S.A.Vakarov, D.A.Gruzdev, G.L.Levit, V.P.Krasnov, V.N.Charushin, O.N.Chupakhin
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Synthesis of enantiomerically pure 2-aryloxy carboxylic acids and their derivatives

Sergey A. Vakarov,[a] Dmitry A. Gruzdev,[a, b] Galina L. Levit,[a, b] Victor P. Krasnov,[a]* Valery N. Charushin,[a, b] Oleg N. Chupakhin [a, b]

[a] I.Ya.Postovsky Institute of Organic Synthesis, Ural Branch of theRussian Academy of Sciences, ul. S.Kovalevskoi 22/Akademicheskaya 20, 620990 Ekaterinburg, Russian Federation
[b] Ural Federal University named after the First President of Russia B.N.Yeltsin, ul. Mira 19, 620002 Ekaterinburg, Russian Federation

Recent publications on the key preparation methods of the enantiomers of 2-aryloxy carboxylic acids are summarized and comparative analysis of the methods is given. The information is arranged according to the type of the starting compound, being classified into syntheses from enantiomerically pure chiral precursors and syntheses from prochiral precursors, which imply generation of an asymmetric centre in the substrate molecule. Data on the chemical resolution of racemic mixtures of the title compounds are addressed in a separate Section. Attention is focused on the preparation of practically valuable 2-aryloxy acids. Examples of biologically active derivatives of 2-aryloxy carboxylic acids are given.
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1. Introduction

Development of rational methods for the synthesis of enantiomerically pure 2-aryloxy-substituted carboxylic acids and their derivatives is of interest because of high practical value of compounds of this class. These acids are precursors or structural fragments of some agrochemicals and physiologically active compounds (Fig. 1). It is well known that biological activity depends on the configuration of the chiral centre in the 2-aryloxy acid molecule.[1–3] For example, the *R*-isomer of lofexidine is 10 times as active as its optical antipode. Nevertheless, both this compound and lactisole, a sweet taste receptor inhibitor, are used in the form of racemates.

2-Aryloxy carboxylic acid derivatives have a significant synthetic potential as chiral (or prochiral) synthons. In recent years, the range of stereoselective reactions with participation of chiral reagents based on iodinated 2-aryloxy carboxylic acids has continuously expanded.[4–6] Enantiomerically pure 2-aryloxy acids also provide the basis for

S.A.Vakarov. Candidate of Chemical Sciences, Researcher at the IOS UrB RAS.
Telephone: +7(343)362 – 3579, e-mail: savakarov@ios.uran.ru
Current research interests: carboxylic acids, asymmetric synthesis, medicinal chemistry, stereochemistry.
D.A.Gruzdev. Candidate of Chemical Sciences, Researcher at the IOS UrB RAS and UrFU.
Telephone: +7(343)362 – 3579, e-mail: gruzdev-da@ios.uran.ru
Current research interests: amino acids, asymmetric synthesis, medicinal chemistry, purine derivatives, stereochemistry.
G.L.Levit. Doctor of Chemical Sciences, Leading Researcher at the IOS UrB RAS and UrFU.
Telephone: +7(343)362 – 3057, e-mail: ca512@ios.uran.ru
Current research interests: amino acids, medicinal chemistry, synthesis of biologically active compounds, stereochemistry.
V.P.Krasnov. Doctor of Chemical Sciences, Professor, Head of Laboratory of the IOS UrB RAS.
Telephone: +7(343)362 – 3057, e-mail: ca@ios.uran.ru
Current research interests: amino acids, asymmetric synthesis, medicinal chemistry, drug design, stereochemistry.
V.N.Charushin. Academician of the Russian Academy of Sciences, Doctor of Chemical Sciences, Professor, Director of the IOS UrB RAS, Professor at the UrFU.
Telephone: +7(343)369 – 3058, e-mail: charushin@ios.uran.ru
O.N.Chupakhin. Academician of the Russian Academy of Sciences, Doctor of Chemical Sciences, Professor, Scientific Advisor of the IOS UrB RAS, Professor UrFU.
Telephone: +7(343)369 – 3058
Current research interests of the authors: medicinal chemistry, nucleophilic substitution of hydrogen, chemistry of heterocyclic compounds, chemistry of organofluorine compounds.

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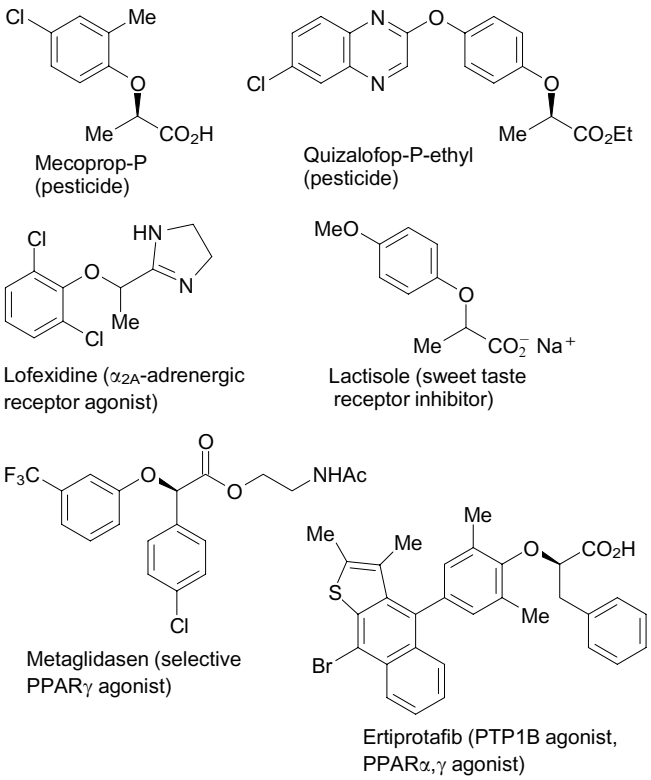


Figure 1. Biologically active 2-aryloxy acids and their derivatives.

the preparation of 2-hydroxy acids, which are used in organic synthesis as chiral building blocks.[7,8] Recently, we have found [9,10] that some 2-aryloxy acid derivatives can serve as efficient chiral reagents for kinetic resolution (KR) of racemic heterocyclic amines.

Therefore, the search for effective synthetic routes to individual stereoisomers of 2-aryloxy carboxylic acids is a relevant task. Meanwhile, despite the practical value of these compounds and the importance of development of synthetic routes to them, no analytical reviews on the preparation of 2-aryloxy acids as single enantiomers have yet been published. Various approaches to enantiomerically pure 2-aryloxy acids are described in the literature, with a large number of publications being devoted to enzymatic reactions used to prepare stereoisomers of 2-aryloxy carboxylic acids.[11–20] Nevertheless, non-enzymatic methods are also important for the preparation of single enantiomers of these compounds. This review is devoted to the achievements in the chemical synthesis of enantiomerically pure 2-aryloxy-substituted carboxylic acids and their derivatives.

Methods for the preparation of enantiomers of 2-aryloxyalkanoic acids can be divided into three main groups according to the type of substrate:

(1) syntheses from enantiomerically pure chiral precursors;

(2) syntheses from prochiral compounds with generation of an asymmetric centre in the substrate molecule;

(3) resolution of racemic mixtures.

The following designations and abbreviations are used:

acac — acetylacetonate,
B — base,
BINAP — 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl,
C — conversion,
CAN — cerium(IV) ammonium nitrate,
Cat — catalyst,
DBAD — di-*tert*-butyl azodicarboxylate,
de — diastereomeric excess,
DEA — *N*,*N*-diethylaniline,
DEAD — diethyl azodicarboxylate,
DIAD — diisopropyl azodicarboxylate,
DIPEA — *N*,*N*-diisopropyl-*N*-ethylamine,
DKR — dynamic kinetic resolution,
dr — diastereomeric ratio,
EDCI — 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide,
ee — enantiomeric excess,
HBTM — homobenzotetramisole,
KR — kinetic resolution,
MS — molecular sieves,
MW — microwave radiation,
NaBARF — sodium tetrakis[3,5-bis(trifluoromethyl)-phenyl]borate,
Naph — naphthyl,
NBD — norborna-2,5-diene,
PKR — parallel kinetic resolution,
PPAR — peroxisome proliferator-activated receptor,
PEA — 1-phenylethylamine,
rt — room temperature,
s — selectivity factor,
Tf — trifluoromethanesulfonyl (triflyl),
TMS — trimethylsilyl,
Ts — *p*-toluenesulfonyl (tosyl).

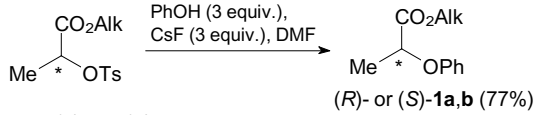
2. Synthesis from chiral precursors

The availability of enantiomerically pure 2-hydroxy carboxylic acids, *e.g.*, lactic and mandelic acids, and the possibility of isolating them from natural sources make it possible to synthesize the enantiomers of 2-aryloxy acids by replacing the hydroxy group by a phenolic moiety (directly by the Mitsunobu reaction or *via* sulfonylation followed by nucleophilic substitution). Appropriate 2-halogen derivatives can also serve as the starting compounds in the synthesis of enantiomerically enriched 2-aryloxy carboxylic acids. The key problem restricting the use of S_N2 nucleophilic substitution reactions for the preparation of compounds with high enantiomeric purity is incomplete inversion of configuration of the chiral centre. Nucleophilic substitution reactions often proceed under drastic conditions (in the presence of strong bases at high temperature) and can be accompanied by racemization and side reactions, for example, elimination. For this reason, publications devoted to the synthesis of enantiomers of aryloxy acids by S_N2 reactions focus attention on the selection of the leaving group and reaction conditions.

The approach based on displacement of the *p*-toluenesulfonate (tosylate, OTs) group in alkyl esters of O-sulfonylated (*S*)- and (*R*)-lactic acids by phenol in the presence of excess CsF in DMF was used to prepare enantiomerically pure (*R*)- and (*S*)-2-aryloxy esters **1a**,**b** (Scheme 1).[21] These products are of interest as structural fragments of chiral β_3-adrenergic receptor agonists, for example, compound **2**.[22]

The reaction of O-trifluoromethanesulfonylated n-butyl 2-hydroxybutyrate (1.2 equiv.) with *meta*-substituted phenol **3** gives biologically active (*R*)-2-aryloxy ester **4** (commercial code K-13675), which is an peroxisome

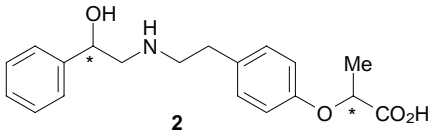
Scheme 1



(*R*)- or (*S*)-**1a**,**b** (77%)

Alk = Et (**a**), Me (**b**)

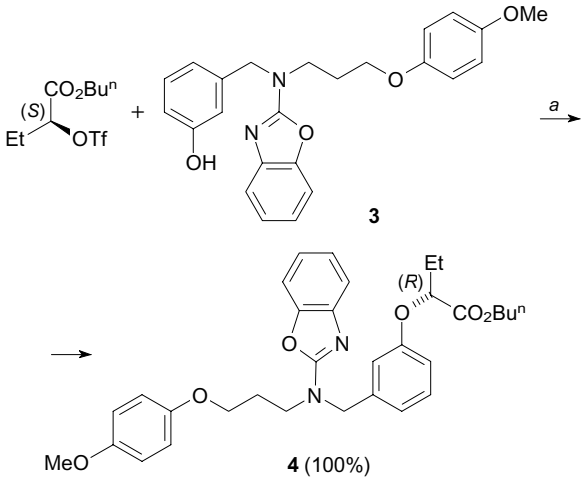
Structure 2



2

proliferation receptor agonist (PPAR) (Scheme 2).[23] The nucleophilic substitution reaction was conducted in acetonitrile in the presence of K_2CO_3; the target product was formed in a quantitative yield with an enantiomeric excess (*ee*) of 99%.

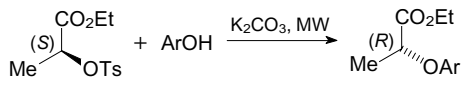
Scheme 2



(*a*) K_2CO_3 (1.2 equiv.), MeCN; OTf is trfluoromethanesulfonate (triflate)

A broad range of 2-aryloxy esters (*R*)-**1** with *ee* from 88.7% to 93.6% (according to chiral HPLC) were prepared in 75% – 95% yields by microwave (MW) assisted reactions of ethyl (*S*)-*O*-tosyllactate with various phenols in the presence of K_2CO_3 (Scheme 3).[24]

Scheme 3

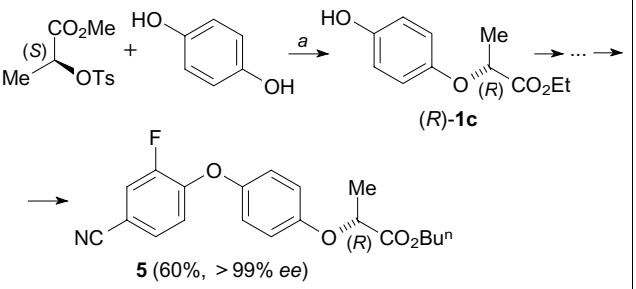


1 [75% – 95%, (88.7% – 93.6%) *ee*]

Ar = Ph, 2-ClC$_6$H$_4$, 4-ClC$_6$H$_4$, 3-BrC$_6$H$_4$, 4-BrC$_6$H$_4$, 3-O$_2$NC$_6$H$_4$, 4-O$_2$NC$_6$H$_4$, 2-Me-4-ClC$_6$H$_3$, 3-Me-4-ClC$_6$H$_3$, 2,4-Cl$_2$C$_6$H$_3$, 3,4-Cl$_2$C$_6$H$_3$, 3,5-Cl$_2$C$_6$H$_3$, 2,4-Br$_2$C$_6$H$_3$, 2,6-(MeO)$_2$C$_6$H$_3$, 2,3,5-Me$_3$C$_6$H$_2$, 3,5-Me$_2$-4-ClC$_6$H$_2$

The nucleophilic displacement of the tosyloxy group of methyl (*S*)-*O*-tosyllactate under the action of hydroquinone is accompanied by inversion of configuration and affords (*R*)-aryloxy ester **1c** in 75% yield (Scheme 4).[25] This

Scheme 4

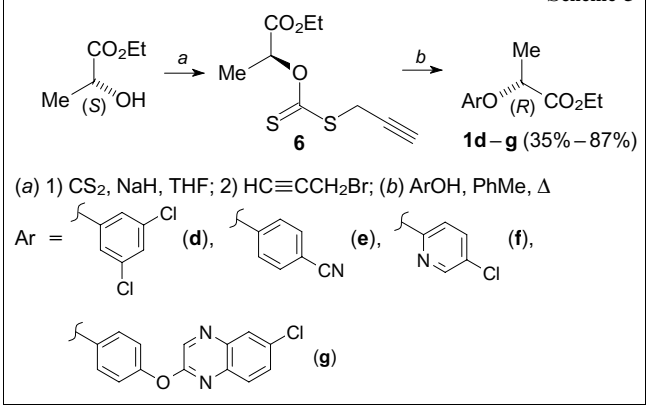


(*a*) NaOH, EtOH

(*R*)-aryloxy ester was used in the synthesis of compound **5** — the low-toxic enantiomerically pure herbicide Cyhalofop-butyl.

In 2016, a new original approach was proposed[26] for the preparation of enantiomers of aryloxy esters (*R*)-**1d** – **g** (Scheme 5). The reaction of enantiomerically pure ethyl L-lactate with carbon disulfide in the presence of sodium hydride followed by treatment of the reaction product with propargyl bromide affords xanthate **6**, which reacts with phenols to be converted to enantiomerically pure 2-aryloxy esters. Compound **1g** (Quizalofop-P-ethyl) is used as a herbicide.

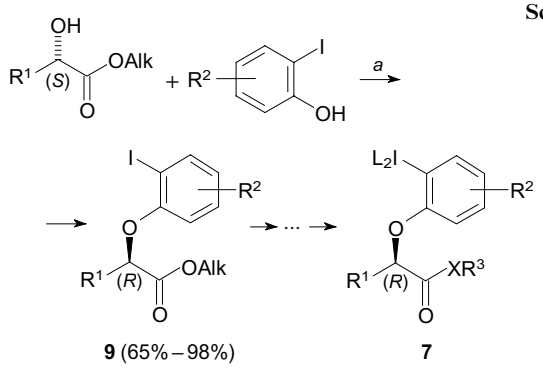
Scheme 5



A popular approach to the synthesis of 2-aryloxy carboxylic acids from optically pure precursors consists in the Mitsunobu reaction of single enantiomers of 2-hydroxy esters with phenols. During this reaction, the stereo configuration of the 2-hydroxy ester moiety is inverted. However, there are known examples where this reaction is accompanied by partial racemization or even retention of configuration.[27 – 29] The enantiomeric purity of 2-aryloxy carboxylic acid derivatives obtained by the Mitsunobu reaction does not receive adequate researchers' attention. Examples of using this reaction in the route towards enantiomerically pure 2-aryloxy acids are presented below.

Among 2-aryloxy acids, special place is occupied by iodo derivatives, which serve as chiral reagents and catalysts in diverse redox processes. The key method for their preparation is the Mitsunobu reaction involving 2-hydroxy acids and phenols. Scheme 6 depicts the general approach to the synthesis of iodinated 2-aryloxy acids **7**. Derivatives of 2-aryloxy acids **8** were prepared in a similar way. In all cases, 2-aryloxy esters **9** were obtained by the Mitsunobu reaction from 2-hydroxy esters and substituted phenols in

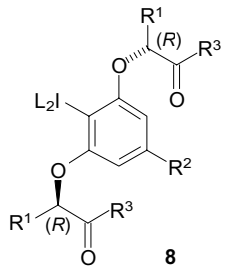
Scheme 6



9 (65% – 98%) **7**

(*a*) DIAD or DEAD, PPh_3, THF; L: none, OAc; X = O, NH; R^1 = Me, Pr^i, Bn; R^2 = H, Me, Ph; R^3 = Me, Et, Pr^i, Bu^t, (1*R*,2*S*,5*R*)-menthyl

Structures 8



8

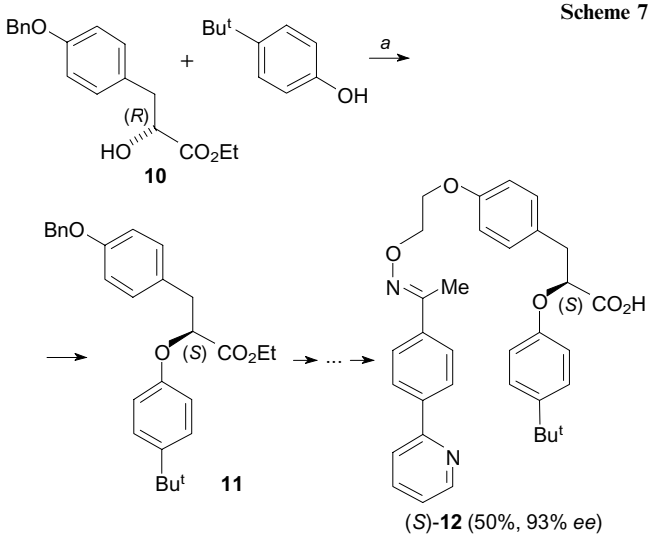
L: none, OAc
R^1 = Me, Pr^i, Bn; R^2 = H, Me, F, CF_3, 3,5-$(F_3C)_2C_6H_3$;
R^3 = OAlk, NHAlk, NHAr, $NAlk_2$, N(cyclo-Alk)

the presence of diethyl azodicarboxylate (DEAD) or diisopropyl azodicarboxylate (DIAD) and triphenylphosphine.[30 – 47]

The Mitsunobu reaction is often used to prepare single enantiomers of physiologically active 2-aryloxy acid derivatives such as serotonin receptor agonists; adrenergic receptor agonists and antagonists; PPAR modulators; phosphoinositide 3-kinase (PI3K) inhibitors; antiviral, anti-inflammatory, antimicrobial and antiprotozoal agents; and natural products.

The reaction of (*R*)-hydroxy ester **10** (96% *ee*) with 4-*tert*-butylphenol (1.5 equiv.) in the presence of di-*tert*-butyl azodicarboxylate (DBAD) and triphenylphosphine immobilized on a resin gives (*S*)-aryloxy ester **11** (Scheme 7).[48] The overall yield of the product reaches 50%.

Scheme 7

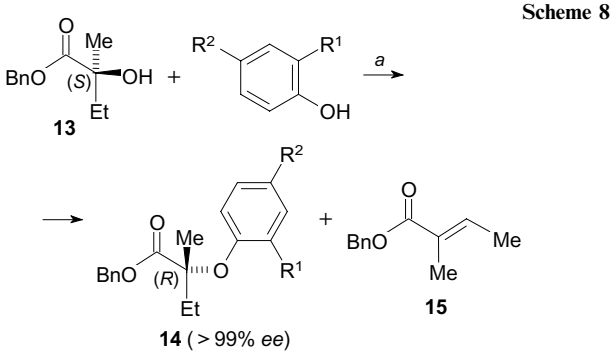


(*a*) DBAD (1.5 equiv.), PPh_3 (2.1 equiv.), THF

Ester **11** served as the starting compound for the preparation of (*S*)-2-aryloxy acid **12**, a selective PPARγ agonist, with 93% *ee* (the total yield was 50% according to HPLC).

The Mitsunobu reaction between benzyl ester (*S*)-**13** and substituted phenols (1.1 equiv.) resulted in the formation of enantiomerically pure (*R*)-aryloxy esters **14** in 51% – 58% yields (Scheme 8).[49] In all cases, the reaction was accompanied by the formation of benzyl tiglate (**15**). For *p*-benzyloxy-substituted aryloxy ester **14a** (R^1 = H, R^2 = OBn) as an example, the absence of racemization during the Mitsunobu reaction was shown by HPLC analysis [(*R*)-ester *ee* > 99%].

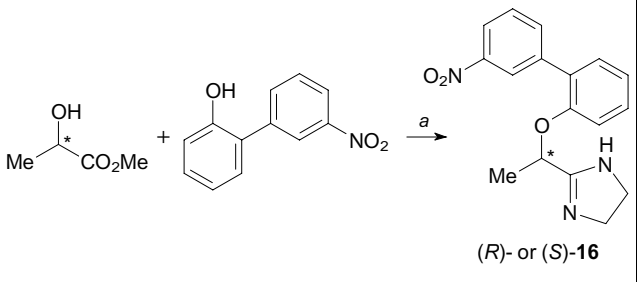
Scheme 8



(*a*) DIAD (1.2 equiv.), PPh_3 (1.2 equiv.), PhMe, 100 °C, 2 – 5 h; R^1 = H, Me, OMe: R^2 = H, CN, NO_2, OBn, Me

The reaction of methyl (*R*)- and (*S*)-lactates with 2-(3-nitrophenyl)phenol in the presence of DEAD and PPh_3 afforded 2-aryloxy ester, which was allowed to react with ethylenediamine in the presence of trimethylaluminium to give imidazoline derivative **16**, an α_2-adrenergic receptor agonist, as the (*S*)- or (*R*)-enantiomers in up to 54% yield (Scheme 9).[50] The optical purity of the products was > 98% according to HPLC and ^{1}H NMR spectroscopy.

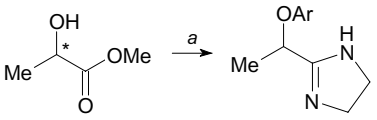
Scheme 9



(*a*) 1) DEAD, PPh_3, THF; 2) $H_2N(CH_2)_2NH_2$, Me_3Al, PhMe

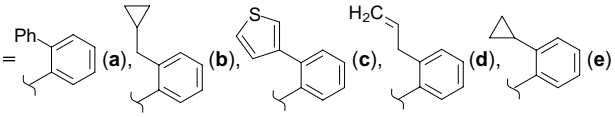
The synthesis of related compounds **17a – e** under similar conditions was accompanied by the loss of enantiomeric purity (Scheme 10). These compounds could be obtained in an enantiopure form by fractional crystallization of their dibenzoyl L- and D-tartrate salts.[51] The (*R*)- and (*S*)-enantiomers of biphenyline **17a** (96% and 89% *ee*, respectively)[52] and cyclomethyline **17b** (~ 85% *ee*)[53] were synthesized by the Mitsunobu reaction in a total yield of up to

Scheme 10



17a – e

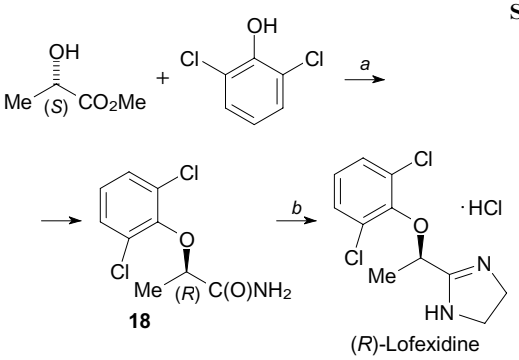
(*a*) 1) ArOH, DEAD or DIAD, PPh_3, THF; 2) $H_2N(CH_2)_2NH_2$, Me_3Al, PhMe;

Ar = 

40%. The single isomers of biphenyline **17a** were obtained by fractional crystallization of (+)- and (−)-di-*O*,*O*′-(*p*-toluoyl)tartrate salts.

Vartak and Crooks[54] proposed a synthetic route towards (*R*)-lofexidine, an α_2-adrenergic receptor agonist (Scheme 11). The initial displacement of the hydroxy group in methyl (*S*)-lactate by 2,6-dichlorophenol *via* the Mitsunobu reaction resulted in the formation of 2-aryloxy ester, which was converted to amide **18**; on treatment with trimethyloxonium tetrafluoroborate and ethylenediamine, the latter was converted to the target product. The overall yield of (*R*)-lofexidine was 80% (~ 100% *ee* according to polarimetric data).

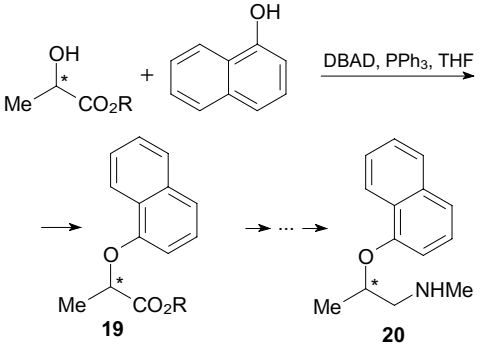
Scheme 11



(*a*) 1) DEAD, PPh_3, THF; 2) NH_3, EtOH; (*b*) 1) Me_3OBF_4, CH_2Cl_2, Et_2O; 2) $H_2N(CH_2)_2NH_2$, Me_3Al, EtOH; 3) HCl (conc.), EtOH, Et_2O

The individual (*R*)- and (*S*)-enantiomers of alkyl 2-(1-naphthyloxy)propionates **19**, precursors of serotonin receptor agonists **20**, were synthesized from 2-hydroxy esters in the presence of DBAD and PPh_3 in up to 95% yields (Scheme 12).[55] The optical purity of the target (*S*)- and (*R*)-amines **20** was 97% and 92%, respectively.

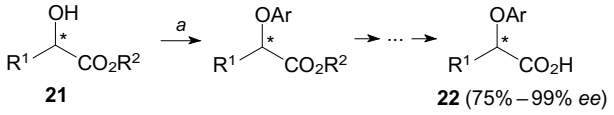
Scheme 12



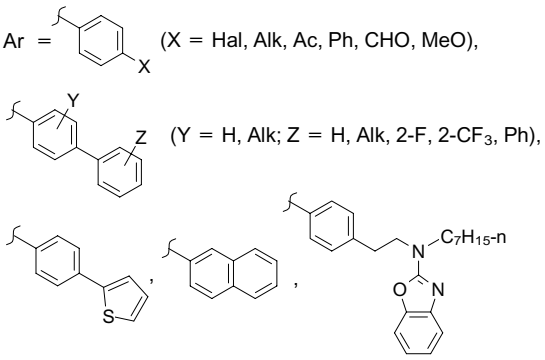
R = Me (*S*), Et (*R*)

The Mitsunobu reaction of enantiopure hydroxy esters **21** with substituted phenols resulted in the formation of enantiomerically enriched 2-aryloxy esters in 40% – 92% yields; the products were used to synthesize a broad range of PPAR agonists **22** (Scheme 13).[56 – 58]

Scheme 13

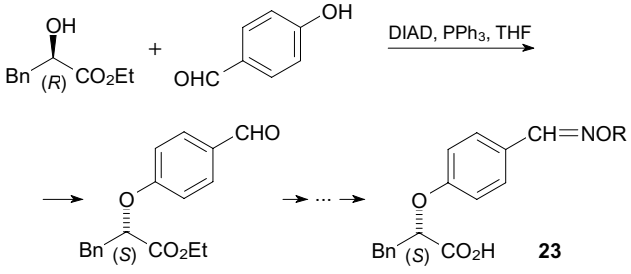


(*a*) ArOH, DEAD or DIAD, PPh_3, THF or PhMe; R^1 = Me, Pr^n, Bn; R^2 = Me, Et;

Ar = 

The same method was used to prepare a series of compounds **23** possessing the properties of PPAR agonists (Scheme 14).[59] The optical purity of the intermediate (*S*)-2-aryloxy ester **24** determined by chiral HPLC was 96%.

Scheme 14

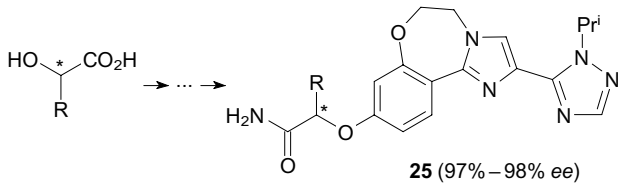


R = H, Pr^n

The appropriate enantiopure 2-hydroxy acids were employed for the synthesis of amides **25**, phosphoinositide 3-kinase α-isoform inhibitors using the Mitsunobu reaction (Scheme 15).[60] The enantiomeric purity of the resulting amides was > 97% according to supercritical fluid chromatography (Chiralpak AS column); the overall yield of compounds **25** reached 85%.

Optical isomers of 2-aryloxy acids are also formed upon nucleophilic substitution in commercially available optically pure 2-halocarboxylic acids on treatment with phenols or phenoxide ions displacing the halogen atom. A considerable obstacle hampering the use of this synthetic approach is racemization during the reaction. Aikins *et al.*[61] reported nucleophilic substitution of the chlorine atom in (*S*)-2-

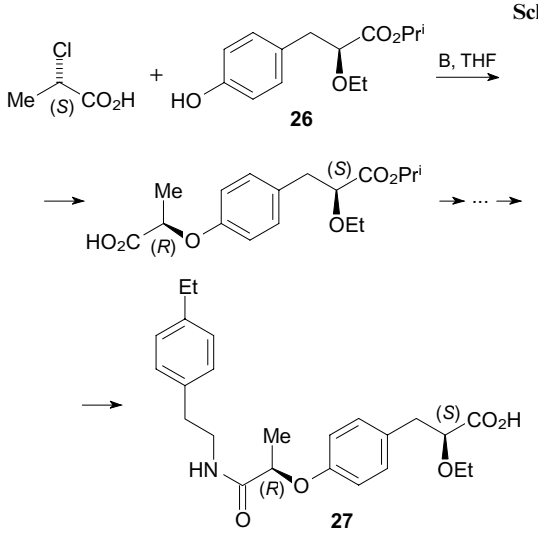
Scheme 15



R = Me, Et

chloropropionic acid on treatment with (*S*)-ester **26** (Scheme 16). The authors studied the effects of the leaving group, the base and reaction conditions on the yield and isomeric purity of the target (*R*,*S*)-2-aryloxy acid **27**. The best results were achieved using NaH as a base in refluxing THF or using Na in THF at 50 °C [diastereomeric excess (*de*) of product (*R*,*S*)-**27** was 97%]. Other conditions resulted in a noticeable epimerization or a low yield of the product. Crystallization of the (*R*)-1-naphthylethylamine salt of (*R*,*S*)-acid **27** (97% *de*) increased *de* to 100%. Houpis *et al.*[62] used sodium trimethylsilyl oxide (TMSONa) as a base in the nucleophilic substitution reaction. The reaction was accompanied by complete inversion of configuration of the chiral centre in the acid moiety; the yield of product (*R*,*S*)-**27** (*de* > 99%) was 87%. Acid **27** is a key intermediate in the synthesis of PPAR agonist.

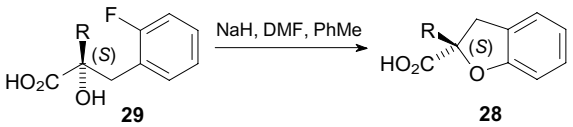
Scheme 16



B is base

A method for the synthesis of enantiopure 2-alkyl-substituted benzofuran-2-carboxylic acids **28** is based on intramolecular nucleophilic substitution reaction of (*S*)-fluoroarenes **29** with fluorine being displaced by a hydroxy group (Scheme 17).[63] The cyclization does not affect the chiral centre of 2-hydroxy acid. The resulting 2,3-dihydrobenzofuran-2-carboxylic acids are precursors for the synthesis of promising PPAR agonists.

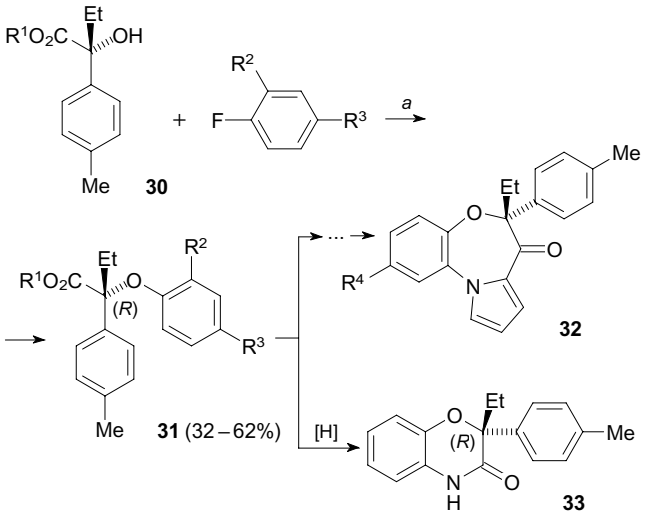
Scheme 17



R = Et, Pri

Nucleophilic substitution of fluorine was used to prepare intermediates for the synthesis of a number of chiral heterocycles (Scheme 18).[64] Esters **30** react with fluoronitrobenzenes in the presence of sodium hydride and 15-crown-5 to afford (*R*)-2-aryloxy esters **31**, which were converted to benzoxazepine **32** and benzoxazine **33** derivatives.

Scheme 18



(*a*) NaH, 15-crown-5, THF; R^1 = Me, (–)-menthyl; R^2 = NO_2, pyrrol-1-yl; R^3 = H, NO_2; R^4 = H, Br, I

3. Synthesis from prochiral precursors

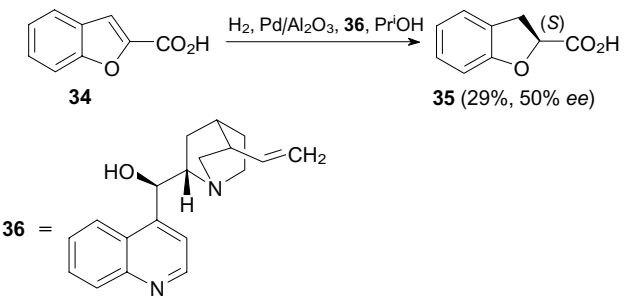
An important modern approach to the preparation of enantiopure compounds is based on reactions accompanied by the formation of an asymmetric centre in a prochiral substrate. The unremitting interest in asymmetric catalysis is caused by wide possibilities for modifying chiral catalysts and relatively low cost of achiral substrates. Currently, there are known catalysts and reagents for obtaining chiral compounds in enantiopure form in high yields.[65 – 67] The drawbacks of this approach are related to the facts that chiral catalysts usually have a sophisticated structure and are difficult to synthesize; furthermore, it is not always possible to regenerate and reuse the catalysts. Product purification from the catalyst may also be labour-consuming, especially for metal complex catalysts.

Over the past 15 years, a considerable progress has been achieved in the asymmetric synthesis of substituted carboxylic acids, including 2-hydroxy acids and related compounds.[68 – 70] Enantioselective hydrogenation of α,β-unsaturated acids in the presence of transition metal-based chiral catalysts has been studied most extensively. The studied reactions include regio- and stereoselective hydroformylation of aryloxy alkenes and insertion of carbenoids into the O – H bond of phenols.

In 2003, alumina-supported palladium was proposed as a catalyst for asymmetric reduction of benzofuran-2-carboxylic acid (**34**) to give product **35** (Scheme 19).[71]

Chirality was induced by cinchonidine (**36**). The influence of the reaction conditions on the yield and enantiomeric purity of dihydro derivative (*S*)-**35** was studied. The

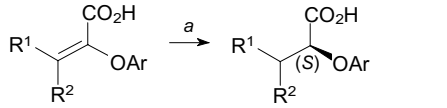
Scheme 19



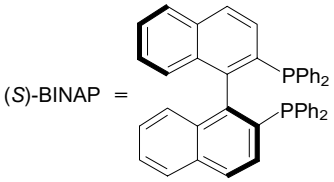
best results (29% yield, 50% *ee*) were obtained when the reaction was carried out in isopropyl alcohol for 23 h at a substrate **34** to catalyst ratio of 22 : 1.

The catalytic complex based on ruthenium(II) chloride and commercially available diphosphine, (*S*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl [(*S*)-BINAP], was used for enantioselective hydrogenation of α,β-unsaturated aryloxy acids (*Z*)-**37** (R^1 = H) and (*Z*)-**38** (R^1 = Me) (Scheme 20).[72] The hydrogen reduction of these alkenes catalyzed by [(*S*)-BINAP]$RuCl_2$ gave rise to (*S*)-2-aryloxy acids **39** (R^1 = H) and **40** (R^1 = Me) (13 examples) in 65% – 99% yields and with 61% – 95% *ee* (chiral HPLC data). Hydrogenation of *p*-methoxyphenoxy-substituted 2,3-dimethylcrotonic acid **38a** ($R^1 = R^2$ = Me) was markedly less stereoselective (32% *ee*).

Scheme 20



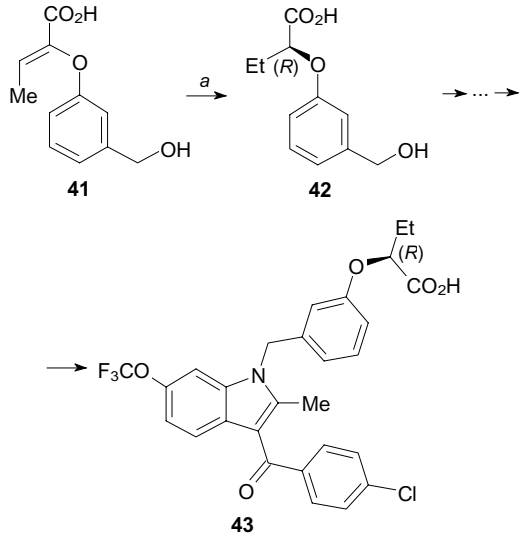
(*a*) H_2, [(*S*)-BINAP]$RuCl_2$ (20 mol.%), Et_3N, MeOH; R^1 = H (**37**, **39**), Me (**38**, **40**); R^2 = Me, n-C_5H_{11}; Ar = Ph, 2-MeC_6H_4, 4-MeC_6H_4, 2-$MeOC_6H_4$, 4-$MeOC_6H_4$, 2-FC_6H_4, 4-FC_6H_4, 2-ClC_6H_4, 3-BrC_6H_4, 2-IC_6H_4, 3-IC_6H_4, 4-$O_2NC_6H_4$;



Hydrogenation of α,β-unsaturated acid **41** catalyzed by 0.5 mol.% [(*R*)-BINAP]$RuCl_2$ affords compound (*R*)-**42** in up to 99% yield and with up to 94% *ee* (Scheme 21).[73] Temperature rise and increasing pressure have an adverse effect on the enantiomeric excess of the target product. Decreasing amount of the catalyst does not affect the optical purity of the product, but increases the reaction time. Enantiomerically pure selective PPARγ modulator **43** was derived from 2-aryloxy acid (*R*)-**42**.

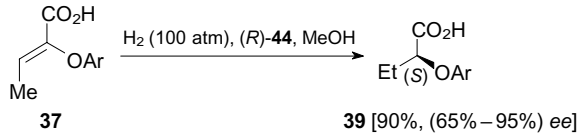
Chiral ruthenium(II) phosphine complex (*R*)-**44** proved to be an efficient catalyst for asymmetric hydrogenation of 2-aryloxycrotonic acids (*Z*)-**37** (Scheme 22).[74] The reduction of the double bond catalyzed by (*R*)-**44** (0.5 mol.%) resulted in the formation of (*S*)-aryloxybutyric acids **39** in

Scheme 21

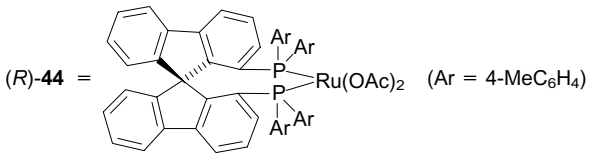


(*a*) H_2, [(*R*)-BINAP]$RuCl_2$, Et_3N, MeOH

Scheme 22



Ar = Ph, 2-MeC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 2-$MeOC_6H_4$, 2-ClC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-$Bu^tC_6H_4$, 3,5-$F_2C_6H_3$, 3,5-$(F_3C)_2C_6H_3$, 2-Naph; Naph is naphthyl;

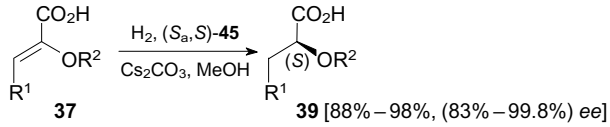


90% – 93% yields [the conversion (*C*) reaches 100%] with an optical purity of 65% – 95% (chiral HPLC data). The enantioselectivity of hydrogenation of 2-phenoxycrotonic acid **37a** (Ar = Ph) is comparable with that obtained earlier using the [(*S*)-BINAP]$RuCl_2$ catalyst.[72] The stereoselectivity of reduction depends on the structure of the aryl moiety of the substrate. Indeed, hydrogenation of 2-*o*-tolyloxycrotonic (**37b**, Ar = 2-MeC_6H_4) and 2-(2-naphthyloxy)crotonic (**37c**, Ar = 2-naphthyl) acids leads to lower *ee* of the products (65% and 80%, respectively). Meanwhile, hydrogenation of *para*- and *meta*-substituted acids is usually more selective.

In the presence of catalyst (S_a,*S*)-**45**, stereoselective hydrogenation of quite a few (*Z*)-2-aryloxycrotonic and (*Z*)-2-aryloxycinnamic acids **37** was carried out (26 examples, Scheme 23).[75]

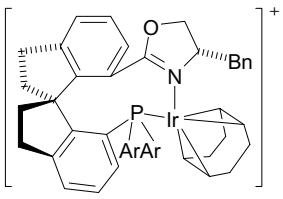
In relation to 2-phenoxycrotonic acid **37a** (R^1 = Me, R^2 = Ph), it was demonstrated that the presence of a base is a necessary condition for the reaction to proceed; the best result was attained with Cs_2CO_3. The reduction leads to (*S*)-2-aryloxy acids **39** in 88% – 98% yield and with 96% – 99.8% *ee* (chiral HPLC). In the case of 2-phenoxyacrylic acid **37d** (R^1 = H, R^2 = Ph), the hydrogenation product has 83% *ee*. An increase in the length of the alkyl substituent at

Scheme 23



R^1 = H, Me, Et, Ph, 2-MeC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 3-$MeOC_6H_4$, 4-$MeOC_6H_4$, 3-$F_3CC_6H_4$, 4-$F_3CC_6H_4$, 1-Naph, 2-Naph, 2-furyl;
R^2 = Ph, 3-MeC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 3-BrC_6H_4, 4-$Bu^tC_6H_4$, 3,5-$F_2C_6H_3$, 2-Naph

(S_a,*S*)-**45** =



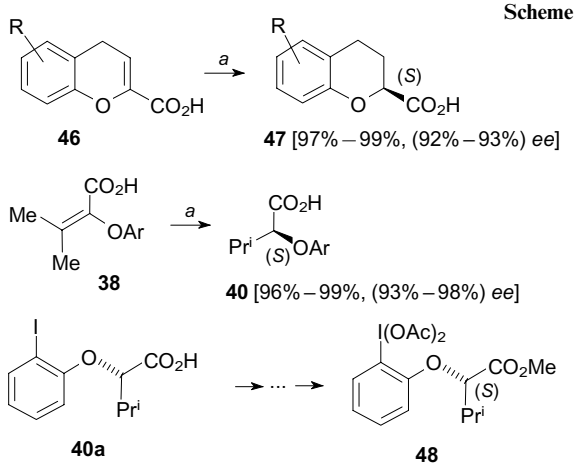
BAr^-_F

(Ar = 3,5-$Bu^t_2C_6H_3$, A_F = C_6F_5)

the β-position of crotonic acid decreases the reactivity of the substrate. Indeed, hydrogenation of 3-ethyl-2-phenoxyacrylic acid **37e** (R^1 = Et, R^2 = Ph) gives only traces of the target product.

Catalyst (S_a,*S*)-**45** was utilized for the enantioselective reduction of benzopyran-2-carboxylic acids (**46**)[76] and 2-aryloxy-3-methylcrotonic acids (**38**)[77] (Scheme 24).

Scheme 24



(*a*) H_2, (S_a,*S*)-**45**, B, MeOH; R = H, 6-Me, 7-OMe, 6-F; Ar = Ph, 2-MeC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 2-IC_6H_4, 2-Naph

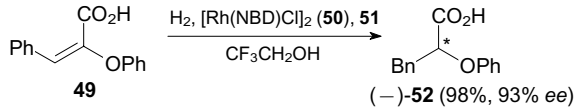
(*S*)-2-Aryloxy carboxylic acids **40** and **47** were obtained in 96% – 99% yield and with 92% – 98% optical purity. 2-Iodophenoxy derivative of isovaleric acid **40a** (Ar = 2-IC_6H_4) with 95% *ee* served as the starting compound in the synthesis of stereoselective oxidant **48**.

Hydrogenation of 2-phenoxy-*cis*-cinnamic acid **49** in the presence of rhodium complex **50** and ferrocene-based chiral catalyst ChenPhos (**51**) was used to prepare (−)-2-aryloxy acid **52** (93% *ee*) in 98% yield (Scheme 25).[78]

Solinas *et al.*[79] investigated the regio- and stereoselective hydroformylation of aryl vinyl ethers **53** catalyzed by chiral Rh^I complexes (Scheme 26).

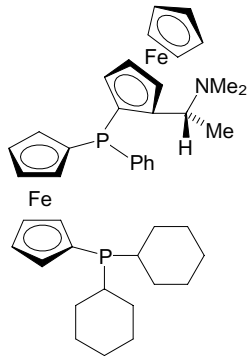
The reaction of the ethers with carbon monoxide and hydrogen produced 2-aryloxypropanals **54** (5 examples). It was demonstrated that the chiral complex based on rhodium and (*R*,*S*)-BINAPHOS ligand (**55**) is the most efficient

Scheme 25

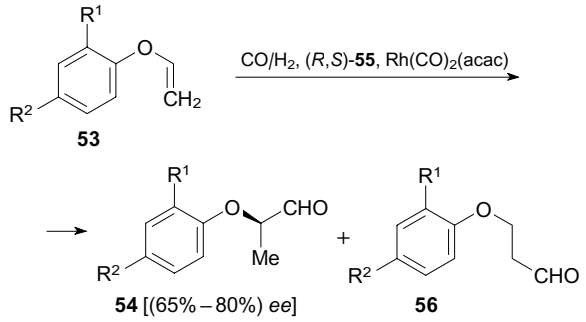


NBD is norborna-2,5-diene;

51 =

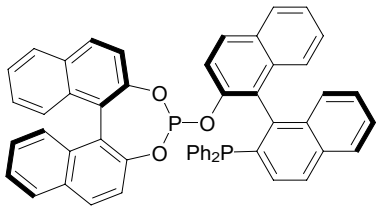


Scheme 26



R^1 = H, Me, Cl; R^2 = H, Cl, OPh;

55 =

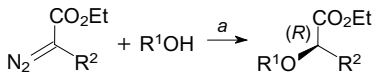


catalyst for this reaction. The hydroformylation afforded a mixture of 2- and 3-substituted propanals **54** and **56** with a conversion of 35% – 56% (the yield is not indicated in the original publication). The content of the target 2-substituted aldehydes **54** in the reaction products was 63% – 71%, while *ee* varied from 65% to 80% (according to GLC on a chiral stationary phase).

Enantioselective insertion of carbenoids into the O – H bonds of a broad range of phenols was reported.[80] The reaction of phenols with 2-diazo esters **57a**,**b** in the presence of ligand (S_a,*S*,*S*)-**58**, copper(I) salt, sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBARF) and molecular sieves (MS) furnished 2-aryloxy esters **1** and **59** (19 examples) in 62% – 88% yields and with ⩾ 95% *ee* according to chiral HPLC (Scheme 27).

This reaction was shown to afford predominantly *R*-enantiomers of 2-aryloxy esters. The nature of the substituent in position 2 of diazo ester **57** has a strong influence on the enantioselectivity of the carbenoid insertion. Indeed, the reaction of unsubstituted phenol with ethyl 2-diazo-2-

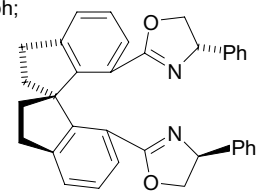
Scheme 27



57a,**b** **1**, **59** [68% – 87%, (10.0% – 99.6%) *ee*]

(*a*) – CuCl, (S_a,*S*,*S*)-**58**, NaBARF, MS, CH_2Cl_2; R^2 = Me (**57a**, **1**), Ph (**57b**, **59**); R^1 = Ph, 3-BrC_6H_4, 4-BrC_6H_4, 4-ClC_6H_4, 2-MeC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 4-$Bu^tC_6H_4$, 3-$MeOC_6H_4$, 4-$MeOC_6H_4$, 2-PhC_6H_4, 3-PhC_6H_4, 3-$MeO_2CC_6H_4$, 2,4-$Me_2C_6H_3$, 3,5-$Me_2C_6H_3$, 1-Naph, 2-Naph;

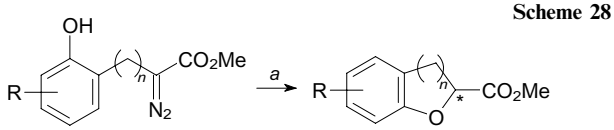
(S_a,*S*,*S*)-**58** =



phenylacetate **57b** (R^2 = Ph) was less stereoselective (10% *ee*) than the reactions of the other compounds, while benzyl 2-diazobutyrate underwent only β-elimination under these conditions. Meanwhile, the nature of substituents in the phenol molecule has a slight effect on the stereochemical outcome.

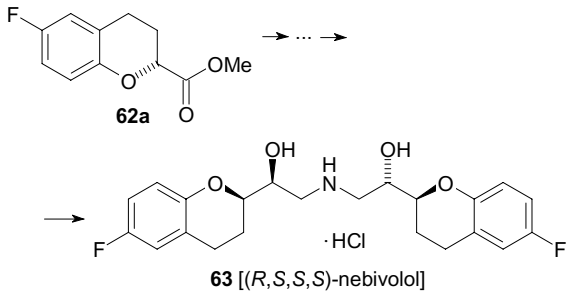
Spirobis(indanes) (S_a,*S*,*S*)-**58** and (S_a)-**60** were employed as catalysts of the intramolecular version of the carbenoid insertion into the O – H bond of phenols (Scheme 28).[81]

Scheme 28



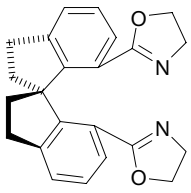
61 **62** [86% – 99%, (94% – 98%) *ee*]

(*a*) $[Cu(MeCN)_4]PF_6$, (S_a,*S*,*S*)-**58** or (S_a)-**60**, NaBARF, CH_2Cl_2; *n* = 1 – 3; R = H, F, Br, Me, OMe



63 [(*R*,*S*,*S*,*S*)-nebivolol]

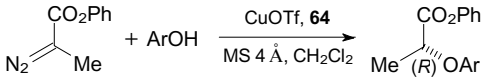
(S_a)-**60** =



Diazo esters **61** were converted to a number of cyclic 2-aryloxy esters **62** in 86% – 99% yields and with 94% – 99% *ee*. It was shown that the reaction mainly gives *R*-enantiomers. Enantiomerically pure fluorinated ester **62a** (*n* = 2, R = 6-F, 96% *ee*) was used to obtain (*R*,*S*,*S*,*S*)-nebivolol (**63**), a β-adrenergic blocker.

Osako *et al.*[82] studied the stereoselective carbenoid insertion into the O – H bond of several phenols in the presence of a copper(I) complex, chiral hydrogenated imidazoindolephosphine **64** and 4 Å molecular sieves (Scheme 29). The reaction of phenols with phenyl 2-diazopropionate **57c** gave (*R*)-2-aryloxy acids **65** in 15% – 67% yield and with 24% – 91% *ee* (chiral HPLC). The highest enantioselectivity (91% *ee*) was attained with *o*-cresol being used as the substrate. Phenyl 2-diazopropionate reacted with *p*-chloro- and *p*-trifluoromethyl-substituted phenols to give products in lower yields and with lower stereoselectivity (64% and 24% *ee*, respectively).

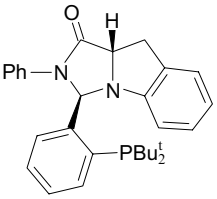
Scheme 29



57c **65** [15% – 67%, (24% – 91%) *ee*]

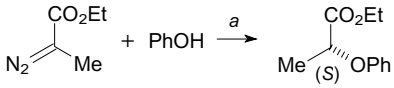
Ar = Ph, 4-ClC_6H_4, 2-MeC_6H_4, 4-MeC_6H_4, 4-$Bu^tC_6H_4$, 2-$MeOC_6H_4$, 3-$MeOC_6H_4$, 4-$MeOC_6H_4$, 2-PhC_6H_4, 4-$PhOC_6H_4$, 4-$F_3CC_6H_4$, 1-Naph, 2-Naph;

64 =



Planar chiral paracyclophane derivatives (S_P)-**66** were tested as catalysts of the enantioselective insertion of ethyl 2-diazopropionate into the phenol O – H bond in the presence of a copper(I) salt, NaBARF and 5 Å molecular sieves.[83] The highest *ee* (80%) for ethyl (*S*)-2-phenoxypropionate (**1a**) was attained when isopropyl-substituted paracyclophane **66** (R = Pr^i) was used (Scheme 30).

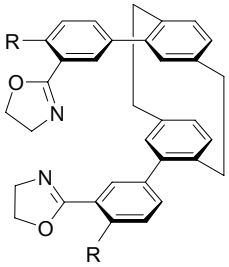
Scheme 30



57a **1a** (65% – 73%, up to 80% *ee*)

(*a*) CuCl, **66**, NaBARF, MS 5 Å, CH_2Cl_2

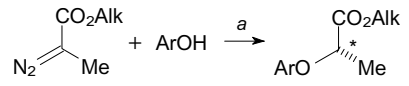
66 =



(R = Ph, 3,5-$Me_2C_6H_3$, Pr^i)

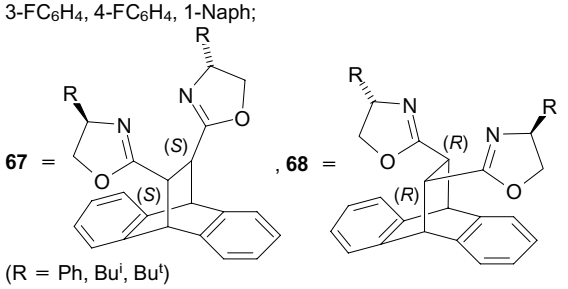
Le Maux *et al.*[84] reported a similar enantioselective insertion of carbenoids into phenols of various structures in which chiral induction was accomplished by copper(I) and copper(II) complexes with bicyclo bisoxazolines **67** and **68** (Scheme 31). The authors investigated the effects of copper salt (nature of the anion and valence of the metal),

Scheme 31



57a,**d** **1** [< 82%, (78% – 94%) *ee*]

(*a*) $Cu(OTf)_2$, **67** or **68**, NaBARF, MS, CH_2Cl_2; **57**: Alk = Et (**a**), Bu^t (**d**); Ar = Ph, 2-MeC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 2-FC_6H_4, 3-FC_6H_4, 4-FC_6H_4, 1-Naph;

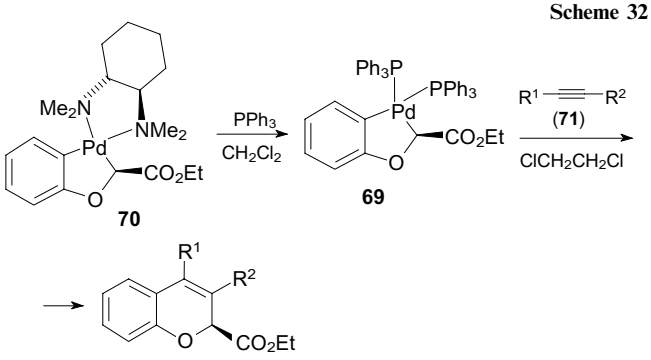


(R = Ph, Bu^i, Bu^t)

the catalyst structure and the addition of NaBARF and molecular sieves on the stereochemical outcome and the product yield for the reaction of phenols with ethyl and *tert*-butyl 2-diazopropionates **57a**,**d**. The highest *ee* values of 2-aryloxy esters **1** (up to 94%) were attained using $Cu(OTf)_2$ as the source of copper in the presence of NaBARF and molecular sieves.

The approach based on the reaction of palladium-containing heterocycles **69**, obtained from complexes **70**, and activated alkynes **71** was used to prepare enantiomerically enriched 3,4-disubstituted benzopyran-2-carboxylates **72** (4 examples, Scheme 32).[85] Ligand exchange in the diastereomerically enriched (64% *de*) oxapalladacycle **70** under the action of triphenylphosphine gave compound **69** in 91% yield. The reaction of this product with alkynes **71** resulted in pyran ring formation, with *ee* of the products being 32% – 56% (chiral HPLC).

Scheme 32

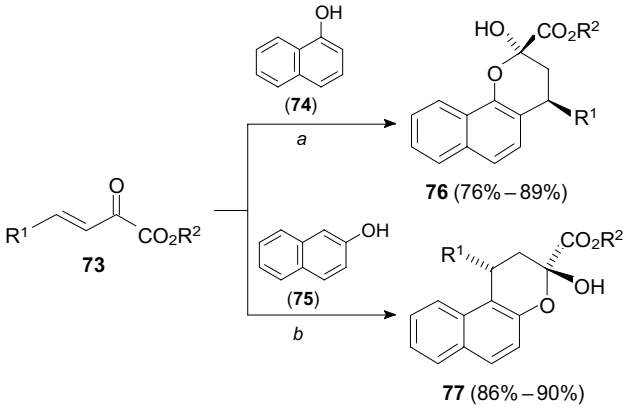


72 [52% – 72%, (32% – 56%) *ee*]

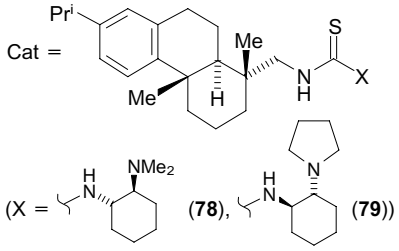
R^1 = Me, Bu^n, Ph; R^2 = CO_2Me, CO_2Et

The enantioselective Friedel – Crafts alkylation reaction between β,γ-unsaturated α-keto esters **73** and 1-naphthol (**74**) or 2-naphthol (**75**) furnished 2-hydroxy-substituted 2-aryloxy esters **76** and **77** (17 examples, Scheme 33).[86] The best results of stereoselective alkylation were achieved using catalysts **78** and **79**. The alkylation catalyzed by (1*S*,2*S*)-**78** and (1*R*,2*R*)-**79** afforded (2*S*,4*R*)- and (2*R*,4*S*)-2-aryloxy esters, respectively. The assignment of configuration of the reaction products was based on X-ray diffraction data. The optical purity of chromanes **76** and **77** was

Scheme 33



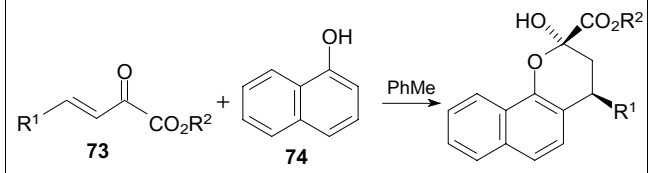
(*a*) **78** or **79**, Et_2O; (*b*) **79**, Et_2O;
R^1 = Ph, 3-MeC_6H_4, 2-FC_6H_4, 4-FC_6H_4, 2-ClC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 2-F-5-BrC_6H_3, 2-Br-5-FC_6H_3, 2-Naph, 2-furyl, 2-thienyl;
R^2 = Me, Et, Bn;



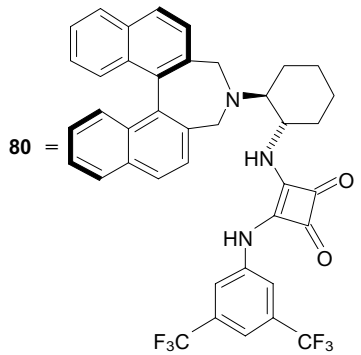
79% – 96%, and the diastereomeric ratio (*dr*) of the products varied from > 20 : 1 to 3 : 1.

Asymmetric alkylation of 1-naphthol (**74**) with α-keto esters **73** in the presence of 2.5 mol.% catalyst **80** gave chromanes **76** (86% – 97% *ee*) in 62% – 95% yield (Scheme 34).[87]

Scheme 34



R^1 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 2-FC_6H_4, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 2-F-5-BrC_6H_3, 2-Br-5-FC_6H_3, 2-Naph, 2-furyl, 2-thienyl; R^2 = Me, Et;



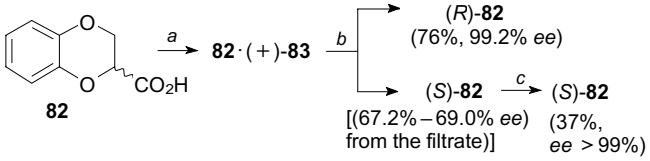
4. Preparation of 2-aryloxy carboxylic acid enantiomers by resolution of racemates

4.1. Classical methods for resolution of racemic 2-aryloxy carboxylic acids

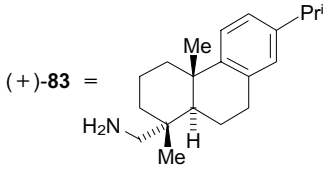
One of the methods for preparation of enantiomerically pure 2-aryloxy carboxylic acids is resolution of racemic mixtures. According to this approach, first of all, it is necessary to prepare diastereomeric salts, amides or esters of racemic 2-hydroxy acids with appropriate chiral reagents [*e.g.*, α-phenylethylamine (PEA, **81**)]. Then the diastereomers are separated by non-stereospecific techniques (fractional crystallization, chromatography). Lately, these methods have found limited use due to low productivity (repeated crystallizations and large amounts of solvents are required) and the risk of optical purity loss during recovery of the target compounds from diastereomers.

The enantiomers of 1,4-benzodioxane-2-carboxylic acid (**82**) were isolated using (+)-dehydroabietylamine (**83**) as a chiral resolving agent (Scheme 35).[88] Amine **83** was already applied for this purpose; however, the yield of the *R*-isomer of the acid did not exceed 2%.[89] The resolution of racemic 2-aryloxy acid **82** is based on different solubilities of the salts formed by the *S*- and *R*-enantiomers with (+)-dehydroabietylamine in methanol under prolonged reflux. As a result, the *R*-enantiomer of acid **82**, the salt of which is less soluble, was isolated in 76% yield and with 99.2% *ee*. Acid (*S*)-**82** (*ee* > 99%) was obtained in an overall yield of 37% after isolation of the salt remaining in the filtrate and recrystallization from toluene.

Scheme 35

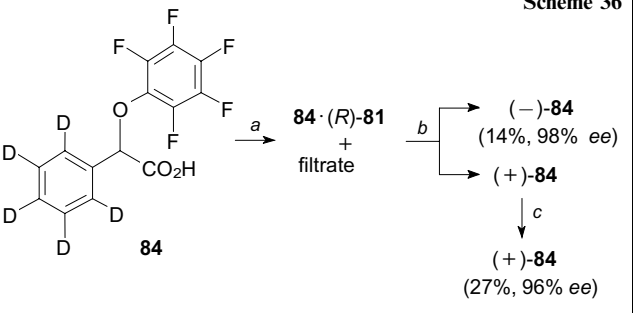


(*a*) (+)-**83** · AcOH (0.6 equiv.), NaOH, MeOH; (*b*) 1) MeOH, Δ; 2) NaOH; 3) H^+; *c* is crystallization from toluene



Pentafluorophenyl derivatives of deuterated mandelic acid **84** are of interest as chiral solvating agents for ^{1}H NMR spectroscopy. A method proposed for preparing (+)- and (−)-enantiomers of this compound is based on formation of salts with (*R*)- and (*S*)-1-phenylethylamine (**81**) (Scheme 36).[90] After two recrystallizations and treatment of salt **84** · (*R*)-**81** with 2 M HCl, 2-aryloxy acid (−)-**84** was isolated with an optical purity of 98% and in 14% yield. The reaction of enantiomerically enriched (+)-acid isolated from the mother liquor with (*S*)-**81** resulted in the formation of salt **84** · (*S*)-**81**; the (+)-acid was recovered from the salt with 96% optical purity and in 27% yield. Acid (−)-**84** was employed as a chiral solvating agent for determining *ee* values of a number of antimalarial drugs by ^{1}H NMR spectroscopy.

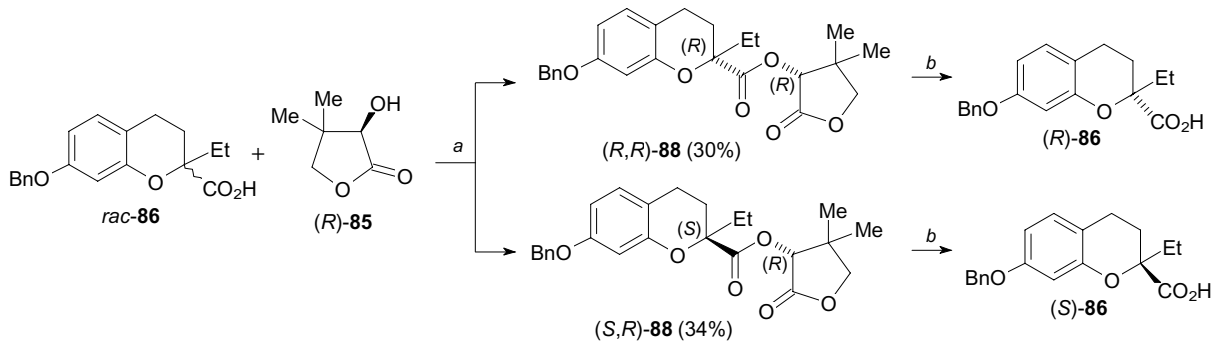
Scheme 36



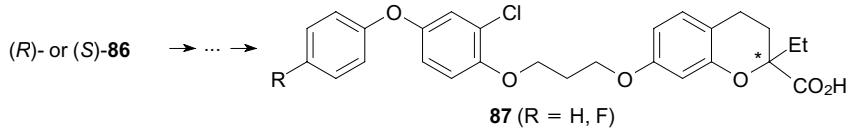
(*a*) (*R*)-**81**, crystallization from EtOH; (*b*) 2 M HCl, EtOAc; (*c*) 1) (*S*)-**81**, EtOH; 2) crystallization from EtOH; 3) 2 M HCl, EtOAc

(*R*)-Pantolactone (**85**) was utilized for the resolution of benzofuran-2-carboxylic acid derivative *rac*-**86**, an intermediate on the synthesis of PPAR agonists **87** (Scheme 37).[91] Esterification of acid *rac*-**86** with enantiopure alcohol (*R*)-**85** in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) gave a diastereomeric mixture of esters (*R*,*R*)- and (*S*,*R*)-**88**. Chromatographic

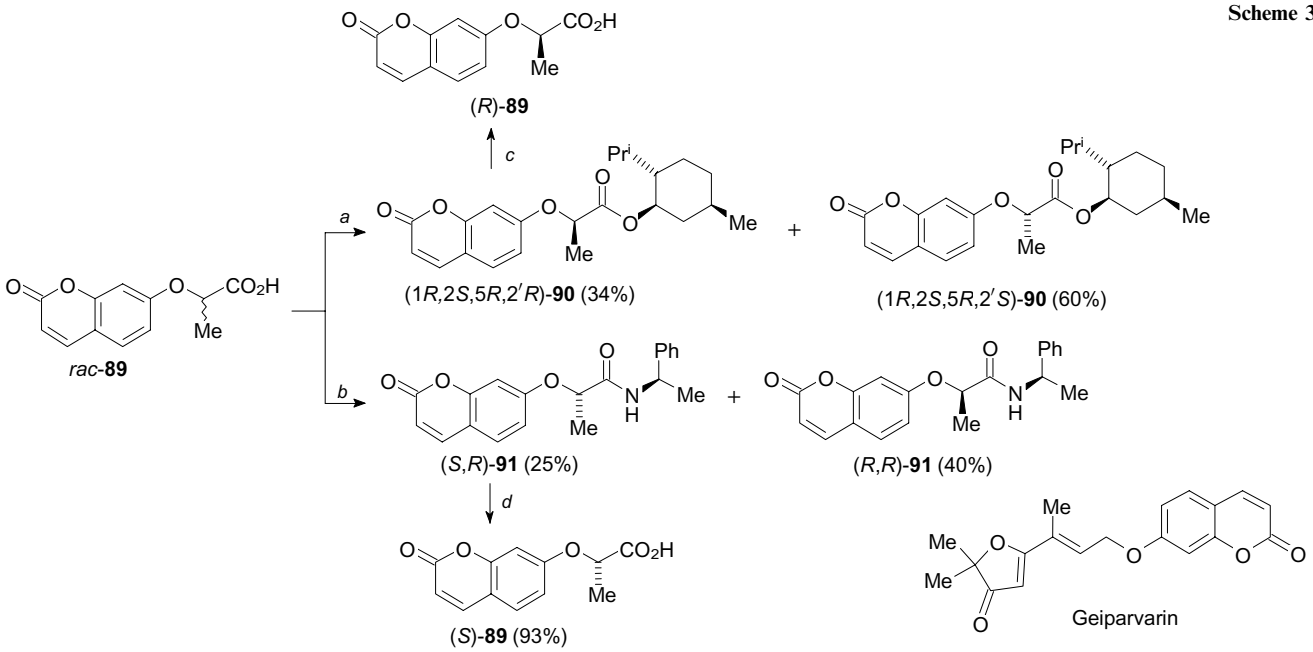
Scheme 37



(*a*) EDCI, CH_2Cl_2; (*b*) NaOH, Pr^iOH



Scheme 38



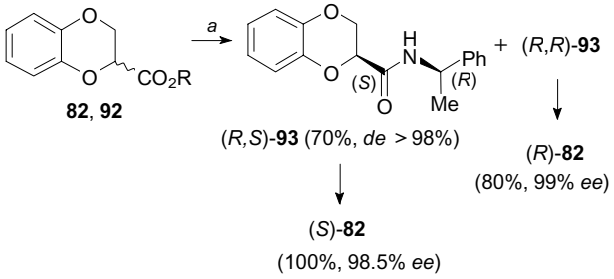
(*a*) 1) $SOCl_2$, $CHCl_3$, Δ; 2) L-menthol, Et_3N, $CHCl_3$, Δ; (*b*) 1) $SOCl_2$, $CHCl_3$, Δ; 2) (*R*)-**81**, $CHCl_3$, Δ; (*c*) NaOH, MeCN, H_2O, rt, 5 days; (*d*) 6 M HCl, Δ

separation of these esters followed by alkaline hydrolysis of single diastereomers afforded *R*- and *S*-enantiomers of 2-aryloxy acid **86**. The configuration assignment for the esters and the acids was based on X-ray diffraction study of (*S*,*R*)-ester **88**.

Racemic 2-aryloxy acid **89** was resolved by coupling with optically pure L-menthol and (*R*)-1-phenylethylamine [(*R*)-**81**] followed by fractional crystallization and hydrolysis of the pure diastereomers (Scheme 38).[92] Recrystallization of ester **90** from ethanol produced the individual diastereomer with *S*-configuration of the chiral centre in the acid moiety (X-ray diffraction data) in an overall yield of 60%. The menthyl ester of *R*-isomeric acid was isolated from the filtrate in 34% yield. Alkaline hydrolysis of diastereomers of esters **90** proceeded in 74% yield, with the optical purity of the resulting isomers of acid **89** being > 98%. Amides (*R*,*R*)- and (*S*,*R*)-**91** were isolated in 40% and 25% yields, respectively, by fractional crystallization. The acid hydrolysis of the *S*,*R*-diastereomer gave product (*S*)-**89** in 93% yield. Compounds (*R*)- and (*S*)-**89** are intermediates in the synthesis of analogues of geiparvarin — a natural coumarin derivative.

Fumagalli *et al.*[93] reported the use of (*R*)-phenylethylamine [(*R*)-**81**] as a chiral reagent for the resolution of enantiomers of 1,4-benzodioxane-2-carboxylic acid (**82**) (Scheme 39). The reaction of methyl ester **92** (R = Me) with an excess of this amine in THF in the presence of magnesium chloride gave a mixture of diastereomeric (*R*,*S*)- and (*R*,*R*)-amides **93**. Crystallization of the equimolar mixture of (*R*,*S*)- and (*R*,*R*)-amides from toluene gave amide (*R*,*S*)-**93** in 70% yield (*de* > 98% according to reversed-phase HPLC); both diastereomers of compound **93** were recovered from the filtrate by column chromatography (*de* > 99%). The overall yield of *R*,*S*-amide was 95%, while that of the *R*,*R*-diastereomer was 80%. The acid hydrolysis of amides gave the corresponding enantiomers of acid **82** without racemization.

Scheme 39



(*a*) (*R*)-**81**, $MgCl_2$, THF; R = H (**82**), Me (**92**)

4.2. Methods based on kinetic resolution of racemic 2-aryloxy carboxylic acids

Currently, non-enzymatic methods for the separation of optical isomers are used more and more often in the practice of organic synthesis. Among the most important methods is optical kinetic resolution (KR). Over the past two decades, KR has become a widely used modern method for the preparation of enantiopure compounds.[94,95] Kinetic resolution is based on the difference between the rates of reaction of substrate enantiomers with a chiral resolving agent or with some other compound under the action of a chiral catalyst.[96] The KR efficiency can be increased by using a modification of the method, namely, dynamic kinetic resolution (DKR), which implies *in situ* racemization of the slowly reacting isomer. Provided that the racemization rate is higher than the rate of the product formation and that the reaction selectivity is high, the theoretical yield of the enantiomerically enriched product amounts to 100%.[97–99] One more way to increase the efficiency of KR is parallel kinetic resolution (PKR). In this case, the racemic substrate reacts with a reagent representing an equimolar

mixture of *quasi*-enantiomers, that is, compounds with similar structures but opposite stereo configurations.[100, 101]

The preparation of optical isomers of 2-aryloxyalkanoic acids by means of KR is mainly accomplished using two approaches. One approach is based on nucleophilic displacement of halogen atoms in racemic esters of 2-halo acids by phenols accompanied by DKR. Dynamic kinetic resolution during nucleophilic substitution of halogen in configurationally labile 2-halogenated acids is often used in the synthesis of chiral 2-substituted carboxylic acids.[102]

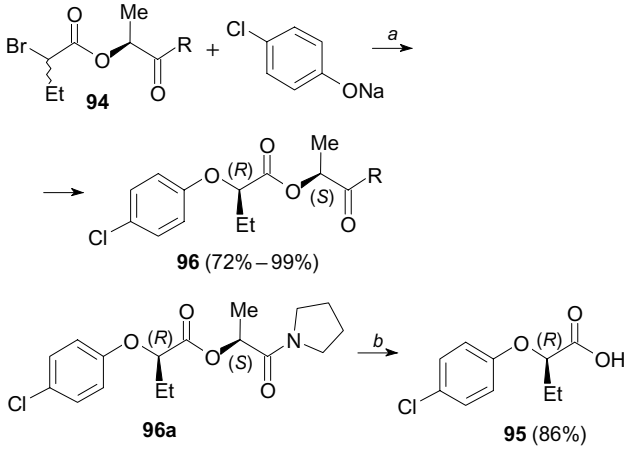
The second approach implies the reaction of activated racemic 2-aryloxy acid derivatives with chiral compounds (alcohols, amines, imides) or achiral compounds in the presence of chiral acyl transfer catalysts.

The dynamic kinetic resolution during nucleophilic substitution of bromine in 2-bromobutyric acid esters **94** was used to prepare (*R*)-2-(*p*-chlorophenoxy)butyric acid (**95**), exhibiting a hypolipidemic activity (Scheme 40).[103] The reaction of diastereomeric α-bromo esters **94** containing N-substituted lactamide moieties with sodium 4-chlorophenoxide under various conditions affords 2-aryloxy acid derivatives **96** with *dr* ranging from 70 : 30 to 98 : 2. Conducting the reaction at 0 °C promotes higher *dr* values of the products compared with the reaction carried out at 60 °C. Alkaline hydrolysis of diastereomerically enriched ester **96a** (96% *de*) yielded enantiopure acid (*R*)-**95** (according to polarimetric data).

An approach was proposed for the preparation of single *R*- and *S*-enantiomers of 2-phenoxypropionic acid (**97a**). It is based on diastereoselective PKR of pentafluorophenyl ester **98** induced by a mixture of *quasi*-enantiomeric oxazolidinones **99** and **100** taken in 1 : 1 ratio in the presence of n-butyllithium (Scheme 41).[104] The PKR furnished a mixture of diastereomeric adducts *syn*-**101** – *anti*-**101** (83 : 17 ratio, 62% yield) and *syn*-**102** – *anti*-**102** (82 : 18, 54% yield). Hydrolysis of compounds *syn*-**101** and *anti*-**101**, isolated in the diastereomerically pure form by flash column chromatography, afforded single *S*- and *R*-enantiomers of the target acid **97a**, respectively.

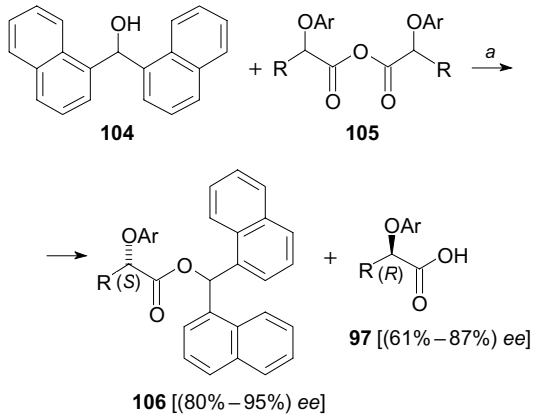
A tetramisole derivative, (*S*)-homobenzotetramisole [HBTM, (*S*)-**103**], was proposed as a chiral acylation catalyst for the KR of racemic 2-substituted carboxylic acids (Scheme 42).[105] Di(1-naphthyl)methanol (**104**) (0.5 equiv.) reacted with symmetrical anhydrides **105** based on racemic 2-aryloxyalkanoic acids in the presence of diisopropylethylamine (DIPEA) as a base. The enantioselective acylation gave predominantly the *S*-enantiomers of esters **106** and the *R*-enantiomers of acids **97**. The highest selectivity (95% *ee*) was attained for dichlorophenoxy-substituted propionic acid **97b** (R = Me, Ar = 2,4-$Cl_2C_6H_3$), with the selectivity factor (*s*) being 74 and the conversion of the corresponding substrate being 39% (the yield is not indicated).[105] The kinetic resolution of unsubstituted 2-phenoxypropionic acid anhydride giving πρωδυψτ **97a** was less efficient (*s* = 42). With increasing size of the alkyl substituent in position 2 of anhydrides **105** (R = Et, Pr^i), the stereoselectivity of acylation also decreased; indeed, for

Scheme 40



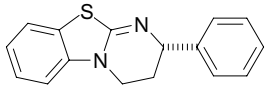
(*a*) Et_3N, (n-$C_6H_{13})_4NI$, THF; (*b*) LiOH, H_2O, THF, 0 °C;
R = NBn_2, NMe_2, cyclo-$N(CH_2)_5$

Scheme 42

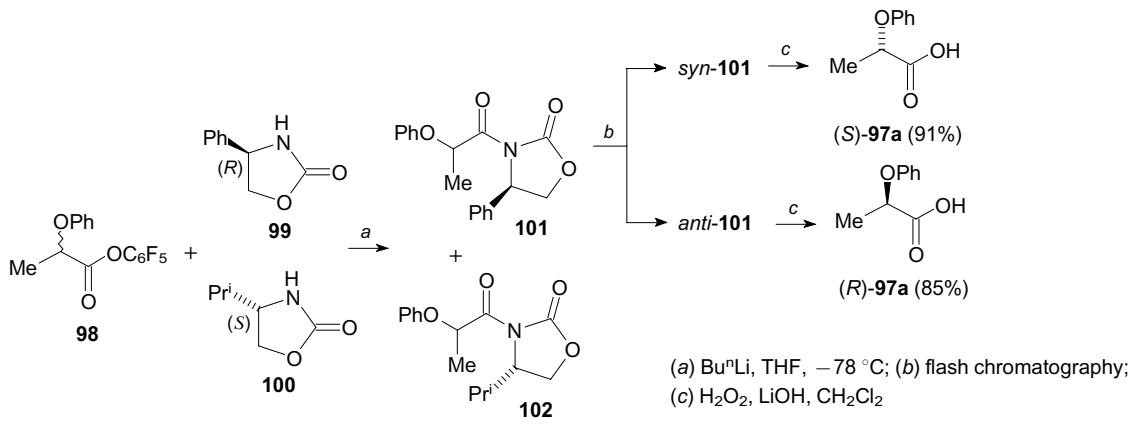


(*a*) (*S*)-**103** (0.05 equiv.), DIPEA (1 equiv.), PhMe, 24 h

(*S*)-**103** =



Scheme 41

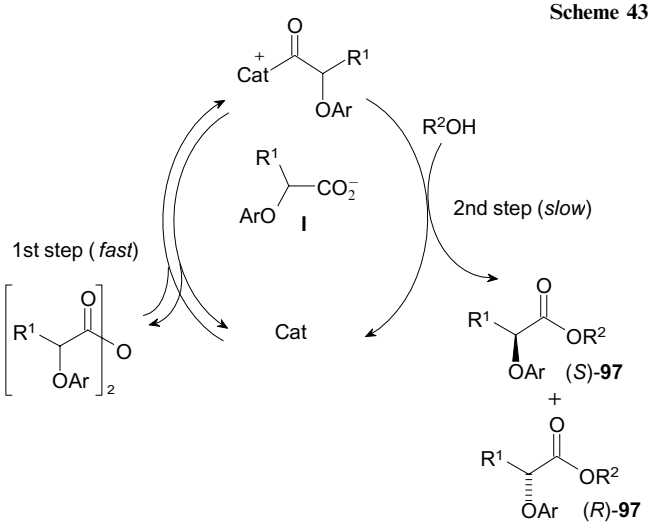


(*a*) Bu^nLi, THF, −78 °C; (*b*) flash chromatography;
(*c*) H_2O_2, LiOH, CH_2Cl_2

R = Et, $s = 26$, while for R = Pr^i, $s = 18$.[106] A minor change in the structure of the acylation catalyst resulted in a considerable decrease in the selectivity factor: $s = 8.3$ when using benzotetramisole (*R*)-**107**.[106]

A two-step catalytic cycle was proposed for the acylation of alcohols with 2-substituted acid anhydrides in the presence of a tetramisole derivative as the catalyst (Scheme 43). In the first (fast) step, symmetrical anhydride reacts with the catalyst (Cat) to give intermediate **I**. In the second (slow) step, this intermediate acylates the alcohol, thus furnishing the product and regenerating the catalyst. In the opinion of the authors, stereoselectivity of the reaction is determined by the second step of the catalytic cycle, because the stereochemical outcome is substantially affected by the nature of alcohol used.[105, 107]

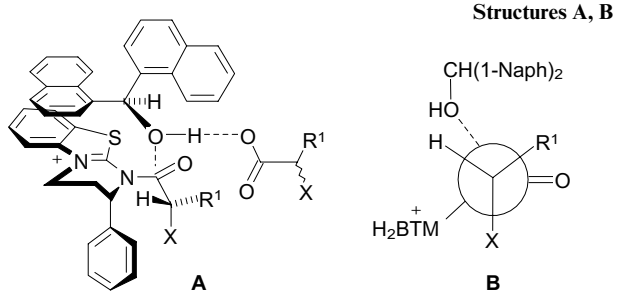
Scheme 43



A possible model of the transition state (structure **A**) arising during acylation of alcohol **104** with anhydrides of 2-substituted acids in the presence of (*S*)-homobenzotetramisole [(*S*)-**103**] is presented below.[105, 107]

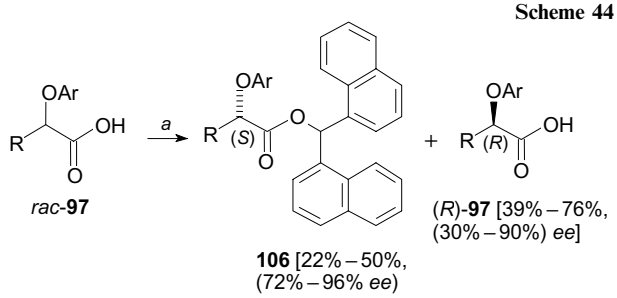
This model is analogous to the transition state model proposed previously for the KR of benzylic alcohols [108, 109] and obeys the Felkin – Anh rule (structure **B**). Presumably, an important role in the stereoselectivity for the studied catalysts belongs to π-stacking.[107] This assumption is in line with the results [107, 109] of quantum chemical calculations of the relative energies of transition states arising during the stereoselective acylation.

Structures A, B



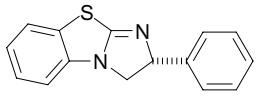
The kinetic resolution of 2-aryloxy acids **97** *via* acylation of achiral alcohol **104** in the presence of tetramisole (*R*)-**107** was described (Scheme 44, 19 examples).[110] The carboxyl group of aryloxy acids was activated by pivalic anhydride [$(Bu^tCO)_2O$]. The KR gave (*S*)-2-aryloxy esters **106** with

Scheme 44



(*a*) **104** (0.5 equiv.), $(Bu^tCO)_2O$ (1.2 equiv.), DIPEA (1.8 equiv.), (*R*)-**107** (0.05 equiv.), THF, 24 h; R = Me, Et, Pr^n; Ar = Ph, 2-MeC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 2-ClC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 2,4-$Cl_2C_6H_3$, 2,6-$Cl_2C_6H_3$, 2-FC_6H_4, 2-BrC_6H_4, 2-$MeOC_6H_4$, 2-$O_2NC_6H_4$, 2-PhC_6H_4, 2-Me-4-ClC_6H_3, 1-Naph, 2-Naph;

(*R*)-**107** =



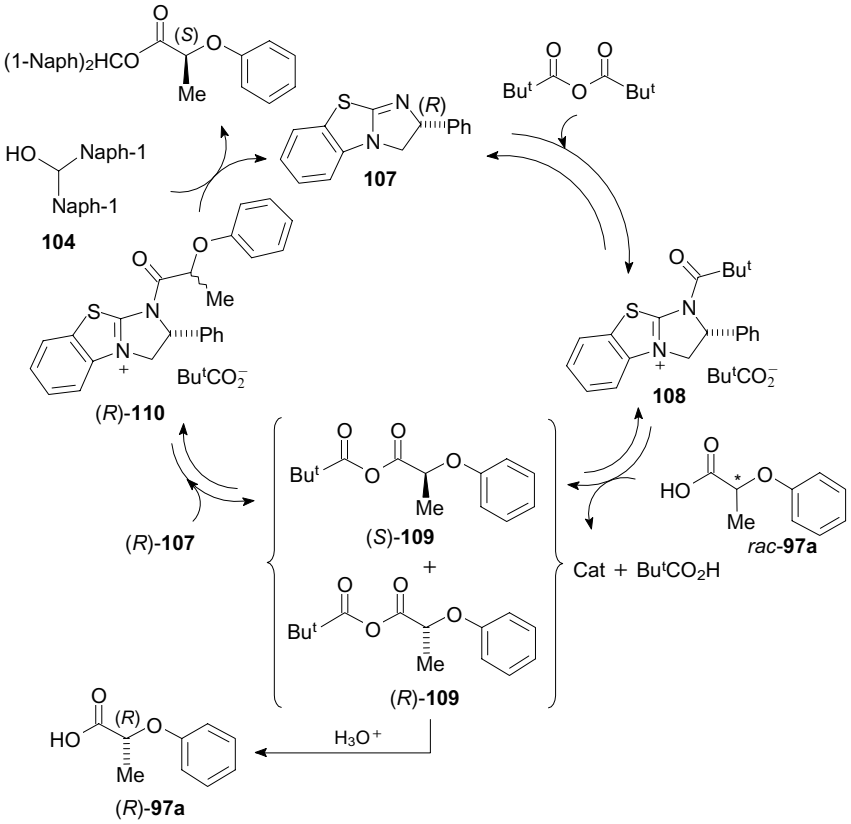
72% – 96% *ee* and acids (*R*)-**97** with 30% – 90% *ee*. The stereoselectivity of acylation of alcohol **104** with mixed anhydrides obtained from 2-aryloxy acids was shown to considerably depend on the nature of substituents and the pattern of substitution in the aromatic ring. The kinetic resolution was more efficient for *ortho*-substituted acids ($s = 35 – 131$) than for *meta*- and *para*-substituted homologues ($s = 14 – 17$). The observed selectivity was higher in the case of acids containing a bulky group in the *ortho*-position (for R = Me and Ar = 2-BrC_6H_4, $s = 110$; for R = Me and Ar = 2-PhC_6H_4, $s = 131$). The product of acylation of alcohol **104** with a sterically hindered isovaleric acid derivative (R = Pr^i, Ar = 2-PhC_6H_4) could not be obtained under the given conditions, and the starting acid was recovered in the racemic form.

A possible catalytic cycle of esterification of 2-aryloxy acid with alcohol **104** in the presence of pivalic anhydride and acyl transfer catalyst (*R*)-**107** is shown in Scheme 45.[110] Pivalic anhydride reacts with benzotetramisole (*R*)-**107** to give zwitter-ion **108**. This intermediate reacts with racemic 2-phenoxy acid to afford mixed anhydride **109**, which is converted to the second intermediate **110** in the presence of catalyst (*R*)-**107**. The acylation of di(1-naphthyl)methanol (**104**) (0.5 equiv.) with *N*-acylbenzotetramisole salt **110** leads to enantiomerically enriched (*S*)-ester; presumably, exactly this step determines the reaction enantioselectivity. By treatment of the reaction mixture with 1 M hydrochloric acid, the unreacted mixed anhydride **109** is converted to enantiomerically enriched (*R*)-2-phenoxypropionic acid (**97a**). To explain the predominant formation of *S*-enantiomeric esters in this reaction, quantum chemical calculations were carried out for the relative energies of the transition states arising upon the reaction of mixed anhydrides with nucleophile **104** in the presence of catalyst (*R*)-**107**.[110]

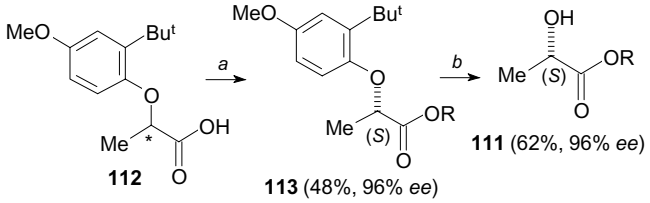
The kinetic resolution *via* acylation in the presence of benzotetramisole (*R*)-**107** was employed to obtain enantiomerically enriched (*S*)-lactate **111** (Scheme 46).[110] Initially, 2-aryloxy acid **112** is converted to ester (*S*)-**113** with 96% *ee* and in 48% yield ($s = 158$). The oxidative elimination of the aromatic group induced by cerium(IV) ammonium nitrate (CAN) allows for isolation of the target lactate in 62% yield, with the optical purity being retained.

The KR principle was implemented by Zhang *et al.*,[111] who explored the catalytic alkylation of the *N*,*N*-diphenylamide of 2-phenoxypropionic acid (**114**) (Scheme 47). The

Scheme 45

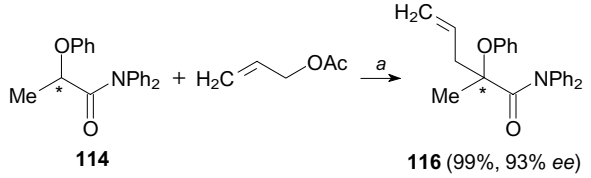


Scheme 46

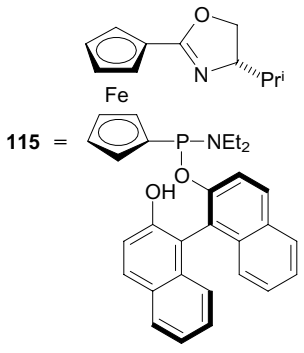


(*a*) **104** (0.5 equiv.), $(Bu^tCO)_2O$, DIPEA, (*R*)-**107** (0.05 equiv.), THF, 24 h; (*b*) CAN, DMF, H_2O; R = $CH(Naph\text{-}1)_2$

Scheme 47



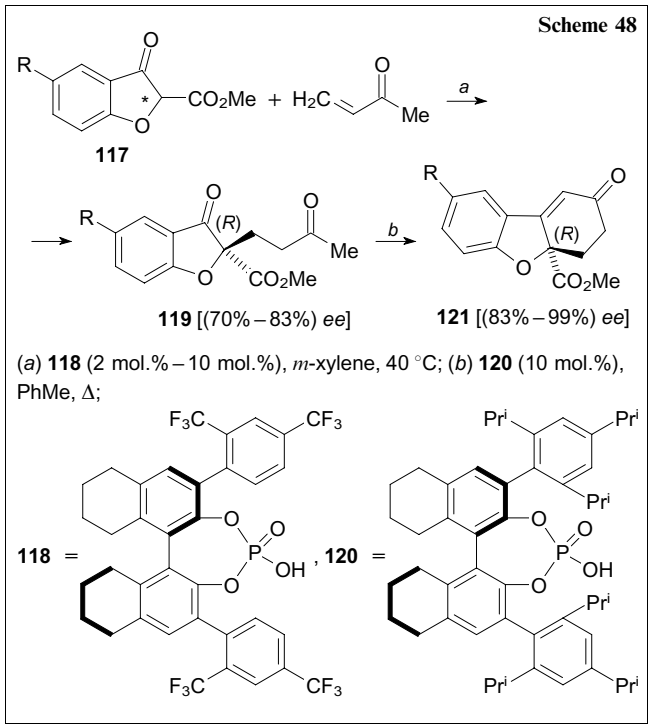
(*a*) **115** (2 mol.%), [{$Pd(C_3H_5)Cl$}$_2$] (1 mol.%), $LiN(SiMe_3)_2$, LiCl, THF;



reaction of starting racemic amide with allyl acetate in the presence of chiral catalyst **115** is stereoselective and results in the formation of enantiomerically enriched alkylation product **116** (93% *ee*) in 99% yield.

Kinetic resolution occured during the Robinson annulation of β-ketoesters **117** (Scheme 48).[112] The first step of annulation implies the stereoselective Michael reaction of β-ketoesters with methyl vinyl ketone in the presence of chiral catalyst **118**. The Michael addition affords enantio-

Scheme 48



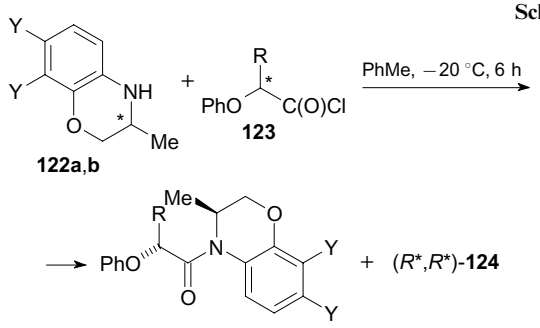
(*a*) **118** (2 mol.% – 10 mol.%), *m*-xylene, 40 °C; (*b*) **120** (10 mol.%), PhMe, Δ;

merically enriched adducts **119** (70%–83% *ee*). In the second step, adducts **119** undergo intramolecular aldol condensation in the presence of catalyst **120** with elimination of water. Successive enantioselective transformations gave products **121** in 53%–72% yields and with 83%–99% *ee*.

The kinetic resolution of racemates as a result of diastereoselective acylation is a convenient method for the preparation of enantiomerically pure compounds.[113,114] Originally, this method was used to isolate enantiomerically pure amines,[115–117] and recently it was applied to obtain the *R*-isomer of 2-phenoxypropionic acid **97a**.[10]

The stereoselective acylation of heterocyclic aromatic amines **122a**,**b** with 2-phenoxy acyl chlorides **123** was reported [Scheme 49, 6 examples, (*R*,*S*)/(*R*,*R*)-diastereomer ratio is given].[9]

Scheme 49

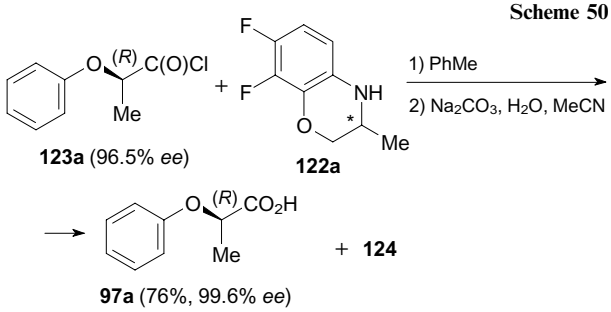


(*R*,*S*)-**124** [(29%–69%), up to 99.8 : 0.2 *dr*]

122: Y = F (**a**), H (**b**); R = Me, Pr^i, Bn

The reaction stereoselectivity was evaluated using the following approach: a racemic amine was reacted with a racemic acylating agent. This approach refers to mutual kinetic resolution;[118] in this case, the ratio of the resulting diastereomeric products **124** is equal to the selectivity factor *s*.[119] It was ascertained that benzoxazines **122** react with 2-phenoxy acyl chlorides **123** stereoselectively, with the selectivity factor reaching 499. These results formed the ground for a method for enantiomeric enrichment of scalemic (*R*)-**97a** (96.5% *ee*).[10] The reaction of chloride **123a** prepared from scalemic (*R*)-2-phenoxypropionic acid (**97a**) with 0.15 equiv. of racemic difluorinated benzoxazine derivative **122a** (Y = F) resulted in a mixture of diastereomeric amides **124**. Treatment of the unreacted chloride with a sodium carbonate solution gave enantiopure target (*R*)-acid **97a** (99% *ee*) (Scheme 50). The proposed approach demonstrates the applicability of mutual KR (Ref. 118) for the isolation of single enantiomers of a 2-aryloxy acid.

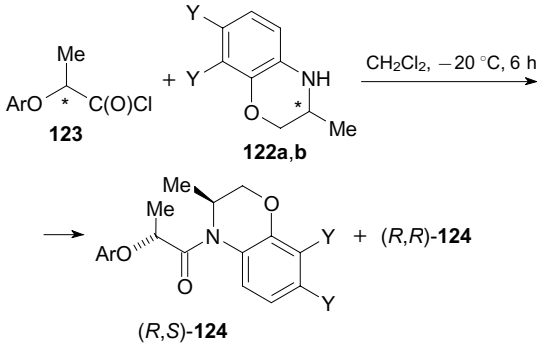
Scheme 50



More recently, amines **122a**,**b** were used for the KR of 2-alkoxy acids and showed a moderate stereoselectivity (*s* of up to 32).[120]

To clarify the mechanisms responsible for the stereoselectivity of acylation of 3-methylbenzoxazines **122a**,**b**, quantum chemical modelling of reactions of these amines with 2-aryloxy acyl chlorides **123** was carried out (Scheme 51).[121]

Scheme 51



Y = H, F; Ar = Ph, 4-$O_2NC_6H_4$, 4-$MeOC_6H_4$

The reaction of racemic benzoxazines **122** with racemic reagents **123** in dichloromethane at −20 °C furnished diastereomerically enriched amides **124**, with the selectivity factor varying from 20 to 85. The calculation of Gibbs energy difference ($\Delta\Delta G$) between the diastereomeric transition states at the COSMO-CH_2Cl_2-B3LYP-D3-gCP/def2TZVP level of theory demonstrated good agreement with experimental data. The calculated transition state geometry unambiguously indicated a significant role of aromatic interactions in the observed stereoselectivity, since stabilizing π-stacking was found in the preferable *R*,*S*-transition state.

5. Conclusion

Analysis of the published data demonstrates that enantiomerically pure compounds, in general, and 2-aryloxy carboxylic acid derivatives, in particular, are finding more and more extensive use in organic synthesis. The diversity of applications of enantiomerically pure 2-aryloxy acids is impressive, ranging from reagents for determining the enantiomeric purity to intermediates in the synthesis of valuable biologically active compounds and agrochemicals.

The data presented in the review demonstrate the successful development of preparation methods for the enantiomers of 2-aryloxy carboxylic acids, including both traditional approaches to resolution of racemates and asymmetric synthesis. The methods described in contemporary publications make it possible to produce the target acids with optical purity above 99%. It is important to note that synthetic chemists have found approaches to enantiomerically pure 2-aryloxy acids that require no sophisticated or expensive reagents. However, applicability of one or another approach considerably depends on the structure of the target 2-aryloxy acid. It is not always possible to obtain structurally similar compounds with equal efficiency. In addition, the mechanisms of spatial selectivity of the reactions are still obscure. In view of the high practical value of many compounds of this class, one can state with confidence that the development and study of rational pathways towards enantiomerically pure 2-aryloxy carboxylic acids

will continue to attract attention of synthetic organic chemistry professionals.

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