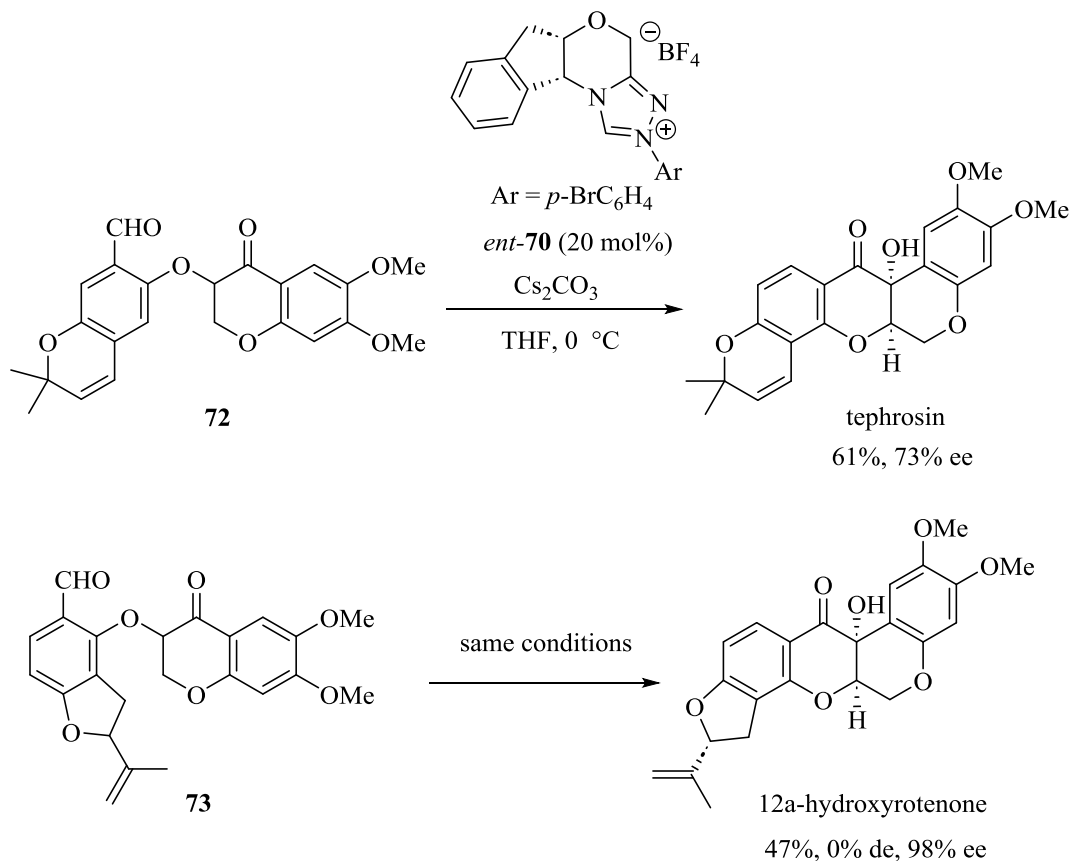
In 2016, Wang and Zhu described a DKR process based on an asymmetric two-component Ugi-type reaction of 3-(arylamino)isobenzofuran-1(3H)-ones **54** with isonitriles **53** catalyzed at $0\text{ }^\circ\text{C}$ in DCE by 10 mol% of chiral phosphoric acid **55** (Scheme 13) [100]. This resulted within 1 hour in the formation of chiral 3-oxo-2-arylisindoline-1-carboxamides **56** with 74-99% yields and 82-96% ee. These bicyclic products constitute the skeleton of numerous bioactive products, such as analgesic pentacyclic drug (*S*)-(+)-lennoxamine (Scheme 13).



Scheme 13. Synthesis of the skeleton of (*S*)-(+)-lennoxamine.

Later in 2019, Fang et al. employed chiral *N*-heterocyclic carbene catalyst *ent*-**70** to promote the intramolecular benzoin reaction of ketoaldehydes evolving through DKR [136]. The process was carried

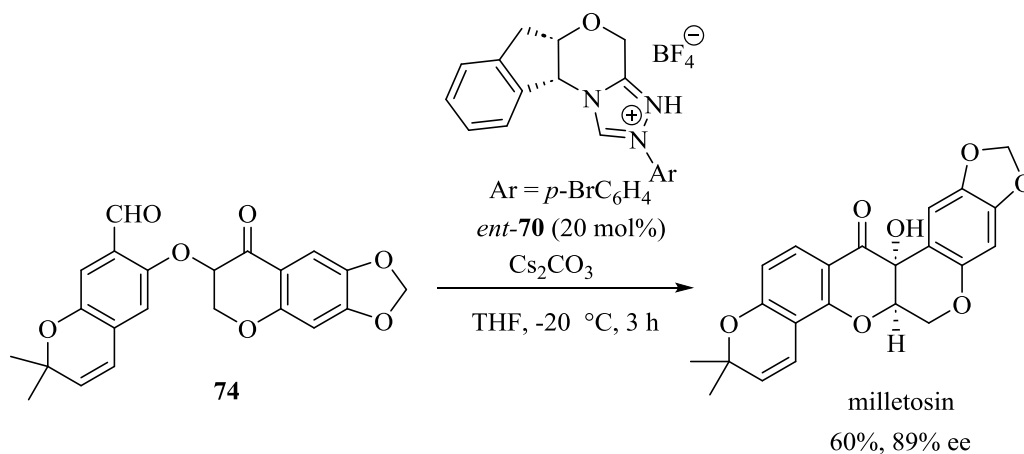
out at 0 °C in THF in the presence of 20 mol% of this catalyst along with Cs₂CO₃ as base. This DKR methodology was applied to the synthesis of tephrosin and 12a-hydroxyrotenone, which are two bioactive natural heterocycles. As presented in Scheme 14, the benzoin reaction of ketoaldehyde **72** allowed natural and bioactive chiral tephrosin to be synthesized in 3 hours with 61% yield and 73% ee. The same reaction conditions were also applied to the benzoin reaction of ketoaldehyde **73** which allowed bioactive 12a-hydroxyrotenone to be synthesized with 47% yield and 98% ee albeit as a mixture of diastereomers (0% de).



Scheme 14. Synthesis of tephrosin and 12a-hydroxyrotenone.

2.7. Synthesis of Hexacyclic Products

In 2019, the scope of the precedent methodology was also employed to prepare another natural bioactive product, namely hexacyclic milletosin (Scheme 15) [136]. Indeed, the treatment at -20 °C instead of 0 °C of ketoaldehyde **74** with 20 mol% of chiral *N*-heterocyclic carbene catalyst *ent*-**70** allowed the direct synthesis of milletosin with 60% yield and 89% ee within 3 hours.



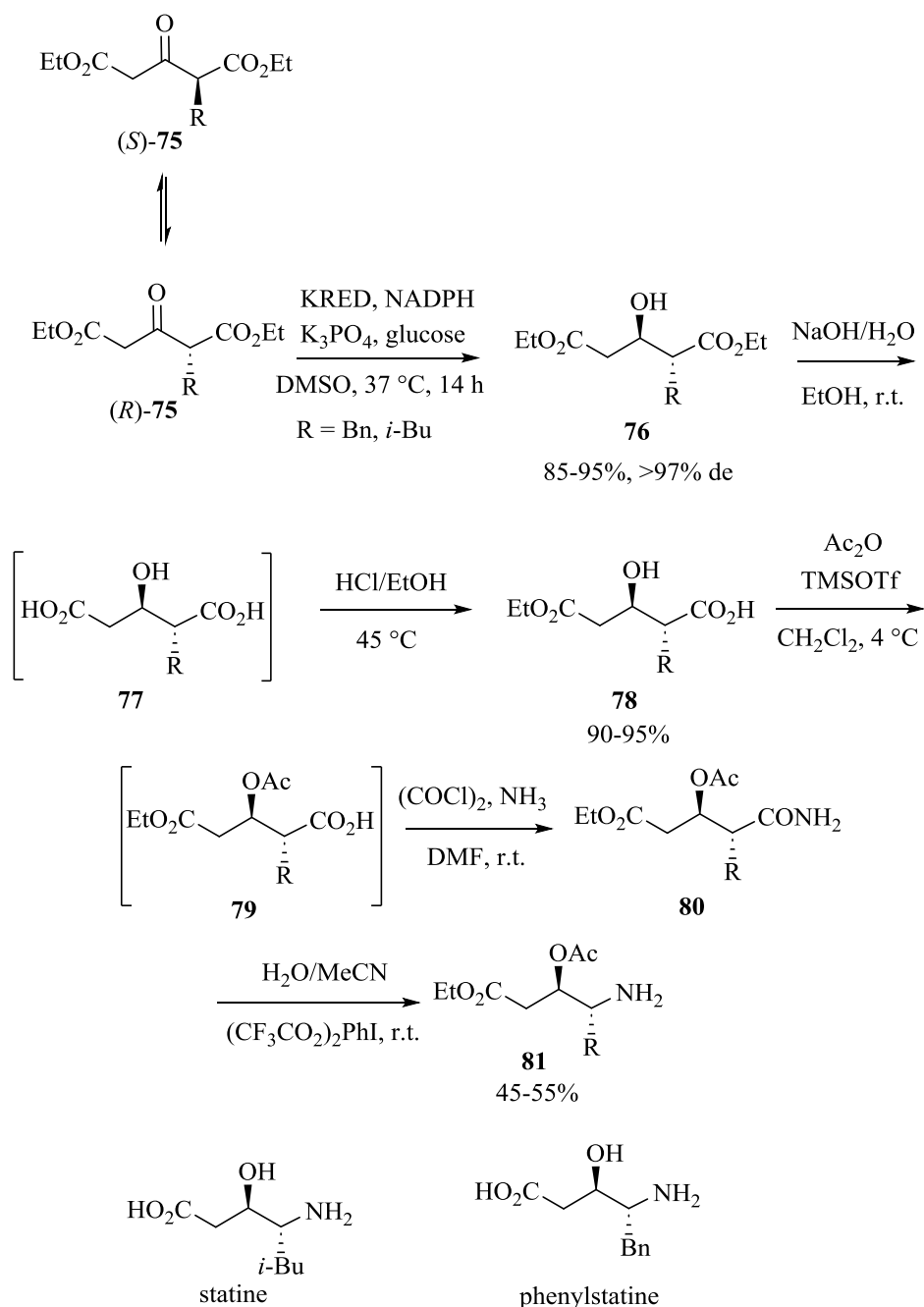
Scheme 15. Synthesis of milletosin.

3. ENZYMATIC DKRS

In recent years, the use of biocatalysts in many types of organic transformations has become an attractive green alternative to conventional chemical transformations [137-141]. Especially, intensive progress has been made in the last decade in the combination of enzymes with the concept of green DKR [16, 18, 25, 63-66]. Indeed, enzymatic reactions are commonly performed under atmospheric pressure and at ambient temperature, avoiding side reactions related to more extreme conditions, such as isomerization, racemization, epimerization, or rearrangements. Furthermore, biocatalytic processes are often remarkably enantio- and regioselective in comparison with more unpredictable chemical reactions. Today, a number of key intermediates for medicinal chemistry are prepared from enzymatic DKR methodologies.

3.1. Synthesis of Acyclic Products

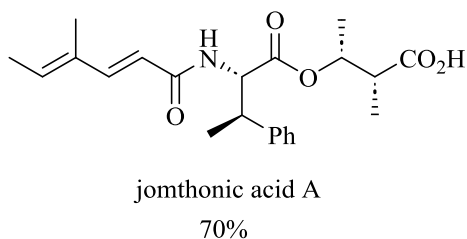
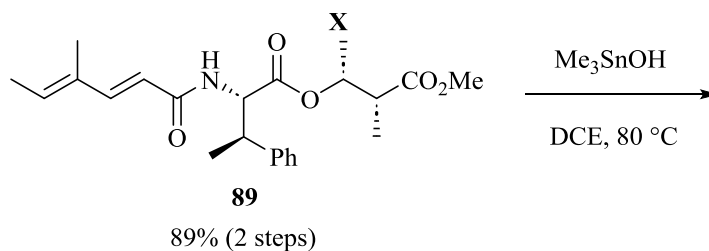
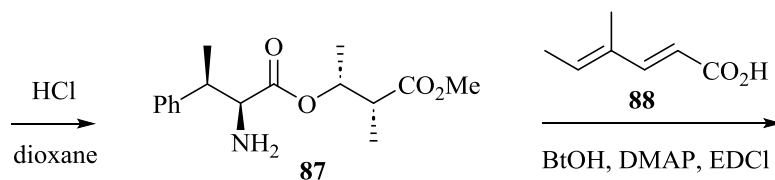
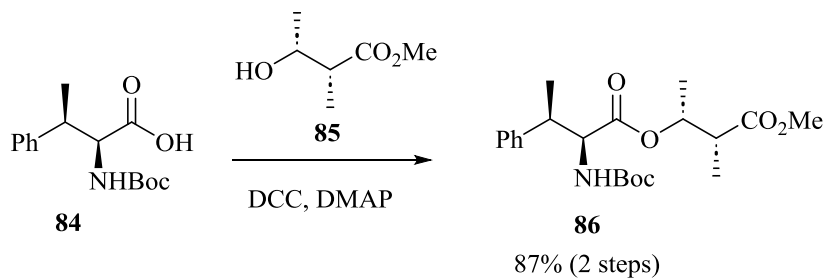
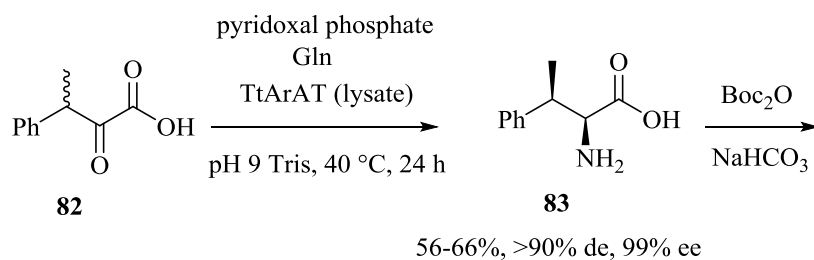
Along with their biologic role in the synthesis of important nitrogen-containing compounds, such as proteins, peptide hormones, and neurotransmitters, amino acids are one of the most important synthons employed in the pharmaceutical industry for the preparation of bioactive agents [142]. Many natural as well as unnatural amino acids have been synthesized through DKRs [143-145]. Moreover, they represent versatile building blocks in modern drug discovery [146]. Among them, γ -alkyl β -hydroxy- γ -amino acids constitute the skeletons of many natural products, such as statine. This product has been identified as a new class of anti-HIV agents. In 2003, Kambourakis and Rozzell reported a synthesis of statine and phenylstatine, which was based on a KRED-mediated reduction of 2-alkyl-substituted 3-ketoglutarate diesters **75** (Scheme 16) [147]. This first step was carried out at 37 °C in the presence of KRED-10000 in DMSO, leading to the corresponding alcohols **76** as single diastereomers with 85-95% yields within 14 hours. The DKR resulted from the rapid isomerization of the two enantiomeric diesters **75**. The second step of the synthesis involved the regioselective hydrolysis of **76** into monoesters **78**. In a first time, diesters **76** were converted by treatment with NaOH into the corresponding diacids **77** which were subsequently submitted to HCl in ethanol at 45 °C to afford monoethyl 2-alkyl-3-hydroxyglutarate **78** with excellent yields (90-95%). The last step of the synthesis was the conversion of monoacids **78** into desired amines **81**. It was achieved by a former protection of the alcohol group into an acetate in **78** by treatment with acetic anhydride and TMSOTf to give **79** in quantitative yields (>95%). The latter acetates were then converted into the corresponding amides **80** by treatment with oxalyl chloride and ammonia gas. Finally, these amides underwent Hofmann rearrangement in the presence of [bis(trifluoroacetoxy)iodo]benzene to give expected free amines **81**, namely acetates of statine (R = *i*-Bu) and phenylstatine (R = Bn) obtained with 45-55% yields.



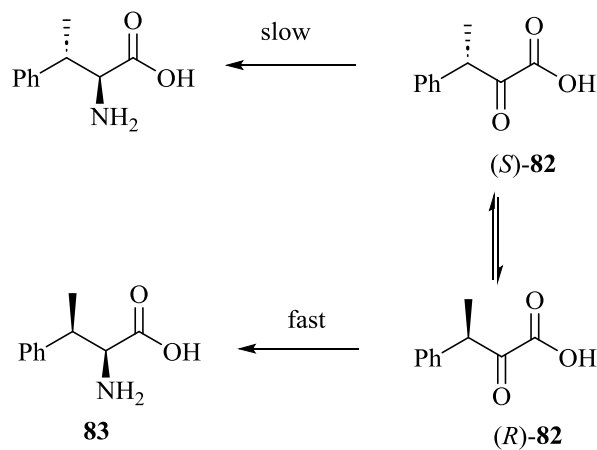
Scheme 16. Synthesis of statine and phenylstatine.

Enzymatic reactions have proven to be effective in the synthesis of β -branched amino acids exhibiting multiple stereocenters [148]. In this context, Renata et al. reported in 2021 the first biocatalytic DKR focusing on the production of non-canonical β -branched α -amino acids [149]. It dealt with the transamination of β -methylphenylpyruvic acid **82** using the thermophilic enzyme TtArAT from *Thermus thermophilus*. Remarkably, this thermostable aromatic amino acid aminotransferase allowed at 40 °C and pH 9 the synthesis of enantiopure (99% ee) β -methylphenylalanine **83** as an almost single (>90% de) *syn*-diastereomer with 56-66% yield (Scheme 17). In the mechanism detailed in Scheme 17, the two substrate enantiomers rapidly interconverted but only the (R) -configured one could preferentially undergo productive reaction with TtArAT. This novel highly efficient methodology was used as first step in the first synthesis of natural jomthonic acid A, which is an antidiabetic and antiatherogenic agent. The second step of the sequence dealt with the Boc protection of the amine group in **83** which was achieved in the presence of Boc₂O. The thus-formed protected amine **84** was further treated with chiral alcohol **85** arising from a diastereoselective α -methylation of methyl (R) -3-hydroxybutyrate. This coupling reaction was performed in the presence of DMAP and DCC to give within 24 hours the corresponding ester **86** with 87% yield (2

steps). Subsequently, the latter was submitted to deprotection by treatment with HCl in dioxane, which led to free amine **87**. Then, the peptide coupling between **87** and dienic acid **88** was performed in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI), 1-hydroxy-1H-benzotriazole (BtOH), and DMAP, providing ester **89** with 89% yield (2 steps). Finally, the selective methyl ester hydrolysis of **89** performed in the presence of Me₃SnOH delivered expected jomthonic acid A.



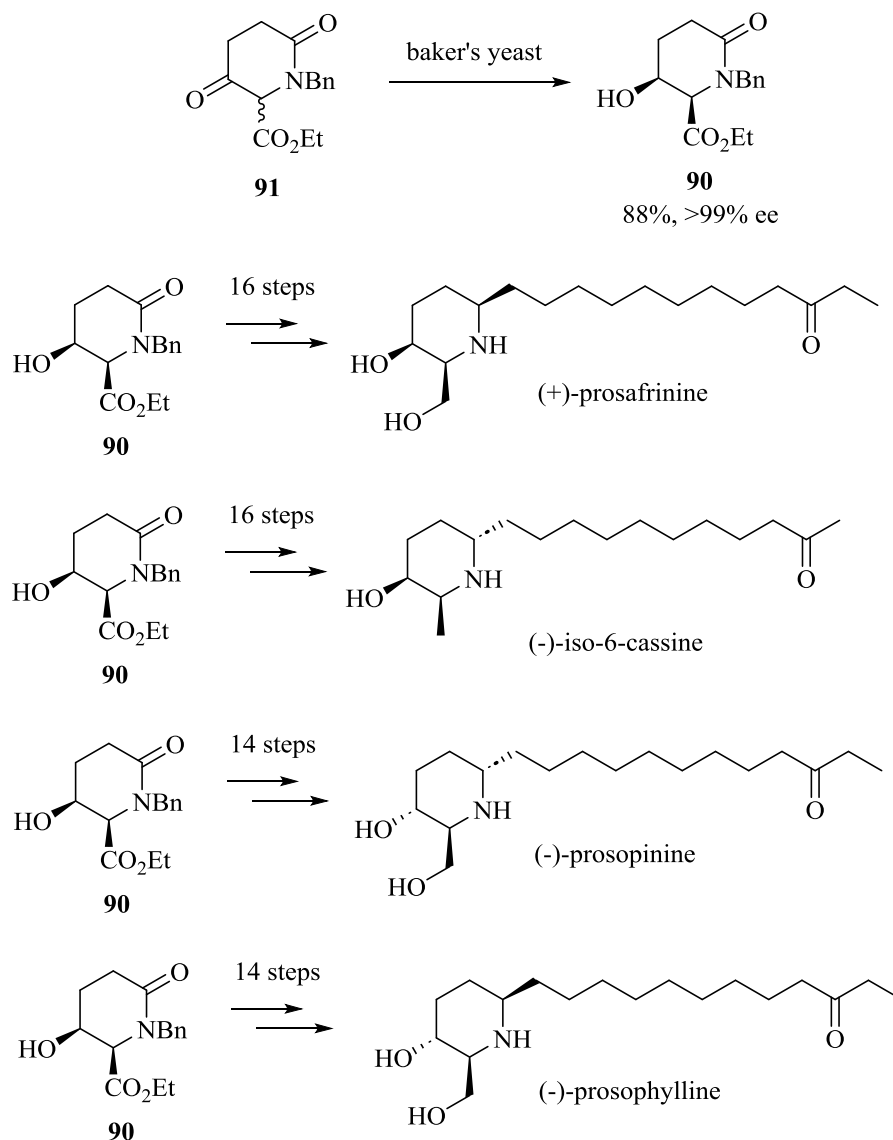
mechanism:



Scheme 17. Synthesis of jomthonic acid A.

3.2. Synthesis of Monocyclic Products

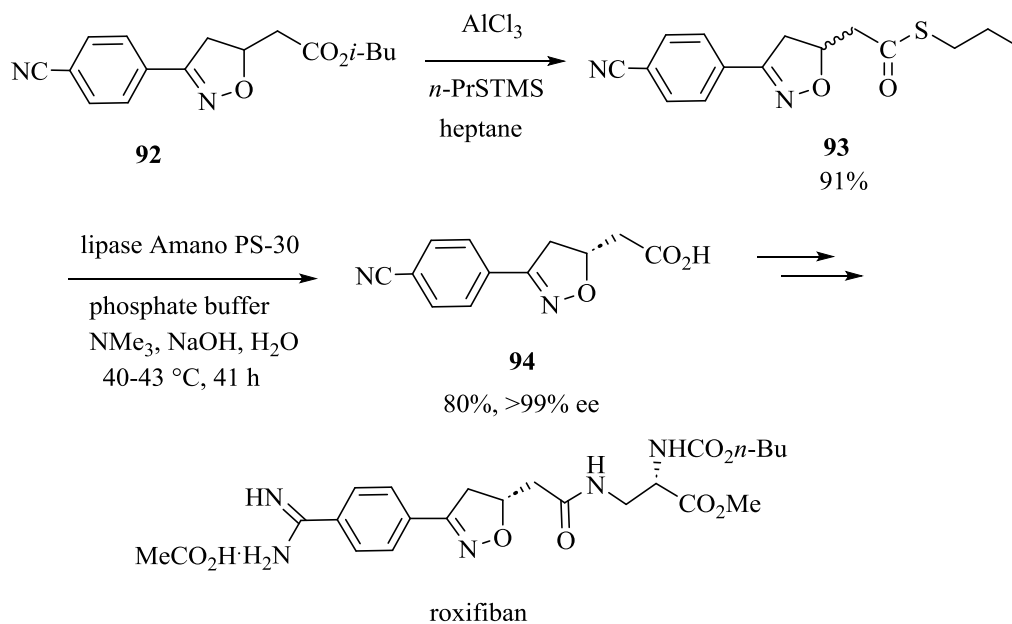
The synthesis of functionalized piperidines is challenging since these molecules are present in the skeletons of numerous pharmaceuticals. Among them, Toyoota and Momose described in 1990s a novel route to chiral 3-piperidinol alkaloids, such as (+)-prosafrinine, (-)-iso-6-cassine, (-)-prosopinine, and (-)-prosophylline [150-151]. The four syntheses of these important products all began from the same novel 2-piperidone building block **90**, which was prepared through baker's yeast reduction of the corresponding β -keto ester **91** (Scheme 18). This DKR reaction was performed with 88% yield and complete enantioselectivity (>99% ee). Chiral alcohol **90** could be further converted through sixteen additional steps into (+)-prosafrinine and (-)-iso-6-cassine, and through fourteen steps into (-)-prosopinine and (-)-prosophylline (Scheme 18).



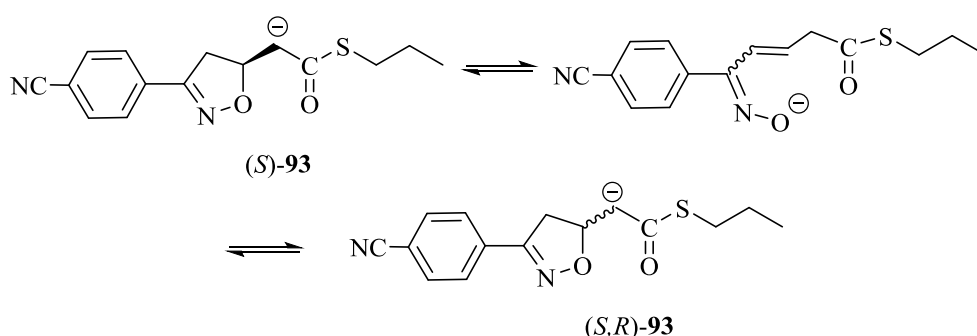
Scheme 18. Synthesis of (+)-prosafrinine, (-)-iso-6-cassine, (-)-prosopinine, and (-)-prosophylline.

Later, lipases have been employed to catalyze key DKR steps in the total synthesis of different monocyclic products. For example in 2004, Pesti et al. employed a biocatalytic DKR hydrolysis to prepare a key intermediate in the synthesis of roxifiban, which is a potent antagonist of the platelet glycoprotein IIb/IIIa receptor [152]. The DKR substrate was thioester **93**, previously synthesized from ester **92**, which was submitted to a lipase-catalyzed hydrolysis (Scheme 19). Thioester **93** enabled racemization to occur under sufficiently mild conditions to also allow the enzymatic resolution to be achieved. The racemization of thioester **93** during the DKR arose from easy retro-Michael/Michael reaction equilibrium between the

isoxazoline ring and derived acrylate, as illustrated in Scheme 19. Using lipase Amano PS-30 in the presence of trimethylamine as base to undergo racemization, the reaction afforded expected enantiopure key acid **87** with 80% yield after 41 hours.

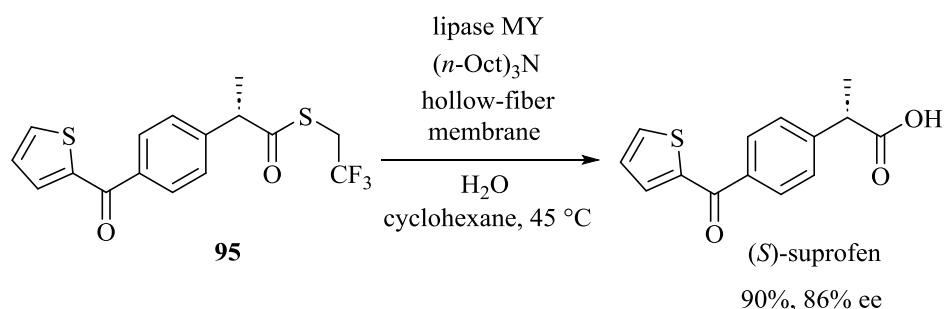


racemization of **93** through retro-Michael/Michael reaction:



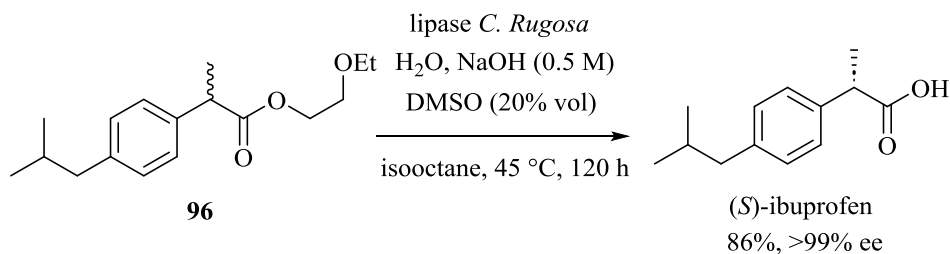
Scheme 19. Synthesis of a key intermediate in the synthesis of roxifiban.

In the same year, Tsai et al. reported a synthesis of anti-inflammatory agent (*S*)-suprofen via lipase-catalyzed hydrolysis of the corresponding 2,2,2-trifluoroethyl ester **95** performed in aqueous cyclohexane at 45 °C [153]. In this DKR, lipase MY from *Candida rugosa* was immobilized on polypropylene powders, and trioctylamine was added as racemization agent. A hollow-fiber membrane was employed to continuously extract the desired (*S*)-suprofen into an aqueous solution containing NaOH. Under these conditions, (*S*)-suprofen was synthesized with 86% ee and 90% yield (Scheme 20).



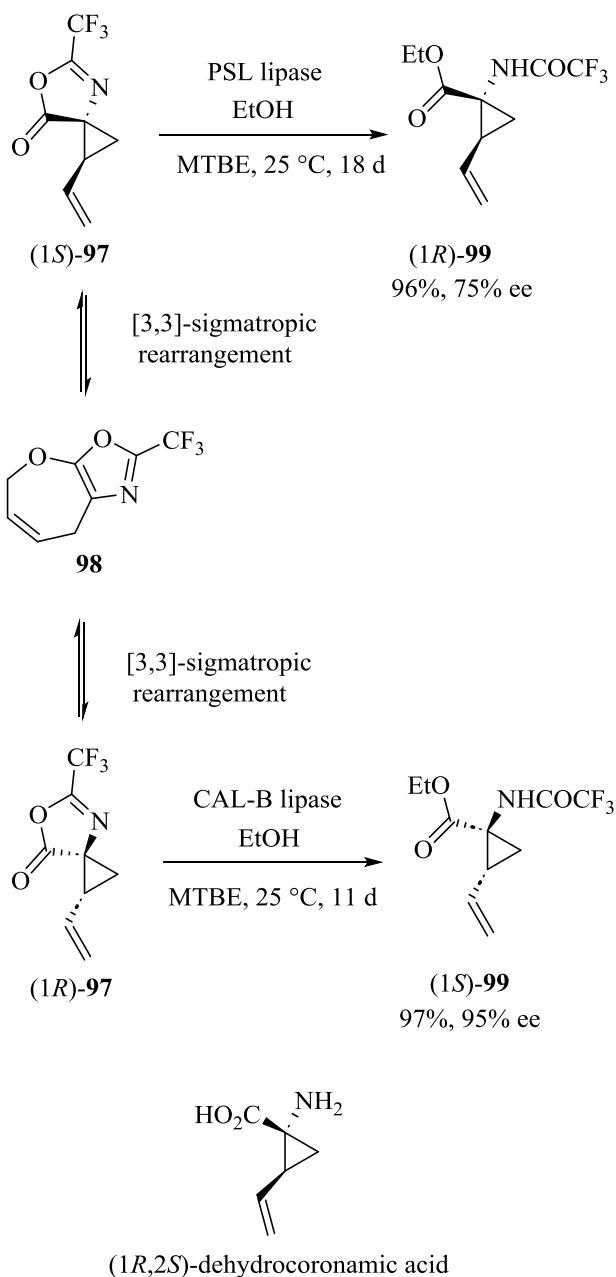
Scheme 20. Synthesis of (*S*)-suprofen.

Later in 2006, Kamaruddin et al. reported a related enzymatic DKR applied to the synthesis of another anti-inflammatory agent, namely (*S*)-ibuprofen [154]. The reaction consisted of a lipase-catalyzed hydrolysis of the corresponding racemic ethoxyethyl ester **96** performed at 45 °C in isoctane in the presence of 20% of DMSO as co-solvent, water, and sodium hydroxide (0.5 M). These conditions allowed the smooth *in situ* racemization of the remaining (*R*)-ibuprofen ester substrate, thus producing within 120 hours expected enantiopure (>99% ee) (*S*)-ibuprofen in 86% yield (Scheme **21**).



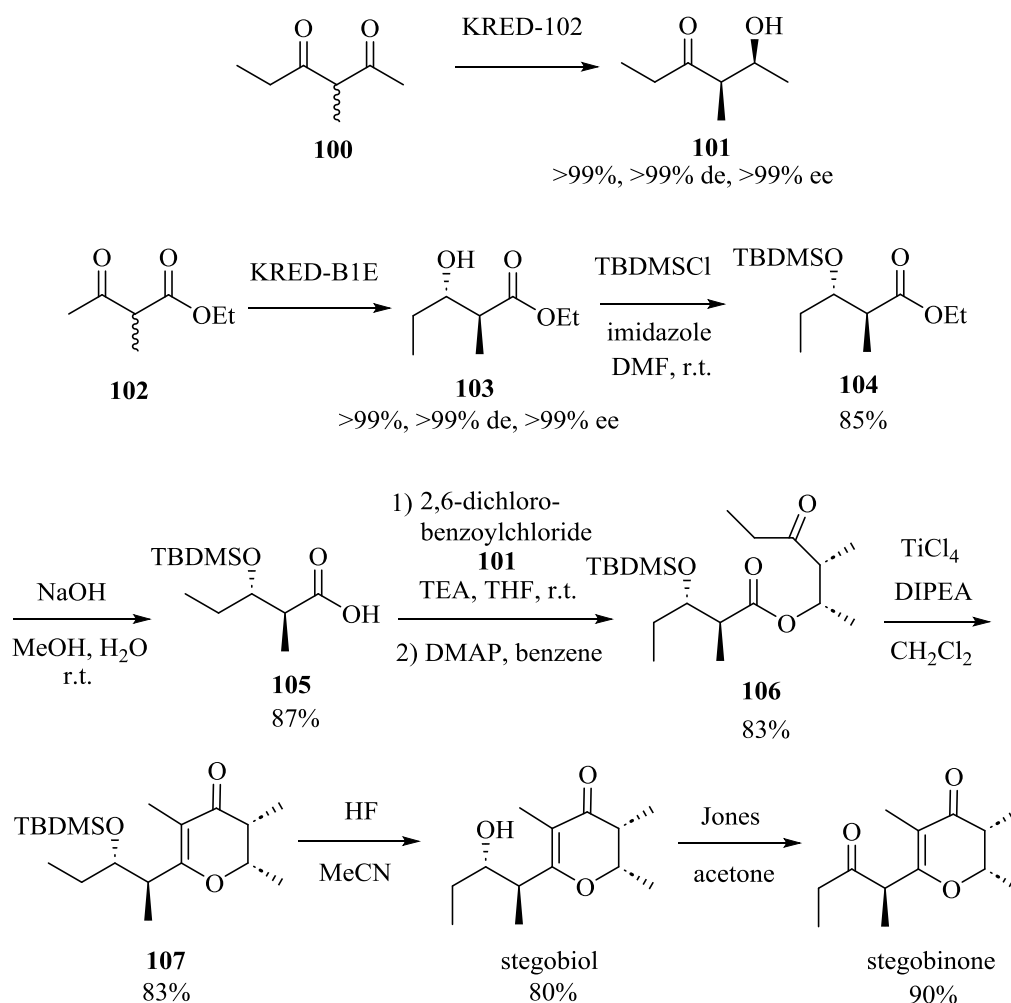
Scheme 21. Synthesis of (*S*)-ibuprofen.

(1*R*,2*S*)-Dehydrocoronamic acid constitutes the skeleton of many Hepatitis C NS3 NS4A protease inhibitors among which many are antiviral drugs. Consequently, efficient asymmetric synthesis of this functionalized quaternary three-membered amino-acid is challenging. In 2014, Fox et al. described a novel hydrolase-catalyzed DKR of cyclopropyl azlactone **97** to prepare chiral dehydrocoronamic acid precursors [155]. As illustrated in Scheme **22**, cyclopropyl azlactone **97** was easily racemized through a spontaneous concerted [3,3]-sigmatropic rearrangement into achiral dihydrooxepine intermediate **98**. The azlactone **97** was subsequently treated respectively with CAL-B or PSL lipases in MTBE as solvent and in the presence of ethanol. Under transesterification conditions with ethanol, both enantiomers of the expected precursor **99** of dehydrocoronamic acid were obtained in 96-97% yields and 75-95% ee. Indeed, enantiomer (1*R*)-**99** was obtained with 96% yield and 75% ee from the treatment of (1*S*)-**97** with PSL lipase during 18 days, while enantiomer (1*S*)-**99** generated from the treatment of (1*R*)-**97** with CAL-B lipase was produced with 97% yield and 95% ee after 11 days. This novel methodology based on a facile racemization of dehydrocoronamic acid allowed the asymmetric synthesis of either enantiomer of the significant dehydrocoronamic acid precursors **99** through enzyme-mediated DKRs.



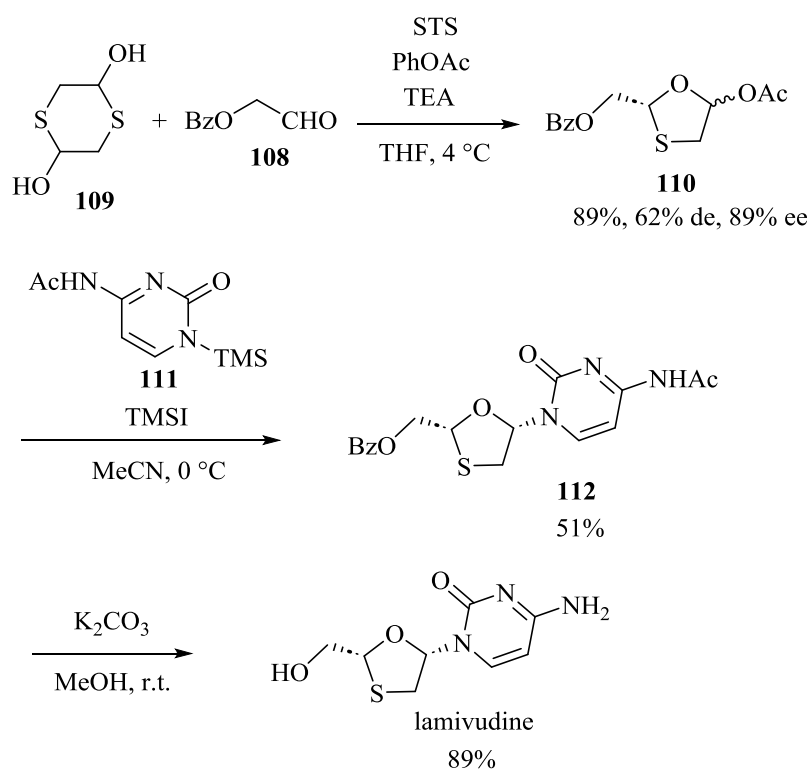
Scheme 22. Synthesis of a precursor of dehydrocoronamic acid.

In 2012, Kalaitzakis and Smonou employed another type of enzymes, namely NADPH-dependent ketoreductases (KREDs), to promote the enzymatic stereoselective synthesis of stegobiol and stegobinone which are natural sex pheromones of the drugstore beetle [156]. The key steps of the synthesis were the enzymatic reductions of α -methyl-1,3-diketone **100** and α -methyl- β -keto ester **102**, respectively (Scheme 23). The regio- and stereoselective transformation of diketone **100** into diastereo- (>99% de) and enantiopure (>99% ee) hydroxy ketone **101** with a quantitative yield was achieved by using enzyme KRED-102. Simultaneously, the reduction of β -keto ester **102** was achieved in the presence of enzyme KRED-B1E to afford quantitatively diastereo- (>99% de) and enantiopure (>99% ee) hydroxy ester **103**. In order to be coupled with **101**, compound **103** was previously converted into intermediate **105** through successive protection with TBDMSCl followed by hydrolysis with an overall yield of 74%. Then, intermediates **101** and **105** were coupled to give ester **106** with 83% yield, which was further converted into TBDMS-protected cyclic product **107** with 67% yield by treatment with TiCl_4 and DIPEA in dichloromethane. Then, deprotection of the latter product in the presence of HF in acetonitrile provided stegobiol with 80% yield. Subsequent oxidation of stegobiol with Jones reagent delivered stegobinone with 90% yield.



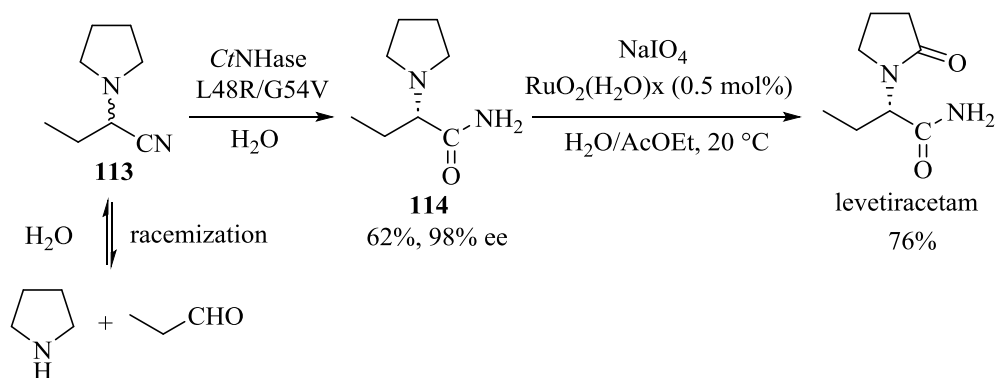
Scheme 23. Synthesis of stegobiol and stegobinone.

Lamivudine is an anti-HIV nucleoside agent also effective against chronic Hepatitis B. In 2013, Ramström et al. disclosed a short three-step synthesis of this product, the first step of which was an enzymatic DKR mediated by surfactant-treated subtilisin Carlsberg (STS) [157]. As illustrated in Scheme 24, this enzyme catalyzed a domino addition/cyclization/acetylation reaction between benzoyl protected aldehyde **108** and 1,4-dithiane-2,5-diol **109**. This cascade was carried out at 4 °C in THF in the presence of PhOAc and TEA as base, which resulted in the formation of desired chiral 1,3-oxathiolane **110** with 89% yield and 89% ee as a mixture of two diastereomers (62% de). This key intermediate was subsequently submitted to a Vorbrüggen coupling reaction with silylated *N*⁴-acetylcytosine **111** in the presence of TMSI in acetonitrile at 0 °C to give the corresponding nucleoside analog **112** with 51% yield. Finally, deprotection of the latter by treatment with K₂CO₃ in methanol at room temperature delivered expected lamivudine with 89% yield.



Scheme 24. Synthesis of lamivudine.

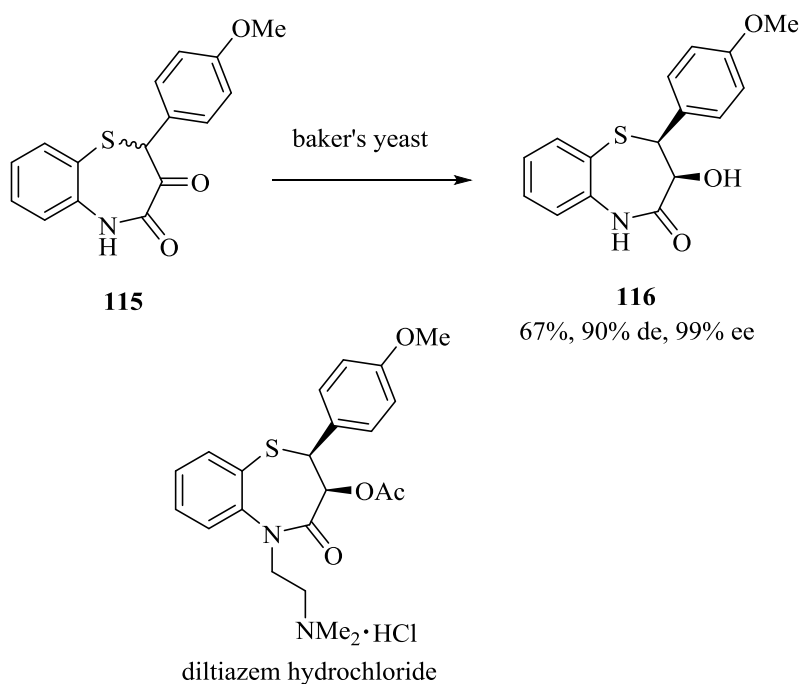
Levetiracetam is an active antiepileptic drug. In 2021, a novel economic synthesis of this pharmaceutical product was developed by Winkler and Waldvogel on the basis of an enzymatic DKR [158]. This was achieved by using *Comamonas testosteroni* nitrile hydratase L48R/G54V exhibiting a high (*S*)-selectivity to hydrolyze racemic nitrile **113** into the corresponding chiral amide **114** with 62% yield and 98% ee (Scheme 25). This enantiopure product was further converted into expected levetiracetam through ruthenium-catalyzed oxidation with periodate, using only 0.5 mol% of hydrated ruthenium(IV) oxide as catalyst. The oxidation, performed in aqueous ethyl acetate at 20 °C, occurred regioselectively in position α to the amine, thus producing the desired drug with 76% yield.



Scheme 25. Synthesis of levetiracetam.

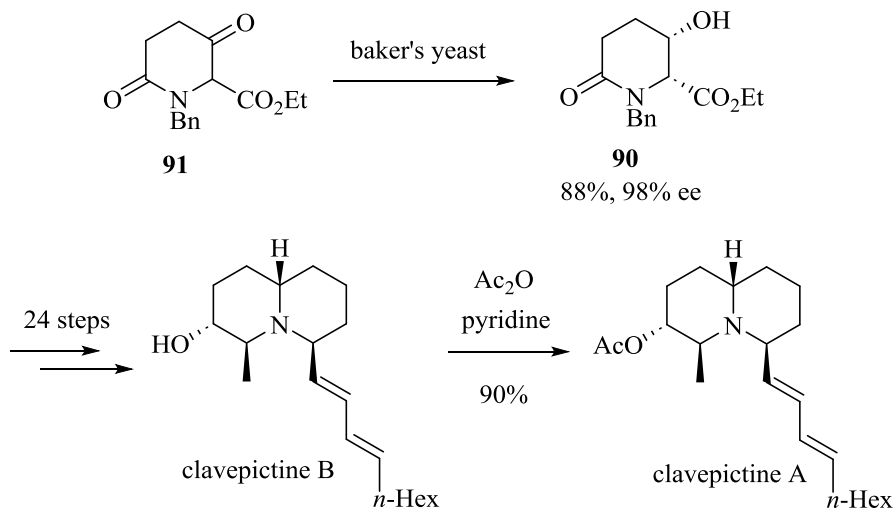
3.3. Synthesis of Bicyclic Products

Diltiazem is a calcium channel blocker which is employed in the treatment of arrhythmia and hypertension. In 1995, Matsumae et al. described a synthesis of diltiazem precursor **115** based on a DKR reduction performed in the presence of baker's yeast alcohol dehydrogenase [159]. As illustrated in Scheme 26, the ketone group of bicyclic substrate **115** was reduced into the corresponding alcohol, thus resulting in the formation of expected chiral diltiazem precursor **116** with both remarkable enantio- (99% ee) and diastereoselectivities (90% de) albeit combined with a moderate yield of 67%.



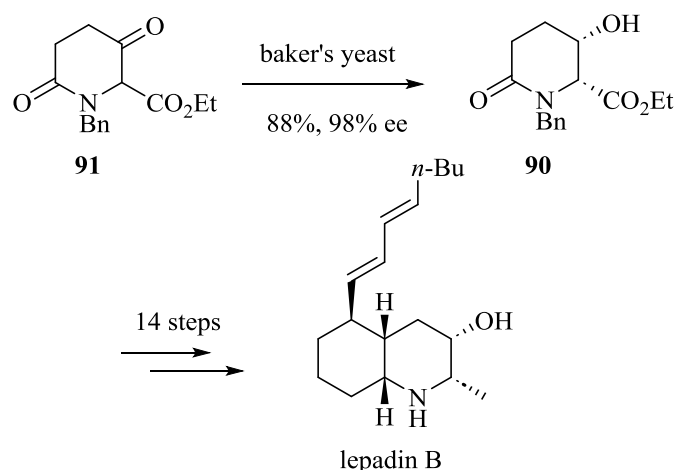
Scheme 26. Synthesis of a precursor of diltiazem hydrochloride.

In 1996, Momose et al. reported the first total synthesis of anti-tumor agents clavепictines A and B [160]. The first step of the synthesis of these quinolizidine alkaloids dealt with a baker's yeast reduction of β -keto ester **91** into the corresponding chiral 3-piperidinol **90** achieved with 88% yield and 98% ee, which was earlier described in 1995 by the same authors (Scheme 27) [151]. This key building block was converted into expected clavепictines B and A through twenty four and twenty five additional steps, respectively. Furthermore, the absolute configuration of both alkaloids was determined for the first time.



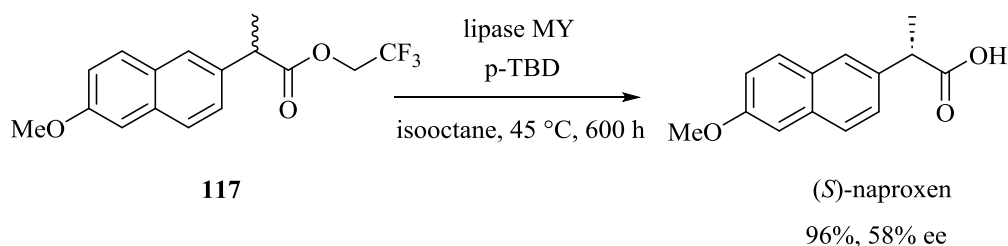
Scheme 27. Synthesis of clavепictines B and A.

In 1999, the same group also developed the synthesis of alkaloid lepadin B, which is an inducer of immunogenic cell death [161-162]. The sequence started from the same chiral building block **90** as that employed in the precedent synthesis of clavепictines A and B [150]. In this case, this 3-piperidinol **90**, obtained with 88% yield and 98% ee from baker's yeast reduction of β -keto ester **91**, was submitted to a series of fourteen additional steps to deliver expected lepadin B (Scheme 28).



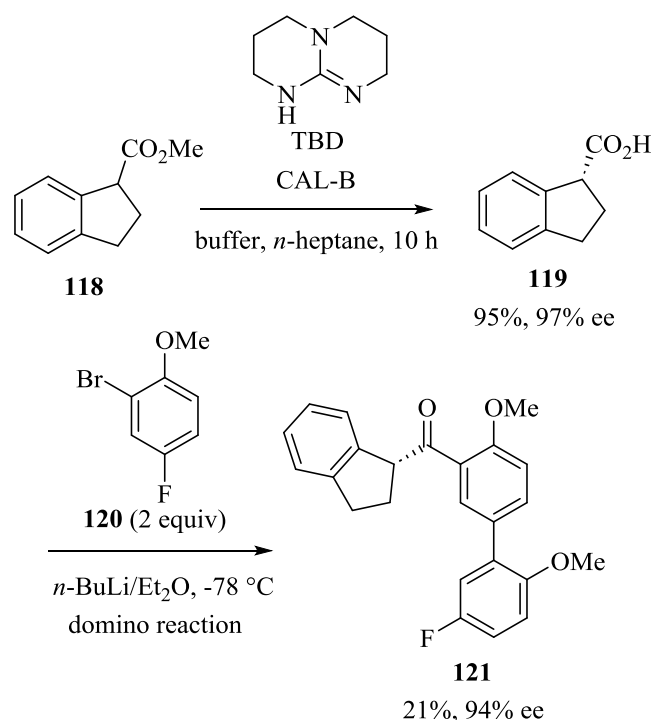
Scheme 28. Synthesis of lepadin B.

In 2003, Tsai et al. reported a synthesis of anti-inflammatory agent naproxen via lipase-catalyzed hydrolysis of the corresponding 2,2,2-trifluoroethyl ester **117** performed in micro-aqueous isooctane at 45 °C [163]. In this method, lipase MY from *Candida rugosa* was immobilized on polypropylene powders, and 1,5,7-triazabicyclo[4,4,0]dec-5-ene (p-TBD) bound to polystyrene crosslinked with 2% divinylbenzene was added as an *in situ* racemization agent [164]. Under these conditions, a 96% yield of the desired (*S*)-naproxen was obtained after 600 hours albeit combined with a moderate enantioselectivity of 58% ee (Scheme 29).



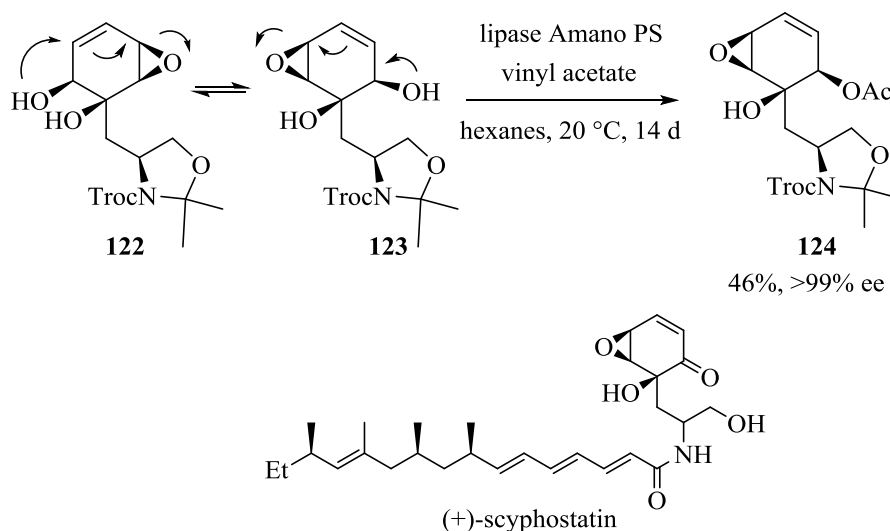
Scheme 29. Synthesis of (*S*)-naproxen.

2,3-Dihydro-1-*H*-indene-1-carboxylic acid constitutes the skeleton of aryl indan-1-yl ketones among which are inhibitors of peptidyl-prolyl-cis/trans-isomerases. In this context, Pietruszka et al. developed in 2009 a novel route to this type of molecules on the basis of an enzymatic DKR (Scheme 30). It involved the hydrolysis of bicyclic methyl ester **118** carried out in the presence of *Candida antarctica* lipase B (CAL-B) combined with a base, such as 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) as the racemization agent (Scheme 30) [165]. The process delivered the expected almost enantiopure (97% ee) indanecarboxylic acid **119** in 95% yield within 10 hours. The latter product was further converted through a domino reaction with two equivalents of aryl bromide **120** into expected biaryl indan-1-yl ketone **121** with 21% yield and 94% ee, constituting a lead product for novel inhibitors of peptidyl-prolyl-cis/trans-isomerases.



Scheme 30. Synthesis of a lead product for human peptidyl-prolyl-*cis/trans*-isomerase inhibitors.

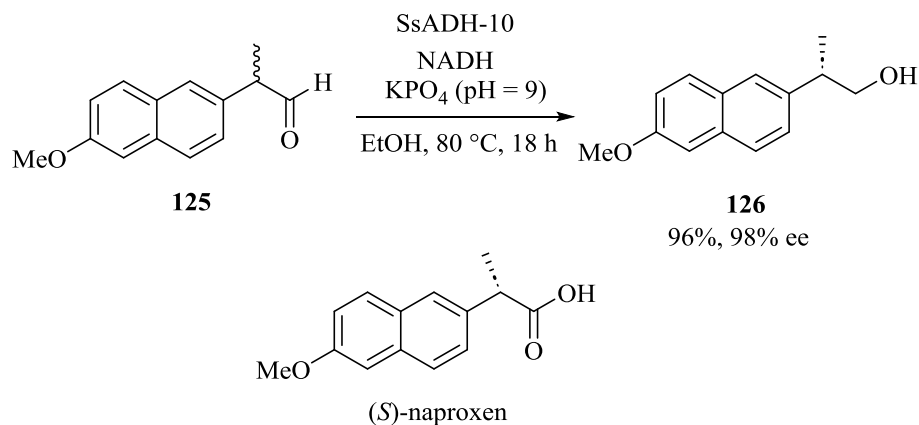
(+)-Scyphostatin can be considered as the most potent inhibitor of neutral sphingomyelinase, employed against inflammation and neurological and immunological disorders [166]. In 2010, Hoye et al. developed a novel synthesis of the epoxycyclohexene core of this product on the basis of a DKR coupled to a reversible vinylogous Payne rearrangement of a mixture of the pseudoenantiomeric epoxycyclohexenols **122** and **123** depicted in Scheme 31 [167]. The DKR employed lipase Amano PS, producing enantiopure epoxy-alkenol **124** in 46% yield, as illustrated in Scheme 31. It must be noted that this DKR is noteworthy, because it created four stereocenters in a single step in spite of its long reaction time of 14 days.



Scheme 31. Synthesis of the epoxycyclohexene core of (+)-scyphostatin.

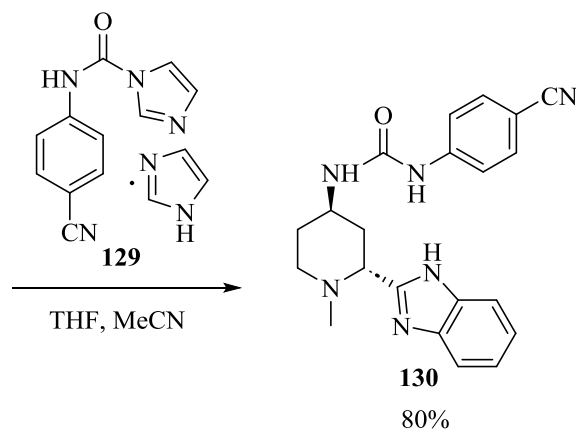
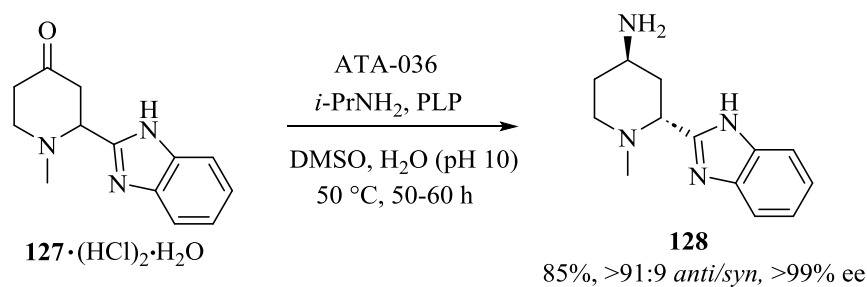
Highly stereoselective alcohol dehydrogenases (ADHs) have been widely employed in reductive DKR processes of diverse α -substituted chiral carbonyl compounds toward the formation of optically pure α -alkyl- β -hydroxy esters, α -alkyl- β -hydroxy ketones, α -amino- β -hydroxy esters, halohydrins among other products. In these methodologies, the stereoselective reduction of the carbonyl group is combined with the *in situ* racemization of the substrate, thus allowing the final products bearing two stereocenters to be obtained as single stereoisomers among the four theoretically possible ones. In 2010, other substrates, such as α -substituted aldehydes, were successfully submitted to NADH reductive DKR by Berkovitz and Blum,

thus leading to the corresponding chiral α -substituted primary alcohols with 57-99% yields and 61-99% ee [168]. The process employed at 80 °C a thermostable alcohol dehydrogenase from *Sulfolobus sulfataricus* (SsADH-10) at pH 9. Especially, the reaction of 2-arylpropionaldehyde **125** afforded enantiopure (98% ee) α -substituted primary alcohol **126** with 96% yield after 18 hours, which constituted a precursor of (*S*)-naproxen (Scheme 32).

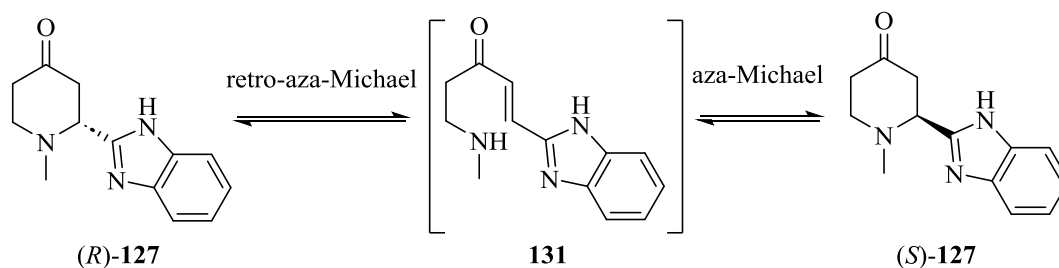


Scheme 32. Synthesis of a precursor of (*S*)-naproxen.

In 2014, Peng et al. described an enzymatic DKR as key step in the synthesis of smoothed receptor inhibitor **130** used as an anticancer agent (Scheme 33) [169]. This involved the transamination of 2-substituted 4-piperidinone **127** performed with commercial transaminase enzyme ATA-036 at 50 °C in a phosphate buffer DMSO mixture and in the presence of isopropylamine. This produced within 50-60 hours the corresponding enantiopure (>99% ee) primary amine **128** in 85% yield as major *anti*-diastereomer (>82% de). The racemization of the starting 4-piperidinone **127** could proceed through an achiral ring-opened intermediate **131** generated by a retro-aza-Michael/aza-Michael addition, as detailed in Scheme 33. Then, amine **128** reacted with *N*-carbamoylimidazole **129** in the presence of TEA in THF to form expected smoothed receptor inhibitor **130** with 80% yield. It must be noted that the complete synthesis required only five steps and produced **130** in 40% overall yield without requiring any chromatography, thus, making this synthesis suitable for large scale industrial production.

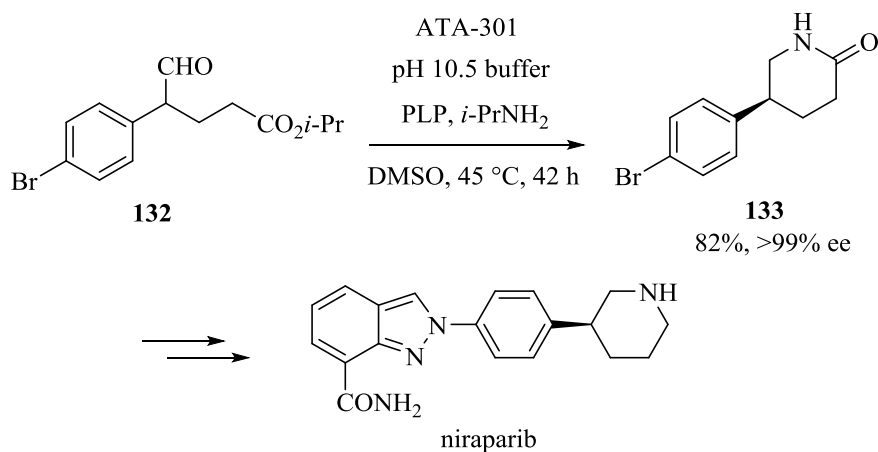


racemization of **127**:



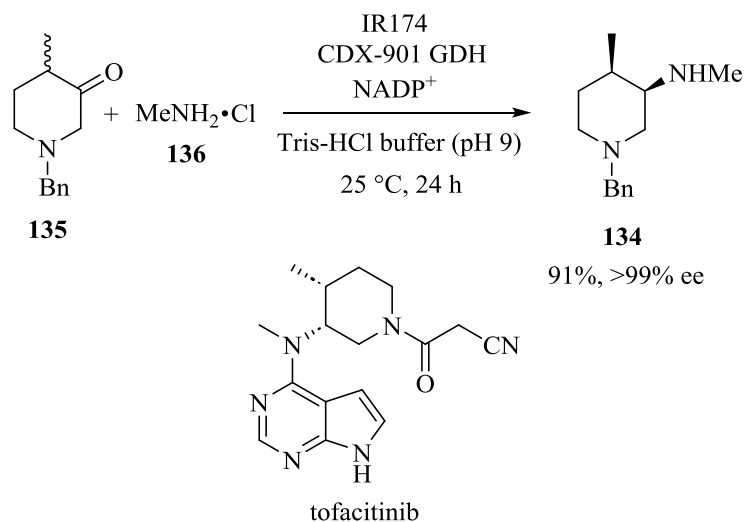
Scheme 33. Synthesis of a smoothed receptor inhibitor.

In the same year, a lactam precursor **133** of anticancer drug niraparib was synthesized by Chung and Bulger on the basis of a novel DKR amination [170]. As presented in Scheme 34, this amination followed by an intramolecular cyclization of aldehyde **132** was achieved by treatment with transaminase enzyme ATA-301 in the presence of PLP and isopropylamine as amine donor. The DKR process furnished within 42 hours enantiopure (>99% ee) lactam **133** with 82% yield. This product was further converted into expected anticancer agent niraparib.



Scheme 34. Synthesis of niraparib.

Tofacitinib is a bicyclic protein tyrosine kinase inhibitor used against active psoriatic arthritis, rheumatoid arthritis, and ulcerative colitis. The challenge in its synthesis is related to the presence of two contiguous stereocenters exhibited by a piperidine moiety. In 2022, Zhu and Yao described a green synthesis of key bicyclic intermediate **134** for the synthesis of tofacitinib, which involved an enzymatic DKR reductive amination of piperidine **135** with imine reductase IR174 (Scheme 35) [171]. In the presence of methylamine hydrochloride **136**, the reaction afforded within 24 hours enantiopure (>99% ee) amine **134** as single *cis*-diastereomer (>98% ee) with 91% yield.



Scheme 35. Synthesis of a key intermediate for the synthesis of tofacitinib.

CONCLUSION

This review highlights major developments in the application of green organocatalytic and enzymatic DKRs in the total synthesis of biorelevant scaffolds. It illustrates the diversity of useful bioactive products that can be easily synthesized under these green conditions. Although impressive advances have been achieved in asymmetric synthesis, and especially in catalysis, the resolution of racemates is still widely employed in industry to reach chiral molecules, in spite of its major disadvantage related to the limitation of the yield to 50%. Solving this major drawback, DKR has become a serious alternative to conventional methods for asymmetric synthesis by allowing yields of up to 100 % yield to be achieved. In the last two decades, the combination of the two powerful concepts, namely DKR and green organocatalysis, has triggered an increasing and impressive interest from both the industrial and the academic perspective. This original approach has permitted a range of chiral biorelevant molecules to be synthesized with high enantioselectivities by using organocatalysts, such as amino acids, 4-(dialkylamino)pyridines, phosphoric acids, N-heterocyclic carbenes among others. Furthermore along with chiral organocatalysts, many types of enzymes have been successfully employed to promote DKR processes commonly performed under particularly mild conditions and often remarkably enantioselectively, with significant applications in the synthesis of biologically important products. With the need of more ecologic synthetic technologies, the fields of organocatalytic as well as enzymatic DKRs, avoiding the use of toxic and expensive metals, will undoubtedly even more expand its scope with the employment of other types of organocatalysts and enzymes and develop novel transformations, thus allowing powerful greener and more economic strategies to reach other biologically important molecules. These methodologies allow the preparation of chiral bioactive products with the exclusion of any trace of hazardous metals. Although the first examples of organocatalysed dynamic kinetic resolution processes were described in the last decade, a wide number of chiral organocatalysts are nowadays available to achieve excellent levels of stereocontrol that could only previously be achieved using biocatalysts.

LIST OF ABBREVIATIONS

ADP: adenosine diphosphate
 AIBN: azobisisobutyronitrile
 Ar: aryl
 BINOL: 1,1'-bi-2-naphthol
 Boc: *tert*-butoxycarbonyl

Bn: benzyl
Bt: benzotriazole
BTM: bis(triazolyl)- phenylmethanol ??? non
Bz: benzoyl
Cy: cyclohexyl
DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene
DCC: dicyclohexylcarbodiimide
DCE: 1,2-dichloroethane
de: diastereomeric excess
DIPEA: diisopropylethylamine
DKR: dynamic kinetic resolution
DMAP: dimethylaminopyridine
DMF: dimethylformamide
DMSO: dimethylsulfoxide
EDCI: 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
ee: enantiomeric excess
Gln: glutamine
HIV: human immunodeficiency virus
KRED: ketoreductase
MOM: methoxymethyl
Naph: naphthyl
MS: molecular sieves
MTBE: methyl *tert*-butyl ether
NADP: nicotinamide adenine dinucleotide phosphate
Oct: octyl
PCSK: proprotein convertase subtilisin/kexin
Piv: pivaloyl
PLP: pyridoxal-5-phosphate
r.t.: room temperature
TBAB: tetrabutylammonium bromide
TBD: 1,5,7-triazabicyclo[4.4.0]dec-5-ene
TBDMS: *tert*-butyldimethylsilyl
TEA: triethylamine
THF: tetrahydrofuran
Tf: trifluoromethanesulfonyl
TMS: trimethylsilyl
Tol: tolyl
Ts: 4-toluenesulfonyl (tosyl)
Xantphos: 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

- [1] Robinson, D. E. J. E.; Bull S. D. Kinetic resolution strategies using non-enzymatic catalysts. *Tetrahedron: Asymmetry* **2003**, *14*, 1407-1446.
- [2] Breuer, M.; Ditrich, K.; Habicher, T.; Hauer B.; Keßeler M.; Stürmer R.; Zelinski T. Industrial methods for the production of optically active intermediates. *Angew. Chem., Int. Ed. Engl.* **2004**, *43*, 788-824.
- [3] Vedejs E.; Jure, M. Efficiency in nonenzymatic kinetic resolution. *Angew. Chem., Int. Ed. Engl.* **2005**, *44*, 3974-4001.

- [4] Fogassy, E.; Nogradi, M.; Kozma, D.; Egri, G.; Palovics, E.; Kiss, V. Optical resolution methods. *Org. Biomol. Chem.* **2006**, *4*, 3011-3030.
- [5] Turner, N. J. Controlling chirality. *Curr. Opin. Biotechnol.* **2003**, *14*, 401-406.
- [6] Turner N. J. Directed evolution of enzymes for applied biocatalysis. *Trends Biotechnol.* **2003**, *21*, 474-478.
- [7] Alexeeva, M.; Carr, R.; Turner, N. J. Directed evolution of enzymes: new biocatalysts for asymmetric synthesis. *Org. Biomol. Chem.* **2003**, *1*, 4133-4137.
- [8] Schnell, B.; Faber, K.; Kroutil, W. Enzymatic racemization and its application to synthetic biotransformations. *Adv. Synth. Catal.* **2003**, *345*, 653-666.
- [9] Turner, N. J. Enzyme catalyzed deracemization and dynamic kinetic resolution reactions. *Curr. Opin. Chem. Biol.* **2004**, *8*, 114-119.
- [10] Gadler, P.; Glueck, S. M.; Kroutil, W.; Nestl, B. M.; Larissegger-Schnell, B.; Ueberbacher, B. T.; Wallner, S. R.; Faber, K. Biocatalytic approaches for the quantitative production of single stereoisomers from racemates. *Biochem. Soc. Trans.* **2006**, *34*, 296-300.
- [11] Noyori, R.; Tokunaga, M.; Kitamura, M. Stereoselective Organic Synthesis via Dynamic Kinetic Resolution. *Bull. Chem. Soc. Jpn* **1995**, *68*, 36-56.
- [12] Ward, R. S. Dynamic kinetic resolution. *Tetrahedron: Asymmetry* **1995**, *6*, 1475-1490.
- [13] Caddick, S.; Jenkins, K. Dynamic resolutions in asymmetric synthesis. *Chem. Soc. Rev.* **1996**, *25*, 447-456.
- [14] Stecher, H.; Faber, K. Biocatalytic deracemization techniques: dynamic resolution and stereoinversions. *Synthesis* **1997**, 1-16.
- [15] Huerta, F. F.; Minidis, A. B. E.; Bäckvall, J.-E. Racemisation in asymmetric synthesis. Dynamic kinetic resolution and related processes in enzyme and metal catalysis. *Chem. Soc. Rev.* **2001**, *30*, 321-331.
- [16] Pellissier H. Dynamic Kinetic Resolution. *Tetrahedron* **2003**, *59*, 8291-8327.
- [17] Bräse, C. S. *Asymmetric Synthesis - The Essentials*, Wiley-VCH: Weinheim, **2006**.
- [18] Pellissier, H. Recent Developments in Dynamic Kinetic Resolution. *Tetrahedron* **2008**, *64*, 1563-1601.
- [19] Kamal, A.; Azhar, M. A.; Krisnaji, T.; Malik, M. S.; Azeeza, S. Approaches based on enzyme mediated kinetic to dynamic kinetic resolutions: A versatile route for chiral intermediates. *Coord. Chem. Rev.* **2008**, *252*, 569-592.
- [20] Ahn, Y.; Ko, S.-B.; Kim, M.-J.; Park, J. Racemization catalysts for the dynamic kinetic resolution of alcohols and amines. *Coord. Chem. Rev.* **2008**, *252*, 647-658.
- [21] Martin-Matute, B.; Bäckvall, J.-E. In: *Asymmetric Organic Synthesis with Enzymes*, Wiley-VCH: Weinheim, **2008**, pp 87-113.
- [22] Martin-Matute, B.; Bäckvall, J.-E. In: *Organic Synthesis with Enzymes. In Non-aqueous Media*, Wiley-VCH: Weinheim, **2008**, pp 113-144.
- [23] Kamaruddin, A. A.; Uzir, M. H.; Aboul-Enein, H. Y.; Halim, H. N. A. Chemoenzymatic and microbial dynamic kinetic resolutions. *Chirality* **2009**, *21*, 449-467.
- [24] Pellissier, H. *Chirality from Dynamic kinetic resolution*; Royal Society of Chemistry: Cambridge, **2011**.
- [25] Pellissier, H. Recent Developments in Dynamic Kinetic Resolution. *Tetrahedron* **2011**, *67*, 3769-3802.
- [26] Pellissier, H. Organocatalyzed Dynamic Kinetic Resolution. *Adv. Synth. Catal.* **2011**, *353*, 659-676.
- [27] Rachwalski, M.; Vermue, N.; Rutjes, F. P. J. T. Recent advances in enzymatic and chemical deracemisation of racemic compounds *Chem. Soc. Rev.* **2013**, *42*, 9268-9282.
- [28] Pellissier, H. Recent developments in organocatalytic dynamic kinetic resolution. *Tetrahedron* **2016**, *72*, 3133-3150.
- [29] Pellissier, H. Organocatalytic Dynamic Kinetic Resolution. An Update. *Eur. J. Org. Chem.* **2022**, *26*, 120-169.
- [30] Pellissier, H. *Organocatalytic Dynamic kinetic resolution*, Royal Society of Chemistry: Cambridge, **2022**.
- [31] Noyori, R. *Asymmetric Catalysts in Organic Synthesis*, Wiley-VCH: New-York, **1994**.
- [32] Beller, M.; Bolm, C. *Transition Metals for Organic Synthesis*, Wiley-VCH: Weinheim, **1998**, Vols I and II.
- [33] Ojima, I. *Catalytic Asymmetric Synthesis*, second ed.; Wiley-VCH: New-York, **2000**.
- [34] Negishi, E *Handbook of Organopalladium Chemistry for Organic Synthesis*, John Wiley & Sons, Inc.: Hoboken NJ, **2002**; Vol. 2, pp 1689-1705.
- [35] Beller, M.; Bolm, C. *Transition Metals for Organic Synthesis*, 2nd ed.; Wiley-VCH: Weinheim, **2004**.
- [36] Tietze, L. F.; Hiriyakkanavar, I.; Bell, H. P. Enantioselective Palladium-Catalyzed Transformations. *Chem. Rev.* **2004**, *104*, 3453-3516.
- [37] Ramon, D. J.; Yus, M. In the Arena of Enantioselective Synthesis, Titanium Complexes Wear the Laurel Wreath. *Chem. Rev.* **2006**, *106*, 2126-2208.
- [38] Pellissier, H.; Clavier, H. Enantioselective Cobalt-Catalyzed Transformations. *Chem. Rev.* **2014**, *114*, 2775-2823.
- [39] Pellissier, H. Recent developments in enantioselective scandium-catalyzed transformations. *Coord. Chem. Rev.* **2016**, *313*, 1-37.
- [40] Pellissier, H. Enantioselective Silver-Catalyzed Transformations. *Chem. Rev.* **2016**, *116*, 14868-14917.
- [41] Pellissier, H. Recent developments in enantioselective lanthanide-catalyzed transformations. *Coord. Chem. Rev.* **2017**, *336*, 96-151.

- [42] Pellissier, H. Enantioselective Magnesium-Catalyzed Transformations. *Org. Biomol. Chem.* **2017**, *15*, 4750-4782.
- [43] Pellissier, H. Recent developments in enantioselective cobalt-catalyzed transformations. *Coord. Chem. Rev.* **2018**, *360*, 122-168.
- [44] Pellissier, H. Recent Developments in Enantioselective Iron-Catalyzed Transformations. *Coord. Chem. Rev.* **2019**, *386*, 1-31.
- [45] Pellissier, H. Recent Developments in Enantioselective Vanadium-Catalyzed Transformations. *Coord. Chem. Rev.* **2020**, *418*, 213395.
- [46] Pellissier, H. Recent developments in enantioselective zinc-catalyzed transformations. *Coord. Chem. Rev.* **2021**, *439*, 213926.
- [47] Pellissier, H. Recent developments in enantioselective titanium-catalyzed transformations. *Coord. Chem. Rev.* **2022**, *463*, 214537.
- [48] Hajos, Z. G.; Parrish, D. R. Asymmetric synthesis of bicyclic intermediates of natural chemistry. *J. Org. Chem.* **1974**, *39*, 1615-1621.
- [49] Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. New Strategies for Organic Catalysis: The First Highly Enantioselective Organocatalytic Diels-Alder Reaction. *J. Am. Chem. Soc.* **2000**, *122*, 4243-4244.
- [50] List, B.; Lerner, R. A.; Barbas, C. F. Proline-Catalyzed Direct Asymmetric Aldol Reactions. *J. Am. Chem. Soc.* **2000**, *122*, 2395-2396.
- [51] Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis—From Biomimetic Concepts to Powerful Methods for Asymmetric Synthesis*, Wiley-VCH: Weinheim, **2005**.
- [52] Taylor, M. S.; Jacobsen, E. N. Asymmetric Catalysis by Chiral Hydrogen-Bond Donors. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520-1543.
- [53] Dalko, P. I. *Enantioselective Organocatalysis*, Wiley-VCH: Weinheim, **2007**.
- [54] Pellissier, H. Asymmetric organocatalysis. *Tetrahedron* **2007**, *63*, 9267-9331.
- [55] *Chem. Rev.* **2007**, *107*, 5413-5883, Special Issue on Organocatalysis (List, B., Ed.).
- [56] Doyle, A. G.; Jacobsen, E. N. Small-Molecule H-Bond Donors in Asymmetric Catalysis. *Chem. Rev.* **2007**, *107*, 5713-5743.
- [57] Dondoni, A.; Massi, A. Asymmetric Organocatalysis: From Infancy to Adolescence. *Angew. Chem., Int. Ed.* **2008**, *47*, 4638-4660.
- [58] Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. Asymmetric Aminocatalysis—Gold Rush in Organic Chemistry. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138-6171.
- [59] Pellissier, H. *Recent Developments in Asymmetric Organocatalysis*, Royal Society of Chemistry: Cambridge, **2010**.
- [60] Mahrwald, R. *Enantioselective Organocatalyzed Reactions*, Vols. I and II, Springer: Berlin, **2011**.
- [61] Sahoo, B. M.; Banik, B. K. Organocatalysis: Trends of Drug Synthesis in Medicinal Chemistry. *Current Organocatalysis* **2019**, *6*, 92-105.
- [62] Xiang, S-H.; Tan, B. Advances in asymmetric organocatalysis over the last 10 years. *Nature Commun.* **2020**, *11*, 3786-3791.
- [63] Zhang, Y.; Cai, H.; Gan, X.; Jin, Z. N-Heterocyclic carbene-catalyzed enantioselective (dynamic) kinetic resolutions and desymmetrizations. *Sci China Chem.* **2024**, *67*, 482-511.
- [64] Marwa, A.; Kelly, T.; Ghanem, A. Applications of enzymatic and non-enzymatic methods to access enantiomerically pure compounds using kinetic resolution and racemisation. *Tetrahedron* **2012**, *68*, 6781-6802.
- [65] Applegate, G. A.; Berkowitz, D. B. Exploiting Enzymatic Dynamic Reductive Kinetic Resolution (DYRKR) in Stereocontrolled Synthesis. *Adv. Synth. Catal.* **2015**, *357*, 1619-1632.
- [66] Díaz-Rodríguez, A.; Lavandera, I.; Gotor, V. Why Leave a Job Half Done? Recent Progress in Enzymatic Deracemizations. *Curr. Green Chem.* **2015**, *2*, 192-211.
- [67] Musa, M. M.; Hollmann, F.; Mutti, F. G. Synthesis of enantiomerically pure alcohols and amines via biocatalytic deracemisation methods. *Catal. Sci. Technol.* **2019**, *9*, 5487-5503.
- [68] Ward, D. E.; Jheengut, V.; Akinnusi, O. T. Enantioselective Direct Intermolecular Aldol Reactions with Enantiotopic Group Selectivity and Dynamic Kinetic Resolution. *Org. Lett.* **2005**, *7*, 1181-1184.
- [69] Ward, D. E.; Jheengut, V.; Beye, G. E. Thiopyran Route to Polypropionates: An Efficient Synthesis of Serricornin. *J. Org. Chem.* **2006**, *71*, 8989-8992.
- [70] Guercio, G.; Bacchi, S.; Goodyear, M.; Carangio, A.; Tinazzi, F.; Curti, S. Synthesis of the NK1 Receptor Antagonist GW597599. Part 1: Development of a Scalable Route to a Key Chirally Pure Arylpiperazine. *Org. Process Res. Dev.* **2008**, *12*, 1188-1194.
- [71] Guercio, G.; Manzo, A. M.; Goodyear, M.; Bacchi, S.; Curti, S.; Provera, S. Synthesis of the NK1 Receptor Antagonist GW597599. Part 2: Development of a Scalable Route to a Key Chirally Pure Arylpiperazine. *Org. Process Res. Dev.* **2009**, *13*, 489-493.
- [72] Guercio, G.; Bacchi, S.; Perboni, A.; Leroi, C.; Tinazzi, F.; Bientinesi, I.; Hourdin, M.; Goodyear, M.; Curti, S.; Provera, S.; Cimarosti, Z. Synthesis of the NK1 Receptor Antagonist GW597599. Part 3: Development of a Scalable Route to a Key Chirally Pure Arylpiperazine Urea, A Happy End. *Org. Process Res. Dev.* **2009**, *13*, 1100-1110.
- [73] Brands, K. M. J.; Davies, A. J. Crystallization-Induced Diastereomer Transformations. *Chem. Rev.* **2006**, *106*, 2711-2733.
- [74] Sonawane, H. R.; Bellur, N. S.; Ahuja, J. R.; Kulkarni, D. G. Recent developments in the synthesis of optically active α -arylpropanoic acids: an important class of non-steroidal anti-inflammatory agents. *Tetrahedron: Asymmetry* **1992**, *3*, 163-192.
- [75] Shiina, I.; Ono, K.; Nakata, K. Non-enzymatic dynamic kinetic resolution of racemic α -arylalkanoic acids: an advanced asymmetric synthesis of chiral nonsteroidal anti-inflammatory drugs (NSAIDs). *Catal. Sci. Technol.* **2012**, *2*, 2200-2205.

- [76] Ortiz, A.; Benkovics, T.; Beutner, G. L.; Shi, Z.; Bultman, Nye, J.; Sfougataki, C.; Kronenthal, D. R. Scalable Synthesis of the Potent HIV Inhibitor BMS-986001 by Non-Enzymatic Dynamic Kinetic Asymmetric Transformation (DYKAT). *Angew. Chem., Int. Ed.* **2015**, *54*, 7185-7188.
- [77] Vedejs, E.; Chen, X. Kinetic Resolution of Secondary Alcohols. Enantioselective Acylation Mediated by a Chiral (Dimethylamino)pyridine Derivative. *J. Am. Chem. Soc.* **1996**, *118*, 1809-1810.
- [78] Spivey, A. C.; Maddaford, A. ASYMMETRIC CATALYSIS OF ACYL TRANSFER BY LEWIS ACIDS AND NUCLEOPHILES. A REVIEW. *Org. Prep. Proced. Int.* **2000**, *32*, 331-365.
- [79] Dalko, P. I.; Moisan, L. Enantioselective Organocatalysis. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726-3748.
- [80] France, S.; Guerin, D. J.; Miller, S. J. Letcka, T. Nucleophilic Chiral Amines as Catalysts in Asymmetric Synthesis. *Chem. Rev.* **2003**, *103*, 2985-3012.
- [81] Wurz, R. P. Chiral Dialkylaminopyridine Catalysts in Asymmetric Synthesis. *Chem. Rev.* **2007**, *107*, 5570-5595.
- [82] Xie, M.-S.; Li, N.; Tian, Y.; Wu, X.-X.; Deng, Y.; Qu, G.-R.; Guo, H.-M. Dynamic Kinetic Resolution of Carboxylic Esters Catalyzed by Chiral PPY N-Oxides: Synthesis of Nonsteroidal Anti-Inflammatory Drugs and Mechanistic Insights. *ACS Catal.* **2021**, *11*, 8183-8196.
- [83] Ford, D. D.; Kamlet, A. S.; Limberakis, C.; Pearsall, A.; Piotrowski, D. W.; Quinn, B.; Rothstein, S.; Salan, J.; Wei, L.; Xiao, J. *Org. Process Res. Dev.* **2017**, *21*, 1990-2000.
- [84] Piotrowski, D. W.; Kamlet, A. S.; Dechert-Schmitt, A.-M. R.; Yan, J.; Brandt, T. A.; Xiao, J.; Wei, L.; Barrila, M. T. Regio- and Enantioselective Synthesis of Azole Hemiaminal Esters by Lewis Base Catalyzed Dynamic Kinetic Resolution. *J. Am. Chem. Soc.* **2018**, *138*, 4818-4823.
- [85] Xie, M.-S.; Shan, M.; Li, N.; Chen, Y.-G.; Wang, X.-B.; Cheng, X.; Tian, Y.; Wu, X.-X.; Deng, Y.; Qu, G.-R.; Guo, H.-M. Chiral 4-Aryl-pyridine-N-oxide Nucleophilic Catalysts: Design, Synthesis, and Application in Acylative Dynamic Kinetic Resolution. *ACS Catal.* **2022**, *12*, 877-891.
- [86] Nugent, T. C.; Seemayer, R. An Efficient Enantiopure Synthesis of a Pivotal Precursor to Substance P Antagonists. *Org. Process Res. Dev.* **2006**, *10*, 142-148.
- [87] Schreiner, P. R. Metal-free organocatalysis through explicit hydrogen bonding interactions. *Chem. Soc. Rev.* **2003**, *32*, 289-296.
- [88] Akiyama, T.; Itoh, J.; Fuchibe, K. Recent Progress in Chiral Brønsted Acid Catalysis. *Adv. Synth. Catal.* **2006**, *348*, 999-1010.
- [89] Akiyama, T. Stronger Brønsted Acids. *Chem. Rev.* **2007**, *107*, 5744-5758.
- [90] Kampen, D.; Reisinger, C. M.; List, B. Chiral Brønsted acids for asymmetric organocatalysis. *Top. Curr. Chem.* **2010**, *291*, 395-456.
- [91] Akiyama, T.; Mori, K. Stronger Brønsted Acids: Recent Progress. *Chem. Rev.* **2015**, *115*, 9277-9306.
- [92] Rahman, A.; Lin, X. Development and application of chiral spirocyclic phosphoric acids in asymmetric catalysis. *Org. Biomol. Chem.* **2018**, *16*, 4753-4777.
- [93] Liu, W.; Yang, X. Recent Advances in (Dynamic) Kinetic Resolution and Desymmetrization Catalyzed by Chiral Phosphoric Acids. *Asian J. Org. Chem.* **2021**, *10*, 692-710.
- [94] Terada, M. Chiral Phosphoric Acids as Versatile Catalysts for Enantioselective Transformations. *Synthesis* **2010**, 1929-1982.
- [95] Zamfir, A.; Schenker, S.; Freund, M.; Tsogoeva, S. B. Chiral BINOL-derived phosphoric acids: privileged Brønsted acid organocatalysts for C-C bond formation reactions. *Org. Biomol. Chem.* **2010**, *8*, 5262-5276.
- [96] Zhao, R.; Shi, L. Promising Combination for Asymmetric Organocatalysis: Brønsted Acid-Assisted Chiral Phosphoric Acid Catalysis. *ChemCatChem* **2014**, *6*, 3309-3311.
- [97] Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. Complete Field Guide to Asymmetric BINOL-Phosphate Derived Brønsted Acid and Metal Catalysis: History and Classification by Mode of Activation; Brønsted Acidity, Hydrogen Bonding, Ion Pairing, and Metal Phosphates. *Chem. Rev.* **2014**, *114*, 9047-9153.
- [98] Maji, R.; Mallojjala, S. C.; Wheeler, S. E. Chiral phosphoric acid catalysis: from numbers to insights. *Chem. Soc. Rev.* **2018**, *47*, 1142-1158.
- [99] Li, X.; Song, Q. Recent advances in asymmetric reactions catalyzed by chiral phosphoric acids. *Chem. Lett.* **2018**, *29*, 1181-1192.
- [100] Zhang, Y.; Ao, Y.-F.; Huang, Z.-T.; Wang, D.-X.; Wang, M.-X.; Zhu, J. Chiral Phosphoric Acid Catalyzed Asymmetric Ugi Reaction by Dynamic Kinetic Resolution of the Primary Multicomponent Adduct. *Angew. Chem., Int. Ed.* **2016**, *55*, 5282-5285.
- [101] Nolan, S. P. *N-Heterocyclic Carbenes in Synthesis*, Wiley: Weinheim, **2006**.
- [102] Grossmann, A.; Enders, D. N-Heterocyclic Carbene Catalyzed Domino Reactions. *Angew. Chem., Int. Ed.* **2012**, *51*, 314-325.
- [103] Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F. An overview of N-heterocyclic carbenes. *Nature* **2014**, *510*, 485-496.
- [104] Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Tomislav, R. Organocatalytic Reactions Enabled by N-Heterocyclic Carbenes. *Chem. Rev.* **2015**, *115*, 9307-9387.
- [105] Tietze, L. F. Domino Reactions in Organic Synthesis. *Chem. Rev.* **1996**, *96*, 115-136.
- [106] Tietze, L. F.; Rackelmann, N. Domino reactions in the synthesis of heterocyclic natural products and analogs. *Pure Appl. Chem.* **2004**, *76*, 1967-1983.
- [107] Zhu, J.; Bienaymé, H. *Multicomponent Reactions*, Wiley-VCH: Weinheim, **2005**.

- [108] Ramon, D. J.; Yus, M. Asymmetric Multicomponent Reactions (AMCRs): The New Frontier. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602-1634.
- [109] Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis*, Wiley-VCH: Weinheim, **2006**.
- [110] Pellissier, H. Asymmetric domino reactions. Part B: Reactions based on the use of chiral catalysts and biocatalysts. *Tetrahedron* **2006**, *62*, 2143-2173.
- [111] Padwa, A.; Bur, S. K. The domino way to heterocycles. *Tetrahedron* **2007**, *63*, 5341-5378.
- [112] Touré, B. B.; Hall, D. G. Natural product synthesis using multicomponent reaction strategies. *Chem. Rev.* **2009**, *109*, 4439-4486.
- [113] *Chem. Soc. Rev.* **2009**, *38*, Special Issue on Rapid formation of molecular complexity in organic synthesis.
- [114] Orru, R. V. A.; Ruijter, E. *Synthesis of Heterocycles via Multicomponent Reactions, Topics in Heterocyclic Chemistry*, Vols. I and II, Springer: Berlin, **2010**.
- [115] Tietze, L. F. *Domino Reactions - Concepts for Efficient Organic Synthesis*, Wiley-VCH: Weinheim, **2014**.
- [116] Zhu, J.; Wang, Q.; Wang, M. *Multicomponent Reactions in Organic Synthesis*, Wiley: Weinheim, **2014**.
- [117] Herrera, R. P.; Marques-Lopez, E. *Multicomponent Reactions: Concepts and Applications for Design and Synthesis*, Wiley: Weinheim, **2015**.
- [118] Snyder, S. A. *Science of Synthesis. Applications of Domino Transformations in Organic Synthesis*, Thieme Verlag: Stuttgart, **2016**; Vols 1-2.
- [119] Enders, D.; Grondal, C.; Hüttl, M. R. M. Asymmetric Organocatalytic Domino Reactions. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570-1581.
- [120] Alba, A.-N.; Companyo, X.; Viciano, M.; Rios, R. Organocatalytic Domino Reactions *Curr. Org. Chem.* **2009**, *13*, 1432-1474.
- [121] De Graaff, C.; Ruijter, E.; Orru, R. V. A. Recent developments in asymmetric multicomponent reactions. *Chem. Soc. Rev.* **2012**, *41*, 3969-4009.
- [122] Pellissier, H. Recent Developments in Asymmetric Organocatalytic Domino Reactions. *Adv. Synth. Catal.* **2012**, *354*, 237-294.
- [123] Clavier, H.; Pellissier, H. Recent Developments in Enantioselective Metal-Catalyzed Domino Reactions. *Adv. Synth. Catal.* **2012**, *354*, 3347-3403.
- [124] Pellissier, H. Stereocontrolled Domino Reactions. *Chem. Rev.* **2013**, *113*, 442-524.
- [125] Pellissier, H. *Asymmetric Domino Reactions*, Royal Society of Chemistry: Cambridge, **2013**.
- [126] Volla, C. M. R.; Atodiressei, I.; Rueping, M. Catalytic C-C Bond-Forming Multi-Component Cascade or Domino Reactions: Pushing the Boundaries of Complexity in Asymmetric Organocatalysis. *Chem. Rev.* **2014**, *114*, 2390-2431.
- [127] Pellissier, H. Recent Developments in Enantioselective Metal-Catalyzed Domino Reactions. *Adv. Synth. Catal.* **2016**, *358*, 2194-2259.
- [128] Chanda, T.; Zhao, J. C.-G. Recent Progress in Organocatalytic Asymmetric Domino Transformations. *Adv. Synth. Catal.* **2018**, *360*, 2-79.
- [129] Pellissier, H. Recent developments in enantioselective metal-catalyzed domino reactions. *Adv. Synth. Catal.* **2019**, *361*, 1733-1755.
- [130] Pellissier, H. *Asymmetric Metal Catalysis in Enantioselective Domino Reactions*, Wiley: Weinheim, **2019**.
- [131] Enders, D.; Breuer, K.; Raabe, G.; Runsink, J.; Teles, J. H.; Melder, J.-P.; Ebel, K.; Brode, S. Preparation, Structure, and Reactivity of 1,3,4-Triphenyl-4,5-dihydro-1H-1,2,4-triazol-5-ylidene, a New Stable Carbene. *Angew. Chem., Int. Ed.* **1995**, *34*, 1021-1023.
- [132] Knight, R. L.; Leeper, F. J. Comparison of chiral thiazolium and triazolium salts as asymmetric catalysts for the benzoin condensation. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1891-1893.
- [133] Wang, Z.; Pan, D.; Li, T.; Jin, Z. N-Heterocyclic Carbene (NHC)-Organocatalyzed Kinetic Resolutions, Dynamic Kinetic Resolutions, and Desymmetrizations. *Chem. Asian J.* **2018**, *13*, 2149-2166.
- [134] De Risi, C.; Bortolini, O.; Di Carmine, G.; Ragno, D.; Massi, A. Kinetic Resolution, Dynamic Kinetic Resolution and Asymmetric Desymmetrization by N-Heterocyclic Carbene Catalysis. *Synthesis* **2019**, *51*, 1871-1892.
- [135] Cohen, D. T.; Johnston, R. C.; Rosson, N. T.; Cheong, P. H.-Y.; Scheidt, K. A. Functionalized cyclopentenes through a tandem NHC-catalyzed dynamic kinetic resolution and ambient temperature decarboxylation: mechanistic insight and synthetic application. *Chem. Commun.* **2015**, *51*, 2690-2693.
- [136] Perveen, S.; Yang, S.; Meng, M.; Xu, W.; Zhang, G.; Fang, X. Asymmetric total synthesis of rotenoids via organocatalyzed dynamic kinetic resolution. *Commun. Chem.* **2019**, *2*, 8.
- [137] Sukumaran, J.; Hanefeld, U. Enantioselective C-C bond synthesis catalyzed by enzymes. *Chem. Soc. Rev.* **2005**, *34*, 530-542.
- [138] Patel, R. N. Synthesis of chiral pharmaceutical intermediates by biocatalysis. *Coord. Chem. Rev.* **2008**, *252*, 659-701.
- [139] Hauer, B. Embracing Nature's Catalysts: A Viewpoint on the Future of Biocatalysis. *ACSCatal.* **2020**, *10*, 8418-8427.
- [140] Hall, M. Enzymatic strategies for asymmetric synthesis. *RSC Chem. Biol.* **2021**, *2*, 958-989.
- [141] Wu, S.; Snajdrova, R.; Moore, J. C.; Baldenius, K.; Bornscheuer, U. T. Biocatalysis: Enzymatic Synthesis for Industrial Applications. *Angew. Chem., Int. Ed.* **2021**, *60*, 88-119.
- [142] Blaskovich, M. A. T. Unusual Amino Acids in Medicinal Chemistry. *J. Med. Chem.* **2016**, *59*, 10807-10836.

- [143] May, O.; Verseck, S.; Bommaris, A.; Drauz, K. Development of Dynamic Kinetic Resolution Processes for Biocatalytic Production of Natural and Nonnatural L-Amino Acids. *Org. Process Res. Dev.* **2002**, *6*, 452-457.
- [144] Servi, S.; Tessaro, D.; Pedrocchi-Fantoni, G. Chemo-enzymatic deracemization methods for the preparation of enantiopure non-natural α -amino acids. *Coord. Chem. Rev.* **2008**, *252*, 715-726.
- [145] Kim, C.; Park, J.; Kim, M.-J. In: *Comprehensive Chirality*; 1st ed.; Carreira, E. M.; Yamamoto, H., Eds; Elsevier, **2012**; pp 156-180.
- [146] Heninot, A.; Collins, J. C.; Nuss, J. M. The Current State of Peptide Drug Discovery: Back to the Future?. *J. Med. Chem.* **2018**, *61*, 1382-1414.
- [147] Kambourakis, S.; Rozzell, J. D. Chemo-Enzymatic Method for the Synthesis of Statine, Phenylstatine and Analogues. *Adv. Synth. Catal.* **2003**, *345*, 699-705.
- [148] Xue, Y.-P.; Cao, C.-H.; Zheng, Y.-G. Enzymatic asymmetric synthesis of chiral amino acids. *Chem. Soc. Rev.* **2018**, *47*, 1516-1561.
- [149] Li, F.; Yang, L.-C.; Zhang, J.; Chen, J. S.; Renata, H. Stereoselective Synthesis of β -Branched Aromatic α -Amino Acids by Biocatalytic Dynamic Kinetic Resolution. *Angew. Chem., Int. Ed.* **2021**, *60*, 17680-17685.
- [150] Toyooka, N.; Yoshida, Y.; Yotsui, Y.; Momose, T. 2-Piperidone Type of Chiral Building Block for 3-Piperidinol Alkaloid Synthesis. *J. Org. Chem.* **1999**, *64*, 4914-4919.
- [151] Toyooka, N.; Yoshida, Y.; Momose, T. Enantio- and diastereodivergent synthesis of all four diastereomers of the 2,6-disubstituted 3-piperidinol chiral building block. *Tetrahedron Lett.* **1995**, *36*, 3715-3718.
- [152] Pesti, J. A.; Yin, J.; Zhang, L.-h.; Anzalone, L.; Waltermire, R. E.; Ma, P.; Gorko, E.; Confalone, P. N.; Fortunak, J.; Silverman, C.; Blackwell, J.; Chung, J. C.; Hrytsak, M. D.; Cooke, M.; Powell, L.; Ray, C. Efficient Preparation of a Key Intermediate in the Synthesis of Roxifiban by Enzymatic Dynamic Kinetic Resolution on Large Scale. *Org. Process Res. Dev.* **2004**, *8*, 22-27.
- [153] Wang, L. W.; Cheng, Y. C.; Tsai, S. W. Process modeling of the lipase-catalyzed dynamic kinetic resolution of (*R,S*)-suprofen 2,2,2-trifluoroethyl thioester in a hollow-fiber membrane. *Bioprocess Biosyst. Eng.* **2004**, *27*, 39-49.
- [154] Fazlena, H.; Kamaruddin, A. H.; Zulkali, M. M. D. Dynamic kinetic resolution: alternative approach in optimizing S-ibuprofen production. *Bioprocess Biosyst. Eng.* **2006**, *28*, 227-233.
- [155] Chaplin, D. A.; Fox, M. E.; Kroll, S. H. B. *Chem. Commun.* **2014**, *50*, 5858-5860.
- [156] Kalaitzakis, D.; Smonou, I. Chemoenzymatic Synthesis of Stegobinone and Stegobiol, Components of the Natural Sex Pheromone of the Drugstore Beetle (*Stegobium paniceum* L.). *Eur. J. Org. Chem.* **2012**, 43-46.
- [157] Hu, L.; Schaufelberger, F.; Zhang, Y.; Ramström, O. Efficient asymmetric synthesis of lamivudine via enzymatic dynamic kinetic resolution. *Chem. Commun.* **2013**, *49*, 10376-10378.
- [158] Arndt, S.; Grill, B.; Schwab, H.; Steinkellner, G.; Pogorevčnik, U.; Weis, D.; Nauth, A. M.; Gruber, K.; Opatz, T.; Donsbach, K.; Waldvogel, S. R.; Winkler, M. The sustainable synthesis of levetiracetam by an enzymatic dynamic kinetic resolution and an ex-cell anodic oxidation. *Green Chem.* **2021**, *23*, 388-395.
- [159] Matsumae, H.; Douno, H.; Yamada, S.; Nishida, T.; Ozaki, Y.; Shibatani, T.; Tosa, T. Microbial asymmetric reduction of (*RS*)-2-(4-methoxyphenyl)-1,5-benzothiazepin-3,4(2*H,5H*)-dione, the key intermediate in the synthesis of diltiazem hydrochloride. *J. Ferment. Bioeng.* **1995**, *79*, 28-32.
- [160] Toyooka, N.; Yotsui, Y.; Yoshida, Y.; Momose, T. Enantioselective Total Synthesis of the Marine Alkaloids Clavepictines A and B. *J. Org. Chem.* **1996**, *61*, 4882-4883.
- [161] Toyooka, N.; Okumura, M.; Takahata, H. Enantioselective Total Synthesis of the Marine Alkaloid Lepadine B. *J. Org. Chem.* **1999**, *64*, 2182-2183.
- [162] Toyooka, N.; Okumura, M.; Takahata, H.; Nemoto, H. Construction of 4a,8a-*cis*-octahydroquinolin-7-one core using an intramolecular aldol type of cyclization: An application to enantioselective total synthesis of lepadin B. *Tetrahedron* **1999**, *55*, 10673-10684.
- [163] Lin, H.-Y.; Tsai, S.-W. Dynamic kinetic resolution of (*R,S*)-naproxen 2,2,2-trifluoroethyl ester via lipase-catalyzed hydrolysis in micro-aqueous isooctane. *J. Mol. Catal. B* **2003**, *24-25*, 111-120.
- [164] Wen, W.-Y.; Ng, I.-S.; Tsai, S.-W. J. Lipase-catalyzed dynamic hydrolytic resolution of (*R,S*)-2,2,2-trifluoroethyl α -chlorophenyl acetate in water-saturated isooctane. *Chem. Technol. Biotechnol.* **2006**, *81*, 1715-1721.
- [165] Pietruszka, J.; Simon, R. C.; Kruska, F.; Braun, M. Dynamic Enzymatic Kinetic Resolution of Methyl 2,3-Dihydro-1*H*-indene-1-carboxylate. *Eur. J. Org. Chem.* **2009**, 6217-6224.
- [166] Claus, R. A.; Dorer, M. J.; Bunck, A. C.; Deigner, H. P. Inhibition of Sphingomyelin Hydrolysis: Targeting the Lipid Mediator Ceramide as a Key Regulator of Cellular Fate. *Curr. Med. Chem.* **2009**, *16*, 1978-2000.
- [167] Hoye, T. R.; Jeffrey, C. S.; Nelson, D. P. Dynamic Kinetic Resolution During a Vinyllogous Payne Rearrangement: A Concise Synthesis of the Polar Pharmacophoric Subunit of (+)-Scyphostatin. *Org. Lett.* **2010**, *12*, 52-55.
- [168] Friest, J. A.; Maezato, Y.; Broussy, S.; Blum, P.; Berkowitz, D. B. Use of a Robust Dehydrogenase from an Archaeal Hyperthermophile in Asymmetric Catalysis—Dynamic Reductive Kinetic Resolution Entry into (*S*)-Profens. *J. Am. Chem. Soc.* **2010**, *132*, 5930-5931.
- [169] Peng, Z.; Wong, J. W.; Hansen, E. C.; Puchlopek-Dermenci, A. L. A.; Clarke, H. J. Development of a Concise, Asymmetric Synthesis of a Smoothed Receptor (SMO) Inhibitor: Enzymatic Transamination of a 4-Piperidinone with Dynamic Kinetic Resolution. *Org. Lett.* **2014**, *16*, 860-863.
- [170] Chung, C. K.; Bulger, P. G.; Kosjek, B.; Belyk, K. M.; Rivera, N.; Scott, M. E.; Humphrey, G. R.; Limanto, J.; Bachert, D. C.; Emerson, K. M. Process Development of C–N Cross-Coupling and Enantioselective Biocatalytic Reactions for the Asymmetric Synthesis of Niraparib. *Org. Process Res. Dev.* **2014**, *18*, 215-227.

[171] Zhan, Z.; Xu, Z.; Yu, S.; Feng, J.; Liu, F.; Yao, P.; Wu, Q.; Zhu, D. Stereocomplementary Synthesis of a Key Intermediate for Tofacitinib via Enzymatic Dynamic Kinetic Resolution-Reductive Amination. *Adv. Synth. Catal.* **2022**, *364*, 2380-2386.